

Novel Regioselective Synthesis of 6-(3-Hydroxy-1-propenyl)-2-phenyl-2,3-dihydrobenzo[*b*]-1,4-dioxin-3-methanol

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A novel regioselective synthesis of neolignan, 6-(3-hydroxy-1-propenyl)-2-phenyl-2,3-dihydrobenzo[*b*]-1,4-dioxin-3-methanol, is described. 2-[bromo(phenyl)methyl]-oxirane upon condensation with 3,4-dihydroxybenzaldehyde gave regioselectively (±)-*trans*-3-hydroxymethyl-2-phenyl-2,3-dihydrobenzo[*b*]-1,4-dioxin-6-carbaldehyde, which upon reaction with dihydropyran in dichloromethane using (PPTS) gave 2-phenyl-3-(tetrahydro-2-pyranyloxy-methyl)-2,3-dihydrobenzo[*b*]-1,4-dioxin-6-carbaldehyde. This compound by a Wittig reaction with ethoxycarbonylmethylene-triphenylphosphorane gave stereoselectively ethyl 3-[*trans*-2-phenyl-3-(tetrahydro-2-pyranyloxymethyl)-2,3-dihydrobenzo[*b*]-1,4-dioxin-6-yl]-2-propenoate, which upon reduction with DIBAL-H afforded the title compound.

The neolignans (isoamericanol A, americanol A, isoamericanin A and americanin A isolated from *Phytolacca americana*) are found to have neurotropic and acetylcholine enhancing activity.[1] The neolignans possess a phenyl propane segment in two regioisomeric forms: 1) 3-aryl-2-hydroxymethyl-2,3-dihydrobenzo[*b*]-1,4-dioxin and 2) 2-aryl-3-hydroxymethyl-2,3-dihydrobenzo[*b*]-1,4-dioxin that cannot be distinguished from the ^{1}H NMR spectrum.

Earlier methods for constructing the key neolignan skeleton, i.e. 3-aryl-2-hydroxymethyl-2,3-dihydrobenzo[*b*]-1,4-dioxin or 2-aryl-3-hydroxymethyl-2,3-dihydrobenzo[*b*]-1,4-dioxin, involve i) the coupling of catechols or monoprotected catechol ethers with α,β-dibromodihydrocinnamates, epoxy coniferyl alcohols or ethyl-2-bromo-3-(3,4-dimethoxy)-phenyl-3-oxo propionates,[2–4] and ii) the coupling of substituted catechols with coniferyl alcohols using Ag_2O, Ag_2CO_3 or $K_3[Fe(CN)_6]$–NaOAc as catalysts.[5–7] Recently, it was reported that horse radish peroxidase (HRP) incubation of caffeic acid led to the formation of this skeleton.[8] Most of these methods involve a protection-deprotection sequence. The Ag_2O coupling method suffers from a regioisomeric problem, resulting in both regioisomers. The yields in all of the above methods are much less (30–50%). We have recently reported a general method for the synthesis of 2-aryl-3-hydroxymethyl-2,3-dihydrobenzo[*b*]-1,4-dioxins by the reaction of 2-[bromo(phenyl)methyl]oxirane with catechols, where we could not solve the regioisomer problem umambiguously.[9]

In the present paper, we report on a revision of the regioselectivity assigned to **3** in our earlier paper.[9] The regioselectivity assignment is now based on an X-ray analysis of the key intermediate **3** (Fig. 1), which is 2-aryl-3-hydroxymethyl-2,3-dihydrobenzo[*b*]-1,4-dioxin (**3**). We earlier reported on the structure of **3** as being 3-aryl-2-hydroxymethyl-2,3-dihydrobenzo[*b*]-1,4-dioxin. This paper also reports on a regioselective route for the synthesis of an analog of americanol A starting from **3**.

(±)-*threo*-2-[Bromo(phenyl)methyl]oxirane (**1**) on condensation with 3,4-dihydroxybenzaldehyde (**2**) in acetone–K_2CO_3 gave regioselectively (±)-*trans*-3-hydroxymethyl-2-phenyl-2,3-dihy drobenzo[*b*]-1,4-dioxin-6-carbaldehyde (**3**) (Fig. 1) in 70% yield, mp 104 °C, ^{1}H NMR δ 3.45 and 3.78 (m, 2H, CH_2OH), 4.05 (m, H-3), 4.62 (t, OH), 5.20 (d, J = 9 Hz, H-2), 7.10 (d, J = 9 Hz, H-8), 7.40 (m, H-5,7 and Ph), 9.85 (s, CHO). The doublet due to the H-2 (5.20, J = 9 Hz) shows that the substituents at C-2 (Ph) and C-3 (CH_2OH) are *trans*. Compound **3** upon a reaction with dihydropyran in dichloromethane using pyridinium–*p*-toluene sulfonate (PPTS) as a catalyst gave **4**, which was subjected to a Wittig synthesis with stabilized ylide, ethoxycarbonylmethylenetriphenylphosphorane (**5**),[10] to give stereoselectively *trans* α,β-unsaturated ester, ethyl 3-[2-phenyl-3-(tetrahydro-2-pyranyloxymethyl)-2,3-dihydrobenzo[*b*]1,4-dioxin-6-yl]-2-propenoate (**6**) in 75% yield (Scheme 1).

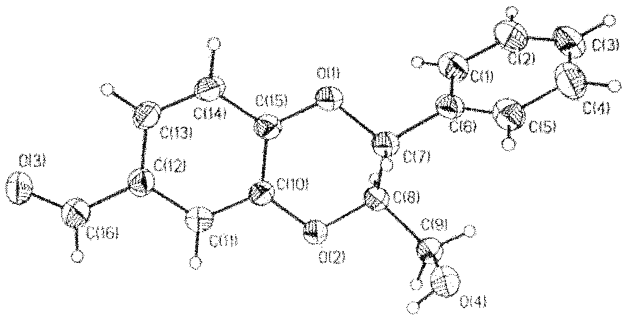
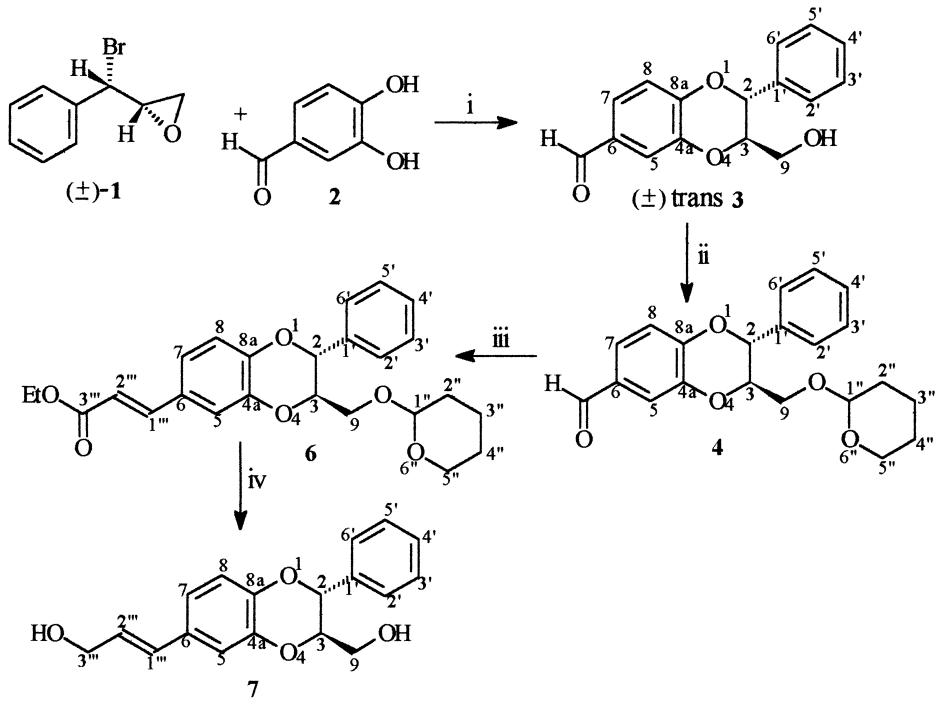


Fig. 1. X-ray structure of **3**.

In the ^{1}H NMR of **6**, the protons due to a *trans* double bond appeared at δ 6.20 (d, J = 18 Hz, H-2‴) and 7.50 (d, J = 18 Hz, H-3‴) and OCH_2CH_3 appeared at δ 1.35 (t, J = 8.0 Hz), 4.15 (q, J = 8 Hz). The other ^{1}H NMR signals of **6** are 1.50–1.60 (m, H-2″, 3″ and 4″), 3.40 and 3.80 (m, 2H, CH_2–O), 3.55 (m, H-5″), 4.50 (m, H-3), 4.55 (m, H-1″), 5.05 (d, J = 9 Hz, H-2), 6.85 (d, J = 9 Hz, H-8), 7.00 (m, H-5, 7) and 7.35 (m, H-2′, 3′, 4′, 5′, 6′). In the ^{13}C NMR of **6** the dioxane ring carbons C-



Scheme 1. i. Acetone/K_2CO_3, ii. DHP/PPTS, DCM, RT, iii. PPh_3=CHCOOEt (**5**), Benzene reflux, iv. DIBAL-H, DCM, 0 °C

2, C-3, CH_2O resonated at δ 77.0, 65.9, 61.8, respectively. The tetrahydropyran ring carbons, C-1″ appeared at δ 99.0 and C-2″, 3″, 4″, 5″ appeared at δ 30.0, 19.5, 24.5, 60.0, respectively. The *trans* α,β-unsaturated ester carbons, C-3‴, C-2‴, C-1‴ resonated at δ 142.2, 117.5, 167.5, respectively, and the CH_3 and OCH_2 appeared at δ 14.0, 60.0, respectively.

Compound **6** upon reduction with DIBAL-H (3 equivalents) in dry dichloromethane at 0 °C afforded the title compound **7** (Scheme 1) in 75% yield. This step involves the conversion of α,β-unsaturated ester to alcohol as well as THP deprotection. The structure of **7** was established from its spectral data.

In the ^{1}H NMR ($CDCl_3$ + DMSO-d_6) the diastereotopic methylene protons of the 3-CH_2OH appeared as two multiplets at δ 3.45 and 3.75. The H-3 appeared at δ 4.00 as a multiplet, while the H-2 appeared at δ 5.05 (d, J = 9 Hz), indicating a *trans* relation to the phenyl group and CH_2OH at the C-2 and C-3 positions. The -OCH_2- appeared at δ 4.20 and the H-2″ at δ 6.15 as a multiplet, while H-3 resonated at δ 6.45 (d, J = 16 Hz). The aromatic protons resonated at δ 6.85–7.30.

In conclusion, the synthesis of **7** starting from oxirane **1** and 3,4-dihydroxybenzaldehyde (**2**) constitutes a new approach to a neolignan skeleton. About 75% yields were observed in every step and the reaction was highly regioselective. Efforts towards the total synthesis of neolignans and flavonolignans are in progress with this approach. As this work is being communicated, a total stereoselective and regioselective synthesis of a lignan has been reported.[11,12]

Experimental

The melting points were recorded on open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer infrared model 337. ^{1}H NMR spectra were recorded at 200 MHz and ^{13}C NMR were recorded at 50.3 MHz on a Varian Gemini spectrometer. Mass spectra were recorded on a UG micromass 7070 H instrument.

Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambride CB2 1EZ, UK and the copies can be obtained on request, free of charge, by quoting the publication citation and deposition numbers xxx-yyyy. The detail of structures have been deposited as Document number 74058 at Office of the Editor of Bull. Chem. Soc. Jpn.

(±)-*trans*-3-Hydroxymethyl-2-phenyl-2,3-dihydrobenzo[*b*]-1,4-dioxin-6-carbaldehyde (3):[9] A mixture of (±)-*threo* 2-[bromo(phenyl)methyl]oxirane (**1**) (2.12 g, 10 mmol), 3,4-dihydroxybenzaldehyde (**2**) (1.34 g, 10 mmol), anhydrous K_2CO_3 (5 g, 35 mmol) and dry acetone (40 mL) was refluxed for 24 h. The reaction mixture was cooled, filtered and evaporated. The product was extracted with solvent ether. The ether was washed with chilled aqueous KOH (2%), water, and brine, dried over Na_2SO_4 and concentrated. The crude product was purified over a silicagel column by eluting with petroleum ether:ethyl acetate (9:1) to give **3** as colorless crystals (1.8 g, 70%). Mp 104 °C (Ref. 9, Mp 104 °C). ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 3.45 and 3.78 (m, -OCH_2-), 4.05 (m, H-3), 5.20 (d, J = 9 Hz, H-2), 4.62 (t, OH), 7.10 (d, J = 9.0 Hz, H-8), 7.40 (m, H-5, 7, 2′, 3′, 4′, 5′, 6′), 9.85 (s, CHO). ^{13}C NMR ($CDCl_3$) δ 60.0 (CH_2OH), 76.3 (C-3), 77.9 (C-2), 117 (C-8), 117.3 (C-5), 123.7 (C-7), 127.0 (C-2′, 6′), 128.2 (C-3′, 5′), 128.6 (C-6), 130.1 (C-1′), 143.5 (C-8a), 148.9 (C-4a), 191.0 (C=O). MS *m*/*z* 270 (M^+) (100), 252 (28), 239 (7), 149 (78), 133 (53), 115 (42), 105 (50) and 91 (78). The regioisomer 2-hydroxymethyl-3-phenyl-2,3-dihydrobenzo[*b*]-1,4-dioxin-6-carbaldehyde was not formed in the reaction. An X-ray analysis of **3** showed it to be 3-hydroxymethyl-2-phenyl-2,3-dihydrobenzo[*b*]-1,4-dioxin-6-carbaldehyde (Fig. 1).

2-Phenyl-3-(tetrahydro-2-pyranyloxymethyl)-2,3-dihydrobenzo[*b*]-1,4-dioxin-6-carbaldehyde (4): A mixture of 3-hydroxymethyl-2-phenyl-2,3-dihydrobenzo[*b*]-1,4-dioxin-6-carbaldehyde (**3**) (2.42 g, 10 mmol), dihydropyran (1.3 mL, 15

mmol), PPTS (50 mg) and dichloromethane was stirred for 4 h at 35 °C. The dichloromethane was removed. The product was extracted with ether and washed with water and brine, then dried over Na_2SO_4 and concentrated. The crude compound on purification over a silica gel column by eluting with petroleum ether:ethyl acetate (9.5:5) gave **4** as a yellow semisolid (2.8 g, 85% yield). ^{1}H NMR ($CDCl_3$) δ 1.65–1.90 (m, H-2″, 3″, 4″), 3.50 (m, -CH_2O-), 3.65 (m, H-5″), 4.00 (m, H-3), 4.95 (m, H-1″), 5.15 (d, J = 9 Hz, H-2), 7.05 (d, J = 10 Hz, H-8), 7.40 (m, H-5, 7, 2′, 3′, 4′, 5′, 6′), 9.85 (s, CHO). Found: C, 71.10; H, 6.23%. Calcd for $C_{21}H_{22}O_5$: C, 71.18; H, 6.21%.

Ethyl 3-[2-phenyl-3-(tetrahydro-2-pyranyloxymethyl)-2,3-dihydrobenzo[*b*]-1,4-dioxin-6-yl]-2-propenoate (6): A mixture of 2-phenyl-3-(tetrahydro-2-pyranyloxymethyl)-2,3-dihydrobenzo[*b*]-1,4-dioxin-6-carbaldehyde (**4**) (1.63 g, 5 mmol) and ethoxycarbonylmethylenetriphenylphosphorane (**5**) (1.5 g, 5 mmol) and benzene (25 mL) was refluxed for 4 h. Benzene was removed under reduced pressure. The residue was chromatographed over a silica gel column by eluting with petroleum ether:ethyl acetate (8:2) to give **6** (3 g, 75% yield) as a white solid. Mp 105 °C. IR (KBr) 3035, 2990, 1710, 1590, 1150 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, CH_3), 1.50–1.60 (m, H-2″, 3″, 4″), 3.40 and 3.80 (m, CH_2OH), 3.55 (m, H-5″), 4.15 (q, J = 7 Hz, OCH_2), 4.50 (m, H-3), 4.55 (m, H-1″), 5.05 (d, J = 9 Hz, H-2), 6.20 (d, J = 18 Hz, H-2‴), 7.50 (d, J = 18 Hz, H-3‴), 6.85 (d, J = 9 Hz, H-8), 7.00 (m, H-5, 7), 7.35 (m, H-2′, 3′, 4′, 5′, 6′). ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 19.0 (C-3″), 22.5 (C-4″), 30.0 (C-2″), 60.0 (C-5″, OCH_2), 61.8 (CH_2OH), 65.9 (C-3), 77.0 (C-2), 99.0 (C-1″), 116.5 (C-5, 2‴), 117.0 (C-8), 122.0 (C-7), 127.8 (C-2′, 6′), 127.9 (C-6), 128.1 (C-3′, 5′), 129.1 (C-4′), 136.0 (C-1′), 143.9 (C-8a), 144.0 (C-3‴), 146.0 (C-4a), 167.0 (C=O). MS *m*/*z* 340 (M^+−85) (20), 219 (8), 133 (10), 117 (14), 85 (100). Found: C, 68.73; H, 6.40%. Calcd for $C_{25}H_{28}O_6$: C, 68.80; H, 6.42%.

6-(3-Hydroxy-1-propenyl)-2-phenyl-2,3-dihydrobenzo[*b*]-1,4-dioxin-3-methanol (7): To a solution of ethyl 3-[2-phenyl-3-(tetrahydro-2-pyranyloxymethyl)-2,3-dihydrobenzo[*b*]-1,4-dioxin-6-yl]-2-propenoate (**6**) (100 mg, 0.23 mmol) in dichloromethane was slowly added diisobutylaluminium hydride (0.7 mL, 0.7 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 5 h, and then quenched with saturated aq sodium potassium tartrate. The compound was extracted with dichloromethane (20 mL × 3). The dichloromethane was washed with water and brine, then dried over Na_2SO_4 and concentrated. The product was purified by a silica gel column by eluting with petroleum ether:ethyl acetate (7:3) afforded **7** as white solid (75% yield). Mp 96 °C. IR (KBr) 3421, 3032, 2918, 1653, 1211, 1094, 1021 cm^{-1}. ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 3.45 and 3.70 (m, CH_2OH), 4.00 (m, H-3), 4.20 (d, 2H, J = 8 Hz, H-1″), 5.05 (d, J = 9 Hz, H-2), 6.15 (m, H-2″), 6.45 (d, J = 16 Hz, H-3″), 6.85 (m, H-5, 7), 6.98 (s, H-8), 7.30 (m, H-2′, 3′, 4′, 5′, 6′). MS *m*/*z* 298 (M^+) (20), 270 (12), 133 (35), 105 (55). Found: C, 72.45; H, 6.02%. Calcd for $C_{18}H_{18}O_4$: C, 72.48; H, 6.04%.

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