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Convenient Syntheses of Neurotrophic Americanol A and Isoamericanol A by HRP Catalyzed Oxidative Coupling of Caffeic Acid

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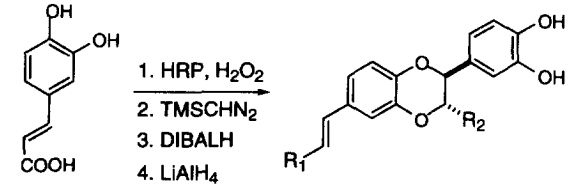
Abstract: Extremely simple syntheses of americanol A (**1**) and isoamericanol A (**2**) having intriguing neurotrophic properties have been accomplished by HRP catalyzed oxidative coupling of caffeic acid.

A unique group of the neo-lignans such as americanol A (**1**), isoamericanol A (**2**), americanin A (**3**) and isoamericanin A (**4**), which are characterized by having a 1,4-benzodioxane ring in their molecules and have a diversity of significant biological activities, occurs exclusively in the seeds of *Phytolacca americana* L.[1,2] Among them, americanol A (**1**) and isoamericanol A (**2**) exhibit interesting neurotrophic properties, i.e., the promotion of neurite sprouting and the enhancement of choline acetyltransferase activity in neuronal cell culture of the fetal rat cerebral hemishpere.[1c,3] Americanin A (**3**) and isoamericanin A (**4**) were already synthesized by employing the stepwise ether formation for the construction of the benzodioxane ring.[4] The biomimetic approach to the formation of the benzodioxane ring was demonstrated in the synthesis of a flavonolignan, silybin, by silver oxide-mediated[5] and horseradish peroxidase (HRP)[6] catalyzed oxidative couplings between dihydroquerecetin and conifenyl alcohol. Few enzymatic dimerization of caffeic acid regarded as a biosynthetic precursor for the neo-liganans **1** ~ **4**, however, has been investigated.[7] In this paper, we report the first syntheses of americanol A (**1**) and isoamericanol A (**2**) starting from the 1,4-benzodioxane dicarboxylic acids **5** and **6**, obtained directly by the HRP[8] catalyzed oxidative dimerization of caffeic acid.

Caffeic acid (1.80 g, 10 mmol), was incubated with HRP (1000 units, type II from Sigma, USA) in phosphate buffer (0.1M, pH 6.0) containing 18% 1,4-dioxane in the presence of H_2O_2 (1eq, 30 mL) at 20°C. After being stirred for 2 hrs, the reaction was quenched with 1M $NaHSO_3$ and then adjusted to pH 7.0 with



Caffeic acid

1 $R_1 = R_2 = CH_2OH$
3 $R_1 = CHO$, $R_2 = CH_2OH$
5 $R_1 = R_2 = CO_2H$
5a $R_1 = R_2 = CO_2Me$
5b $R_1 = CH_2OH$, $R_2 = CO_2Me$

2 $R_1 = R_2 = CH_2OH$
4 $R_1 = CHO$, $R_2 = CH_2OH$
6 $R_1 = R_2 = CO_2H$
6a $R_1 = R_2 = CO_2Me$
6b $R_1 = CH_2OH$, $R_2 = CO_2Me$

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1M NaOH. This solution was acidified to pH 3.0 with 1M $KHSO_4$ and extracted with ethyl acetate. Purification of the residue by HPLC[9] furnished the desired coupling products **5** (180 mg, 10%) and **6** (144 mg, 8%), and previously known 1-(3,4-dihydroxyphenyl)-6,7-dihydroxy-1,2-dihydro-2,3-naphthalenedicarboxylic acid (270 mg, 15%)[7] along with 30% of recovered caffeic acid. The structures of **5** and **6**[10] were established by 2 D NMR data. The subsequent methylation of **5** and **6** with $TMSCHN_2$ yielded the corresponding methyl diesters **5a** and **6a**, the conjugated esters of which could be reduced with DIBAL–H, giving rise to the esters **5b** and **6b**. They were, therefore, subjected again to $LiAlH_4$ reduction to afford **1** and **2** in 30 % and 40 % overall yields, respectively. The spectral data of **1** and **2** were superimposed with those of natural americanol A and isoamericanol A.

In summary, the efficient biomimetic syntheses of americanol A and isoamericanol A have been achieved by HRP catalyzed oxidative phenol coupling of caffeic acid. We have shown that HRP has a preference for the C-O coupling leading to the 1,4-benzodioxane ring formation, which are not readily accessible from caffeic acid by usual oxidative coupling methods.[11]

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2. Americanin A (**3**) shows an interesting antiheptatotoxic activity similar to that of silybin belonging to flavonolignan having a 1,4-benzodioxane ring,[1d] whereas isoamericanin A (**4**) can increase the release of endogenous prostaglandin I_2 from the rat aorta.[1b]
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8. HRP, an oxidative enzyme, is well known to catalyze oxidative phenolic coupling of many aromatic substrates to give the C–O and/or C–C coupled products. For recent examples see: a) Bolzacchini, E.; Brunow, G.; Meinardi, S.; Orlandi, M.; Rindone, B.; Rummakko, P.; Setala, H. *Tetrahedron Lett.* **1998**, *39*, 3291–3294. b) Ma, You-A.; Guo, Zhi-W.; Sih, C. J. *Tetrahedron Lett.* **1998**, *39*, 9357–9360. c) Schmitt, M. M.; Schüler, E.; Braun, M.; Häring, D.; Schreier, P. *Tetrahedron Lett.* **1998**, *39*, 2945–2946. d) Sridhar, M.; Vadivel, S. K.; Bhalerao, U. T. *Tetrahedron Lett.* **1997**, *38*, 5695-5696. e) Guo, Zhi-W.; Salamonczyk, G. M.; Hang, K.; Machiya, K.; Sih, C. J. *J. Org. Chem.* **1997**, *62*, 6700–6701. f) Donnelly, D. M. X.; Murphy, F. G; Polonski, J.; Prange, T. *J. Chem. Soc. Perkin Trans. I* **1987**, 2719–2722.
9. Column: Cosmosil 5C18 AR-II (ϕ 20 x 250 mm); solvent: CH_3CN–H_2O (1 : 2.5, 7 mL/min)); detector: UV 254 nm; **5** (RT 16. 2 min) and **6** (RT 19.6 min).
10. **5**: IR (KBr) cm^{-1}: 3300 (OH), 1684 (C=O), 1607, 1507 (Ar). ^1H NMR (CD_3OD): δ 7.56 (d, J=15.9, 1H), 7.17 (d, J = 1.9, 1H), 7.13 (dd, J = 8.5, 1.9, 1H), 6.96 (d, J = 8.5, 1H), 6.83 (br s, 1H), 6.74 (br s, 2H), 6.32 (d, J = 15.9, 1H), 5.16 (d, J = 5.1, 1H), 4.90 (d, J = 5.1, 1H); ^{13}C NMR (CD_3OD): δ 170.9, 170.6, 147.0, 146.5, 146.0, 145.8, 144.6, 129.9, 128.5, 123.4, 120.1, 118.4, 117.8, 117.6, 116.3, 115.4, 77.7, 77.1. **6**: IR (KBr) cm^{-1}: 3185 (OH), 1688 (C=O), 1607, 1507 (Ar); ^1H NMR (CD_3OD): δ 7.57 (d, J = 16.1, 1H), 7.17 (d, J = 1.8, 1H), 7.15 (dd, J = 8.4, 1.8, 1H), 7.00 (d, J = 8.4, 1H), 6.83 (d, J = 1.8, 1H), 6.72 (d, J = 1.8, 1H), 6.71 (s, 1H), 6.32 (d, J = 16.1, 1H), 5.37 (d, J = 3.3, 1H), 5.00 (d, J = 3.3, 1H); ^{13}C NMR (CD_3OD): δ 170.6, 170.1, 146.8, 146.2, 146.0, 145.8, 144.8,. 130.0, 128.1, 123.3, 119.7, 118.4, 117.5 (2 × C), 116.1, 115.1, 76.6, 76.3.
11. Autoxidation of caffeic acid at pH 8.5 resulted in the formation of a mixture of the 1,4-benzodioaxne-type dimers which had the cis oriented substituents on the dioxane ring. Cillies, J. J. L.; Singletone, V. L. *J. Agri. Food Chem.* **1991**, *39*, 1298–1303.