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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[lb] 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 activity[2]. Herein we report the total synthesis of (±) ginkgolide A from an intermediate (**3**) used previously for the total synthesis of (±) ginkgolide B[1] and also the conversion of natural ginkgolide B to ginkgolide A.

Treatment of bislactone **3** with 2.5 equiv of N,N'-thiocarbonyldiimidazole[3] 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 drop wise 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 deoxygenated[4] product 5 (90%). The ^{1}H NMR (500Hz) spectrum of **5** confirmed the presence of two C(l) protons (H_α, δ 2.23; dd, J = 7.0Hz, 14.6Hz; H_β, 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 CH_3OH-H_2O 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 anhydride[5] 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 (±)-**l** thus obtained was identical with'natural ginkgolide A by 500 MHz ^{1}H 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(l) 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 BF_3• Et_2O in CH_2Cl_2 in the presence of thiophenol at −10°C for 1 h provided ginkgolide A (**l**).[7]

REFERENCES AND NOTES

1. (a) Corey EJ; Kang M-C; Desai MC; Ghosh AK; Houpis IN J. Am. Chem. Soc. 1988,110, 649–651; [PubMed: 31527923] (b) Corey EJ; Gavai AV Tetrahedron Lett., preceding paper.
2. (a) Matsumoto T; Sei T Agric. Biol. Chem. 1987,51, 249–250;(b) Major RT. Science 1967,157, 1270. [PubMed: 5341600]
3. Pullukat TJ; Urray G Tetrahedron Lett. 1967, 1953–1954.
4. (a) Barton DHR; McCombie SWJ Chem. Soc., Perkin Trans 11975, 1574–1585;(b) Barton DHR; Motherwell WB Pure Appl. Chem. 1981,53, 15–31.
5. Barton DHR; Brewster AG; Hui RAHF; Lester DJ; Ley SV; Back TG J. Chem. Soc. Chem. Commun. 1978, 952.
6. Satisfactory ^{1}H 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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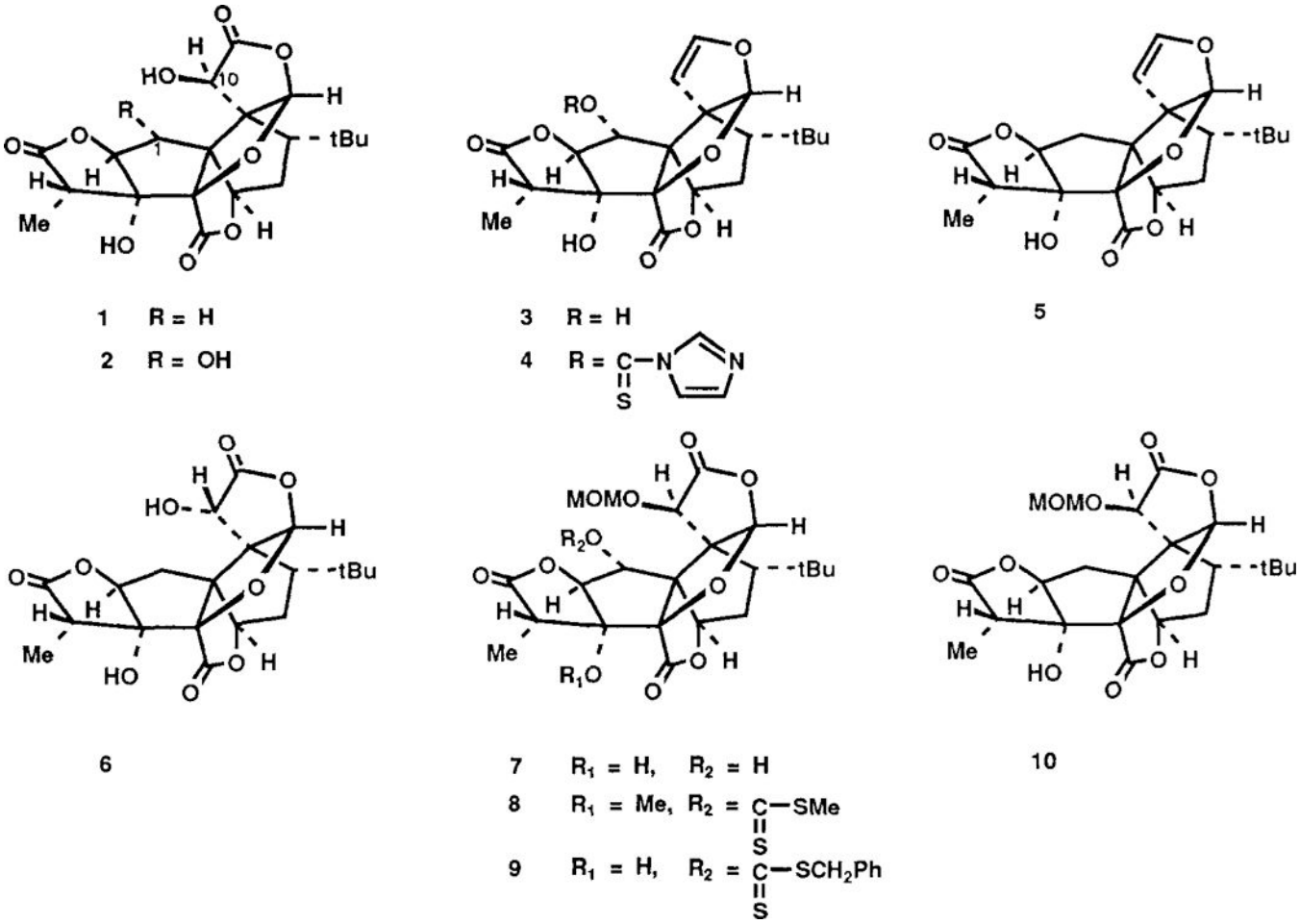

Figure 1.
Synthesis of Ginkgolide A.