Study on the Total Synthesis of Neolignans(I): Synthesis of the Methyl Ethers of Americanin A and Americanol A†

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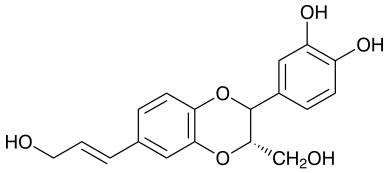
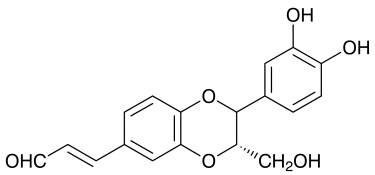
The methyl ethers of americanol A (**8**) and americanin A (**9**) were synthesized from the readily available caffeic acid **4** and ferulic acid **1**; conversion of *cis* **6** to *trans* **7** is a key step.

The neolignans americanol A (**8′**) and americanin A (**9′**), which have been isolated from the seeds of *phytolacca americana* (*phytolaccaceae*),[1,2] show antihepatotoxic activity[3] and increased CHAT activity,[4] and have received considerable attention from synthetic chemists.[5] In order to further confirm the structure, we developed a facile stereoselective synthesis of the methyl ethers of americanol A (**8**) and americanin A (**9**) in which the *cis* isomer was converted into the *trans* isomer by treatment with potassium carbonate.

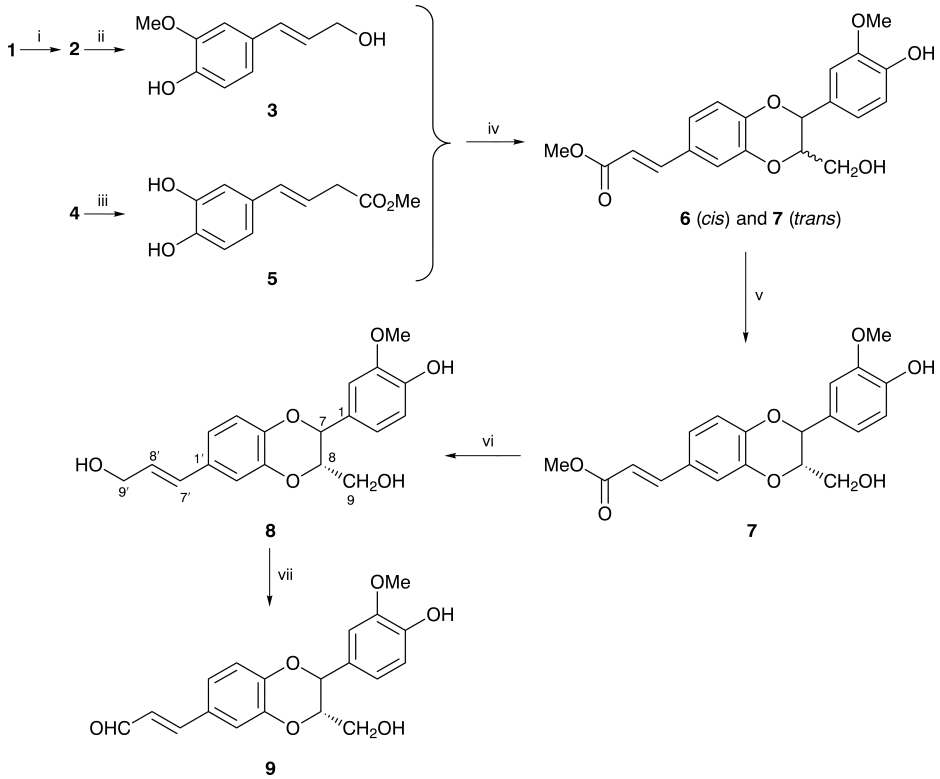


8′



9′

As shown in Scheme 1, ferulic acid **1** was esterified to afford compound **2** which was reduced by $LiAlH_4$ in the presence of $AlCl_3$ to obtain the corresponding unsaturated alcohol **3**,[5] **3** was coupled with **5** which was derived from **4**, to give a mixture of **6** (*cis*) and **7** (*trans*) isomers[6] [*ca* 1:5 by 400 MHz ^{1}H NMR: *cis*, δ 5.35 (H-7), 4.55 (H-8, $J_{7,8}$ = 3 Hz); *trans*, δ 5.01 (H-7), 4.14 (H-8, $J_{7,8}$ = 8 Hz)].[8,9] The mixture with anhydrous K_2CO_3 in dry DMF was stirred at room temperature for 40 min to give **7** exclusively. Then **7** was reduced to afford the first target compound **8** which was oxidized to obtain the second target compound **9**.[7]



Scheme 1 *Reagents and conditions*: i, MeOH, H_2SO_4, reflux, (95%); ii, $LiAlH_4$, $AlCl_3$, (75%); iii, MeOH, H_2SO_4. (95%); iv, $K_3Fe(CN)_6$, NaOAc; v, DMF, K_2CO_3, (iv, v overall yield 31.2%); vi, $LiAlH_4$, $AlCl_3$, (82%); vii, MnO_2, (60.4%)

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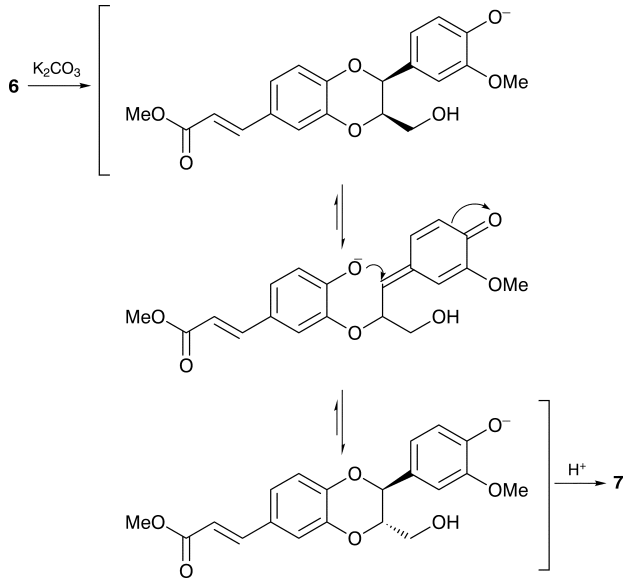
†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.



Scheme 2

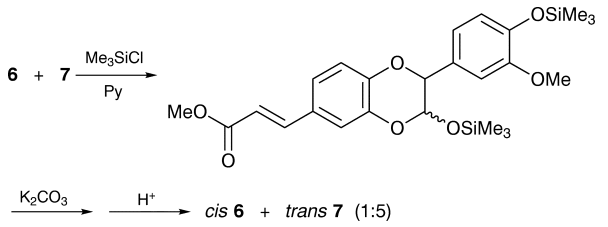
The mechanism of the conversion of **6** to **7** may involve a quinonemethide *via* reversible cleavage of the O—C^7 bond (Scheme 2).

In order to prove our assumption of this mechanism, we established that when the hydroxy group of **6** was protected by Me_3SiCl, conversion of **6** was not observed (Scheme 3).

Experimental

^{1}H NMR spectra were recorded on a Bruker AM400 spectrometer. IR spectra were recorded on a Nicolet170SXFT spectrometer. Mass spectral data were recorded on a VGZAB-HS instrument. Compounds **2**, **3** and **5** were prepared by reported procedures.[4,5]

Methyl-3-(2*R*/*S*,3*R*/*S*)-2-(4-*Hydroxy*-3-*methoxy*)-3-*hydroxylmethyl*-1,4-*benzodioxan*-6-*yl*]*propenoate* (**7**).—To a stirred solution of methyl-3-(3,4-dihydroxy)phenylprop-2-enoate **5** (500 mg, 2.58 mmol) and coniferyl alcohol **3** (511 mg, 2.83 mmol) in 25 ml acetone, sodium acetate (1.84 g, 8.71 mmol in 10 ml water) and then potassium hexacyanoferrate(III) (2.049 g in 15 ml water) were added dropwise during 40 min. The mixture was stirred at 25–30 °C for 4 h, then acidified with dilute hydrochloric acid and diluted with water. The product was extracted with ethyl acetate, washed with water and dried, the solvent was evaporated in vacuum and the residue purified on a silica gel column [ethyl acetate–light petroleum (1:2)] to afford a mixture of isomers **6** and **7** (0.52 g). The mixture was then dissolved in dry DMF and potassium carbonate (740 mg) added. After stirring for 1 h, the reaction solution was acidified with dilute hydrochloric acid, extracted with ethyl acetate, washed with brine, then dried, the solvent was evaporated, and the crude product recrystallized from methanol to give **7** as a white powder (300 mg, yield 31.25%); mp 144–146 °C; Elemental analysis: $C_{20}H_{20}O_7$ requires C, 64.51; H, 5.41. Found: C, 64.4; H, 5.4% ^{1}H NMR [$(CD_3)_2CO$], δ 7.58 (d, 1H, $J = 16$ Hz, H-8′), 7.10–7.20 (3H-Ar), 6.65–6.96 (3H-Ar), 6.41 (dd, 1H, $J = 16$, 4 Hz, H-7′), 5.01 (d, 1H, $J = 8$ Hz H-7), 4.14 (m, 1H, H-8), 3.84 (s, 3H, $COOCH_3$), 3.70 (s, 3H, OCH_3), 3.77 and 3.50 (dd, 2H, $J = 12$, 2 Hz, H-9). MS: m/z 372 (M^+, 100), 354 (69), 205 (25), 137 (46), 124 (22).



Scheme 3

Methyl Ether of Americanol A (**8**).—Compound **7** (290 mg in THF) was added to a solution of stirred $LiAlH_4$ (90 mg) and $AlCl_3$ (100 mg in 20 ml diethyl ether). The mixture was stirred at room temperature for 1.5 h, then saturated NH_4Cl was added, stirred for a while, extracted with ethyl acetate and dried, the solvent was evaporated off and the crude product was purified by flash-chromatography [ethyl acetate–light petroleum (2:1)] to obtain a white powder of **8** (220 mg, yield 82%); mp 186–188 °C; Elemental analysis: $C_{19}H_{20}O_6$ requires C, 66.27; H, 5.85. Found: C, 66.8; H, 5.9% IR (cm^{-1}): (KBr) 3400, 3293, 2928, 1611, 1584, 1505. ^{1}H NMR (400 MHz, CD_3CN): δ 7.20–6.81 (6H, Ar), 6.46 (d, $J = 15.9$ Hz, H-7′), 6.21 (m, $J = 15.9$, 5.4 Hz, 1H, H-8′), 4.87 (d, $J = 8$ Hz, 1H, H-7), 4.10 (m, $J = 5.4$ Hz, 2H, H-9′), 4.11 (m, $J = 7.5$, 5.1 Hz, 1H, H-8), 3.60 (s, 3H, OCH_3), 3.57 and 3.38 (dd, $J = 12.4$, 5.0 Hz, 2H, H-9); MS: m/z 344 (M^+ 44), 326 (78), 180 (62), 162 (77), 137 (100), 124 (62).

Methyl Ether of Americanin A (**9**).—To 30 mg of **8** in 20 ml ether was added 150 mg of activated MnO_2 and the mixture was stirred at room temperature for 18 h. MnO_2 was filtered off and TLC afforded **9** (18 mg, yield 60.4%); mp 167–168 °C; Elemental analysis: $C_{19}H_{18}O_8$ requires C, 66.66; H, 5.30. Found: C, 66.5; H, 5.4%. IR (cm^{-1}): (KBr) 3375, 2924, 2852, 1697, 1661, 1609, 1578, 1505, 1497; ^{1}H NMR [$(CD_3)_2CO$]: δ 3.38 and 3.59 (dd, $J = 2.2$, 5.0 Hz, 2H, H-9), 3.74 (s, 3H, OCH_3), 4.04 (m, 1H, H-7), 4.93 (d, 7.9 Hz, 1H, H-8), 4.10 (dd, 16.8 Hz, 1H, H-7′), 7.48 (d, 16 Hz, 1H, H-8′), 6.79–7.22 (m, 6H, ArH), 9.53 (d, 7.6 Hz, 1H, CHO); MS: m/z 342 (M^+ 100), 324 (42), 137 (33), 124 (19).

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