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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 531–534

Preparation of ginkgolide and F-seco-ginkgolide lactols: the unique reactivity of α-hydroxy lactones toward $NaBH_4$

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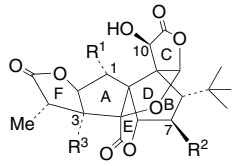
Received 24 September 2004; revised 18 October 2004; accepted 20 October 2004
Available online 2 December 2004

Dedicated to Professor Iwao Ojima on the occasion of his 60th birthday

Abstract—It has been found that $NaBH_4$ smoothly reduces the α-hydroxy-lactone moieties in ginkgolide and F-seco-ginkgolides to lactols. The reaction is rapid and stops at the lactol stage; the coordination of $NaBH_4$ to the conformationally rigid cage structure is involved in both the initiation and termination stages. This facile reduction of ginkgolide lactones yields a variety of new ginkgolide lactols.

Ginkgolides from the *Ginkgo biloba* tree are diterpenes with a rigid cage structure consisting of six five-membered rings and a unique *t*-Bu groups (Fig. 1).[1] Ginkgolides exhibit a variety of biological properties, one of the earliest recognized being their antagonist properties against the platelet activating factor receptor (PAFR).[2,3] Recently, it has been shown that they are potent and selective antagonists of the inhibitory glycine and $GABA_A$ receptors.[4–6] In view of such attractive biological activities, a variety of ginkgolide analogs have been prepared.[7–19] So far, however, the preparation of ginkgolide derivatives has been restricted to the functionalization of hydroxyl groups, that is, selective acylation or alkylation of one of the three hydroxyls in ginkgolide C.[18] Another attractive approach is the modification and deep-seated transformation of the ginkgolide cage skeleton. The extensive degradation studies of native ginkgolides performed during the course of structural determination[20–26] gave rise to dilactone derivative **1** lacking the ring F of original ginkgolides (see structure in Scheme 1). It was obtained readily from ginkgolide C through methylation, acetylation, and hydrogenation. However, since neither the biological activity nor derivatization of **1** had been explored, the current studies were performed in view of its attractive truncated skeleton as a new template for preparation of a new series of derivatives. In addition to the two C-10 and C-7 hydroxyls, the presence of the unusual C-3 ester group renders **1** a unique ginkgolide template. Unexpectedly, it was found that the α-hydroxyl lactone moieties in **1** are readily reduced by sodium borohydride ($NaBH_4$) to produce the corresponding lactols (Scheme 1). In this paper, we report the unique reactivity of $NaBH_4$ toward the α-hydroxyl lactone moieties of ginkgolide and its derivatives, leading to a number of derivatives.



	R^1	R^2	R^3
Ginkgolide A	H	H	OH
Ginkgolide B	OH	H	OH
Ginkgolide C	OH	OH	OH
Ginkgolide J	H	OH	OH
Ginkgolide M	OH	OH	H

Figure 1. Structure of five ginkgolides.

Thus, $NaBH_4$ treatment (1 equiv) of **1** quantitatively provided the C-13 and C-11 lactol derivatives **4** and **5** (Scheme 1). The reaction was completed within 5 min at room temperature, and interestingly, none of the over-reduced dialcohols were obtained even upon exposure to excess $NaBH_4$, and/or prolonged reaction time. It is to be noted that the ester group in **1** was not

Keywords: Ginkgolide; F-seco-ginkgolide; $NaBH_4$; Lactone; Lactol.
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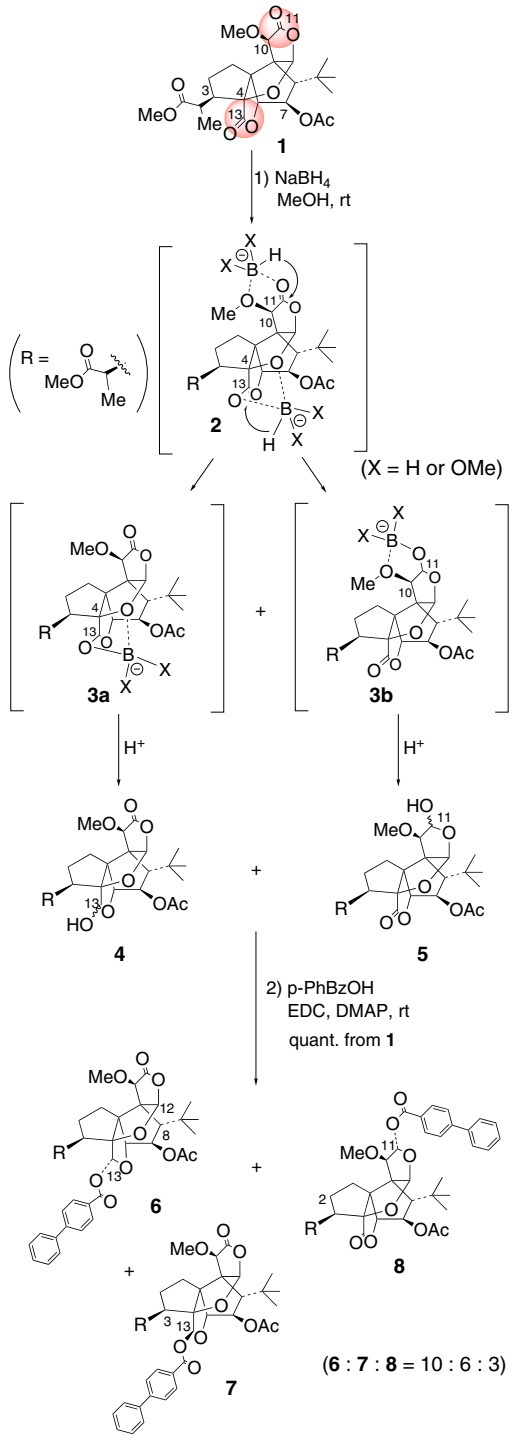
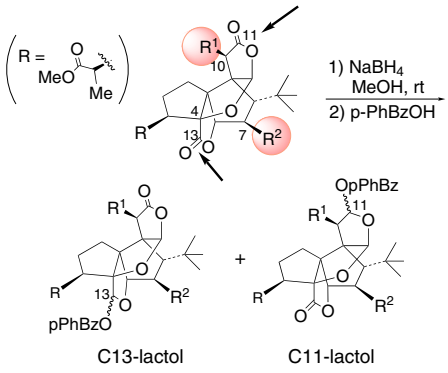
doi:10.1016/j.tetlet.2004.10.113



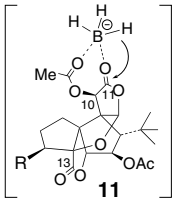
Scheme 1. Reduction of α-hydroxy lactones to lactols.

reduced under these conditions. Since lactol derivatives **4** and **5** exist as 1:1 equilibrium mixtures of lactol hydroxy groups at both C-11 and C-13, the isolation and separation became possible only after acylation. Thus, treatment of **4** and **5** with *p*-phenylbenzoic acid in the presence of EDC and DMAP gave **6**–**8** in a ratio of 10:6:3,[27] each isomer being readily separable by silica gel TLC;[28] the chemoselectivity ratio of reduction at C-13 and C-11 were thus 83:17, respectively (see Table 1).

Table 1. Reduction ratio at α-hydroxy lactones[a]



Subs.	R^1	R^2	Reduction at C13 : C11
1	OMe	OAc	83 : 17
9	OAc	OAc	50 : 50
10	OMe	$OSiEt_3$	80 : 20



[a] Each reaction was performed using 1 equiv of $NaBH_4$ at room temperature for 5 min. The reaction mixtures were directly acylated by *p*-phenylbenzoic acid and the products were analyzed by ^1H NMR. None of over-reduced diols were observed.

The stereochemistry of the 11- and two 13-*p*-phenylbenzoate, **6**–**8**, were assigned from the following NOEs: 13-H/8-H and 13-H/12-H for 13α-benzoate **6**, 13-H/3-H for 13β-benzoate derivative **7**, and 2-H/11-H for **8**. The configuration of the main isomer **6** was also confirmed by new cross metathesis/CD and/or FDCD exciton chirality protocol.[29]

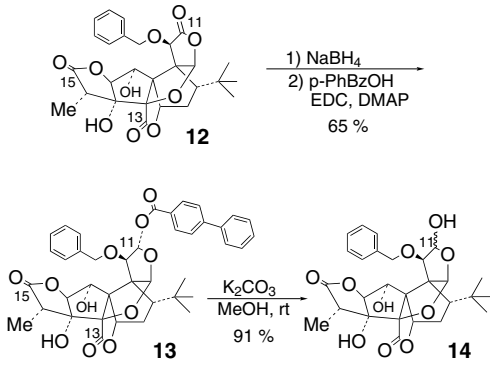
Our studies revealed that the ginkgolide α-hydroxyl lactones are converted smoothly, selectively, and quantitatively into lactols, by reacting with 1 equiv $NaBH_4$ at room temperature for a few minutes.[30] In contrast, it is well known that the reduction of lactones or esters by $NaBH_4$ requires a large excess of the reagent, that is, exceeding 20 equiv, and/or relatively high reaction temperatures.[31–34] Furthermore, when such reduction of lactones proceeds, in most cases the products are the diols resulting from over-reduction of the intermediary lactols, as is the case of polyhydroxylated sugar lactones. It has been reported that the electron withdrawing α-oxygen or coordinating functionalities linked to the carbonyl groups, for example, α-amino acids, accelerate the $NaBH_4$ reduction.[32,35,36] An unique reactivity of ginkgolide lactones is, therefore, most likely caused by the presence of suitably arranged C-4 and C-10 α-oxygens, which are rigidly fixed in the ginkgolide cage-shaped skeleton (Scheme 1). Namely, $NaBH_4$ presumably coordinates tightly with the lactone carbonyls and α-oxygens to yield a complex such as **2** that could accelerate the nucleophilic attack of the hydride toward the lactone carbonyl, which in turn is activated by the hydroxyl inductive effect. The preferred reduction of the 13-lactone (C-13:C-11 = 83:17) is most likely due to the stronger coordination of $NaBH_4$ to this carbonyl. In addition, the obtained lactol hydroxyl and α-hydroxyl could form a strong

borate complex such as **3a** and **3b** which might stabilize the reaction intermediates and prevent further reduction, a phenomenon similar to the well-known partial reduction of lactones by diisobutyl aluminum hydride (DIBAL) at low temperature, that is, −78 °C. Piancatelli and co-worker have also found that glycidic lactones (α-epoxy lactones) are readily reduced to glycidic lactols by $NaBH_4$, although the latter are gradually reduced further to diols upon a prolonged reaction period.[37] Note that the DIBAL reduction of **1** leads to a mixture of products; the mild $NaBH_4$ reduction is thus an efficient alternative to obtain the α-hydroxy lactol derivatives.

We further examined the substituent effects on the $NaBH_4$ reduction at C-7 and C-10 of **1** (Table 1). Interestingly, when the C-10 methoxy substituent of **1** (R^1 substituent) was replaced by the acetoxy group in **9**, the reduction ratio at C-11 carbonyl increased (C-13:C-11 = 50:50), possibly due to better coordination of $NaBH_4$ with the α-acetoxy lactone moiety, which increases the reactivity at C-11 carbonyl (see structure **11**). In contrast, $NaBH_4$ treatment of **10**, in which the 7-acetoxy group in **1** (R^2 substituent) was replaced by the bulkier triethylsiloxy group, provided a C-11 to C-13 lactol ratio similar to that obtained for **1** (C-13:C-11 = 80:20), indicating that the remote C-7 substituents exert no steric and/or electronic influence.

The method was further applied to the natural ginkgolides (Scheme 2). α-Benzyl ginkgolide B (**12**), the most potent ginkgolide antagonist against PAF receptor,[1] was readily reduced by $NaBH_4$ to give C-11 lactol derivative **13** as the major product, which was separated from the minor C-13 lactol by acylation with *p*-phenylbenzoic acid. It is noted that the reduction did not proceed at the C-15 lactone that lacks a α-hydroxyl function. Phenylbenzoate **13** was hydrolyzed to lactol **14** with K_2CO_3 in 91% yield. Similarly, the hydrolysis of *p*-phenylbenzoate derivatives obtained in Scheme 1 and Table 1 readily yielded an equilibrium mixture of the corresponding lactols. The efficient $NaBH_4$ reduction of **1** and **9**–**12** thus provided a variety of ginkgolide lactols and their diastereomeric acylates leading to a total of 25 acylated or alkylated derivatives at 7- and 10-hydroxyl.[38]

In summary, the unique reactivity of the ginkgolide α-protected hydroxy lactones toward the mild and common reducing reagent $NaBH_4$ was observed. The reaction selectively provides lactol derivatives presumably through strong coordination with the conformationally fixed α-protected hydroxyl functionalities. Namely, the restricted reduction of α-protected hydroxy lactones to α-lactols, instead of ring-opening to diols, originates in the unique ginkgolide cage structure carrying critically positioned oxygen atoms. This has given rise to a new series of unique ginkgolide derivatives, the biological evaluation of which will be performed.



Scheme 2. Synthesis of gingkgolide B lactol derivative.

Acknowledgements

This research is supported by the National Institutes of Health, NIH Grant MH 068817 and GM 34509 (K.N. and N.B.). K.T. is grateful to the JSPS Postdoctoral Fellowships for Research Abroad.

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38. Representative procedure of ginkgolide lactol benzoates: To a solution of ginkgolide derivatives (ca. 0.05 mmol) in MeOH (1 mL) was added $NaBH_4$ (1 equiv) at room temperature, and the mixture was stirred for 5 min. The reaction mixture was directly subjected to rapid chromatography on silica gel (50% ethyl acetate in hexane) to afford the corresponding lactol derivatives. To a solution of the lactol mixture obtained above in dichloromethane (1 mL) was added *p*-phenylbenzoic acid (2 equiv), EDC (2.2 equiv), and DMAP (2.2 equiv) at room temperature, and the mixture was stirred for 12 h. The reaction mixture was concentrated in vacuo to give the crude products, which were purified by preparative thin layer chromatography on silica gel to afford the lactol *p*-phenylbenzoate derivatives. Data for **6**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 9H), 1.15 (d, 3H, J = 7.2 Hz), 1.77–1.98 (m, 2H), 2.07 (s, 3H), 2.21–2.28 (m, 1H), 2.57 (d, 1H, J = 12.3 Hz), 2.69–2.80 (m, 1H), 2.93–3.05 (m, 2H), 3.59 (s, 3H), 3.77 (s, 3H), 4.47 (d, 1H, J = 3.3 Hz), 4.58 (s, 1H), 5.14 (dd, 1H, J = 12.3, 3.3 Hz), 5.87 (s, 1H), 6.44 (s, 1H), 7.36–7.48 (m, 3H), 7.61 (d, 2H, J = 7.2 Hz), 7.68 (d, 2H, J = 8.4 Hz), 8.09 (d, 2H, J = 8.4 Hz); HRFABMS calcd for $C_{37}H_{43}O_{11}$ $[M+H]^+$ 663.2805, found 663.2813. Data for **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.24 (d, 3H, J = 7.2 Hz), 1.74–1.98 (m, 3H), 2.00 (s, 3H), 2.37–2.46 (m, 1H), 2.85–2.96 (m, 2H), 3.06 (d, 1H, J = 12.3 Hz), 3.63 (s, 3H), 3.73 (s, 3H), 4.50 (s, 1H), 4.54 (d, 1H, J = 6.0 Hz), 5.01 (dd, 1H, J = 12.3, 6.0 Hz), 6.04 (s, 1H), 6.36 (s, 1H), 7.40–7.52 (m, 3H), 7.65 (d, 2H, J = 7.2 Hz), 7.70 (d, 2H, J = 8.4 Hz), 8.18 (d, 2H, J = 8.4 Hz); HRFABMS calcd for $C_{37}H_{43}O_{11}$ $[M+H]^+$ 663.2805, found 663.2810. Data for **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 9H), 1.23 (d, 3H, J = 6.9 Hz), 1.91–1.95 (m, 1H), 2.05–2.13 (m, 3H), 2.13 (s, 3H), 2.51–2.66 (m, 2H), 2.90–3.01 (m, 1H), 3.40 (s, 3H), 3.72 (s, 3H), 4.66 (d, 1H, J = 7.2 Hz), 4.67 (s, 1H), 5.12 (dd, 1H, J = 12.9, 4.5 Hz), 5.95 (s, 1H), 6.58 (d, 1H, J = 3.3 Hz), 7.40–7.52 (m, 3H), 7.63 (d, 2H, J = 7.2 Hz), 7.71 (d, 2H, J = 8.4 Hz), 8.10 (d, 2H, J = 8.4 Hz); HRFABMS calcd for $C_{37}H_{43}O_{11}$ $[M+H]^+$ 663.2805, found 663.2816. Data for **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.28 (d, 3H, J = 6.9 Hz), 1.93–1.96 (m, 2H), 2.24–2.35 (m, 1H), 2.76 (s, 1H, C3–OH), 3.00 (d, 1H, J = 3.0 Hz, C10–OH), 3.54 (q, 1H, J = 6.9 Hz), 4.43 (dd, 1H, J = 8.1, 3.3 Hz), 4.52 (d, 1H, J = 9.6 Hz), 4.58 (d, 1H, J = 7.8 Hz), 4.69 (d, 1H, J = 9.9 Hz), 5.04 (d, 1H, J = 2.4 Hz), 5.36 (d, 1H, J = 3.0 Hz), 6.00 (s, 1H), 6.73 (d, 1H, J = 2.4 Hz), 7.30–7.34 (m, 2H), 7.37–7.53 (m, 6H), 7.63–7.66 (m, 2H), 7.73 (d, 2H, J = 8.4 Hz), 8.10 (d, 2H, J = 8.4 Hz); HRFABMS calcd for $C_{40}H_{41}O_{11}$ $[M+H]^+$ 697.2649, found 697.2659.