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EXPANDING STRUCTURAL DIVERSITY OF TERPENE TRILACTONES FROM *GINKGO BILOBA* EXTRACT: STUDIES TOWARDS CORE-MODIFIED GINKGOLIDES

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Abstract – Ginkgolides, the unique terpene trilactones from the *Ginkgo biloba* tree, are believed to enhance memory, improve blood circulation and exhibit beneficial effects in the treatment of dementia. Unfortunately, mechanisms of ginkgolide actions at the molecular level are still not determined. Ginkgolide skeleton modifications may provide a plausible approach to address subtle changes in the ligand-receptor interactions. Furthermore, the simplified structure of the ginkgolide skeleton may guide to the leads that will be attractive for drug development. This review covers the modifications of the ginkgolide skeleton, reported to date.

DEDICATED TO THE MEMORY OF PROFESSOR KENJI KOGA

INTRODUCTION

Extracts from *Ginkgo biloba*, one of the oldest living tree species, and therefore, sometimes called a "living-fossil," have long been claimed to enhance memory, improve blood circulation and exhibit beneficial effects in the treatment of dementia.[1] The main active ingredients responsible for these distinctive properties of the extract are believed to be structurally unique terpene trilactones, diterpenoid natural products with a cage-like structure, which were isolated in the late 1960s and termed ginkgolides (Figure 1).[1,2] Six five-membered ring architectures feature a spiro[4.4]nonane carbocyclic unit, three lactones and a tetrahydrofuran ring. Ginkgolides (**A**-**M**) differ by the number and positions of the hydroxy-groups around the skeleton.

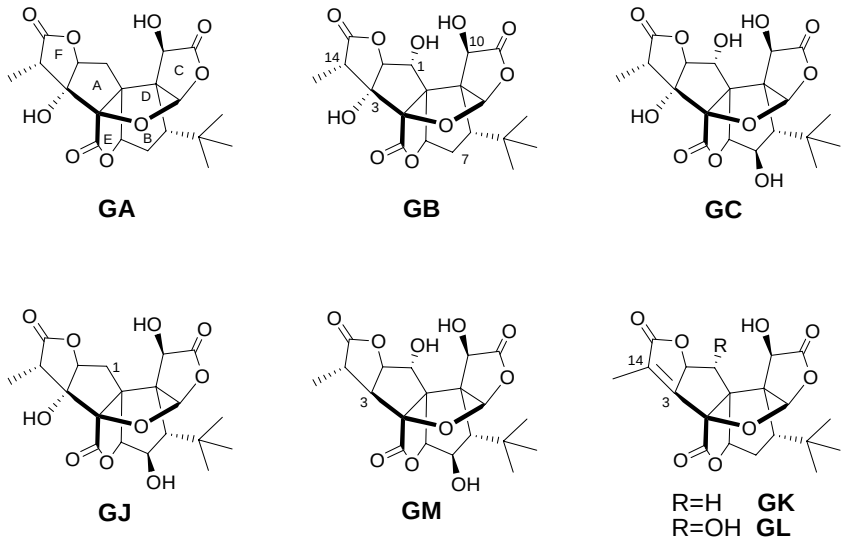


Figure 1.

Effects of ginkgolides on the central nervous system come, at least in part, from their interactions with platelet activating factor receptor, glycine receptor, $GABA_A$ receptor, and peripheral benzodiazepine receptor.[3] In addition, several ginkgolides have shown the ability to inhibit the neurotoxicity of amyloid and prion peptides, thus proving some evidence for the protective effect of ginkgolides, and *Ginkgo biloba* extract, in neurodegenerative diseases, such as Alzheimer's disease.[4] Unfortunately, mechanisms of ginkgolide actions at the molecular level are still not determined.

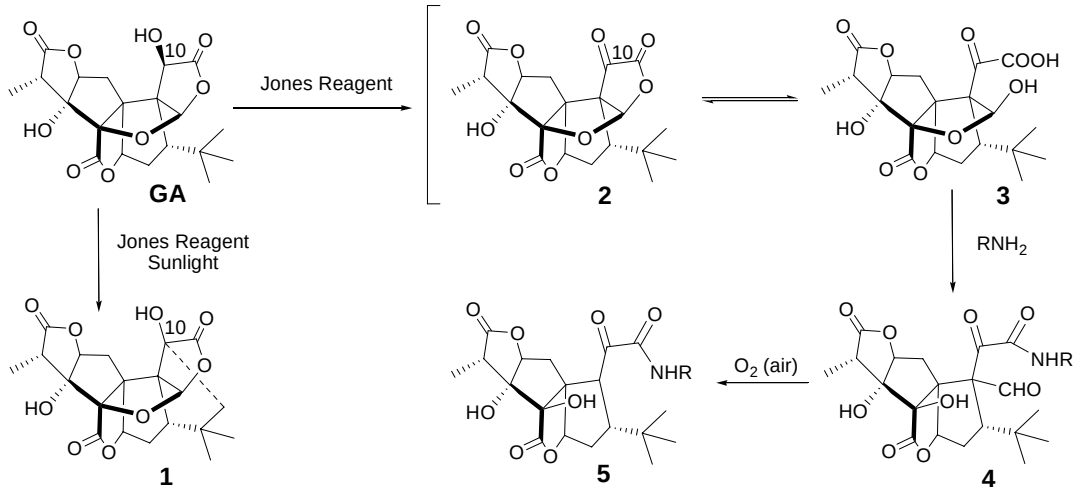
To date, a number of structure-activity relationship (SAR) studies have been carried out in the context of ginkgolide antagonistic activity towards glycine[5] and platelet activating factor receptors.[6] Due to the complex nature of the ginkgolides, SAR studies were primarily focused on functionalization of the hydroxy groups of the ginkgolides, utilizing derivatization at positions 1, 7 and 10 of the ginkgolide skeleton. However, such transformations often result in the formation of ligands that are significantly larger than the ginkgolides themselves, which complicates the rationalization of ligand-receptor interactions. Furthermore, the structural complexity of ginkgolides and their hydroxy-modified derivatives prevents their applications as pharmaceuticals.

On the other side, ginkgolide skeleton modifications provide a plausible approach to address subtle changes in the ligand-receptor interactions. Also, the changes in the ginkgolide skeleton make it possible to set up new reaction centers that would allow further derivatizations for SAR studies. Arguably, the SAR studies on compounds with the simplified ginkgolide skeleton are the leads that may be attractive for drug development.

Over the last several years, a body of accounts has accumulated on the modification of the ginkgolide skeleton. Here, we would like to review publications that utilize, or lead to, structural changes in the ginkgolide core, and do not involve functionalization or modification of the hydroxy groups.

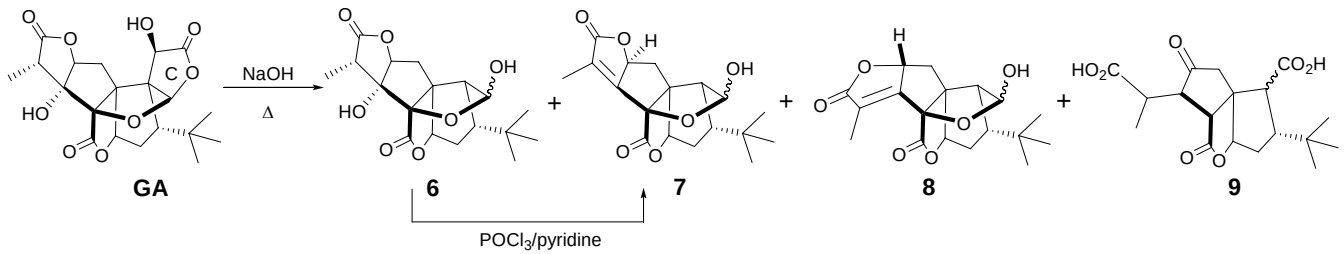
RING-OPENING MODIFICATIONS OF GINKGOLIDES

During the structural studies on ginkgolides, it was discovered that oxidation of **GA** with the Jones reagent yielded two products, which resulted from the modification at the 10-position: the minor product (**1**), which formed upon exposure to light, and the major 10-oxoginkgolide (**2**), which exists in equilibrium with its ring-*C*-open form (**3**).[7] Recently, this oxidation protocol was successfully utilized in the context of preparation of amide derivatives based on the **GA** scaffold.[8] Oxoginkgolide (**2**) reacted with primary amines to form aldehyde (**4**), which was exposed to air to yield amide (**5**) after decarboxylation of an acid intermediate (Scheme 1).



Scheme 1.

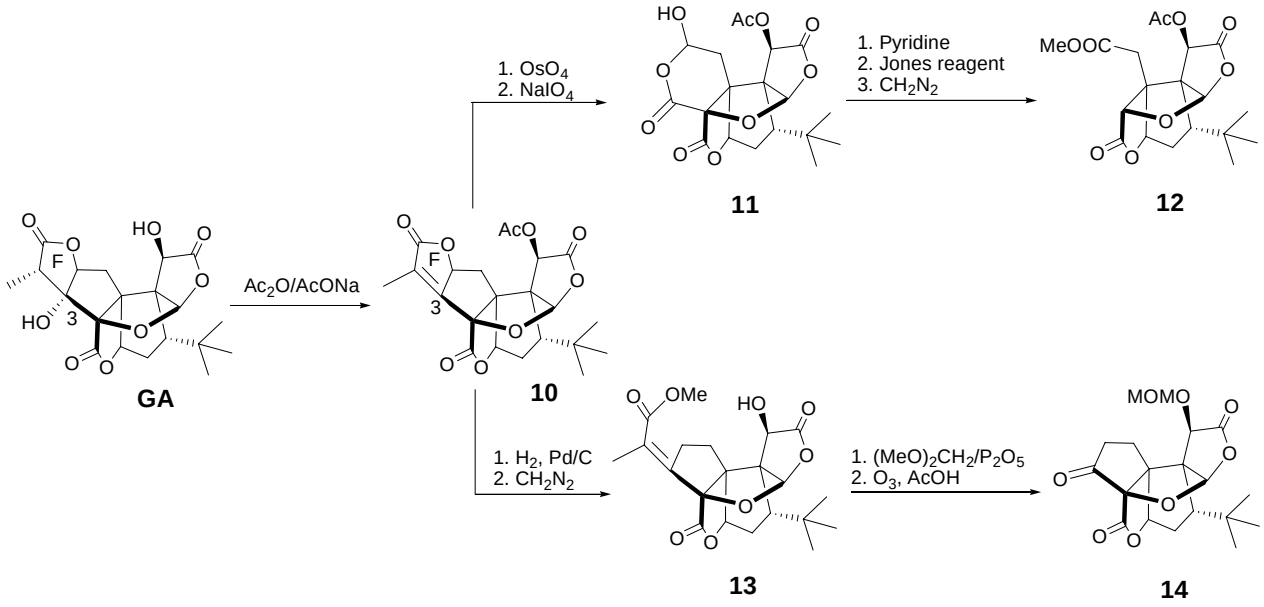
It was demonstrated that lactone *C* of **GA** can be selectively removed upon short exposure to alkaline solution at elevated temperatures leading to formation of diol (**6**).[9] The latter can be selectively dehydrated by reacting with $POCl_3$ in pyridine to yield alcohol (**7**) (Scheme 2).[10] In the recent follow-up study it was shown that conjugated lactone (**7**) could also directly result from reacting **GA** with base (a similar observation was made when this methodology was applied to **GB** instead of **GA**).[11] Also, the formation of two novel products was detected. The first one, dilactone (**8**) resulted from epimerization of dilactone (**7**). The second one, diacid (**9**), is a product of further decomposition of the ginkgolide core (Scheme 2).



Scheme 2.

The presence of a labile tertiary hydroxy group at the 3-position, allows for the introduction of the enone moiety into the ginkgolide skeleton, which can be used as a handle for further modification and functionalization. The elimination strategy was utilized to convert **GA** into unsaturated acetate (**10**),[13] which was then oxidized to give trilactone (**11**) (Scheme 3).[14] The latter was decarboxylated upon reaction with pyridine and subsequent oxidation of aldehyde to an acid, which then was esterified to afford ester (**12**).

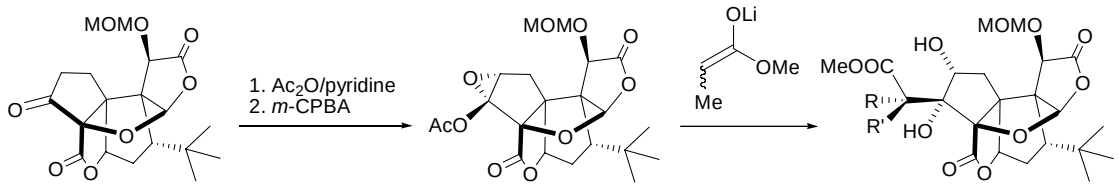
On the other hand, hydrogenation of acetate (**10**) led to ring opening of lactone *F*. The subsequent esterification with diazomethane produced ester (**13**), which was further protected and ozonolyzed to yield ketone (**14**) (Scheme 3).[15]



Scheme 3.

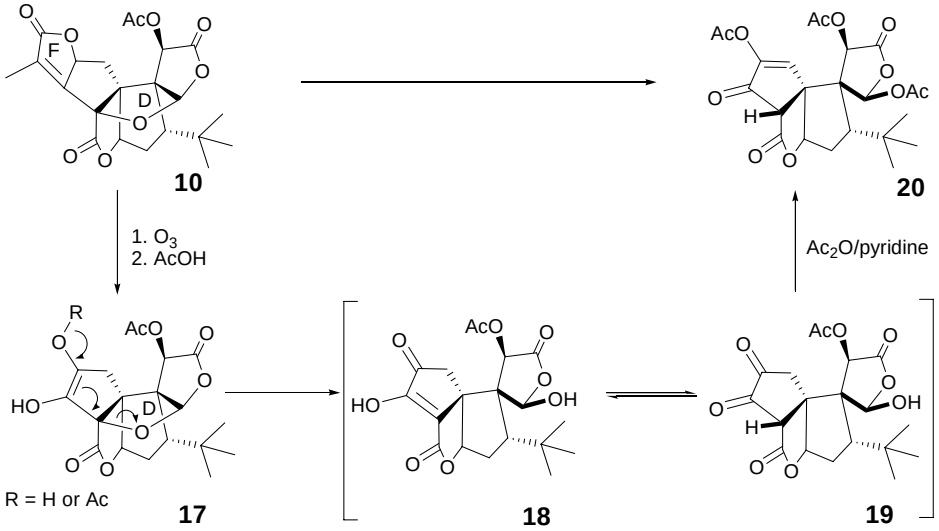
Access to isotopically labeled ginkgolides is essential for future pharmacological studies as well as for monitoring the metabolism of the compounds. Despite the rich functionality of ginkgolides, limited number of chemical incorporation of isotope labeling has been reported to date.[16] Due to the complexity of the ginkgolide structure, it would be logical to utilize core-modification of ginkgolides in order to prepare labeled natural products and their derivatives.

One proposed method involved the ring-opening, degradation and regeneration of the ginkgolide skeleton using isotopically labeled building blocks. Thus, such methodology was developed using GA as the starting material (Scheme 4).[17] Ketone (**14**), prepared from **GA** according to Scheme 3,[15] was converted into the corresponding acetate enol ether, and then subjected to reaction with *m*-CPBA to yield an epoxide (**15**), which reacted with the lithium enolate of methyl propionate to provide a mixture of ester diastereomers (**16a**) and (**16b**). Further activation of the hydroxy group in (**16b**) with MsCl, followed by the ring-closure reaction resulted in **GA**. It was proposed to utilize this sequence in the future using ^{14}C-labeled methyl propionate, which would lead to the labeled **GA** (Scheme 4).[17]



Scheme 4.

Modification of lactone *F* could also facilitate rearrangements in the rest of the ginkgolide skeleton. It was shown that ozonolysis of acetate (**10**), led to an unusual ring-opening of tetrahydropyran ring *D* (Scheme 5).[18]



Scheme 5.

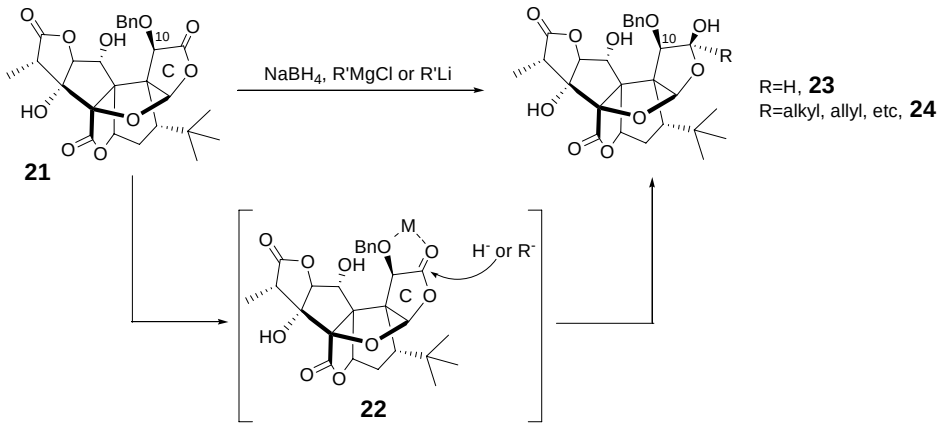
In the proposed mechanism, the enol form (**17**) of initially formed hydroxyketone rearranges into dilactone (**18**), which is in equilibrium with its keto-tautomer (**19**). Enolization of the latter, following by the trapping of the enol with acetic anhydride, leads to triacetate (**20**), which was isolated and characterized.[17]

ADDITION OF THE RINGS

The ginkgolide skeleton modifications discussed above focused on removing parts of the molecule, either the lactone group or other rings. However, it is also possible to add extra rings to the already cage-like skeleton and extend the rigid core of the molecule. The new structures may provide novel binding affinities and clarify ligand-receptor interactions at the molecular level.

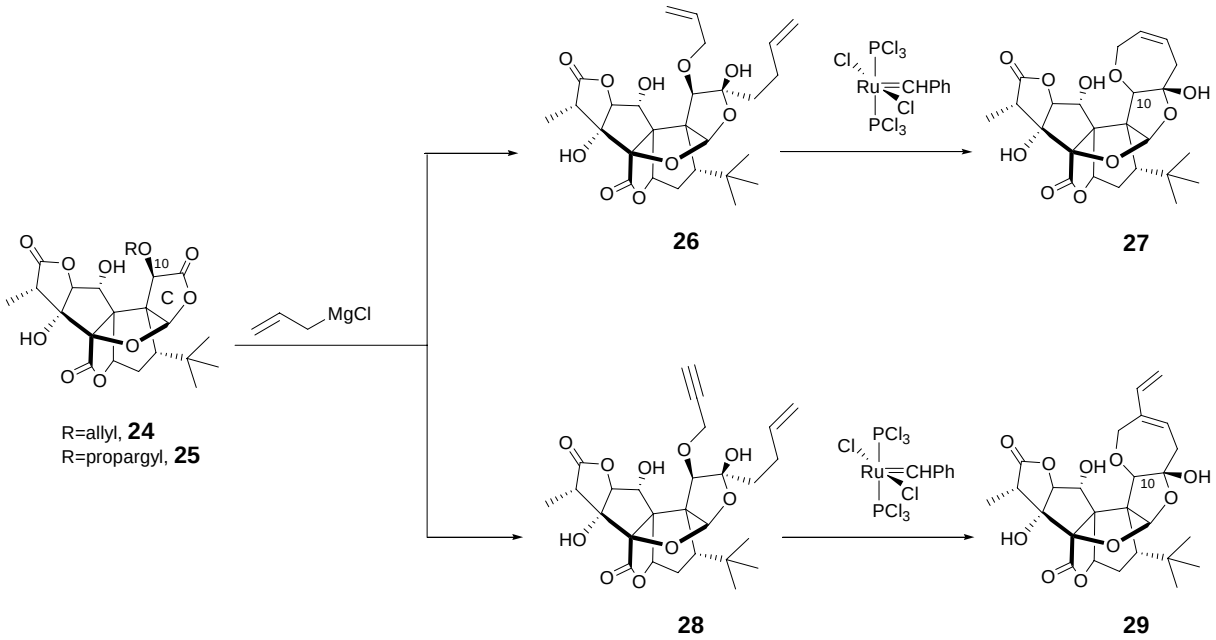
Lactone *C* possesses a unique reactivity towards nucleophilic reagents. For example, in the reaction of 10-Bn-**GB** (**21**) with several reducing reagents, this lactone ring was cleanly converted into the

corresponding lactol (Scheme 6).[19] It was proposed that such selectivity is governed by the formation of complex (**22**), which determines the stereochemistry of the resulting cis-lactols (**23**) and (**24**).



Scheme 6.

This regioselective lactol formation was utilized as a key step for expanding the ginkgolide's core compolexity. 10-Allyl-**GB** (**24**) can be selectively reacted with the allyl-Grignard reagent to produce the corresponding lactol (**26**), which can undergo an intramolecular cross-metathesis reaction to yield a "bowl-like molecule" (**27**) (Scheme 7).[20] The unique cavity of (**28**) provides a scaffold for addressing complexation of this ginkgolide with various species.

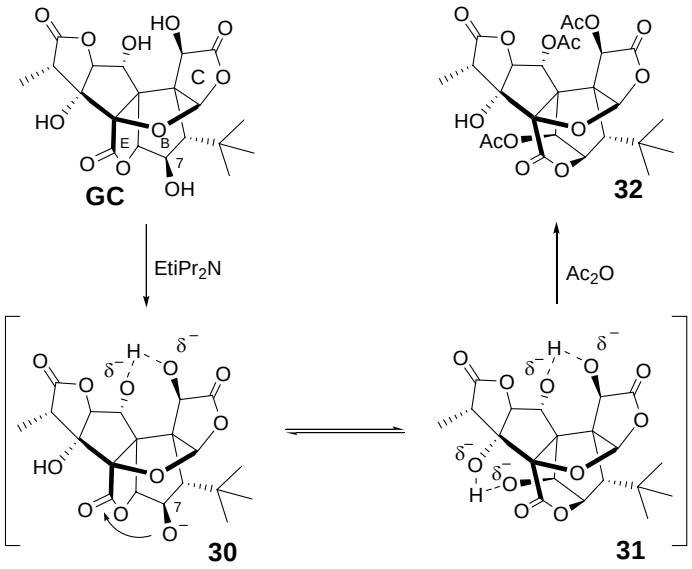


Scheme 7.

In the case where propargyl and allyl moieties are present in the ginkgolide skeleton, as in lactol (**28**), for example, the cross metathesis reaction afforded a diene containing seven membered ginkgolide (**29**) predisposed for further elaborate modifications (Scheme 7).[20]

ISO-GINKGOLIDES

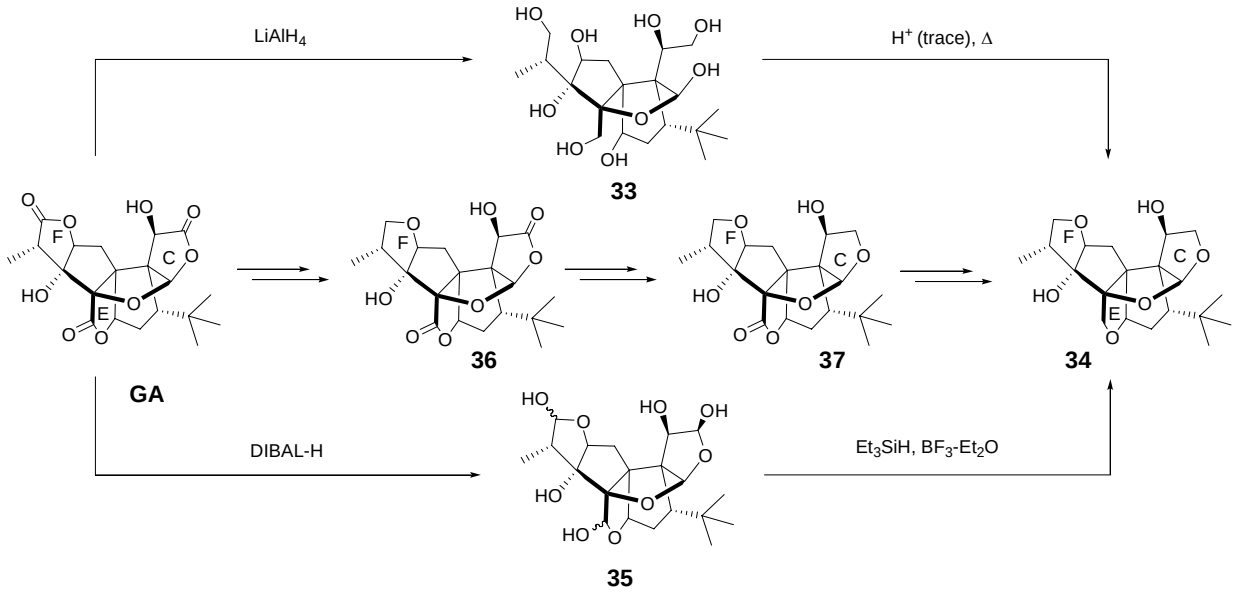
The rearrangement involving lactone *E* and ring *B* was reported during early structural studies. It was found that upon extensive acetylation of **GC** in refluxing Ac_2O/NaOAc, *iso*-tetracetate-**GC** was formed.[7] Furthermore, similar translactonization of lactone *E* also can take place in the presence of the Hunigs base (Scheme 8).[21] Close proximity of the formed anion at the 7-position to the lactone *E* in the intermediate (**30**) allows for the rearrangement of the middle part of the ginkgolide skeleton into (**31**), which can be trapped by electrophiles, such as Ac_2O, to yield *iso*-triacetate (**32**). It is noteworthy that some *iso*-ginkgolides possess antagonistic activity towards the glycine receptor.



Scheme 8

REDUCTION OF LACTONES TO LACTOLS AND ETHERS:

In the late 1960s, a fortuitous reduction of **GA** with $LiAlH_4$ led to the ring-opening of all lactones and the production of octaol (**33**) as an oil (Scheme 9).[9, 22] Pyrolysis of (**33**) in the presence of a trace amount of acid led to ring closure, yielding what has been known as **GA**-triether (**34**). This compound played a crucial role in determining the structure of the ginkgolide skeleton.[9, 22] A convenient reduction protocol featuring DIBAL-H was found to selectively reduce ginkgolide lactones to the corresponding lactols, (**35**), which can be subsequently reduced to the tetrahydrofuran moieties to afford (**34**) (Scheme 9).[23] It also appeared that the reduction of the lactone rings can be achieved in a step-wise fashion, using lesser amounts of DIBAL-H to yield a series of lactone-free ginkgolides, such as **GA**-monoether (**36**) and **GA**-diether (**37**), in moderate yields. The reaction was quite sensitive to the presence of the hydroxy groups, and it was found that in the case of **GB** only two lactone rings, lactone *F* and *C*, could be reduced, and only one in the case of **GC**, namely lactone *F*. Apparently, coordination of bulky aluminum species to the hydroxy-moieties of these ginkgolides contributes to the inefficient preparations.



Scheme 9.

It is interesting to point out that the reduction of **GA** with DIBAL-H started from lactone *F*, continued with lactone *C* and finished with lactone *E*, thus demonstrating a significant degree of substrate-directed regiocontrol in the reaction.[23] In the case of other nucleophiles, such as $NaBH_4$, Grignard and lithium reagents, the addition started from lactone *C* (Scheme 6).[19]

CONCLUSIONS

Core-modification of ginkgolides provides a wide range of functionally and structurally diverse compounds. These modifications may not only find indispensable applications in addressing the modes of ginkgolide actions in biological systems, but they may also be useful for future drug development.

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