

Unique Reactivity of α-Alkoxy Ginkgolide Lactones to Nucleophilic Reagents: Preparation of New Lactol Derivatives

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It has been found that nucleophilic reagents, i.e., $NaBH_4$, Grignard reagents, and alkyl lithium, uniquely react with the α-alkoxy- or acyloxy-lactone moieties in ginkgolide and F-seco-ginkgolides to give rise to lactol derivatives. The reaction is rapid and stops at the lactol stage; the strong coordination of Na, Mg, and Li metals to the conformationally rigid cage structure is involved in both the initiation and termination stages. The $NaBH_4$ reduction of F-seco-ginkgolides gives rise to an equilibrium mixture of α- and β-lactols, the separation of which becomes only possible after acylation by *p*-phenylbenzoic acid. The resulting acyl-lactol stereogenic centers were elucidated by both NOE and the CD/FDCD exciton chirality method utilizing the sterically hindered 7-hydroxyl. On the other hand, the alkylation of ginkgolide B derivatives proceeds regio- and stereoselectively at the C-11 lactone group, resulting from the approach of Grignard and alkyl lithium reagents to the convex face of the cage-shaped ginkgolide molecule. The additional new stereogenic centers of the quaternary lactol hydroxyls have been determined by NOE. This facile alkylation protocol gives rise to a deep-seated skeletal transformation of ginkgolides, resulting in a new class of ball-shaped heptacyclic ginkgolide derivatives via "olefin/olefin" and "olefin/alkyne" ring-closing metathesis.

Ginkgolides from the *Ginkgo biloba* tree are diterpenes with a rigid cage structure consisting of six five-membered rings and a unique *t*-Bu group (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, i.e., 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. Extensive degradation studies of native ginkgolides performed during the course of structural determination[20–26] gave rise to the dilactone derivative **1** lacking ring F of the original ginkgolides (see structure in Scheme 1). However, since neither the biological activity nor the derivatization of F-seco-**1** had been explored, the current studies were performed in view of its attractive truncated skeleton as a new template for the preparation of a new series of derivatives. During this study, unexpectedly, it was found that the α-alkoxy lactone moieties in **1** are readily reduced by sodium borohydride ($NaBH_4$) to produce the corresponding lactols (Scheme 1).[27] In this paper, we report on the unique reactivity of nucleophilic reagents, such as $NaBH_4$, Grignard reagents, or alkyl lithium, towards the α-alkoxy- or acyloxy-lactone moieties of ginkgolide and its derivatives, leading to a new class of ginkgolide derivatives.

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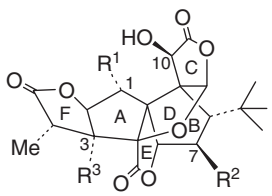

	R^1	R^2	R^3
Ginkgolide A	H	H	OH
Ginkgolide B	OH	H	OH
Ginkgolide C	OH	OH	OH
Ginkgolide J	H	OH	OH
Ginkgolide M	OH	OH	H

Fig. 1. Structure of five ginkgolides.

Results and Discussion

$NaBH_4$ Reduction of F-seco-Ginkgolide and Ginkgolide B Derivatives. The $NaBH_4$ treatment (1 equivalent) of F-seco-ginkgolide **1** quantitatively provided the C-13 and C-11 lactol derivatives **2** and **3** (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 a prolonged reaction time. It is to be noted that the ester groups in **1** were not reduced under these conditions. The isolation and separation of lactol derivatives **2** and **3** that exist as 1:1 equilibrium mixtures of lactol hydroxy groups at both C-11 and C-13, became possible only after acylation. Namely, a treatment of **2** and **3** with *p*-phenylbenzoic acid in the presence of EDC and DMAP gave **4–6** in a ratio of 10:6:3, each isomer being readily separable by silica gel TLC;[28] the chemoselectivity ratio of reduction at C-13 and C-11 was thus 83:17 (see also Table 1). Under these conditions, bis-lactol derivatives were obtained as less than 10% of the products.

The stereochemistry of the 11- and two 13-*p*-phenylbenzoate, **4–6**, were assigned from the following NOEs (Scheme 2): 13-H/8-H and 13-H/12-H for 13α-benzoate **4**, 13-H/3-H for 13β-benzoate derivative **5**, and 2-H/11-H for **6**.

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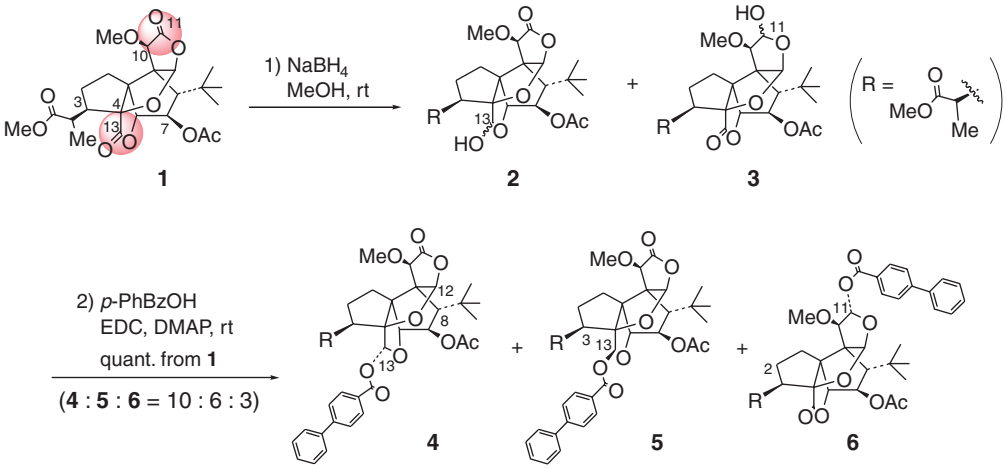
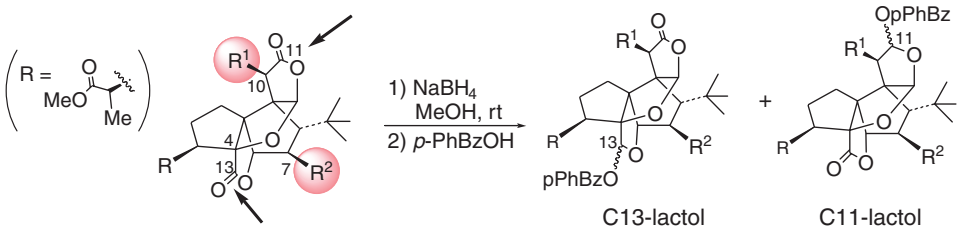
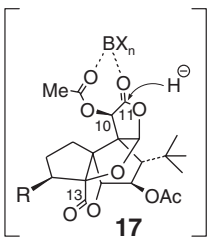


Scheme 1. Reduction of α-alkoxy lactones to lactols.

Table 1. Reduction Ratio at α-Alkoxy or Acyloxy Lactones[a)]



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

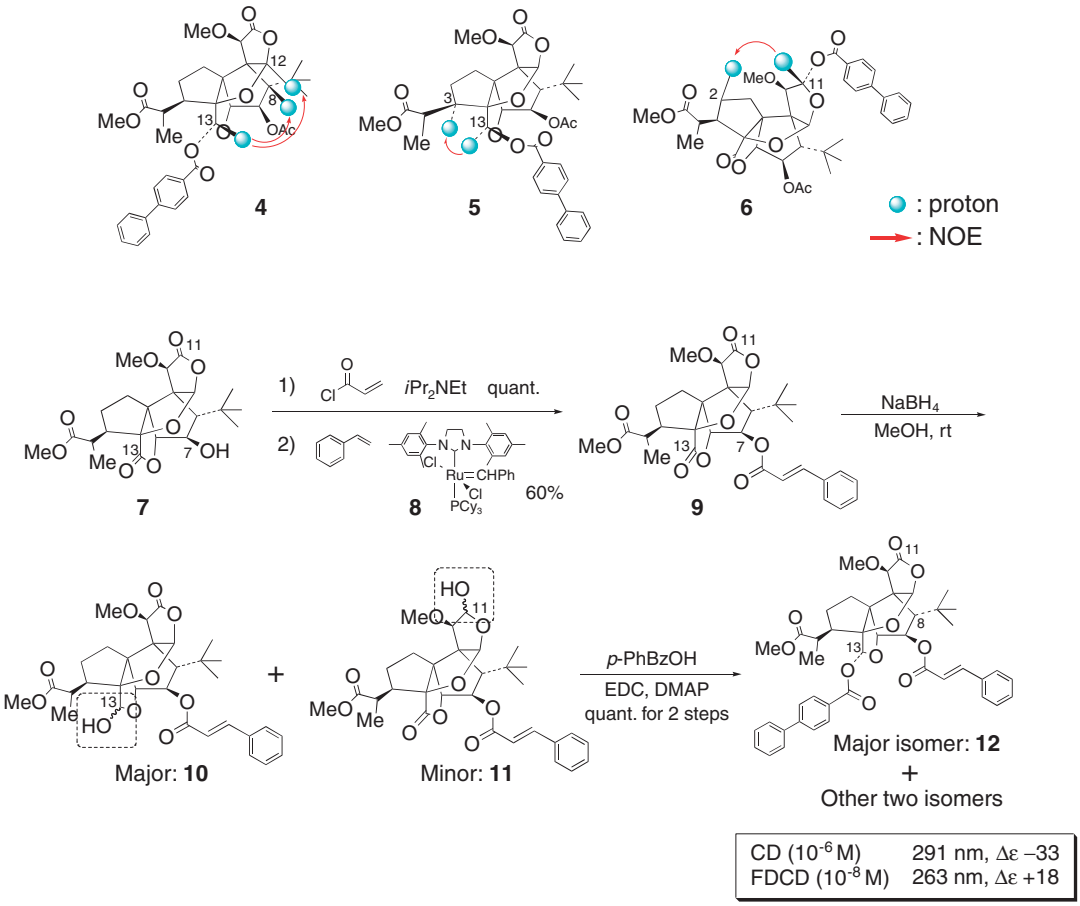


a) Each reaction was performed using 1 equivalent of $NaBH_4$ at room temperature for 5 min. The reaction mixtures were directly acylated by *p*-phenylbenzoic acid and the products were analyzed by ^{1}H NMR. None of over-reduced diols were observed.

The configuration of the main isomer **4**, resulting from $NaBH_4$ reduction of the F-seco-ginkgolide derivative **1**, was also supported by a cross metathesis-CD/FDCD exciton chirality protocol,[29–31] which was performed on the similar derivative **12**, obtained by a similar $NaBH_4$ reduction of the 7-cinnamoyl-F-seco-ginkgolide **9** (Scheme 2).[31] Thus, the lactone groups at C-11 and C-13 in **9**, with the sterically hindered 7-OH acylated with the cinnamate chromophore via cross metathesis,[32,33] were smoothly reduced by $NaBH_4$ to give the corresponding lactols **10** and **11** as four diastereoisomers in quantitative yield. An inseparable equilibrium mixture of **10** and **11** was continuously acylated by *p*-phenylbenzoic acid in the presence of EDC and DMAP to provide **12** as the main diastereoisomer, which was readily separable from the other isomers by silica-gel chromatography.

CD and FDCD of the main isomer **12** show negative exciton coupling between the cinnamate and *p*-phenylbenzoate chromophores, with an amplitude of $A_{CD} = -51$. A conformational analysis of 13α-lactol hydroxyl isomer **12** by MC/MMFF94s method, predicted negative CD exciton chirality, while a similar analysis of the diastereomeric 13β-lactol derivative would give rise to a positive exciton chirality. The structure of the main lactol acylate **12** was thus determined to possess the 13α-lactol hydroxyl.[31]

Our studies revealed that the ginkgolide α-alkoxyl lactones are converted smoothly, selectively, and quantitatively into lactols, by reacting with 1 equivalent $NaBH_4$ at room temperature for a few minutes. In contrast, it is well known that the reduction of lactones or esters by $NaBH_4$ requires a large excess of the reagent, i.e., exceeding 20 equivalents, and/or relatively high reaction temperatures.[34–37] For example, our control experiment showed that the lactone without α-alkoxyls, i.e., Corey lactone (Fig. 2)[29] is not reduced under the condition employed in Scheme 1. 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



Scheme 2. Stereochemical analysis of reduction products **4**–**6** and **12**.

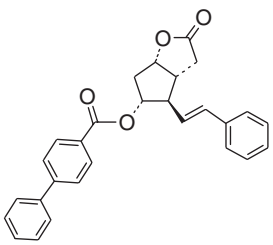
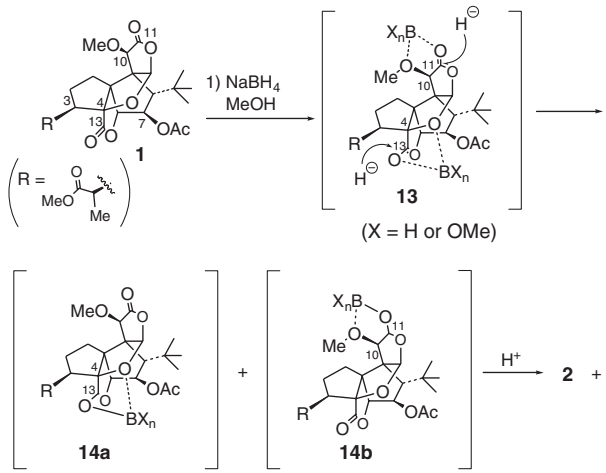


Fig. 2. Structure of Corey lactone.

functionalities linked to the carbonyl groups, e.g. α-amino acids, accelerate the $NaBH_4$ reduction.[35,38,39] An unique reactivity of ginkgolide lactones is therefore most likely caused by the presence of suitably arranged C-4 and C-10 α-oxygen, which are rigidly fixed in the ginkgolide cage skeleton (Scheme 3). Namely, $NaBH_4$ (or its methoxylated reagents, $NaBH_x(OMe)_{4-x}$) presumably coordinates tightly with the lactone carbonyls and α-oxygens to yield a complex such as **13** that could accelerate the nucleophilic attack of the hydride towards the lactone carbonyl, which in turn is activated by the alkoxyl inductive effect. The preferred reduction of the 13-lactone (C-13:C-11 = 83:17) is most likely to be due to the stronger coordination of $NaBH_4$ to this carbonyl. In addition, the obtained lactol hydroxyl and α-alkoxyl could form strong borate complexes, such as **14a** and **14b**, which might stabilize the reaction intermediates and prevent further reduction, a phenomenon similar to the well-known partial reduction of lactones by diisobutylaluminum hydride (DIBAL) at low temperature, i.e., −78 °C. Corsano and Piancatelli 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 by prolonged reaction periods.[40] Note that the DIBAL reduction of **1** leads to a mixture of products; the mild $NaBH_4$ reduction is thus an efficient alternative leading to the α-alkoxy lactol derivatives.

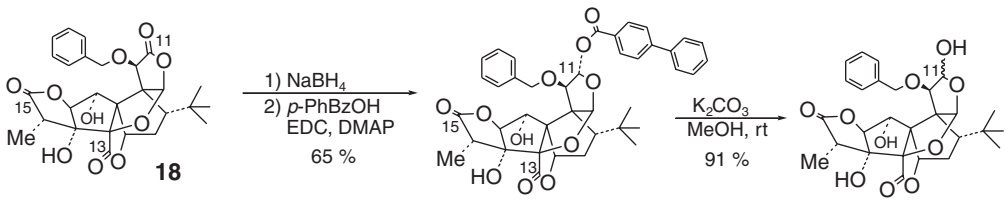


Scheme 3. Possible mechanism of α-alkoxy lactones to lactols.

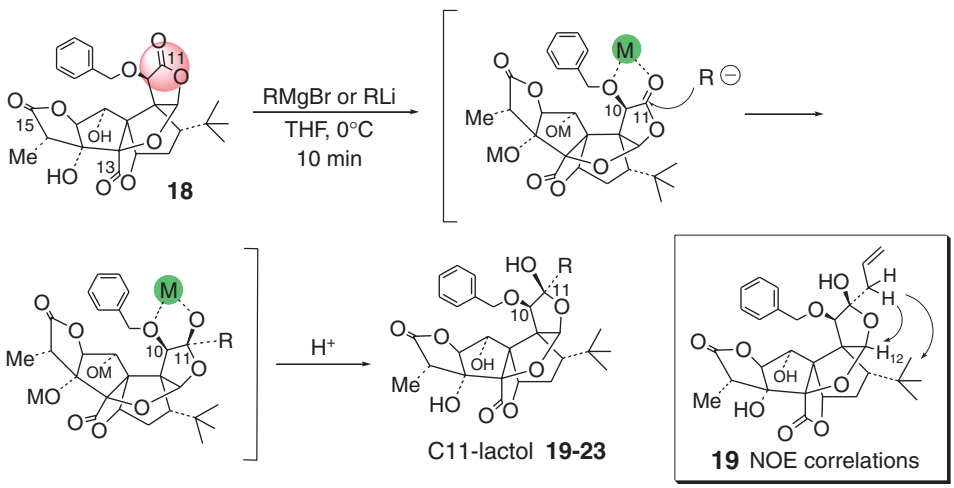
We further examined the substituent effects on $NaBH_4$ reduction at C-7 and C-10 of **1** (Table 1). Interestingly, when the C-10 methoxy substituent of **1** (R^1 substituent) was replaced by the acetoxyl group in **15**, the reduction ratio at C-11 carbonyl increased (C-13:C-11 = 50:50), possibly due to better coordination of $NaBH_4$ with the α-acetoxy lactone moiety, which increases the reactivity at C-11 carbonyl (see structure **17**). In contrast, a $NaBH_4$ treatment of **16**, in which the 7-acetoxyl 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.

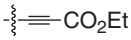
The method was further applied to the natural ginkgolides (Scheme 4). 10-O-Benzylated ginkgolide B (**18**), the most potent ginkgolide antagonist against the PAF receptor,[1] was readily reduced by $NaBH_4$ to give the C-11 lactol derivative as the major product, which was separated from the minor C-13 lactol by acylation with *p*-phenylbenzoic acid (regioselectivity at C-11:C-13 lactones = 10:1). It is noted that the reduction did not proceed at the C-15 lactone, which lacks a α-alkoxyl function. The high regioselectivity at the C-11 lactone over the C-13 lactone, observed in this cage-shaped natural ginkgolide case, is most likely due to the steric hindrance around the C-13 lactone posed by an additional F-ring, so that the $NaBH_4$ reagent is not readily accessible. The phenylbenzoate derivative was then converted into the corresponding lactol by methanolysis with K_2CO_3 in 91% yield. Similarly, the methanolysis of *p*-phenylbenzoate derivatives, obtained according to Scheme 1 and Table 1, readily yielded an equilibrium mixture of the corresponding lactols. The efficient $NaBH_4$ reduction of **1**, **15**, and **16** 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.

Alkylation of Ginkgolide B: Preparation of New Class of Ginkgolide Derivatives. Since we observed an enhanced reactivity of ginkgolide α-alkoxyl lactone towards the hydride ion, we further examined the reaction with other nucleophiles, i.e., Grignard reagent and alkyllithium reagents (Scheme 5). We chose 10-O-benzylated ginkgolide B **18** as a substrate

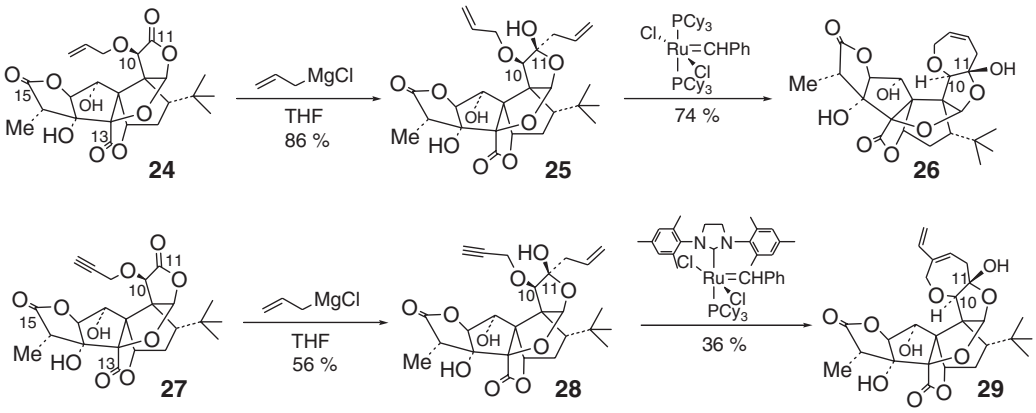


Scheme 4. Synthesis of ginkgolide B lactol derivative.



entry	reagent	R	yield (%)	product
1	 MgBr		86	**19**
2	MeMgBr	Me	50	**20**
3	PhMgBr	Ph	55	**21**
4	*n*-BuLi	*n*-Bu	50	**22**
5	Li—≡—CO_2Et		58	**23**

Scheme 5. Alkylation of 10-O-benzylated ginkgolide B derivatives. Each reaction was performed using 3 equivalents of RMgBr or RLi at 0 °C for 10 min. None of the over alkylated products at C-13 and/or C-15 were observed.



Scheme 6. Preparation of new class of ginkgolide B analogs.

for this alkylation trial. Note that the reaction of **18** with three equivalents of allyl Grignard reagent in THF for 10 min at 0 °C, regio- and stereoselectively provided C-11 quaternary lactol **19** in 86% yield as a single isomer (Scheme 5, Entry 1). Furthermore, the reaction of **18** with methylmagnesium bromide (Entry 2), phenylmagnesium bromide (Entry 3), *n*-butyllithium (Entry 4), and propargyllithium reagent (Entry 5), similarly provided the corresponding C-11 lactols, **20**–**23**, in 50–58% yields, respectively. For Entries 2–5, the unreacted starting materials were recovered under the same alkylation condition as for Entry 1, which led to a slight decrease of the product yields.

These alkylations also proceeded preferentially at the C-11 lactone carrying the α-alkoxyl, the regioselectivity of which is similar to that of $NaBH_4$ reduction (Scheme 4). Furthermore, bis-alkylated products, resulting from the opening of lactol into the keto-alcohol, followed by the alkylation of ketone, were not observed. We could not observe any alkylated products in the control substrate, Corey lactone, under identical conditions (Fig. 2). These results indicate that the strong coordination of Mg and Li metals to the conformationally rigid ginkgolide cage structure is also important for alkylation, in both the initiation and termination stages; it involves a reaction mechanism similar to the $NaBH_4$ reduction, as proposed in Scheme 3. Therefore, the alkylation of ginkgolide C-11 lactone by the ester-containing propargyllithium reagent (Scheme 5, Entry 5), also becomes possible without self-condensation of the reagent under these mild conditions.

The configuration of the new C-11 stereogenic center in **19** was determined from the NOEs of allyl protons with 12-H and with *t*-butyl protons (Scheme 5). The quaternary stereogenic centers at C-11 of other alkylation products, **20**–**23**, were also found to possess the same configuration as that of **19**, determined through a comparison of their characteristic ^{1}H NMR (Experimental Section). As shown in Scheme 5, the highly α-selective alkylation is rationalized by the preferred approach of alkyl nucleophiles from the convex face of the cage-shaped ginkgolide molecule, in which the α-alkoxyl lactone carbonyl is simultaneously activated for a nucleophilic attack by the metal coordination.

The regio- and stereoselective alkylation of α-alkoxyl lactone led to a deep-seated skeletal transformation of the ginkgolide skeleton, yielding a new class of ginkgolide lactol derivatives (Scheme 6). Thus, the allylation of 10-O-allylated ginkgolide B **24**, regio- and stereoselectively provided bis-allyl derivative **25** in 86% yield, while the alkylation of 10-O-propargylated ginkgolide **27** similarly yielded **28** in 56% yield.

The proximately situated two unsaturated moieties, stereoselectively introduced at the C-ring of ginkgolide B, can be utilized for constructing additional seven-membered ring systems via the olefin/olefin and olefin/alkyne ring-closure metathesis. A ruthenium-catalyzed olefin/olefin metathesis[41] of **25** in the presence of the first generation Grubbs' catalyst, successfully provided new ball-shaped heptacyclic ginkgolide **26** in 74% yield. On the other hand, the olefin/alkyne metathesis[42] attempted on **28**, in the presence of the first generation catalyst, only resulted in a recovery of the starting material, even under THF reflux conditions. After optimization of the conditions, regioselective olefin/acetylene metathesis was finally achieved in 36% yield in the presence of the more reactive Grubbs' second-generation catalyst[43–45] in THF at room temperature. Under this condition, compound **28** also participated in self-condensation by cross metathesis between olefins and/or alkyne moieties in **28**, leading to a decrease in the yield of **29**. Note that the presence of the diene moiety in **29**, created during olefin/acetylene metathesis, can be further utilized for functionalization of this intriguing molecule, i.e., Diels–Alder reaction, which enhances the diversity of this new class of ginkgolide analogs.

Conclusion

In summary, the unique reactivity of the ginkgolide α-protected hydroxy lactones toward nucleophilic reagents, Grignard and alkyllithium reagents, and even the mild $NaBH_4$ reducing reagent 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 leads to a new series of ginkgolide derivatives, the biological evaluation of which will be performed.

Experimental

Materials and General Procedures. Anhydrous dichloro-

methane was dried and distilled from CaH_2. Unless otherwise noted, materials were obtained from a commercial supplier and were used without further purification. All reactions were performed in pre-dried glassware under Ar unless noted. Purification was performed either by column chromatography using ICN silica gel (32–63 mesh) or by preparative TLC using silica gel plate, 60 F-254, 0.25 mm, E. Merck. ^{1}H NMR spectra were obtained on Bruker DMX 300 or 400 MHz spectrometers and are reported in parts per million (ppm) relative to TMS (δ), with coupling constants (J) in hertz (Hz). Low- and high-resolution FAB mass spectra were measured on a JEOL JMS-DX303 HF mass spectrometer using a glycerol matrix and Xe ionizing gas. UV–vis spectra were recorded on a Perkin-Elmer Lambda 40 spectrophotometer, and reported as λ_{max} [nm] (ε_{max} [L mol^{-1} cm^{-1}]). The CD spectra were recorded on a JASCO-810 spectrophotometer. The CD spectra were measured in millidegrees and normarized into $\Delta\varepsilon_{max}$ [L mol^{-1} cm^{-1}].

General Procedure of $NaBH_4$ Reduction of Ginkgolide Derivatives: Preparation of Ginkgolide Lactol Benzoates. To a solution of ginkgolide derivatives (ca. 0.05 mmol) in MeOH (1 mL) was added $NaBH_4$ (1 equivalent) 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 as mentioned above in dichloromethane (1 mL) was added *p*-phenylbenzoic acid (2 equivalents), EDC (2.2 equivalents), and DMAP (2.2 equivalents) at room temperature, and the mixture was stirred for 12 h. The reaction mixture was concentrated in vacuo to give crude products, which were purified by preparative thin-layer chromatography on silica gel to afford the lactol *p*-phenylbenzoate derivatives.

F-seco-Ginkgolide C-13 α-Lactol *p*-Phenylbenzoate (4): ^{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.

F-seco-Ginkgolide C-13 β-Lactol *p*-Phenylbenzoate (5): ^{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.

F-seco-Ginkgolide C-11 α-Lactol *p*-Phenylbenzoate (6): ^{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.

Acryloylated Derivative of F-seco-Ginkgolide (7): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.21 (d, 3H, J = 7.2 Hz), 1.84–2.05 (m, 3H), 2.13 (d, 1H, J = 12.8 Hz), 2.54–2.63 (m, 2H), 2.82–2.89 (m, 1H), 3.73 (s, 3H), 3.76 (s, 3H), 4.53 (s, 1H), 4.68 (d, 1H, J = 4.4 Hz), 5.25 (dd, 1H, J = 12.8, 4.4 Hz), 5.94 (dd, 1H, J = 11.8, 1.2 Hz), 5.95 (s, 1H), 6.14 (dd, 1H, J = 17.3, 10.4 Hz), 6.47 (dd, 1H, J = 17.3, 1.2 Hz); HRFABMS calcd for $C_{25}H_{33}O_{10}$ $[M+H]^+$ 493.2074, found 493.2085.

F-seco-Ginkgolide Cinnamate Derivative (9): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H), 1.22 (d, 3H, J = 7.1 Hz), 1.85–2.07 (m, 3H), 2.16 (d, 1H, J = 12.9 Hz), 2.56–2.64 (m, 2H), 2.83–2.90 (m, 1H), 3.73 (s, 3H), 3.77 (s, 3H), 4.54 (s, 1H), 4.71 (d, 1H, J = 4.4 Hz), 5.33 (dd, 1H, J = 12.8, 4.2 Hz), 5.97 (s, 1H), 6.45 (d, 1H, J = 16.0 Hz), 7.40–7.41 (m, 3H), 7.51–7.55 (m, 2H), 7.73 (d, 1H, J = 16.0 Hz).

F-seco-Ginkgolide *p*-Phenylbenzoate Cinnamate Derivative (12): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 1.85–1.97 (m, 2H), 2.27–2.31 (m, 1H), 2.67 (d, 1H, J = 11.2 Hz), 2.75–2.79 (m, 1H), 2.96–3.07 (m, 2H), 3.60 (s, 3H), 3.76 (s, 3H), 4.54 (d, 1H, J = 3.5 Hz), 4.62 (s, 1H), 5.34 (dd, 1H, J = 12.4, 3.5 Hz), 5.92 (s, 1H), 6.44 (d, 1H, J = 16.0 Hz), 6.49 (s, 1H), 7.36–7.71 (m, 13H), 8.10 (d, 2H, J = 8.5 Hz); HRFABMS calcd for $C_{44}H_{46}O_{11}$ $[M]^+$ 789.2677, found 789.2684.

10-O-Benzylated Ginkgolide C-11 α-Lactol *p*-Phenylbenzoate: ^{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.

General Procedure of Alkylation of Ginkgolide Derivatives by Grignard and Alkyllithium Reagents. To a solution of ginkgolide derivatives (ca. 0.05 mmol) in THF (1 mL) was added a 1–2 M solution of Grignard or alkyllithium reagents (3–4 equivalents) in THF (ether) at 0 °C. After the mixture was stirred for 10 min at this temperature, a H_2O and saturated aqueous NH_4Cl solution was added, and the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give the crude product. Column chromatography on silica gel (gradually 33% to 40% ethyl acetate in hexane) gave the corresponding mono-alkylated product as a white solid.

Allylated Product of 10-O-Benzylated Ginkgolide B (19): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 9H), 1.26 (d, 3H, J = 7.1 Hz), 1.86 (dd, 1H, J = 13.3, 3.8 Hz), 1.95 (dd, 1H, J = 14.4, 4.0 Hz), 2.23 (dd, 1H, J = 13.0, 4.0 Hz), 2.45 (d, 1H, J = 3.8 Hz), 2.61–2.76 (m, 3H) including 2.70 (s, 1H), 3.54 (q, 1H, J = 7.1 Hz), 4.34 (d, 1H, J = 8.9 Hz), 4.52 (d, 1H, J = 8.1 Hz), 4.65 (s, 1H), 4.83 (d, 1H, J = 8.9 Hz), 5.22 (d, 1H, J = 3.7 Hz), 5.32 (d, 1H, J = 17.2 Hz), 5.43 (d, 1H, J = 10.3 Hz), 5.51 (s, 1H), 5.64 (dd, 1H, J = 8.1, 3.8 Hz), 5.90–6.01 (m, 1H), 7.31–7.42 (m, 5H); HRFABMS calcd for $C_{30}H_{35}O_9$ $[M-H_2O+H]^+$ 539.2281, found 539.2300.

Methylated Product of 10-O-Benzylated Ginkgolide B (20): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 9H), 1.27 (d, 3H, J = 7.2 Hz), 1.83 (ddd, 1H, J = 13.4, 13.4, 4.9 Hz), 1.98 (dd, 1H, J = 14.4, 4.4 Hz), 2.25 (dd, 1H, J = 13.0, 4.4 Hz), 2.42 (d, 1H, J = 3.9 Hz), 2.56 (s, 1H), 3.53 (q, 1H, J = 7.2 Hz), 3.62 (s, 1H), 4.37 (d, 1H, J = 8.9 Hz), 4.53 (d, 1H, J = 8.1 Hz), 4.62 (s, 1H), 4.84 (d, 1H, J = 8.9 Hz), 5.21 (d, 1H, J = 3.7 Hz), 5.52 (s, 1H), 5.61 (dd, 1H, J = 8.2, 3.9 Hz), 7.30–7.42 (m, 5H); HRFABMS calcd for $C_{28}H_{35}O_{10}$ $[M+H]^+$ 531.2230, found

531.2242.

Phenylated Product of 10-O-Benzylated Ginkgolide B (21): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.25 (d, 3H, $J = 7.2$ Hz), 1.83 (ddd, 1H, $J = 14.0$, 14.0, 3.9 Hz), 2.04 (dd, 1H, $J = 13.6$, 4.6 Hz), 2.25 (dd, 1H, $J = 13.4$, 4.4 Hz), 2.45 (d, 1H, $J = 4.0$ Hz), 2.64 (s, 1H), 3.60 (q, 1H, $J = 7.2$ Hz), 4.05 (d, 1H, $J = 9.3$ Hz), 4.28 (s, 1H), 4.58 (d, 1H, $J = 8.1$ Hz), 4.77 (s, 1H), 4.81 (d, 1H, $J = 9.4$ Hz), 5.24 (d, 1H, $J = 3.6$ Hz), 5.79 (s, 1H), 5.88 (dd, 1H, $J = 8.1$, 4.0 Hz), 7.34–7.47 (m, 8H), 7.65 (d, 2H, $J = 7.8$ Hz); HRFABMS calcd for $C_{33}H_{35}O_9$ $[M - H_2O + H]^+$ 575.2281, found 575.2287.

***n*-Butylated Product of 10-O-Benzylated Ginkgolide B (22):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, 3H, $J = 7.0$ Hz), 1.14 (s, 9H), 1.26 (d, 3H, $J = 7.1$ Hz), 1.41–1.68 (m, 6H), 1.79–1.88 (m, 1H), 1.95 (dd, 1H, $J = 14.3$, 3.8 Hz), 2.24 (dd, 1H, $J = 13.0$, 4.0 Hz), 2.47 (d, 1H, $J = 3.8$ Hz), 2.58 (s, 1H), 3.54 (q, 1H, $J = 7.1$ Hz), 3.57 (s, 1H), 4.35 (d, 1H, $J = 8.9$ Hz), 4.52 (d, 1H, $J = 8.2$ Hz), 4.61 (s, 1H), 4.81 (d, 1H, $J = 8.9$ Hz), 5.22 (d, 1H, $J = 3.6$ Hz), 5.49 (s, 1H), 5.62 (dd, 1H, $J = 8.2$, 3.8 Hz), 7.31 (dd, 1H, $J = 7.0$, 1.7 Hz), 7.38–7.44 (m, 1H), 7.49 (dd, 1H, $J = 7.4$, 7.4 Hz), 7.60 (dd, 1H, $J = 7.4$, 7.4 Hz), 7.81 (d, 1H, $J = 7.0$ Hz); HRFABMS calcd for $C_{31}H_{40}O_{10}Na$ $[M + Na]^+$ 595.2519, found 595.2542.

Propargylated Product of 10-O-Benzylated Ginkgolide B (23): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.26 (d, 3H, $J = 6.9$ Hz), 1.51 (t, 3H, $J = 7.0$ Hz), 1.85 (ddd, 1H, $J = 13.7$, 13.7, 4.1 Hz), 2.02 (dd, 1H, $J = 14.4$, 4.4 Hz), 2.27 (dd, 1H, $J = 13.5$, 4.4 Hz), 2.30 (d, 1H, $J = 4.2$ Hz), 2.58 (s, 1H), 3.46 (q, 1H, $J = 7.0$ Hz), 4.24 (q, 2H, $J = 7.1$ Hz), 4.33 (d, 1H, $J = 9.0$ Hz), 4.43 (d, 1H, $J = 9.0$ Hz), 4.52 (d, 1H, $J = 8.1$ Hz), 5.13 (s, 1H), 5.18 (s, 1H), 5.25 (d, 1H, $J = 3.8$ Hz), 5.35 (dd, 1H, $J = 8.1$, 4.1 Hz), 5.68 (s, 1H), 7.23–7.26 (m, 3H), 7.39–7.41 (m, 2H); HRFABMS calcd for $C_{32}H_{37}O_{12}$ $[M + H]^+$ 613.2285, found 613.2275.

Allylated Product of 10-O-Allylated Ginkgolide B (25): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.26 (d, 3H, $J = 7.1$ Hz), 1.89–1.97 (m, 2H), 2.26 (dd, 1H, $J = 11.6$, 2.6 Hz), 2.54 (dd, 1H, $J = 13.7$, 8.6 Hz), 2.62 (dd, 1H, $J = 13.4$, 6.1 Hz), 2.67 (s, 1H), 2.96 (d, 1H, $J = 3.8$ Hz), 3.52 (q, 1H, $J = 7.0$ Hz), 3.88 (dd, 1H, $J = 10.5$, 5.5 Hz), 3.94 (s, 1H), 4.34 (dd, 1H, $J = 10.4$, 6.8 Hz), 4.48 (s, 1H), 4.61 (d, 1H, $J = 8.2$ Hz), 5.27–5.42 (m, 5H), 5.66 (d, 1H, $J = 8.2$, 3.8 Hz), 5.85–5.97 (m, 2H); HRFABMS calcd for $C_{26}H_{35}O_4$ $[M + H]^+$ 507.2230, found 507.2235.

Allylated Product of 10-O-Propargylated Ginkgolide B (28): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.26 (d, 3H, $J = 7.0$ Hz), 1.61 (s, 1H), 1.91–1.97 (m, 2H), 2.26 (d, 1H, $J = 8.8$ Hz), 2.50–2.67 (m, 3H), 2.73 (s, 1H), 2.98 (d, 1H, $J = 3.8$ Hz), 3.53 (q, 1H, $J = 7.0$ Hz), 4.11–4.17 (m, 3H), 4.46 (dd, 1H, $J = 14.4$, 2.2 Hz), 4.57 (s, 1H), 4.64 (d, 1H, $J = 8.1$ Hz), 5.29 (d, 1H, $J = 17.2$ Hz), 5.35 (s, 1H), 5.39 (d, 1H, $J = 10.0$ Hz), 5.49 (s, 1H), 5.66 (dd, 1H, $J = 8.1$, 3.8 Hz), 5.84–5.92 (m, 1H); FABMS calcd for $C_{26}H_{31}O_9$ $[M - H_2O + H]^+$ 487.19, found 487.18.

Ring-Closing Metathesis of 25. To a solution of **25** (10 mg, 19.7 μmol) in THF (5.0 mL) were added Grubbs' first-generation ruthenium catalyst (3.25 mg, 3.95 μmol) at room temperature, and the mixture was stirred at this temperature for 21 h. The reaction mixture was concentrated in vacuo to give the crude product, which was purified by column chromatography on silica gel (ethyl acetate in hexane, gradually from 33% to 50%) to afford **26** (7.0 mg, 74%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H), 1.27 (d, 3H, $J = 7.1$ Hz), 1.78–1.90 (m, 2H), 2.26 (dd, 1H, $J = 11.9$, 2.7 Hz), 2.35 (dd, 1H, $J = 15.6$, 9.0 Hz), 2.42 (s, 1H), 2.72 (s, 1H), 3.07 (ddd, 1H, $J = 15.6$, 3.1, 3.1 Hz), 3.34 (d, 1H, $J = 3.1$ Hz), 3.49 (q, 1H, $J = 7.0$ Hz), 4.31 (brd, 1H, $J = 17.7$ Hz), 4.53 (dd, 1H, $J = 8.2$, 3.1 Hz), 4.62–4.71 (m, 3H), 5.39 (d, 1H, $J = 3.5$ Hz), 5.49 (dd, 1H, $J = 11.7$, 2.4 Hz), 5.58–5.65 (m, 1H), 5.84 (s, 1H); HRFABMS calcd for $C_{24}H_{31}O_{10}$ $[M + H]^+$ 479.1917, found 479.1928.

Ring-Closing Metathesis of 28. To a solution of **28** (14 mg, 27.7 μmol) in dichloromethane (3.0 mL) were added Grubbs' second-generation ruthenium catalyst (4.71 mg, 5.55 μmol) at room temperature; the mixture was stirred at this temperature for 30 min. The reaction mixture was concentrated in vacuo to give the crude product, which was purified by column chromatography on silica gel (ethyl acetate in hexane, gradually from 25% to 50%) to afford **29** (5.0 mg, 36%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 9H), 1.27 (d, 3H, $J = 7.1$ Hz), 1.79–1.93 (m, 2H), 2.29 (dd, 1H, $J = 12.1$, 3.1 Hz), 2.37 (s, 1H), 2.44 (dd, 1H, $J = 15.2$, 9.0 Hz), 2.68 (s, 1H), 3.12 (brd, 1H, $J = 15.1$ Hz), 3.30 (d, 1H, $J = 3.1$ Hz), 3.47 (q, 1H, $J = 7.0$ Hz), 4.44 (brd, 1H, $J = 17.2$ Hz), 4.53 (dd, 1H, $J = 8.2$, 3.2 Hz), 4.62–4.73 (m, 3H), 4.90 (d, 1H, $J = 17.9$ Hz), 5.04 (d, 1H, $J = 11.3$ Hz), 5.40 (d, 1H, $J = 3.7$ Hz), 5.67 (brd, 1H, $J = 6.9$ Hz), 5.84 (s, 1H), 6.17–6.27 (m, 1H); HRFABMS calcd for $C_{26}H_{31}O_9$ $[M - H_2O + H]^+$ 487.1968, found 487.1964.

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