Chinese Chemical Letters Vol. 12, No. 6, pp. 485 – 486, 2001

First Enantioselective Synthesis of Isoamericanol A and Isoamericanin A

Wen Xin GU, An Xin WU, Xue Gong SHE, Xin Fu PAN*

Department of Chemistry, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000

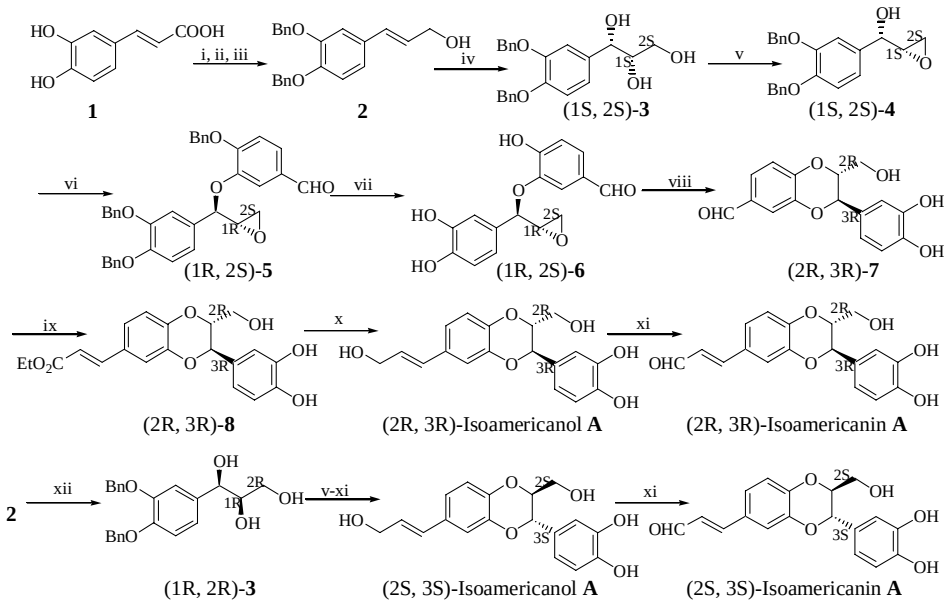
Abstract: The first enantioselective synthesis approach to two chiral 1,4-benzodioxane neolignans isoamericanol A and isoamericanin A was reported.

Keywords: Enantioselective, synthesis, 1,4-benzodioxane, neolignans.

Isoamericanol A and isoamericanin A, two neolignans which have choline acetyltransferase (ChAT) avtivity, were isolated as prostaglandin I_2 inducers from the seeds of *Phytolacca americana L*[1,2]. After its first description as a natural product, isoamericanin A has been synthesized in six steps[3]. Recently, we have developed a convenient synthesis of isoamericanol A and isoamericanin A in racemic form[4]. An unsolved problem is their asymmetric synthesis. Herein, we wish to report the first enantioselective syntheses of chiral neolignans isoamericanol A and isoamericanin A.

As shown in **scheme 1**, caffeic acid **1** was converted to a benzyl cinnamyl unsaturated alcohol **2** in 92% yield by esterification, protection and reduction. Asymmetric dihydroxy (1S, 2S)-**3** was obtained from **2** in 94% e.e. and 88% yield. (1S, 2S)-**3** was treated with *N*–tosylimidazole gave oxirane (1S, 2S)-**4** in 72% yield. Mitsunobu reaction between (1S, 2S)-**4** and 4-benzyloxy-3-hydroxybenzaldhyde gave ether (1R, 2S)-**5** in 81% yield. In this reaction the absolute configuration of C_1-position was converted completely by a S_N2 type nucleophilic displacement of 4-benzyloxy-3-hydroxybenzaldhyde. Three benzyl groups of (1R, 2S)-**5** were removed by hydrogenolysis to afford (1R, 2S)-**6** in 76% yield. (1R, 2S)-**6** underwent cyclization with potassium carbonate to afford (2R, 3R)-**7** in 83% yield. In this reaction an intramolecular nucleophilic attack at C_2-position of oxirane leaded to a complete conversion of the absolute configuration of C_2-position and the formation of 1,4-benzodioxane. In the ^{1}H-NMR spectrum of (2R, 3R)-**7** H-3 gave a doublet signal at δ 5.10 with a coupling constant (J = 8 Hz) indicating a typical of *trans* isomer and *threo* configuration. (2R, 3R)-**7** was treated with monoethyl malonate to afford (2R, 3R)-**8** in 88% yield. (2R, 3R)-**8** was reduced with LAH in the presence of $AlCl_3$ to afford (2R, 3R)-isoamericanol A in 62% yield. (2R, 3R)-isoamericanol A was subjected to oxidation with MnO_2/SiO_2 to afford (2R, 3R)-isoamericanin A in 77% yield.

Scheme 1



Reagents and conditions: i. MeOH, H_2SO_4, 90°C; ii. BnCl, DMF, K_2CO_3, 160°C; iii. LAH, THF, -10°C, (I, ii and iii 91%); iv. AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0°C, (88%); v. *N*–tosylimidazole, NaH, THF, rt, (72%); vi. Diethyl azodicarboxylate (DEAD), Ph_3P, 4-benzyloxy-3-hydroxybenzaldhyde, THF, rt, (81%); vii. Pd/C (5%), H_2, EtOAc, rt, (76%); viii. K_2CO_3, MeOH, rt, (83%); ix. Monoethyl malonate, Py, Piperidine, reflux, (88%); x. THF, LAH, $AlCl_3$, (62%); xi MnO_2/SiO_2, THF, (77%); xii. AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0°C, 20 h, (87%).

Similar, (1R, 2R)-**3** was obtained from **2** in 92% e.e. and 87% yield with the same seven steps treatment. (1R, 2R)-**3** afforded (2S, 3S)-isoamericanol A and (2S, 3S)-isoamericanin A in good yield.

All the spectral data were in good agreement with those of literature report.[1,2] Chiral analysis was performed on chiral chromatographic column.

Acknowledgment

We are grateful to the National Natural Science Foundation of China (No. 29972015) for support.

References

1. Y. Fukuyama, T. Hasegawa, M. Toda, M. Kodama, H. Okazaki, *Chem. Pharm. Bull.*, **1992**, *40* (1), 252.
2. T. Hasegawa, Y. Fukuyama, Y. Asakawa, *Chem. Lett.*, **1987**, 329.
3. H. Tanaka, I. Kato, K. Ito, *Chem. Pharm. Bull.*, **1987**, *35* (9), 3603.
4. X. G. She, W. X. Gu, T. X. Wu, X. F. Pan, *Synth. Commun.*, **1999**, *29* (15), 2625.

Received 16 August, 2000