A Simple Synthesis of Nordihydroguaiaretic Acid and Its Analogues

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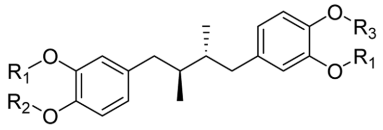
Nordihydroguaiaretic acid (NDGA, **1aa**) is a non-toxic phenolic lignan isolated from the resinous exudations of the North American creosote bush such as *Larrea divaricata* Cav. (Zygophyllaceae).[1] In addition to the usage as an antioxidant in food,[2] interests in NDGA have been continuously increased due to its intriguing pharmacological properties including the inhibitory activity on lipoxygenase,[3] inflammation-inducing systems,[4] herpes simples,[5] HIV,[6] and human papillomavirus,[7] as well as hyperglycemic activity.[8] As a family of NDGA, related compound tetra-*O*-methyl-NDGA (**1ea**) showed tumoricidal activity,[9] and compounds **1ca** and **1eb** (machillin A) showed strong inhibitory activity on melanin biosynthesis.[10]



1aa $R_1 = R_2 = R_3 = H$ (NDGA)
ba $R_1 = CH_3$, $R_2 = R_3 = H$ (dihydroguaiaretic acid)
ca $R_1 = R_2 = CH_3$, $R_3 = H$
da $R_1, R_2 = CH_2$, $R_1, R_3 = CH_2$
ea $R_1 = R_2 = R_3 = CH_3$

Efforts to develop an efficient synthetic method for the preparation of lignan continued for decades. The first preparation of **1aa** was pursued in 1918 many years before it was isolated as a naturally occurring substance by demethylation of hydrogenated dimethyl ether (**1ba**) of (−)-guaiaretic acid.[11] Later, present structure of naturally occurring **1aa** was confirmed through synthesis.[12] More systematic synthesis was reported in 1947 by reacting 1-piperonyl-1-bromoethane and its Griganrd derivative as a key step.[13] Such a method has been modified for decades but failed to increase yield and/or selectivity toward desired stereoisomers.[14] Ti-induced carbonyl-coupling reactions of the substituted phenylacetones, surprisingly, resulted in 1,4-disubstituted-butane-2,3-diols instead of expected McMurry type butenes.[15] Oxidative coupling of β-keto esters,[16] double condensation of piperonal with diethyl succinate followed by a couple of reductive steps,[17] and transition metal-phosphine complex catalyzed Grignard coupling reaction of halothiophenes followed by catalytic reduction,[18] have also been pursued. These methods somewhat improved stereo-selectvity as well as yield, but the cost of the reagents, low yield reactions, lengthy reaction sequences employed might be bottle necks to have a general applicability especially unsymmerically substituted NDGAs.

As a part of our research on biologically important natural products **1** as well as their analogues, we herein described a modified procedure for the preparation of NDGA and related lignans *via* 1,4-di(susbtituted-phenyl)-2,3-dimethyl-butan-2-ol as a key intermediate.

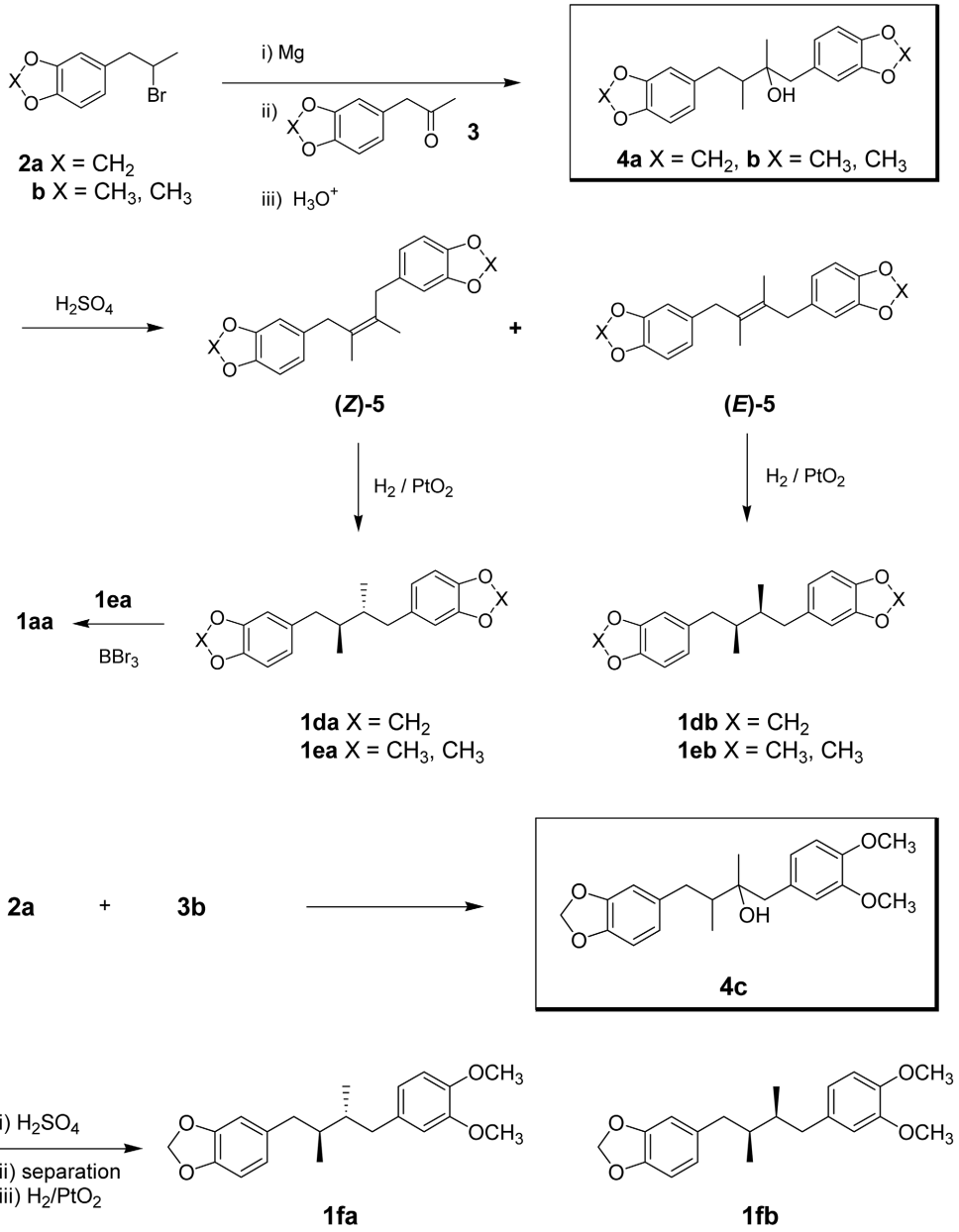
Grignard reagents generated from bromo compounds **2** were reacted with ketones **3** to yield corresponding alcohols **4** in fairly good yields.[19] ^{1}H NMR spectra of **4** showed presence of two diastereomers as a mixture of *erythro*- and *threo*-isomers.[20] Separations of these isomers were not attempted, but instead the mixtures were directly subjected to next step. Dehydration of **4** by concentrated sulfuric acid afforded two regioisomers, (*Z*)-**5** and (*E*)-**5** in a ratio of 3.8 : 6.2 and 3.5 : 6.5 for **5a** and **5b**, respectively in approximately 70% yields. Two regioisomers were readily separable since *E*-isomers are crystalline while *Z*-isomers are oily at room temperature. Structures of (*Z*)-**5** and (*E*)-**5** were confirmed by comparing their ^{1}H NMR spectra and those of the corresponding hydrogenation products to literature values. Catalytic hydrogenation of (*Z*)-**5** in the presence of PtO_2 afforded **1da** and **1ea** while (*E*)-**5** afforded **1db** and **1eb**, respectively, over 85% yields. On the other hand, demethylation of **1ea** with BBr_3 afforded desired NDGA in 75% yield. The prerequisite compounds **2** and **3** were prepared from commercially available 3,4-substituted-1-allylbenzenes by employing previously reported methods.

The generality of the scheme was examined with **2a** and **3b** to provide the corresponding carbinol **4c** in 82% yield. Three-step conversion of **4c** provided new NDGA analogues **1fa** and **1fb** 54% and 45% overall yields, respectively.

In conclusion, a simple procedure for the preparation of NDGA analogues has been established by employing Grignard reagents and readily available ketones as starting materials. Present procedure has an advantage over previously reported methods for preparation of symmetrical as well as unsymmetrically substituted NDGA analogues. Preparation of a series of NDGA analogues is currently in progress and will be due in near future.

Experimental Section

Melting points were determined using a Fischer-Jones melting points apparatus and are not corrected. IR spectra were obtained using a Perkin-Elmer 1330 spectrophoto-



meter. NMR spectra were obtained using a Bruker-250 spectrometer 250 MHz or 400 MHz for ^{1}H NMR and 62.5 MHz or 100 MHz for ^{13}C NMR and are reported as parts per million (ppm) from the internal standard tetramethylsilane (TMS). The starting materials **2a**,[13] **2b**,[21] **3a**,[22] and **3b**[23] were prepared by employing previously reported method. Chemicals and solvents were commercial reagent grade and used without further purification. Elemental analyses were taken on a Hewlett-Packard Model 185B elemental analyzer.

1,4-Bis(3,4-methylenedioxyphenyl)-2,3-dimethyl-2-butene (5a) (General Procedure) Into a mixture of Mg turning (0.50 g, 20.5 mmol) in dry ether (20 mL) was slowly added bromo-compound **2a** (5.00 g, 20.5 mmol) in 50 mL of dry ether *via* septum using syringe. To initiate reaction, a crystal of I_2 was added and resulting mixture was refluxed for 1.5 h. After cooling reaction mixture to room temperature, a solution of **3a** (3.00 g, 20.5 mmol) in dry ether (20 mL) was added in a rate of maintaining reaction mixture under reflux. On the completion of addition (~10 min), resulting mixture was heated an additional half hour before allowed the mixture to stand at room temperature for 8 h. To a cooled reaction mixture on ice bath was added 10 g of crushed ice, followed by 2.5 M H_2SO_4 (50 mL). The resulting mixture was extracted with ether (50 mL × 3). Combined organic layers were dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 5.96 g (85%) of oily material, which was pure enough for next step. A mixture of **4a** (3.42 g, 0.01 mol) in 98% H_2SO_4 (20 mL) was heated at 100 °C for 2 h. The reaction mixture was poured to a mixture of ether and ice water (1 : 1, 100 mL). Resulting aqueous layer was extracted with ether (30 mL × 2). The organic layers were combined, washed with water, and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 2.36 g (73%) of oily material, which was crystallized in

refrigerator to give 1.43 g (44%) of solid which was recrystallized from EtOH to give (***E***)-**5aa** as white needles: mp 118-119 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.69 (s, 6H, 2 x CH_3), 3.34 (s, 4H, 2 x CH_2), 5.92 (s, 4H, OCH_2O), 6.63 (d, J = 7.8 Hz, 2H), 6.64 (d, J = 1.8 Hz, 2H), 6.72 (d, J = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 18.86, 40.32, 101.16, 108.49, 109.21, 121.62, 129.32, 134.97, 146.03, 148.03. Anal Cald. for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 74.08; H, 6.23. Mother liquor was chromatographed on silica gel eluting with CH_2Cl_2 to give 0.89 g (27%) of (***Z***)-**5ab** as an oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.63 (s, 6H, 2 x CH_3), 3.40 (s, 4H, 2 x CH_2), 5.90 (s, 4H, OCH_2O), 6.62-6.75 (m, 6H). ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 18.42, 39.65, 100.70, 107.99, 108.80, 121.22, 128.63, 134.37, 145.57, 147.55. Anal Cald. for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 74.06; H, 6.24.

1,4-Bis(3,4-dimethoxyphenyl)-2,3-dimethyl-2-butene (5b) (*E*)-5ba White needles (EtOH, two-step yield 53%): mp 104-105 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.73 (s, 6H, 2 x CH_3), 3.38 (s, 4H, 2 x CH_2), 3.80 (s, 6H, 2 x OCH_3), 3.84 (s, 6H, 2 x OCH_3), 6.68-6.78 (m, 6H). The mother liquor was chromatographed on silica gel eluting with CH_2Cl_2 to give (***Z***)-**5bb** (two-step yield 32%) as an oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.66 (s, 6H, 2 x CH_3), 3.46 (s, 4H, 2 x CH_2), 3.83 (s, 6H, OCH_3), 3.89 (s, 6H, OCH_3), 6.65-6.88 (m, 6H). Anal Cald. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.16; H, 7.94.

(*meso*)-1,4-Bis(3,4-methylenedioxyphenyl)-2,3-dimethylbutane (1da) (General Method) Into a stirred suspension of (***Z***)-**5aa** (100 mg, 0.31 mmol) and PtO_2 (10 mg) in EtOAc (20 mL) in Parr hydrogenation bottle was passed H_2 gas and maintained the pressure at approximately 40 psi. The resulting mixture was shaken for 1.5 h and filtered to remove insoluble materials. The organic layer was washed with water and dried over $MgSO_4$. Evaporation of the solvent afforded 90 mg (90%) of pale yellow oil, which was recrystallized from CH_3OH to give white prisms: mp 135-136 °C (lit.[24] mp 135-136 °C). ^{1}H and ^{13}C NMR data are identical to those of previously reported.

(±)-1,4-Bis(3,4-methylenedioxyphenyl)-2,3-dimethylbutane (1db) White needles: mp 48-49 °C (lit.[25] mp 48-50 °C). ^{1}H and ^{13}C NMR data are identical to those of an authentic sample of the natural product.

(*meso*)-1,4-Bis(3,4-dimethoxyphenyl)-2,3-dimethylbutane (1ea) White needles: mp 101-102 °C (lit.[6] mp 100-101 °C). ^{1}H and ^{13}C NMR data are identical to those of previously reported.

(±)-1,4-Bis(3,4-dimethoxyphenyl)-2,3-dimethylbutane (1eb) Colorless prisms: mp 70-71 °C (lit.[26] mp 70.4-71.2 °C).

(*threo*)-1-(3,4-Methylenedixoyphenyl)-4-(3,4-dimethoxyphenyl)-2,3-dimethylbutane (1fa) White needles: mp 62-63 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.81 (d, J = 6.0 Hz, 6H, 2 x CHCH_3), 1.75 (m, 2H, 2 x CHCH_3), 2.51 (m, 4H, benzylic H), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.90 (s, 2H, O-CH_2-O), 6.54-6.82 (m, 6H). Anal Cald. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.72; H, 7.64.

(*erythro*)-1-(3,4-Methylenedixoyphenyl)-4-(3,4-dimethoxyphenyl)-2,3-dimethylbutane (1fb) Semisolid. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.79 (d, J = 6.0 Hz, 3H, CHCH_3), 0.81 (d, J = 7.0 Hz, 3H, CHCH_3), 1.75 (m, 2H), 2.49 (AB quartet, 4H, benzylic H), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.90 (s, 2H, O-CH_2-O), 6.54-6.82 (m, 6H). Anal Cald. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.76; H, 7.66.

(*meso*)-NDGA (1aa) A solution of **1ea** (358 mg, 1.0 mmol) and BBr_3 (10 mL, 1.0 *M* solution in CH_2Cl_2) in dry CH_2Cl_2 (10 mL) was stirred at −78 °C for 1.5 h under Ar. Reaction mixture was allowed to reach room temperature. Usual work-up afforded pale yellow solid which was chromatographed on silica gel eluting with in CH_2Cl_2. The early fractions afforded cream needles (227 mg) after recrystallization from the eluent: mp 185-186 °C (lit.[11] mp 184-185 °C). ^{1}H NMR (CD_3OD, 250 MHz) δ 0.79 (d, J = 6.0 Hz, 6H, CHCH_3), 1.66 (q, J = 7.0 Hz, 2H, CHCH$_3$), 2.12 (dd, J = 13.0, 9.0 Hz, 2H, benzylic H), 2.61 (dd, J = 13.0, 6.0 Hz, 2H, benzylic H), 4.98 (br. s, 4H, OH), 6.37 (dd, 2H, J = 7.8, 1.2 Hz), 6.62 (d, 2H, J = 1.2 Hz), 6.73 (d, 2H, J = 7.8 Hz).

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