Total Synthesis of Ginkgolide C and Formal Synthesis Ginkgolides A and B

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Ginkgolides are diterpenes isolated from ginkgo biloba that exhibit strong PAF antagonistic activity as well as other interesting neuroprotective properties. These natural products possess a compact, highly oxygenated hexacyclic structure with two adjacent quaternary carbon centers, an unusual tert-butyl group, and up to twelve contiguous stereogenic carbon centers. The molecular architecture of ginkgolides, coupled with their remarkable biological profile, continues to be a source of fascination but also presents a formidable challenge for chemical synthesis. Herein, we reported the first total synthesis of ginkgolide C and the formal syntheses of ginkgolides A and B. The key to achieving these syntheses is a careful orchestration of carbon-carbon bond formation, guided by the compact nature of the ginkgolide structure.

Ginkgolides are complex polyoxygenated diterpenoids isolated from the leaves and root bark of the ginkgo biloba tree, also known as the maidenhair tree or as the “Living Fossil” as its fossils date back to the Jurassic period (170M years) (Figure 1A). Ginkgolides A (1), B (2), C (3) and M (4) (for minor) were first isolated by Furukawa in 1932 and their structures were subsequently elucidated in 1967 by Nakanishi.1,2 In 1987, Weinges et al. discovered, isolated and characterized ginkgolide J (5).3 More recently, the Wang and Peng groups independently isolated ginkgolides K, L, P and Q.4,5 Ginkgolides, especially ginkgolide B (2), are strong antagonists to the platelet-activating factor (PAF) receptor (PAFR) which is known as a potent inflammatory factor that plays a role in acute and chronic inflammation.6 It has been also reported that ginkgolides could serve as effective therapies against central nervous system illnesses such as Alzheimer’s and Parkinson’s disease,7,8 multiple sclerosis9 and it is also useful in migraine prophylaxis.10

The compact and highly oxygenated polycyclic molecular structure of ginkgolides including six 5-membered rings, two adjacent quaternary carbon centers and an unusual tert-butyl group. Although their therapeutic profile is remarkable, their daunting structures present a significant challenge for chemical synthesis, for which only a handful of synthetic studies of these molecules have been performed,11 including the total syntheses of ginkgolide A (1) and B (2) by the groups of Corey12 and Crimmins.13 To the best of our knowledge, there are no reports for the total synthesis of ginkgolide C (3), the most complex diterpene of the family, which bears 12 contiguous stereocenters, and eleven oxygenated carbons. This diterpene would provide a unique synthetic platform for the advancement of new strategies and methods. Herein, we report the first total synthesis of (+)-ginkgolide C (3) as well as the formal syntheses of (+)-ginkgolide A (1) and (+)-ginkgolide B (2).

Our synthetic analysis was guided by the compact nature of ginkgolides for which careful planning of carbon-carbon bond formation is required. As shown in Figure 1B, ginkgolide C (3) could be obtained from intermediate 6 via an aldol reaction to form the C-C bond between C3 and C13 and oxidation reactions at C1, C3, C11 and C12. At the outset, ketone 6 would arise from a 5-exo dig cyclization on the alkyn e at C15 preceded by a stereoselective cuprate addition of a tert-butyl group at C8 on enone 7. The latter would be a pivotal intermediate for the synthesis of ginkgolides A (1), B (2) and C (3).

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**Figure 1.** (A) Structure of Ginkgolides. (B) Retrosynthetic analysis and key disconnection.
We felt that the stereoselective construction of the adjacent quaternary carbon centers (C5 and C9) should be addressed early in the synthesis. To this end, a Sonogoshira coupling reaction using phenylacetylene 10 (C14-C15) followed by alkylation with 9 on spiroalkane 8 (C9-C12) would be considered to install the contiguous quaternary carbon centers. The Pd coupling reaction would not only serve to construct the D-ring lactone, but also to create a steric environment favoring a diastereoselective nucleophilic addition at C9 on spiroalkane 8. The latter could be easily prepared from ketone 11 and allyl alcohol 12, both commercially available, via a Claisen rearrangement securing the first quaternary carbon center at C5 and a ring-closing metathesis (RCM) between C7 and C8 forming the B ring.

The synthesis commenced by the conversion of ketone 11 (51%) [one-pot] to generate ketone 3 (59%), both X = H, Y = OMe.
**SCHEME 2. Total Synthesis of Ginkgolide C (1)**

Reagents and Conditions: 1. SeO₂ (2 equiv), dioxane 110 °C, 18 h then DMP (2 equiv), dioxane/DCM (1:1) 60 °C, 1 h. 2. tBuLi (4 equiv), CuCN (2 equiv), TMSI (2 equiv), THF -78 °C then TBAF -78 °C to 25 °C, 30 min then NaOH (1M), THF/MeOH/H₂O (3:1:1) 75 °C, 18 h. 3. KHMDS (1.3 equiv), THF -78 °C then Davis’ oxaziridinide (1.25 equiv), THF -78 °C to 25 °C 15 min. 4. MOMBr (3 equiv), TBAI (1 equiv), DIPEA (6 equiv), DCM, sealed tube 55 °C, 18 h. 5. RuCl₃-xH₂O (10 mol%), NaO₂ (8 equiv), CuCl₂/McCN/H₂O (1:1:2) 35 °C, 30 min. 6. I₂ (2 equiv), K₂CO₃ (2 equiv), DCM sealed tube 60 °C, 18 h. 7. NaBH₄ (10 equiv), THF/H₂O (5:1) 0 °C to 25 °C, 4 h then NaOH (1M, 5 equiv), THF/H₂O, aceton 50 °C, 18 h then AcOH (20% in H₂O, 80 equiv), 0 °C to 25 °C, 1 h. 8. IBX (8 equiv), MPO (8 equiv), DMSO 75 °C, 18 h. 9. DMP (1.5 equiv), DCM 0 °C to 25 °C, 18 h. 10. PhSeCl (2 equiv), HCl (4 M in dioxane, 7 equiv), EtOAc/THF 25 °C, 18 h. 11. H₂O₂ (5 equiv), pyridine (10 equiv), DCM/H₂O (10:1) 25 °C, 1 h. 12. PPTS (10 equiv), pyridine (5 equiv), Ac₂O (5 equiv), PhCl 135 °C, 18 h. 13. PhCOOH (2.4 equiv), DBU (1.2 equiv), DCM -25 °C, 10 min. 14. EtOAc/Bu (10 equiv), LDA (7.5 equiv), THF/HMPA (4:1) -78 °C to -30 °C, 12 h. 15. CSA (5 equiv), DCM 25 °C, 18 h. 16. DMDO (excess), acetone/H₂O 25 °C, 20 h. 17. Br₂ (40 equiv), NaOAc (150 equiv), AcOH/H₂O 25 °C, 20 h. 18. K₂CO₃ (3 equiv), MeOH 25 °C, 18 h. Abbreviations: DMDO = dichloromethane; DIPEA = disopropylethylamine; DMP = Dess-Martin periodinane; DMS = dimethyl sulfide; DMSO = dimethyl sulfoxide; IBX = 2-iodoxybenzoic acid; MOMBr = bromomethyl methyl ether; MPO = 4-methoxy pyridine N-oxide; PPTS = pyridinium p-toluenesulfonate; TBAF = tetrabutylammonium fluoride; TBAI = tetrabutylammonium iodide; THF = tetrahydrofuran; TMSI = trimethylsilyl iodide. (Scheme 1A). The B-ring was formed via Grubbs II-catalyzedRCM to afford the ring-closed adduct in 78% yield (over 3 steps), after which, the alkene was conjugated with DBU to afford α,β-unsaturated ester 14 in 99% yield. The ketone was converted to enyne 15 by formation of the corresponding vinyl triflate (96%) followed by a Sonogashira coupling with phenylacetylene 10 (99%). The second quaternary carbon was installed stereoselectively via vinylogous deprotonation of α,β-unsaturated ester 15 with KHMDS/18-crown-6 followed by the addition of iodooalkane 9 to afford α-alkylated ester 16 in 93% (dr >20:1).

A chemoselective epoxidation with MCPBA on enyne 16 afforded lactone 17 (through an intramolecular cyclization of the α-epoxide) and β-epoxide 18 in 35% and 51% yields respectively. The lactone 17 was then converted to alcohol 19 in 78% yield via a one-pot process using Ac₂O followed by the addition of TBAF. In parallel, epoxide 18 was treated with KOH in DMSO at 145 °C which incidentally lactonized onto the methyl ester, and deprotected the primary alcohol to afford 19 in a 44% yield. A one-pot oxidation with DMP followed by the addition of trimethyl orthoformate and amberlyst 15 gave the dimethyl acetal 20 in 75% yield. Reduction of the lactone unit with DIBALH led to lactol 21 in 90% yield (dr = 5:1) which, after treatment with anhydrous HCl and then with Ac₂O, produced anomers 22 and 23 in 96% combined yield (dr = 1.6:1). Both anomers 22 and 23 were separated at this point by silica gel chromatography to facilitate further functionalization, purification, and characterization.

At this stage, the formal syntheses of ginkgolide A (1) and B (2) were attempted using anomer 23 (Scheme 1B). The sequence was initiated by converting 23 into the corresponding enone 24 via a one-pot double oxidation with SeO₂ and Dess-Martin periodinane (78% yield, rr = 6.4:1). The stage was set for the stereoselective conjugate addition of the tBu group which required a carefully planned sequence using tBuLi, CuCN followed by the addition of TMSI. The resulting TMS enol ether was then exposed to TBAF yielding ketone 25 (81%) as a single diastereomer. Gratifyingly, a stereoselective reduction with LiBH₄ provided the corresponding alcohol which after the addition of NaOH (1M) underwent a 3-exo-dig cyclization forming the D-ring of 26 in 92% yield. Under these basic conditions the acetate group was hydrolysed liberating the alcohol at C3. Ozonolysis of enol ether 26 yielded the hydroxylactone 27 in 91% yield which was directly oxidized with IBX and 4-methoxy pyridine N-oxide (MPO) leading to enone 28 in 41% yield. This
sequence concluded our 16-step synthesis of Corey’s intermediate (28) which was converted into ginkgolide A (1) and B (2) in 10 and 6 steps, respectively. The capture of a late-stage intermediate in Corey’s synthesis thus completes a formal synthesis of these natural products.

Although the formal syntheses of 1 and 2 were accomplished, we turned our attention to the preparation of the "pièce de résistance” ginkgolide C (3) (Scheme 2). Starting with anomer 22 and using similar allylic oxidation conditions as for 24 (vide supra), the corresponding enone 29 was obtained in 85% yield. Although the conjugate addition of the tert-butyl group afforded the desired enol ether or ketone, it was not possible to achieve the α-oxygenation as originally planned despite considerable experimentation. Further examination of 29 suggests that the phenylacetylene overhangs the enone portion of ring E, thus preventing electrophilic addition to the enol ether or enolate.

We imagined that freeing the B ring from the acetylene group would allow the desired oxygenation reaction to occur. For this purpose, a one-pot reaction was conducted. After the addition of the tert-butyl cuprate reagent, an aqueous solution of NaOH (1M) was then added to the reaction mixture, hydrolyzing the acetate group and at the same time inducing a 5-endo-dig cyclization of the C3 alcohol onto the proximal alkylene to generate the ketone 30 in 80% yield (in one step).

Satisfyingly, subjection of ketone 30 to KHMDS and Davis’ oxaziridine gave the desired α-hydroxyketone (92% yield) as the sole diastereomer which was subsequently protected as a MOM acetal to afford 31 in nearly quantitative yield. Oxidative cleavage of enol ether moiety on 31 with RuO4/NaIO4 led to the formation of lactol 32 and lactone 33 in a 18% and 73% yield respectively. The minor compound 32 was easily converted to lactone 32 with I2 and K2CO3 in 91% yield. The formation of the D-lactone ring was achieved through a one-pot stereoselective reduction with NaBH4, after which, the benzoyl group was cleaved with NaOH (1M), followed by addition of dilute AcOH to enable the lactonization to afford 34 in 83% yield. Although enone 35 was obtained directly by oxidation of alcohol 34 with IBX and MPO in 31% yield, a procedure to obtain a higher overall yield was developed. First, oxidation of the alcohol followed by treatment with anhydrous HCl and PhSeCl to afford the corresponding α-phenyliselenide which upon exposure to H2O2 led to 35 in 75% yield over 3 steps. The conversion of the F-ring cyclic acetal in 35 to the enol moiety was initially attempted in PhCl at 135 °C in the presence of PPTS and pyridine. To our dismay, no expected enol product was isolated, only several side products were observed resulting from the deprotection of MOM group.

We reasoned that the presence of Ac2O under these conditions, an instantaneous acetylation could occur upon deprotection of the MOM group favoring the formation of the desired enol 36 and thus avoiding side reactions. To our delight, enol 36 was isolated in 66% yield. The latter was subjected to trityl hydroperoxide and DBU to give the epoxide 6 in 57% yield.

With our target intermediate 6 in hand, we now entered the endgame portion of the synthesis. Since epoxide 6 is structurally similar to some of Corey and Crimmins’ intermediates, we have drawn on their results for the following transformations. The formation of the last ring was made possible by the addition of the lithium enolate of tert-butylpropionate in THF/HMPA (4:1) (59%) followed by an acid-catalyzed epoxide opening lactonization with CSA to generate lactone 37 in 89% yield. The F-ring lactone was produced via a stereoselective epoxidation with DMDO followed by an oxidation with Br2 and NaOAc in AcOH/H2O (1:1) to afford the penultimate intermediate 38 in 57% yield over 2 steps. Finally, treatment with K2CO3 in MeOH delivered without incident (±)-ginkgolide C (3) in 95% yield which was spectroscopically identical to the natural product.

In summary, the first total synthesis of ginkgolide C (3) was achieved in 27 steps from commercially available starting material, concluding a journey that began more than 10 years ago. Along the way, we also completed the formal syntheses of ginkgolide A (1) and B (2) by intercepting intermediate 28 in 16 steps, which is the shortest synthesis of these ginkgolides to date. This work serves as a platform for further synthetic and biological studies of these complex and unique natural products.

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and analytical data (1H, 13C, HMRS, IR) for all new compounds (PDF)

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