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Regioselective thionocarbonation of ginkgolides: facile preparation of ginkgolide J

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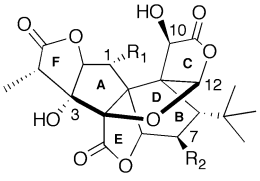
Abstract—Ginkgolide J, a minor constituent of terpene trilactone mixture of *Ginkgo biloba* leaves extract, can be readily prepared from an abundant ginkgolide C in two steps: thionocarbonation and subsequent deoxygenation. Regioselectivity of the first thionocarbonation step can be controlled by a proper choice of the base and solvent combination.

Ginkgo biloba extract, a memory enhancing dietary supplement,[1] has been attracting considerable attention due to its beneficial effects in the treatment of dementia, including Alzheimer's and Parkinson's diseases.[2,3] To date, the mode of action of the extracts remains unclear. In view of multicomponent nature of the extract, studies directed toward elucidation of individual components that mimic the effect of the whole extract are valuable for clarifying biological activities and designing potential therapeutics.

Ginkgolides, **GA**–**GJ** (Fig. 1), which constitute a terpene trilactone fraction of *G. biloba* leave extract, are responsible for a variety of neuromodulatory effects attributed to the extract.[4] For example, **GB** protects neurons from neurotoxicity of amyloid and prion proteins.[5] Both **GA** and **GB** have been shown to inhibit nitric oxide neurotoxicity, and restore the cell growth.[6] **GC** is a potent antagonist of glycine receptor, the protein that mediates inhibition of several regions of central nervous system, including brain stem.[7]



	R_1	R_2
Ginkgolide A (**GA**)	H	H
Ginkgolide B (**GB**)	OH	H
Ginkgolide C (**GC**)	OH	OH
Ginkgolide J (**GJ**)	H	OH

Figure 1. Ginkgolides from *Ginkgo biloba* leaf extract.

Biological potential of **GJ** has been assessed to be of lesser extent than that of other ginkgolides, primarily because it is only a very minor component in the *Ginkgo biloba* extract as well as due to the difficulties associated with its isolation. However, it has recently been demonstrated that **GJ** is capable of completely inhibiting the toxicity of β-amyloid peptides toward neuronal cells,[8] which makes this ginkgolide an appealing lead for developing remedies against Alzheimer's disease. In addition, **GJ** serves as the closest counterpart of homologous **GB** that could provide clarification of subtle ligand–receptor interactions.

To develop the preparation of **GJ**, we envisioned a selective functionalization of 1-hydroxyl group of **GC**, which can be subsequently deoxygenated. The presence of three secondary hydroxyl groups in the **GC** structure might require the use of protecting groups to achieve the desired functionalization. In general, regioselectivity of **GC** functionalization depends on the nature of the electrophile, base and solvent. It was previously shown that **GC** can be selectively silylated into 1-position in DMF.[9] The 10-OH is primarily functionalized upon alkylation or acetylation of **GC** in different solvents and in the presence of different bases,[10] whereas reaction with Tf_2O in pyridine yields 7-OTf **GC**.[11]

In our study, thionocarbonation of **GC** with *O*-phenyl chlorothionoformate in the presence of 2.0 equiv of

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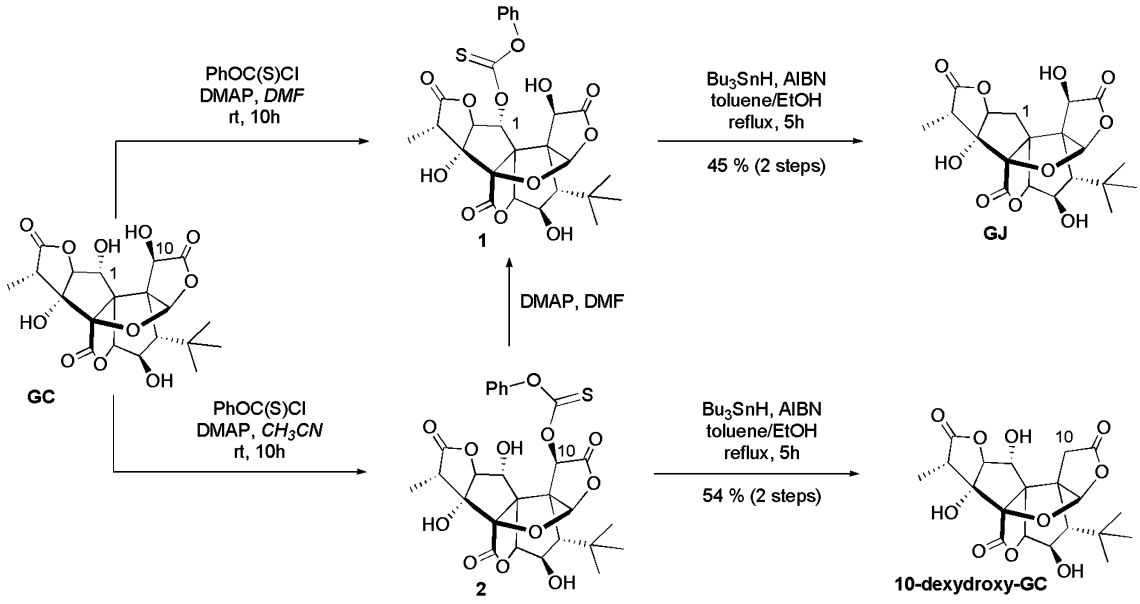

Scheme 1. Regioselective removal of hydroxyl groups via two-step thiocarbonylation/deoxygenation process.

DMAP in DMF led to the desired 1-thionocarbonylated **GC 1** as the major product in good yield; whereas in acetonitrile the reaction yielded thionocarbonate **2** (Scheme 1). Lesser amounts of DMAP resulted in inferior yields of thionocarbonates. Deoxygenation reaction under standard Barton–McCombie conditions of these 1- and 10-thionocarbonates afforded **GJ** and the new deoxygenated ginkgolide 10-dehydroxy-**GC**, respectively.[12]

Based on the results of **GC** thionocarbonation, we explored the effect of solvent on regioselectivity and on the conversion of **GC** into **1** in more detail (Table 1). Similar to acetonitrile (entry 1), dioxane and EtOAc also led to formation of 10-substituted product, thionocarbonate **2** as the main product. Selectivity was completely lost when reaction was performed in either THF or *N*,*N*-dimethylacetamide (entries 4 and 5, respectively), whereas pyridine favored the formation of **1** (entry 6). DMF was the only solvent that selectively yielded thionocarbonate **1** (entry 7).

Table 1. Effect of base/solvent on the regioselective thiocarbonation of **GC**[a]

Entry	Solvent	Base	**1**:**2** (Conversion, %)[b]
1	**CH_3CN**	**DMAP**	**1**:**15** (**85**)
2	Dioxane	DMAP	1:12 (66)
3	EtOAc	DMAP	1:2 (50)
4	THF	DMAP	1:1 (61)
5	NNDA[c]	DMAP	1:1 (60)
6	Pyridine	DMAP	4:1 (35)
7	**DMF**	**DMAP**	**10**:**1** (**90**)
8	DMF	Pyridine	2:1 (74)
9	DMF	*N*-Methylimidazole	1:6 (57)
10	DMF	Et_3N	1:4 (67)

[a] Reaction conditions: GC (20.0 mg, 0.045 mmol), PhOC(S)Cl (12.0 μL, 0.099 mmol), base (0.090 mmol), solvent (0.30 mL), 10 h, rt.
[b] Estimated by ^{1}H NMR of the crude mixture.
[c] *N*,*N*-Dimethylacetamide.

Next, effect of bases on the regioselectivity of thionocarbonation in DMF was investigated using DMAP, pyridine, *N*-methylimidazole and Et_3N (entries 7–10, respectively).[13] The selectivity was low with pyridine (entry 8). However, in the case with *N*-methylimidazole and Et_3N, the regioselectivity switched, leading to the formation of thionocarbonate **2** as the major product. Thus, as evident from Table 1, DMF/DMAP (entry 7) was the only combination that led to almost exclusive formation of **1**, which is the desired intermediate in the preparation of **GJ**.

In the course of this study, we also found that the regioselectivity of thionocarbonation reaction is extremely sensitive to the amount of DMAP (Table 2).

As shown in Table 2, increasing the number of equivalents of DMAP favors the formation of thionocarbonate **1** regardless of the solvent used. These results prompted us to propose that thionocarbonate **2** can be transformed into **1** upon treatment with DMAP. Indeed, the formation of **1** was observed when **2** was treated with DMAP (2.2 equiv) in DMF for 3 h at room temperature (Scheme 1), which is in agreement with the data presented in Table 2. Likewise, **1** was treated with DMAP (2.2 equiv) in CH_3CN—the formation of **2** was not detected after 3 h.

Table 2. Effect of DMAP on the regioselective thiocarbonylation of **GC**[a]

Entry	Solvent	Equivalents of DMAP	**1**:**2**[b]
1	DMF	1.5	2:1
2	DMF	2.0	10:1
3	DMF	5.0	10:1
4	CH_3CN	2.0	1:15
5	CH_3CN	5.0	1:3

[a] Reaction conditions: GC (20.0 mg, 0.045 mmol), PhOC(S)Cl (12.0 μL, 0.099 mmol), solvent (0.30 mL), 10 h, rt.
[b] Estimated by ^{1}H NMR of the crude mixture.

The thionocarbonation protocols were also applied to other ginkgolides. Thionocarbonation of **GA** in the presence of DMAP in both DMF and CH_3CN yielded no products, and unreacted **GA** was recovered in both cases, thus supporting the proposed interplay between 1- and 10-hydroxy groups.[10a] Functionalization of **GB** happened to be less efficient with respect to regioselectivity and conversion, as compared to **GC** and, therefore, was not pursued further.

In conclusion, we have demonstrated that regioselectivity of **GC** thionocarbonation could be controlled by solvent as well as the amount and identity of the base. DMF and DMAP were efficient in promoting the formation of 1-substituted product **1**, whereas the use of CH_3CN in combination with DMAP exclusively afforded 10-substituted product **2**. Deoxygenation of thionocarbonates **1** and **2** afforded **GJ** and the novel analog 10-dehydroxy-**GC**, respectively. The latter compound should be a useful model to probe the contribution of this hydroxyl group in ginkgolide–receptor interactions, since all native ginkgolides carry a hydroxyl group at C-10.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.022.

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12. **GC** to **GJ** conversion (typical experimental procedure): A mixture of **GC** (100 mg, 0.23 mmol) and DMAP (56 mg, 0.46 mmol) was dissolved in DMF (1.5 mL) under argon, and PhOC(S)Cl (60 μL, 0.51 mmol) was added via syringe under vigorous stirring. The reaction mixture was allowed to stir for 10 h at room temperature, quenched with water (50 mL), 1 N HCl (3.0 mL), and washed with EtOAc (3×100 mL). The organic fractions were combined and washed with brine (3×20 mL), dried ($MgSO_4$) and volatiles removed in vacuum. The residue was subjected to column chromatography (1:1, hexane–EtOAc) to afford **1** (93 mg, 70% yield); ^{1}H NMR (400 MHz, CD_3OD) 7.49–7.41 (m, 2H), 7.35–7.28 (m, 1H), 7.18–7.11 (m, 2H), 6.07 (s, 1H), 6.00 (d, $J = 5.0$ Hz, 1H), 5.15 (d, $J = 4.2$ Hz, 1H), 5.12 (s, 1H), 4.92 (d, $J = 5.0$ Hz), 4.32 (dd, $J1 = 12.3$ Hz, $J2 = 4.2$ Hz, 1H), 3.09 (quart, $J = 7.3$, 1H), 1.79 (d, $J = 12.4$ Hz, 1H), 1.26 (d, $J = 7.3$ Hz, 3H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, CD_3OD) 194.0, 177.7, 174.3, 172.2, 155.0, 130.7, 127.8, 122.9, 110.8, 101.3, 93.2, 85.3, 84.5, 81.6, 75.8, 70.1, 67.5, 66.4, 60.0, 42.7, 33.4, 29.6, 9.2. Compound **1** (23 mg, 0.04 mmol) was dissolved in 1.1 mL of toluene–EtOH (9:1) mixture under argon, followed by the addition of AIBN (ca. 1 mg) and Bu_3SnH (42 μL, 0.16 mmol). The mixture was refluxed for 5 h, and then passed through a short KF-containing silica gel column, concentrated and subjected to flash chromatography (2:1, hexane–EtOAc) to give **GJ** (10 mg, 60% yield), whose spectral characteristics were identical to an authentic sample.
13. The effect of Hunig base, *i*-Pr_2EtN, was not studied here, since it was shown previously that in the presence of this base, GC rearranges into *iso*-GC, see Ref. 10b.