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Lactone-free ginkgolides *via* regioselective DIBAL-H reduction†

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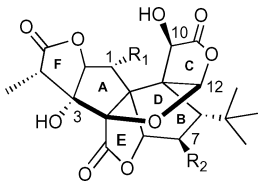
The lactone rings of ginkgolide A are converted into corresponding tetrahydrofuran moieties *via* DIBAL-H reduction followed by deoxygenation of the formed lactols with Et_3SiH–$BF_3{\cdot}Et_2O$ to produce a series of lactone-free ginkgolides.

Ginkgolides (Fig. 1),[1] the main active ingredients of *Ginkgo biloba* extract, are attracting considerable attention in recent years due to their unique biological properties.[1,2]



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

Fig. 1 Major ginkgolides from *Ginkgo biloba* leaf extract.

Extensive derivatization of ginkgolide hydroxyl-functionalities has been performed over the years to further extend their applications as ligands.[1,3] A complement to these efforts is modification of the ginkolide structure itself, to yield core-modified ginkgolides. The first example of a skeletal modification was reported in the late 60s, when "**GA** triether" **1**‡ was accidentally obtained upon $LiAlH_4$ reduction (to an octaol) followed by pyrolysis; this triether played a central role in establishing the pentacyclic cage skeleton.[4] Recently, we have shown that lactone C of **GB** derivatives can be exclusively transformed into the corresponding lactol *via* nucleophilic attack by $NaBH_4$ or Grignard reagents.[5]

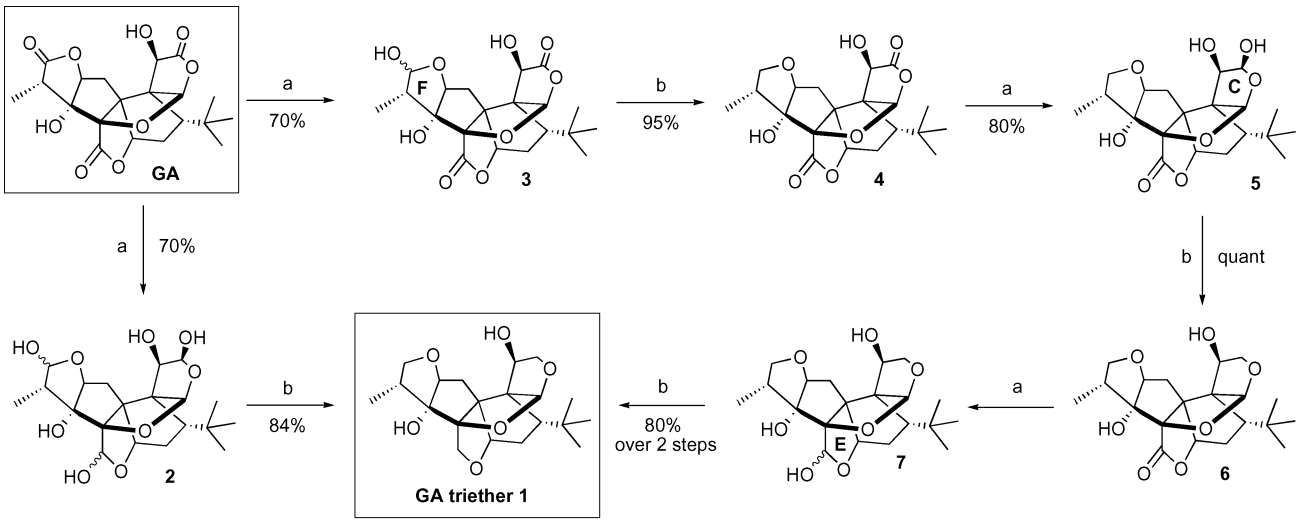
From a biomedical point of view, our interest in *Ginkgo biloba* extract and ginkgolides has in part been driven by the findings that they are able to suppress the progression of Alzheimer's disease.[6] However, to the best of our knowledge, only native ginkgolides have been used in those studies, and structure–activity relationships are yet to be established.

We have recently demonstrated that **GA** triether **1** is capable of mimicking the effect of **GA** in protecting hippocampal neuronal cell cultures from the β-amyloid induced impairment of long-term potentiation.[7] An increased hydrophobicity of **1** should also facilitate its cell wall permeability, thus making it a more viable candidate than **GA** for treatment of the dementia. These preliminary data prompted us to explore the ginkgolide lactone-to-ether conversions in more detail.

We found that the 1967 preparation of **GA** triether **1** gave irreproducible results and was inapplicable for milligram-scale preparations. Furthermore, the formation of other partially reduced ginkgolides, such as **GA** mono- and diethers was not detected. Accordingly, the following reactions were performed to prepare ginkgolides that are lacking lactone moieties.

Among common reducing agents that are known to reduce lactone moieties,[8] such as DIBAL-H, BH_3, $LiAlH_4$–$AlCl_3$ and $LiAlH_4$–$BF_3{\cdot}Et_2O$, DIBAL-H was found to give the minimum amount of side products, while reducing the lactone rings. After adjustment of the excess DIBAL-H to 25 equivalents, all **GA** was consumed and trilactol **2** was isolated as the major product (Scheme 1). According to ^{1}H NMR data, the reduction of lactone C took place in a stereoselective manner, whereas both lactones F and E were transformed into *ca.* 1 : 1 mixture of epimers. **GA** trilactol **2** was subsequently converted into **GA** triether **1** using Et_3SiH–$BF_3{\cdot}Et_2O$. This preparation, with a 58% overall yield, was reproducible and applicable in 10 mg–0.5 g

† Electronic supplemental information (ESI) available: Experimental procedures and characterization data. See http://dx.doi.org/10.1039/b509129b



Scheme 1 Preparation of lactone-free GA derivatives. *Reagents and conditions*: (a) DIBAL-H, THF, −78 °C; (b) Et_3SiH, BF_3–Et_2O, CH_2Cl_2, −78 °C to rt, see text for details.

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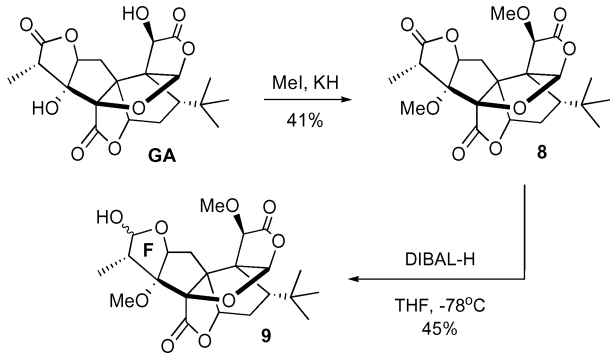
scale. We also attempted a one-pot conversion of **GA** to **GA** triether without success due to formation of an inseparable mixture of **GA** ethers. Adoption of the two-step procedure, *i.e.*, **GA** to **2** to triether **1** (Scheme 1), for the preparation of lactone-free **GB** and **GC** also turned out to be impractical, in view of difficulties in separating the multiple polyol species.

We, therefore, decided to explore the stepwise reduction of **GA** lactone moieties (Scheme 1). From the preparative point of view, ginkgolide's cage-like skeleton, with three lactone rings of potentially different reactivities towards reducing agents, creates a unique scaffold for regioselective lactone to ether transformations.

Reduction of **GA** using five equivalents of DIBAL-H gave **GA** F-lactol **3** as the major isolable product as a 3 : 2 mixture of epimers, determined by ^{1}H NMR (Scheme 1). Lesser amounts of the reducing agent led to lower yields of **3**.§

The epimeric mixture of lactol **3** was directly subjected to deoxygenation conditions leading to the formation of **GA** monoether **4** in high yield,§ whose reduction produced **GA** monoether C-lactol **5** as a single *syn*-product (determined by NOE). This indicated that the stereochemistry of 10-hydroxy group of lactone C controls the hydride attack. The lactol **5** was quantitatively deoxygenated to give **GA** diether **6**. The reduction of **6** using ten equivalents of DIBAL-H led to a clean production of **GA** diether E-lactol **7** (as a 1 : 1 mixture of epimers as determined by ^{1}H NMR of the crude product), which was directly converted to **GA** triether **1** in high yield.¶

To check whether the hydroxy groups of **GA** would affect the regioselectivity of DIBAL-H reduction, we prepared dimethyl **GA**, **8** (Scheme 2). Notably only the use of KH led to production of **8**, whereas no methylation took place in the presence of NaH, K_2CO_3 or AgOTf–Et_3N, all resulting in recovery of **GA**. The DIBAL-H reduction of dimethyl **GA 8** using established conditions (Scheme 1) produced dimethyl **GA** F-lactol **9** as the major product (7 : 3 mixture of epimers, determined by ^{1}H NMR).



Scheme 2 Preparation of dimethyl **GA** and its reduction to the lactol.

Thus, the DIBAL-H reduction of **GA** first occurs at lactone F, followed by reduction of lactone C and finally lactone E. It appears that this type of reduction is sterically controlled, since lactone F is the least hindered and lactone E is the most hindered.

In conclusion, we have demonstrated that **GA** lactone rings can be transformed into tetrahydrofuran moieties *via* regioselective DIBAL-H reduction–deoxygenation with Et_3SiH–$BF_3{\cdot}Et_2O$, producing a novel series of core-modified ginkgolide analogs. We are currently evaluating biological potential of these lactone-free ginkgolide derivatives

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Notes and references

‡ The term **GA** triether stands for the three lactone rings of **GA** that were converted into ether rings, and does not represent the total number of ether moieties, which in this case is four. Similarly, the terms **GA** mono- and diethers represent cases where the lactone rings of **GA** are transformed into one and two ether moietes, respectively.

§ *Typical experimental procedure*. **GA** (64.5 mg, 0.158 mmol) was dissolved in dry THF (4.0 ml), cooled to −78 °C under argon, and treated with 0.5 ml of DIBAL-H (1 M solution in hexanes). The mixture was allowed to stir for two hours, warmed to room temperature and EtOAc (1.0 ml) was added, followed by 3 M HCl (0.3 ml) and water (5.0 ml). The mixture was extracted with EtOAc (3 × 20 ml). The organic phase was separated, washed with brine (3 × 20 ml), dried (Na_2SO_4), and the solvent was removed under vacuum. **GA** F-lactol **3** was isolated as a white solid by preparative TLC (hexane–acetone 1 : 1) as a *ca.* 3 : 2 mixture of epimers (50.3 mg, 70% yield); ^{1}H NMR (MeOH-d_4): major isomer, δ 5.69 (s, 1H), 5.35 (d, J = 5.0 Hz, 1H), 4.96 (s, 1H), 4.78 (d, J = 3.4 Hz, 1H), 4.63 (t, J = 7.7 Hz, 1H), 2.56 (m, 2H), 2.17 (m, 2H), 1.89 (m, 2H), 1.09 (m, 12H); HRMS (FAB) m/z calcd for $C_{20}H_{29}O_9Na$ 433.1475, found 433.1494 [M + Na]. **GA** F-lactol **3** (50.3 mg, 0.123 mmol) was dissolved in CH_2Cl_2 (6.0 ml), cooled to −78 °C, and Et_3SiH (0.098 ml, 0.61 mmol) was added, followed by $BF_3{\cdot}Et_2O$ (0.039 ml, 0.304 mmol). The reaction mixture was warmed to room temperature over a 12 h period, quenched with saturated $NaHCO_3$ (1.0 ml) and water (5.0 ml) and subsequently extracted with EtOAc (3 × 20 ml). Organic layer was separated, washed with brine (3 × 20 ml), dried (Na_2SO_4) and the solvent was removed under vacuum. **GA** mono ether **4** (45.3 mg, 95% yield) was isolated by preparative TLC (hexane–acetone 1 : 1). ^{1}H NMR (MeOH-d_4): δ 5.97 (s, 1H), 4.97 (s, 1H), 4.75 (d, J = 3.4 Hz, 1H), 4.41 (t, J = 7.8 Hz, 1H), 4.18 (t, J = 7.9 Hz, 1H), 3.63 (dd, J = 10.5, 8.0 Hz, 1H), 2.80 (m, 1H), 2.45 (dd, J = 14.9, 7.0 Hz, 1H), 2.15 (m, 2H), 2.02 (dd, J = 15.0, 8.0 Hz, 1H), 1.86 (dd, J = 13.3, 5.6 Hz, 1H), 1.08 (s, 9H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (MeOH-d_4): 175.18, 173.66, 110.69, 91.89, 89.38, 87.15, 76.24, 69.60, 69.46, 67.54, 38.80, 37.93, 36.30, 32.27, 28.55, 8.51. HRMS (FAB): m/z calcd for $C_{20}H_{27}O_8$ 395.1706, found 395.1707.

¶ This methodology can only be partially applied towards conversion of **GB** and **GC** into the corresponding lactone-free analogs. In case of **GB**, initial reduction led to the F-lactol (55% yield, as mixture of epimers), and subsequent deoxygenation afforded **GB** monoether (53% yield); the second reduction produced C-lactol as a single epimer, however, the conversion to the **GB** diether failed under a variety of conditions. The initial reduction of **GC** produced corresponding **GC** F-lactol (64% yield, as a mixture of epimers), but this failed to undergo subsequent deoxygenation.

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