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# A short synthetic route to nordihydroguaiaretic acid (NDGA) and its stereoisomer using Ti-induced carbonyl-coupling reaction

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**Abstract**—A rapid synthetic approach to natural *meso*-nordihydroguaiaretic acid (NDGA) and its non-*meso* isomer is described from (3,4-dimethoxyphenyl)acetone using as a key step the low-valent Ti-induced carbonyl-coupling reaction of the ketone. The method involves a simple separation of the *E*- and *Z*-isomers that result from the dehydroxylation of the diol product of the coupling. The present approach allows the preparation of various analogs of NDGA. © 2001 Elsevier Science Ltd. All rights reserved.

Nordihydroguaiaretic acid (NDGA, **1**) is a product of the creosote bush or chaparral, *Larrea tridentata* Cav. (Zygophyllaceae), that is widely distributed throughout the arid regions of the southwestern US and northern Mexico.[1] This lignan is a well-studied inhibitor of lipoxygenase[2] and is also associated with a wide range of pharmacological activities, including the inhibition of the human papillomavirus,[3] herpes simplex[4] and HIV,[5] as well as having hyperglycemic activity.[6,7] NDGA was approved by the FDA (Food and Drug Administration) for the treatment of multiple actinic keratoses and was available on the market for a short time before it was withdrawn due to dermatologic side effects.[8] As we were interested in screening **1** and a number of structurally related compounds as inhibitors of relevant signaling and cell cycle targets involved in cancer growth and development, we needed to have a rapid and versatile synthetic method that would allow us to make structural modifications on various parts of the molecule.

A literature search on the synthesis of **1** revealed only a handful of research articles scattered for the past 60 years. The first account on the subject reported by Liebermann et al. was published in 1947[9] describing the dimerization of 1-piperonyl-1-bromoethane by reacting it with its Grignard derivative to produce methylenedioxy–NDGA. In the following half-century, a few patent applications and scientific papers appeared utilizing the same principle but using different reagents. For example, **1** was obtained by the dimerization of 1-(3,4-dihydroxyphenyl)-1-bromopropane in the presence of Mg and $I_2$,[10] or the condensation of dimethoxypropiophenone with the corresponding bromo derivative.[11] Most of these methods produced one or the other stereoisomer or a mixture of both. Carbonyl-coupling reactions using low-valent titanium,[12] which have evolved since as powerful tools in the synthesis of complex natural products, appeared to be an attractive alternative route to both **1** and its non-*meso* isomer **2**. This approach also offers many possibilities to produce a wide variety of derivatives of **1**, since carbonyl containing compounds are easily accessible. In this communication, we wish to report a simple and stereoselective approach to the synthesis of **1** and **2** using as a key step the low-valent Ti-induced carbonyl-coupling reaction of (3,4-dimethoxyphenyl)-acetone (**3**). The resulting butanediol intermediate **4** may be dehydroxylated to give the corresponding *Z*- and *E*-butenes **5a** and **5b**, which in turn may be individually subjected to catalytic hydrogenation to afford **1** and **2**, respectively, after demethylation of the methoxy-derivatives **6a** and **6b** (Scheme 1).

The key carbonyl-coupling reaction of the phenylacetone **3** was carried out using $TiCl_4$ as the source of the low-valent Ti, and Zn dust as the reducing agent. Slow addition of the Zn dust into the solution of **3** and $TiCl_4$ in anhydrous THF under an atmosphere of $N_2$ appeared to be critical for the formation of the butane-

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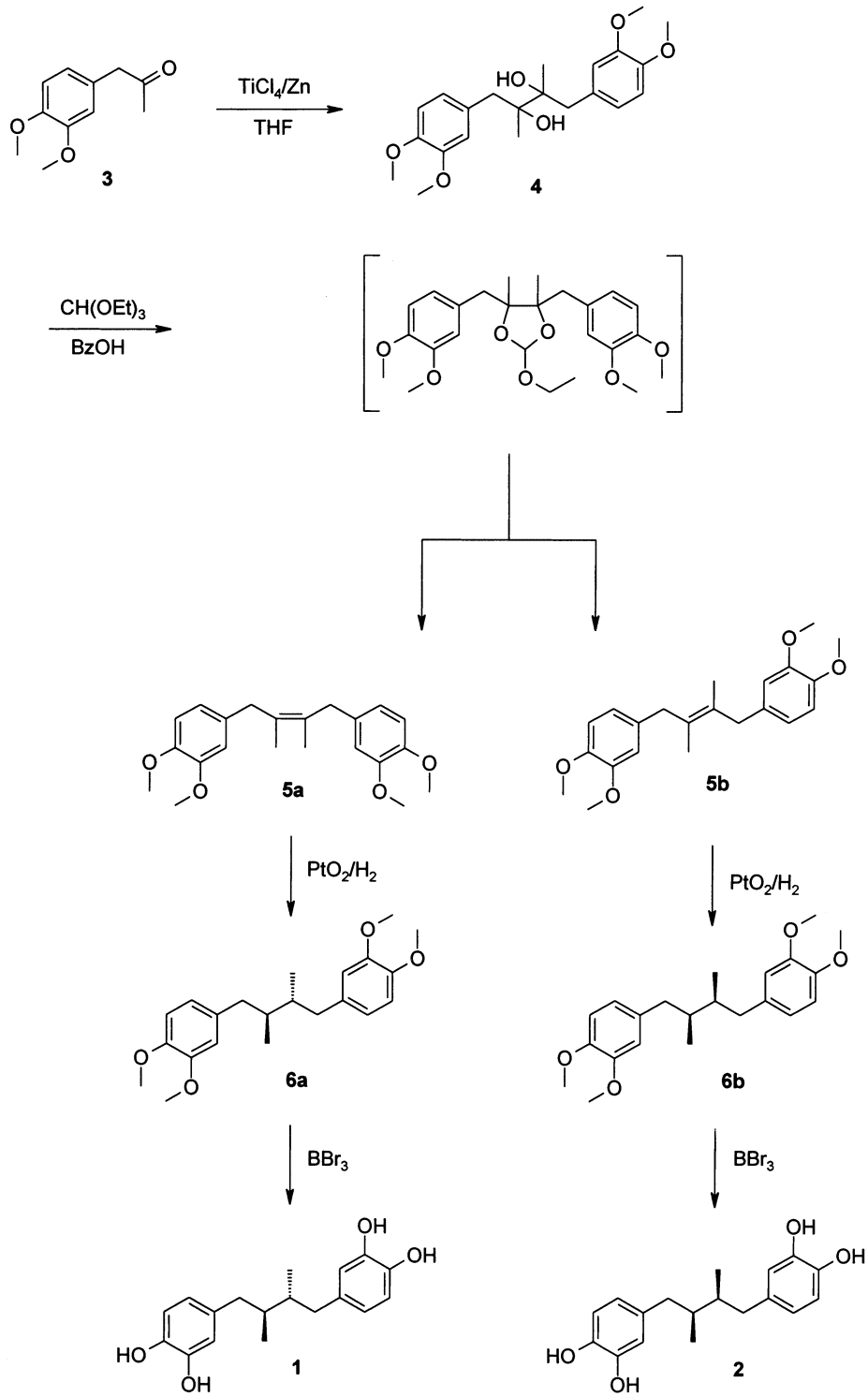


**Scheme 1.**

diol **4**. A relatively faster addition of the Zn resulted in the reduction of the ketone **3** to the corresponding benzyl alcohol.[13] Surprisingly, the formation of the expected McMurry type olefinic products was never observed in our study, even upon prolonged heating of the reaction mixture. The dehydroxylation of **4** was accomplished by heating a mixture of **4** and triethyl orthoformate in the presence of benzoic acid as a catalyst first at 100°C for 2 h followed by 180°C for 4 h. A flash column-chromatographic purification of the crude product gave a 4:6 mixture of **5a** and **5b** in 65% yield. Simple recrystallization of the mixture from EtOH afforded **5b**, whereas **5a** was obtained by evaporation of the mother liquor. The structure of **5a** was assigned based on the $^1$H NMR spectrum of its hydrogenation product **6a**, which was identical to that of the product obtained by the methylation of the naturally-occurring **1**. These data, therefore, allowed us to also

assign the structure of **5b** as the other possible isomer. Attempts to hydrogenate **5b** using Pd/C in AcOH or EtOAc resulted in the formation of a mixture of **6a** and **6b**. No reaction was observed when the dissolving catalyst $(Ph_3P)_3RhCl$ was used in thiophene-free benzene. Finally, hydrogenation of **5b** in the presence of Pt black in EtOAc for 1 h led to a quantitative conversion to **6b** according to HPLC analysis of an aliquot. Similarly, hydrogenation of **5a** with the same catalyst for 2.5 h produced **6a** quantitatively according to HPLC. It was observed that a longer exposure of the starting materials to the catalyst resulted in a complex, UV-inactive mixture. Compounds **6a** and **6b** were demethylated to **1** and **2**, respectively, with $BBr_3$ in anhydrous $CH_2Cl_2$ at −78°C by slowly warming up the reaction mixture to reach room temperature. Synthetic **1** was spectroscopically identical to an authentic sample of the natural product.[14]

In summary, we have succeeded in developing a rapid and versatile synthetic route to the naturally-occurring nordihydroguaiaretic acid and its non-*meso* isomer starting from the commercially available (3,4-dimethoxyphenyl)acetone. The use of this method in the synthesis of a series of diverse analogs of NDGA for biological studies is currently in progress and will be reported in due course.

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13. A typical procedure for the preparation of **4** is as follows: A 100-mL three-neck round-bottom flask equipped with a solid addition funnel, a reflux condenser, and a rubber septum with a stirring bar inside, and a $N_2$ inlet on top of the condenser was charged with 1 g (5.14 mmol) phenylacetone **3** and 50 mL anhydrous THF under an atmosphere of $N_2$. $TiCl_4$ (1.46 g, 7.71 mmol) was transferred and 1.01 g (15.42 mmol) Zn dust that had been placed in the addition funnel was added in small portions over 0.5 h. At the end of the addition, the resulting mixture was refluxed for 3 h, cooled to room temperature and hydrolyzed using 10 mL 10% $K_2CO_3$ solution and stirring for 2 h. The solids were separated by filtration and washed with 50 mL THF. The filtrate and the washings were combined and diluted with 50 mL $H_2O$. The clear solution was concentrated to about 50 mL and extracted with 50 mL EtOAc. The organic layer was washed with 50 mL $H_2O$, dried over anhydrous $Na_2SO_4$ and the solvent was evaporated to yield 0.96 g of a white solid. Recrystallization of the solid from a mixture of hexanes and EtOAc gave 0.74 g **4** as white crystals (73%). $^1H$ NMR (300 MHz) (DMSO-$d_6$): 0.89 (6H, s), 2.62 (2H, d, $J=13.5$ Hz), 2.72 (2H, d, $J=13.3$ Hz), 3.71 (6H, s), 3.72 (6H, s), 4.02 (1H, s), 4.04 (1H, s), 6.74 (2H, d, $J=8.1$ Hz), 6.83 (2H, d, $J=8.1$ Hz), 6.89 (2H, s).
14. NMR data for **1**: $^1H$ NMR (600 MHz) (acetone-$d_6$): 0.82 (6H, d, $J=6.6$ Hz), 1.72 (2H, m), 2.20 (2H, dd, $J=9.0$ and 4.2 Hz), 2.68 (2H, dd, $J=8.4$ and 4.8 Hz), 6.52 (2H, dd, $J=6.0$ and 1.8 Hz), 6.68 (2H, d, $J=1.8$ Hz), 6.73 (2H, d, $J=7.8$ Hz), 7.56 (4H, br. s). $^{13}C$ NMR (150 MHz) (acetone-$d_6$): 16.5, 39.2, 40.1, 115.8, 116.9, 121.2, 134.4, 143.7, 145.6. NMR data for **2**: $^1H$ NMR (600 MHz) (acetone-$d_6$): 0.79 (6H, d, $J=7.2$ Hz), 1.75 (2H, m), 2.29 (2H, dd, $J=8.4$ and 4.8 Hz), 2.52 (2H, dd, $J=7.8$ and 6.0 Hz), 6.45 (2H, dd, $J=6.0$ and 1.8 Hz), 6.62 (2H, d, $J=1.8$ Hz), 6.70 (2H, d, $J=7.8$ Hz), 7.53 (2H, s), 7.57 (2H, s). $^{13}C$ NMR (150 MHz) (acetone-$d_6$): 14.2, 39.1, 41.5, 115.8, 116.8, 121.1, 134.1, 143.8, 145.6.