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 sclerosis[9] 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 Corey[12] 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 alkyne 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**).

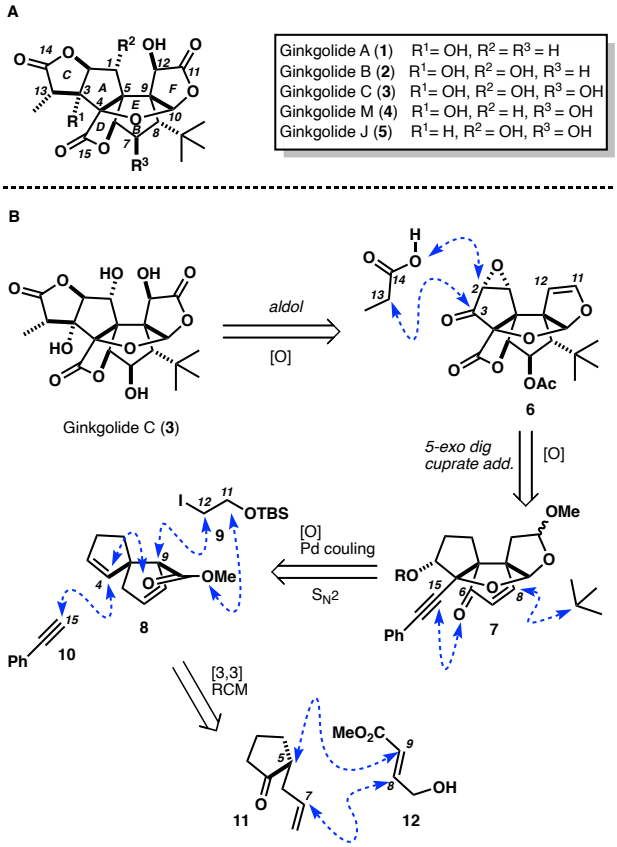
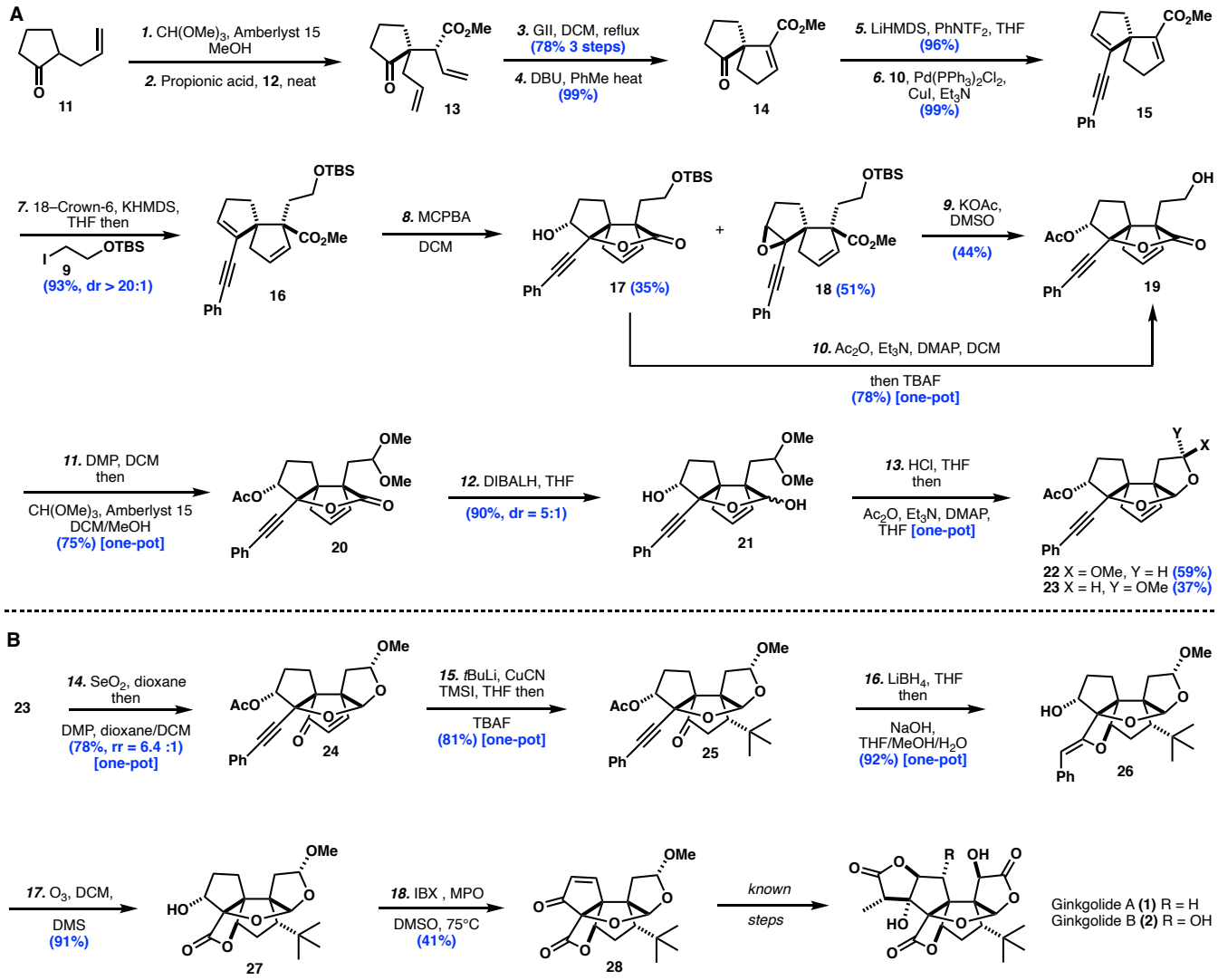


Figure 1. (A) Structure of Ginkgolides. (B) Retrosynthetic analysis and key disconnection

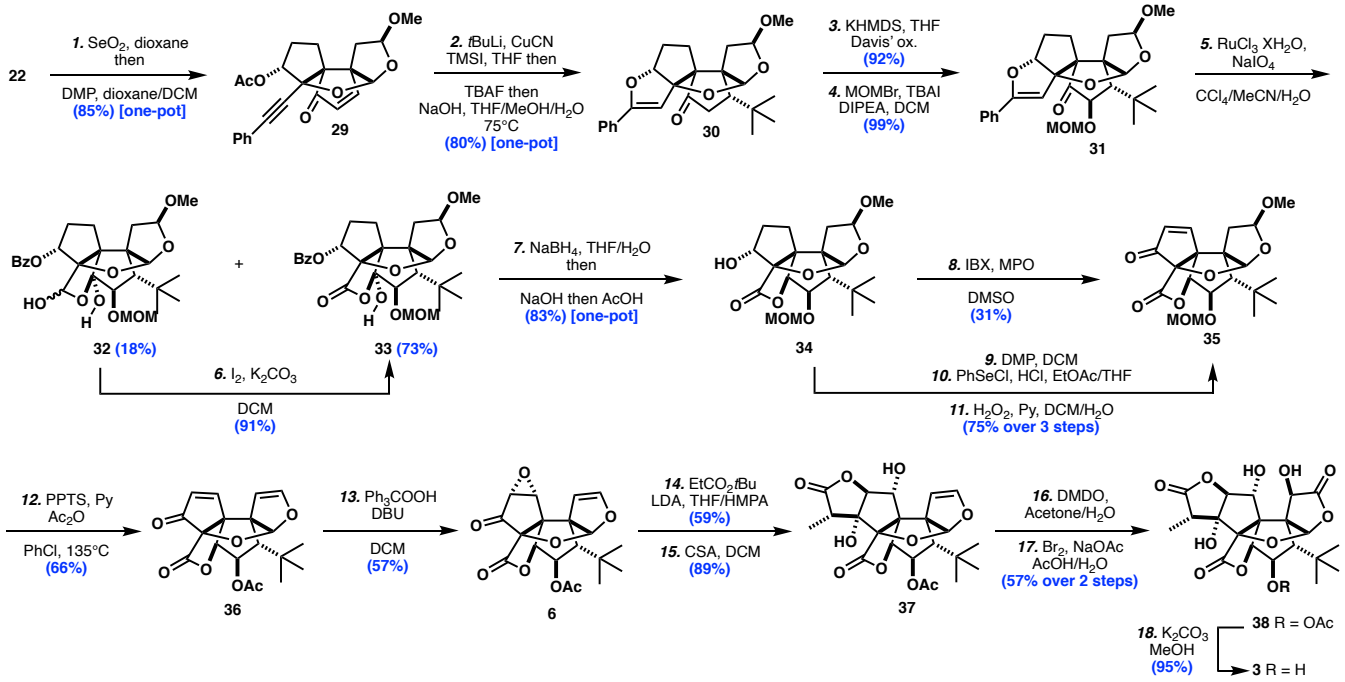
SCHEME 1. Formal Synthesis of Ginkgolide A (1) and B (2)[a]



[a]Reagents and Conditions: ***1.*** $CH(OMe)_3$ (1.25 equiv), amberlyst 15 (5% w/w), MeOH, reflux 30 min ***2.*** **2** (1 equiv), propionic acid (0.1 equiv), 75 °C to 150 °C, 3 h. ***3.*** Grubbs II (0.25 mol%), DCM, reflux. ***4.*** DBU (2 equiv), PhMe, 80 °C. ***5.*** LiHMDS (1.5 equiv), $PhNTf_2$ (1.25 equiv), THF -45 °C, 15 min. ***6.*** **10** (1.3 equiv), $Pd(PPh_3)_2Cl_2$ (1 mol%), CuI (1 mol%), Et_3N 60 °C. ***7.*** 18-crown-6 (2 equiv), KHMDS (2 equiv), THF -78 °C, 1 min then 9 (2 equiv), -78 °C, 1 min. ***8.*** MCPBA (1 equiv), DCM 0 ° to 25 °C, 18 h. ***9.*** KOAc (6 equiv) DMSO 145 °C, 18h. ***10.*** Ac_2O (3 equiv), Et_3N (6 equiv), DMAP (0.1 equiv), DCM 0 °C to 25 °C, 15 min then MeOH (5 equiv), 15 min then TBAF (6 equiv). ***11.*** DMP (1.5 equiv), DCM, 0 °C to 25 °C, 30 min then $CH(OMe)_3$ (5 equiv), amberlyst 15 (20% w/w), DCM/MeOH (1:1) 65 °C, 18h. ***12.*** DIBALH (5 equiv), THF -78 °C to 0 °C, 15 min. ***13.*** HCl 4M in dioxane (1 equiv), THF 0 °C then Ac_2O, Et_3N, DMAP, THF 0 °C to 25 °C, 15 min. ***14.*** SeO_2 (2 equiv), dioxane 110 °C, 18 h then DMP (2 equiv), dioxane/DCM (1:1) 60 °C, 1 h. ***15.*** *t*BuLi (4 equiv), CuCN (2 equiv), TMSI (2 equiv), THF -78 °C then TBAF, -78 °C to 25 °C, 1h. ***16.*** $LiBH_4$ (10 equiv), THF 0 °C to 25 °C, 2 h then NaOH (1M), $THF/MeOH/H_2O$ 85 °C, 18 h. ***17.*** O_3, DCM -78 °C, 30 min then DMS, -78 °C to 25 °C. ***18.*** IBX (6 equiv), MPO (6 equiv), DMSO 75 °C, 18 h. Abbreviations: DBU = 1,8-diazobicyclo[5.4.0]undec-7-ene; DCM = dichloromethane; DIBALH = diisobutylaluminum hydride; DMP = Dess-Martin periodinane; DMS = dimethyl sulfide; DMAP = dimethylaminopyridine; DMSO = dimethyl sulfoxide; GII = Grubbs II catalyst; IBX = 2-iodoxybenzoic acid; KHMDS = potassium bis(trimethylsilyl)amide; LiHMDS = lithium bis(trimethylsilyl)amide; MCPBA = *meta*-chloroperoxybenzoic acid; MPO = 4-methoxypyridine N-oxide; TBAF = tetrabutylammonium fluoride; THF = tetrahydrofuran; TMSI = trimethylsilyl iodide.

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** to the corresponding dimethyl ketal which underwent a Claisen rearrangement with allylic alcohol **12** to generate ketone **3**

SCHEME 2. Total Synthesis of Ginkgolide C (1)[a]



[a]Reagents and Conditions: ***1.*** SeO_2 (2 equiv), dioxane 110 °C, 18 h then DMP (2 equiv), dioxane/DCM (1:1) 60 °C, 1 h. ***2.*** *t*BuLi (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/H_2O (3:1:1) 75 °C, 18 h. ***3.*** KHMDS (1.3 equiv), THF -78 °C then Davis' oxaziridine (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.*** $RuCl_3$-xH_2O (10 mol%), $NaIO_4$ (8 equiv), CCl_4/MeCN/H_2O (1:1:2) 50 °C, 30 min. ***6.*** I_2 (2 equiv), K_2CO_3 (2 equiv), DCM sealed tube 60 °C, 18 h. ***7.*** $NaBH_4$ (10 equiv), THF/H_2O (5:1) 0 °C to 25 °C, 4 h then NaOH (1M, 5 equiv), THF/H_2O, acetone (5:2:1) 50 °C, 18 h then AcOH (20% in H_2O, 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 (2equiv), HCl (4 M in dioxane, 7 equiv), EtOAc/THF 25 °C, 18 h. ***11.*** H_2O_2 (5 equiv), pyridine (10 equiv), DCM/H_2O (10:1) 25 °C, 1 h. ***12.*** PPTS (10 equiv), pyridine (5 equiv), Ac_2O (5 equiv), PhCl 135 °C, 18 h. ***13.*** Ph_3COOH (2.4 equiv), DBU (1.2 equiv), DCM -25 °C, 10 min. ***14.*** $EtCO_2tBu$ (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/H_2O 25 °C, 20 h. ***17.*** Br_2 (40 equiv), NaOAc (150 equiv), AcOH/H_2O 25 °C, 20 h. ***18.*** K_2CO_3 (3 equiv), MeOH 25 °C, 18 h. Abbreviations: DCM = dichloromethane; DIPEA = diisopropylethylamine; DMP = Dess-Martin periodinane; DMS = dimethyl sulfide; DMSO = dimethyl sulfoxide; IBX = 2-iodoxybenzoic acid; MOMBr = bromomethyl methyl ether; MPO = 4-methoxypyridine N-oxide; PPTS = pyridinium p-toluenesulfonate; TBAF = tetrabutylammonium fluoride; TBAI = tetrabutylammonium iodide; THF = tetrahydrofuran; TMSI = trimethylsilyl iodide.

(Scheme 1A).[14] 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.[14] The ketone was converted to enyne **15** by formation of the corresponding vinyl triflate (96%) followed by a Sonogashira coupling with phenylacetylene **10** (99%).[15] 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 iodoalkane **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 Ac_2O 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 Ac_2O, 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 SeO_2 and Dess-Martin periodinane (78% yield, rr = 6.4:1)). The stage was set for the stereoselective conjugate addition of the *t*Bu group which required a carefully planned sequence using *t*BuLi, 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 $LiBH_4$ provided the corresponding alcohol which after the addition of NaOH (1M) underwent a *5-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-methoxypyridine *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.[12] 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 alkyne 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 $RuO_4/NaIO_4$ 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 I_2 and K_2CO_3 in 91% yield. The formation of the D-lactone ring was achieved through a one-pot stereoselective reduction with $NaBH_4$, after which, the benzoyl group was cleaved with NaOH (1M), followed by addition of dilute AcOH enabled 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-phenylselenide which upon exposure to H_2O_2 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 Ac_2O 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.[12] The F-ring lactone was produced via a stereoselective epoxidation with DMDO followed by an oxidation with Br_2 and NaOAc in AcOH/H_2O (1:1) to afford the penultimate intermediate **38** in 57% yield over 2 steps.[13] Finally, treatment with K_2CO_3 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 ginkgolides A (**1**) and (**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, ^{13}C, HMRS, IR) for all new compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest

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