TOTAL SYNTHESIS OF GINKGOLIDE A

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Summary: Ginkgolide A (1) has been synthesized from the trilactone 3 and also from ginkgolide B (2).

Recently we have described the first total syntheses of racemic^{1a} and natural forms^{1b} of ginkgolide B (2), a potent antagonist of platelet activating factor, which shows promise as a therapeutic agent. Ginkgolide A (1), another member of the ginkgolide family, possesses insect antifeedant activity². Herein we report the total synthesis of (\pm) ginkgolide A from an intermediate (3) used previously for the total synthesis of (\pm) ginkgolide B¹ and also the conversion of natural ginkgolide B to ginkgolide A.

Treatment of bislactone 3 with 2.5 equiv of N,N'-thiocarbonyldiimidazole³ in 2 : 1 toluene-pyridine at 45° for 12 h gave selectively the thiocarbonylimidazole derivative 4 (84%) after silica gel (SG) chromatography ($R_f = 0.2$, 1 : 1 EtOAc : hexane). Reduction of 4 with tri-n-butyltin hydride was effected by dropwise addition of a solution of 4 in dioxane over 3 h to 5 equiv of tri-n-butyltin hydride in anhydrous dioxane at reflux to give the deoxygenated⁴ product 5 (90%). The ¹H NMR (500Hz) spectrum of 5 confirmed the presence of two C(1) protons (H_{α} , δ 2.23; dd, J = 7.0Hz, 14.6Hz; H $_{\beta}$, δ 2.02, dd, J = 8.5, 14.6Hz). Reaction of dihydrofuran 5 with osmium tetroxide in pyridine (60°C for 24 h) and workup with aqueous sodium bisulfite gave a diol which was oxidized directly using excess iodine in 10 : 1 CH₃OH-H₂O in the presence of calcium carbonate (23°, 12 h) to provide 10-epi(±) ginkgolide A (6) 48% from (5). The C(10) hydroxy group of 6 was epimerized to form (±)-ginkgolide A (61% overall) by the sequence: (1) oxidation with 3 equiv of benzeneselenic anhydride⁵ and 5 equiv of pyridine in anhydrous chlorobenzene at 80°C for 2 h (TLC R_f 0.5; chromatographed over silicAR CC-7 with 1 : 1 EtOAc-hexane as eluent), and (2) reduction of the resulting α -ketolactone with 5 equiv of sodium borohydride in ethanol at -45° for 15 min. Synthetic (±)-1 thus obtained was identical with "natural ginkgolide A by 500 MHz ¹H NMR, FT-IR, SG-TLC, and FAB mass spectral comparison.

Ginkgolide B (2) has also been converted to ginkgolide A (1) as follows. Ginkgolide B was treated with 5 equiv of chloromethyl methyl ether and 5 equiv of diisopropylethylamine in dry acetonitrile at 23° for 12 h to form 7 and the isomeric C(1) ether (ratio of 3 : 1, 89%). The isomer 7 was separated ($R_f = 0.65$, EtOAc-hexane) by SG chromatography and subjected to xanthate formation by treatment with 5 equiv of potassium hydride in dry THF at 23° for 1 h, followed by stirring with an excess of carbon disulfide (23° for 15 min and 45°C for 30 min), and finally reaction with 5 equiv of benzyl bromide at 23° for 12 h to give 9 (71%). When methyl iodide was used in place of benzylbromide for the alkylation of the thiolate anion, a 75% yield of 8 was obtained. Reduction of 9 with tri-n-butyltin hydride in dioxane at reflux afforded the deoxygenated product 10 (71%). Deprotection of 10 with BF₃•Et₂O in CH₂Cl₂ in the presence of thiophenol at -10°C for 1 h provided ginkgolide A (1).⁷



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- Satisfactory ¹H NMR, infrared and mass spectral data were obtained for each isolated intermediate described herein. Reactions involving air-sensitive reagents or products were conducted under argon atmosphere.
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