The Total Synthesis of (±)-Ginkgolide B

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Abstract: The total synthesis of the potent PAF antagonist ginkgolide B has been accomplished. The complex architecture of ginkgolide B which includes six rings, eleven stereogenic centers, ten oxygenated carbons, and four contiguous fully substituted carbons is a daunting challenge for chemical synthesis. The synthesis of ginkgolide B was accomplished through a stereoselective intramolecular photocycloaddition of enone **5** to construct the congested core of the molecule. The photocycloaddition substrate was prepared through technology for the construction of carboalkoxycyclopentenones previously reported from these laboratories. Regioselective cyclobutane fragmentation and further functionalization of the photoadduct **4** provided the key pentacyclic intermediate. Acid-catalyzed rearrangement and epoxide opening were key transformations in the production of ginkgolide B from the pentacyclic intermediate.

Ginkgo biloba, one of the oldest surviving flora with ancestors dating to 230 million B.C., flourished during the Jurassic Period and has been called the "living fossil" by Charles Darwin.[1] The ginkgo tree survives today because of its extraordinary resilience, having endured several planetary mass extinctions of plant life. Its regenerative powers are supported by a report that a ginkgo tree sprouted anew from its roots at ground zero Hiroshima. Extracts of *G. biloba* have been used as herbal medicines for approximately 5000 years to treat a variety of ailments including coughs, asthma, and circulatory disorders. The traditional Hindu medicine "soma" also contains ginkgo extracts, and recent clinical studies attest to possible benefits of ginkgolides in the delay in the onset of dementia.[2]

Ginkgolides A, B, C, and M (Figure 1), which differ only in the number and location of hydroxyl groups, were first isolated as "bitter principles" of the root bark by Furukawa and co-workers in 1932.[3] The structures of the ginkgolides were first elucidated in 1967 by a series of spectroscopic studies by Nakanishi.[4] The assigned structures were independently confirmed by X-ray crystallography by the Okabe group at Nagoya University.[5] A related C15 compound, bilobalide, was discovered in 1971,[6,7] and in 1987, another member of the ginkgolide family, ginkgolide J, was isolated and characterized.[8] Ginkgolide B is the most potent platelet-activating factor (PAF) antagonist of the ginkgo extracts with an IC_{50} value of 0.6 mM.[9]

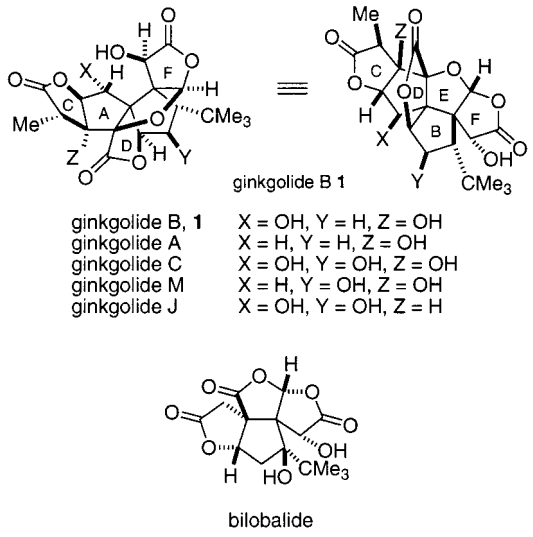

Figure 1.

Because of its portentous molecular architecture, ginkgolide B is an intimidating challenge for chemical synthesis. Included in the ginkgolide skeleton are six rings, eleven stereogenic centers, ten oxygenated carbons, an unusual *tert*-butyl group,[10] and four contiguous fully substituted carbon atoms. At the sterically congested core of the molecule are quaternary carbons C5 and C9, which are jointly embodied in five of the six rings of the molecule. The stereogenically correct installation of the C5 and C9 quaternary carbons and the proper orchestration of functional group manipulation are the most critical issues in regard to a successful synthetic assault. Synthetic studies on the ginkgolides have been relatively limited.[11] The synthesis of bilobalide by Corey and co-workers in 1987 was the first report

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(2) LeBars, P. L.; Katz, M. M.; Berman, N.; Itil, T. M.; Freedman, A. M. Schatzberg, A. F. *J. Am. Med. Assoc.* **1997**, *278*, 1327−1332. Ernst, E.; Pittler, M. H. *Clin. Drug Invest.* **1999**, *17*, 301−308.

(3) Furukawa, S. *Sci. Papers Inst. Phys. Chem. Res. Tokyo* **1932**, *19*, 27.

(4) Nakanishi, K. *Pure Appl. Chem.* **1967**, *14*, 89−113. Sakabe, N.; Takada, S.; Okabe, K. *J. Chem. Soc., Chem. Commun.* **1967**, 259−261.

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(6) Weinges, K.; Bahr, W. *Liebigs Ann. Chem.* **1969**, *724*, 214.

(7) Nakanishi, K.; Habaguchi, K.; Nakadaira, Y.; Woods, M. C.; Maruyama, M.; Major, R. T.; Alauddin, M.; Patel, A. R.; Weinges, K.; Bahr, W. *J. Am. Chem. Soc.* **1971**, *93*, 3544−3546.

(8) Weinges, K.; Hepp, M.; Jaggy, H. *Liebigs Ann. Chem.* **1987**, 521−526.

(9) Braquet, P. *Drugs Future* **1987**, *12*, 643.

(10) Nakanishi, K.; Habaguchi, K. *J. Am. Chem. Soc.* **1971**, *93*, 3546−3547.

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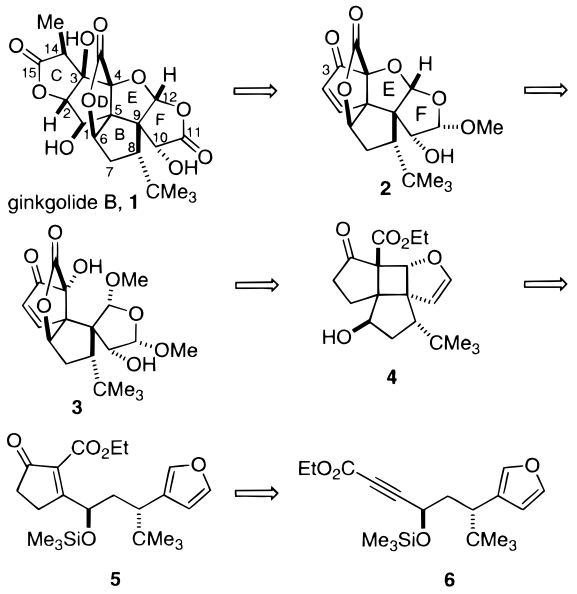
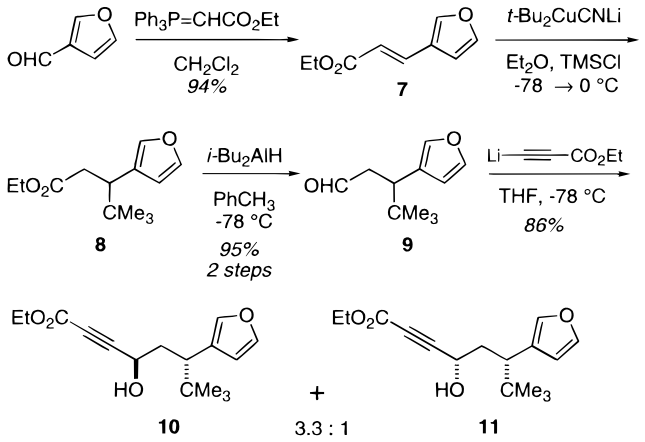
Published on Web 08/18/2000

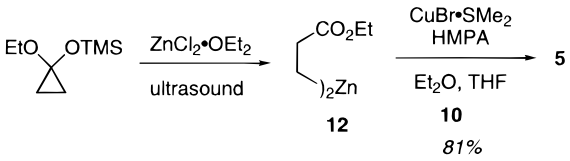
Scheme 1



Scheme 2



Scheme 3



of a synthesis of a member of the ginkgolide family.[12] The Corey group disclosed their successful syntheses of ginkgolides B[13] and A[14] the following year. Corey has also reported on the synthesis and biological activity of several simpler ginkgolide analogues.[11] Work in our laboratories has also led to the completion of the syntheses of bilobalide[15] and, recently, ginkgolide B.[16] Herein is presented a detailed account of the investigations which culminated in the total synthesis of ginkgolide B.

In the original strategic analysis of ginkgolide B (Scheme 1), pentacycle **2** was thought to be a viable intermediate for the attachment of the C ring lactone. Acetal **2** would be obtained from bis(methyl acetal) **3**, via an acid-catalyzed closure of the E ring. The bisacetal **3** would ultimately arise from the regioselective cyclobutane cleavage of tetracycle **4**. The key step in the proposed sequence, a double diastereoselective intramolecular [2+2] photocycloaddition,[17] would provide **4** from enone **5**. The photocycloaddition would serve to not only construct the B ring, but also establish the stereochemistry of the two quaternary centers at C5 and C9 as well as the C4 stereochemistry. Photosubstrate **5** would be obtained from acetylenic ester **6** via a zinc homoenolate conjugate addition/cyclization which was specifically developed for this purpose during the course of this work.[18]

The first objective in the synthesis was the development of a workable synthesis of the acetylenic ester **6**. Synthesis of acetylenic ester **6** began with commercially available 3-furaldehyde which was converted to unsaturated ester **7** via a Wittig reaction with the stabilized ylide, $Ph_3P{=}CHCO_2Et$ (Scheme 2).[15] Exposure of ester **7** to the higher order *tert*-butyl cuprate (*t*-$Bu_2CuCNLi_2$)[19] in the presence of TMSCl provided the ester **8** which was directly treated with *i*-Bu_2AlH to provide the aldehyde **9** in 95% overall yield. Addition of the lithium acetylide of ethyl propiolate to aldehyde **9** resulted in a 3.3:1 separable mixture of the desired anti diastereomer **10** to the syn product **11**.[20]

The completion of the assembly of the photosubstrate **5** from the acetylenic ester **6** was accomplished through a conjugate addition−cyclization protocol using the Kuwajima−Nakamura zinc homoenolate[21] which had been developed in our laboratory specifically for this purpose. The zinc homoenolate **12** was generated via ultrasonic irradiation of [(ethoxycyclopropyl)oxy]-trimethylsilane[22] in the presence of $ZnCl_2{\cdot}OEt_2$ (Scheme 3). Treatment of the homoenolate reagent with $CuBr{\cdot}SMe_2$ followed by addition of the acetylenic ester **10** and HMPA to the reaction mixture resulted in the desired conjugate addition−cyclization in excellent yield.[18] Mechanistically, it is proposed that the zinc/

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(19) Lipshutz, B. H. Sengupta, S. *Org. React*. **1992**, *41*, 135.

(20) Attempts to convert the syn isomer to the anti isomer via the Mitsunobu inversion led only to Michael addition of the acetylenic ester in the hydrolysis step.

(21) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc*. **1984**, *106*, 3368. Nakamura, E.; Aoki, S.; Sekia, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc*. **1987**, *109*, 8056.

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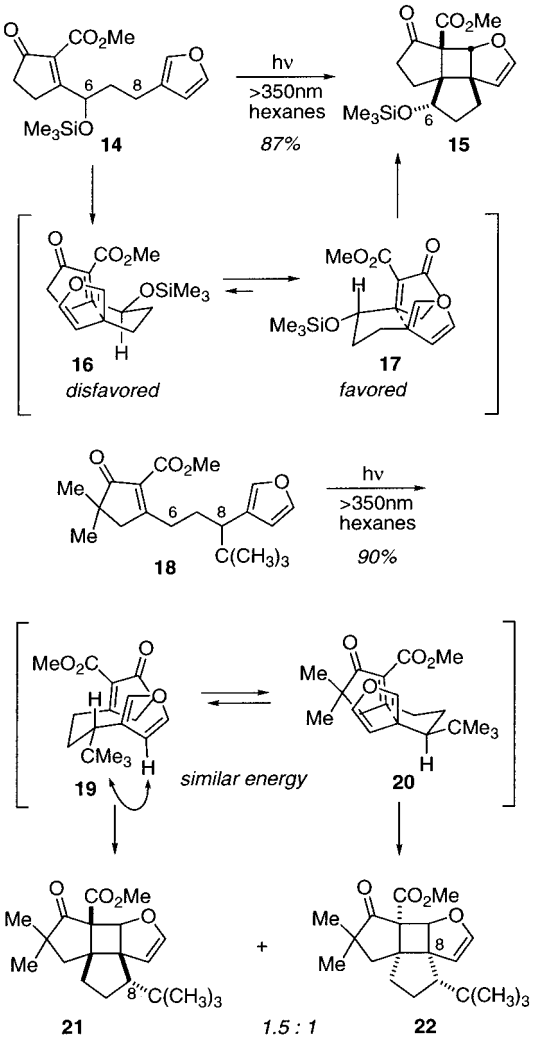
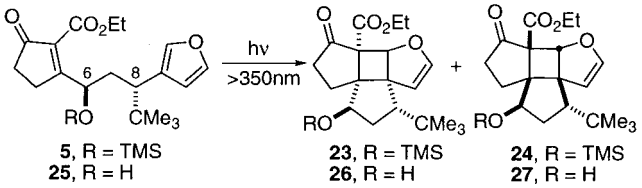
Scheme 4



copper homoenolate effects a syn addition to the acetylene to form the *C*-metalated intermediate which can tautomerize to the *O*-metal allenoate. The allenoate can be trapped by trimethylsilyl chloride, which is generated in situ during formation of the zinc homoenolate. The presence of trimethylsilyl chloride also results in protection of any free hydroxyls present in the molecule. The intermediate silyl allenoate can cyclize, with assistance of the Lewis acidic zinc salts present in the reaction mixture, to form the desired cyclopentenone **5** in greater than 80% yield.

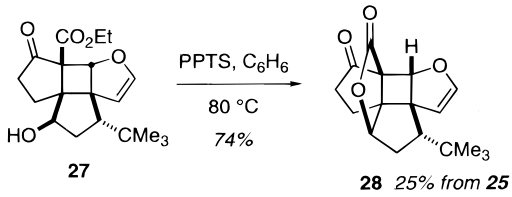
With substrate **5** in hand, the pivotal synthetic operation, a double diastereoselective enone−furan [2+2] photocycloaddition could be investigated.[17] Similar photocycloadditions had been examined on stereochemically simplified systems **14** and **18**,[23] as shown in Scheme 4, to determine the influence of the individual substituents at C6 and C8, the two allylic positions on the tether, on the stereoselectivity of the photocycloaddition. Irradiation of cyclopentenone **14**, which lacked the C8 *tert*-butyl group, gave 87% yield of a single diastereomer **15** in which the methyl ester and silyl ether groups were oriented trans in the photoadduct. Two reasonable conformations for the first bond formation in the triplet excited state are shown in Scheme 4. Both position the trimethylsilyloxy group in a pseudoequatorial orientation on the forming five-membered ring. The chairlike conformation **17** has been calculated[24] to be approximately 2.0 kcal/mol lower in energy than the boatlike conformation **16**. Conformation **17** would lead to the observed product **15**. The enone−furan **18** which includes the *tert*-butyl substituent, but lacks the C6 trimethylsilyloxy group, showed substantially lower selectivity, providing a 1.5:1 ratio of the diastereomeric photocycloadducts **21:22**. Here the two best conformations for the initial ring closure are calculated to be separated by only 0.2 kcal/mol, leading to nearly degenerate conformations **19** and **20**. Apparently the gauche interaction between the *tert*-butyl group and the C4 position of the furan raises the energy of the chairlike conformation **19**, resulting in a nonselective photocycloaddition. The implication which results from these investigations is that the principal controlling factor for asymmetric induction in the enone−furan **5**, required for the ginkgolide B synthesis, is that the influence of the trimethylsilyloxy substituent at the C6 center should override the effect of the *tert*-butyl group.

Scheme 5



	Solvent	ratio	yield
R = Me_3Si, **5**	hexanes/C_6H_6	>25 : 1	*85%*
R = Me_3Si, **5**	MeOH	>25 : 1	*80%*
R = H, **25**	hexanes/C_6H_6	1 .1: 1	*77%*
R = H, **25**	THF	7 : 1	*79%*
R = H, **25**	MeOH	>25 : 1	*75%*

Scheme 6



On the basis of the results of the enone−furans **14** and **18** with monosubstituted tethers, it was not surprising that irradiation of enone **5** selectively produced diastereomer **23** with none of the desired diastereomer **24** detected (Scheme 5). However, when the trimethylsilyl group was removed and the corresponding free hydroxyl was irradiated, a solvent effect on the diastereoselectivity was observed.[25] Specifically, in nonpolar solvents such as hexanes and benzene, a 1.1:1 mixture of **26:27** was observed. The stereochemical assignment of the products was made by exposure of both **26** and **27** to catalytic PPTS in benzene at reflux (Scheme 6). Hydroxy ester **26** was recovered unchanged from the reaction, but **27** was rapidly converted to the bridged lactone **28** in excellent yield. A single-crystal X-ray of lactone **28** further confirmed the assignment.

Further investigation of the photocycloaddition of enone **25** in more polar solvents, such as THF and MeOH, was found, once again, to favor the formation of the undesired product **26**. The rationale for the selectivity trend is found in an examination of the transition states shown in Figure 2. The two lowest energy

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(24) Energy minimizations were performed in MM2 by restricting the interatomic distance of the enone β-carbon and the alkene carbon to 2.5 Å and allowing the conformation to be minimized.

(25) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 10237−10238.

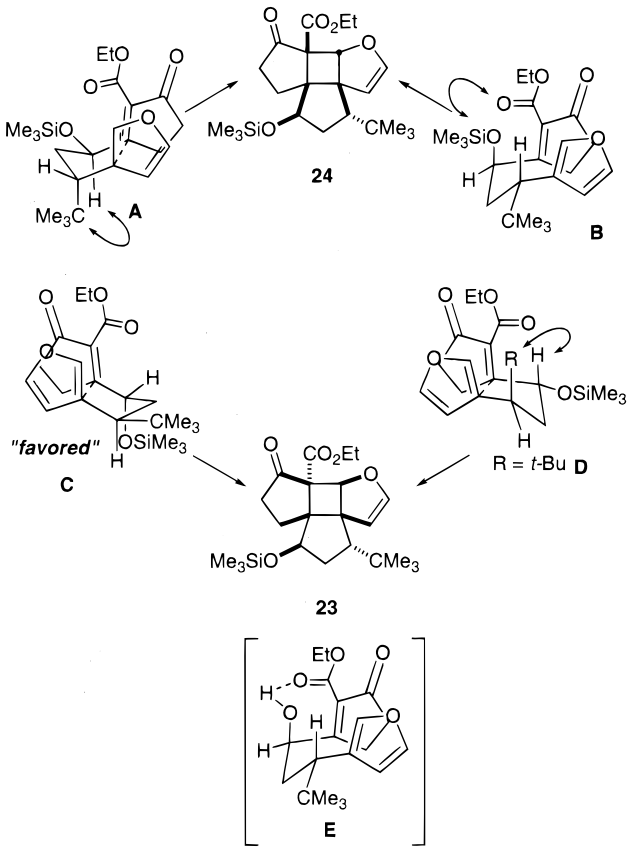


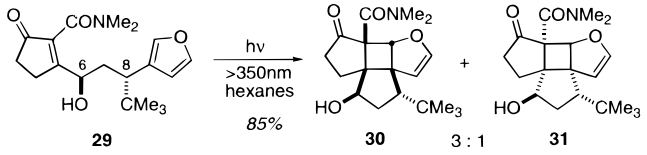
Figure 2.

conformations (**A** and **B**) which would lead to the desired **24** both suffer from severe steric interactions resulting from an axial oriented *tert*-butyl or trimethylsilyloxy group. The chairlike conformation **D**, which would lead to the undesired product **23**, also has a prohibitive nonbonded interaction involving the *tert*-butyl group. The nonbonded destabilization caused by the axial trimethylsilyloxy group in boatlike conformation **C**, which would lead to **23**, is minimized by the long O−Si bond and the possibility for the silyl ether to rotate away from the axial hydrogen. Therefore, it is conformation **C** which is postulated to be the favored transition state, and consequently, **23** is the favored product in the photocycloaddition of **5**.

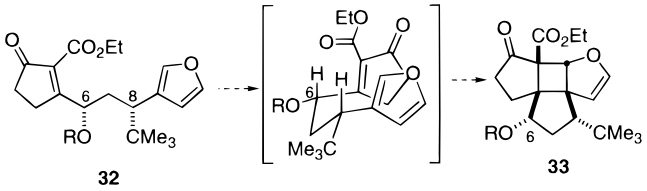
The altered selectivity observed in the alcohol **25** is thought to arise from stabilization of the chairlike conformation **E** which is similar to conformation **B** for the trimethylsilyl ether **5**. The added stabilization of a hydrogen bond between the free hydroxyl and the ester carbonyl as shown may account for the observed solvent effect.

That a hydrogen-bonding interaction between the secondary hydroxyl and the ester carbonyl might be responsible for altering the diastereoselectivity of the photocycloaddition was an encouraging observation. It was postulated that if the hydrogen-bonding interaction could be enhanced, the desired selectivity in the photocycloaddition might be achievable. Since amide carbonyls are more Lewis basic than ester carbonyls, and therefore should be more effective hydrogen bond acceptors, the possibility of using tertiary amides in the photocycloaddition was investigated, as shown in Scheme 7.[26] Indeed, when dimethylamide **29** was irradiated in hexanes, a 3:1 mixture of photocycloadducts **30**:**31** was obtained, indicating that the

Scheme 7



Scheme 8



hydrogen-bonding effect had been enhanced. Other amides, such as the diethylamide and the morpholine amide, gave similar, but slightly diminished selectivities.

While the photocycloadditions of the enone−furans with anti stereochemistry of the tether substituents had led to only modest selectivity for the desired cycloadduct, access to the bridged lactone **28** had been achieved in just seven synthetic steps, and the material produced through the studies on the anti diastereomer served to fuel early investigations on the advanced stages of the synthesis. Nevertheless, the pivotal nature of the photocycloaddition in the synthesis required a more highly selective and efficient cycloaddition. Since the photocycloaddition of **5** and **19** was not selective for the required tetracycle **24**, and the amide photoreactions showed only moderate selectivities, an alternate route to bridged lactone **28** was contemplated.[27] Specifically, it was postulated that a syn diastereomer **32** would permit a transition state in the photocycloaddition in which both the trialkylsilyl ether and the *tert*-butyl group would be in pseudoequatorial orientations in the chairlike conformation (Scheme 8). A matched double-diastereoselective effect was anticipated since the individual substituents each favored pseudoequatorial orientations on the basis of the products observed in the model photocycloadditions. The photocycloaddition of enone **32** was expected to be highly diastereoselective for photocycloadduct **33**. The requirement that the C6 hydroxyl would need to be inverted to construct the D ring lactone was thought to be a minor inconvenience.

A collateral need to improving the selectivity in the photocycloaddition was the supply issue of the photosubstrate. A revision of the early stages of the synthesis was required to access ample quantities of photosubstrate **37**. Several approaches were examined in an attempt to improve access to the syn diastereomer **11**. Ultimately, the most practical sequence, regarding efficient throughput, is illustrated in Scheme 9. Addition of ethynylmagnesium bromide to aldehyde **8** resulted in a 97% yield of a 1.2:1 separable mixture of anti acetylenic alcohol **34** and syn acetylenic alcohol **35**. Attempts to improve the selectivity in favor of the syn diastereomer by changing solvents and metal counterion and using amine additives did not significantly alter the selectivity and often led to lower yield of product.[28] However, since the diastereomers were readily separable by flash chromatography, and the anti diastereomer **34** could be easily converted to the syn diastereomer **35** in near quantitative yield via a Mitsunobu inversion,[29] this strategy was

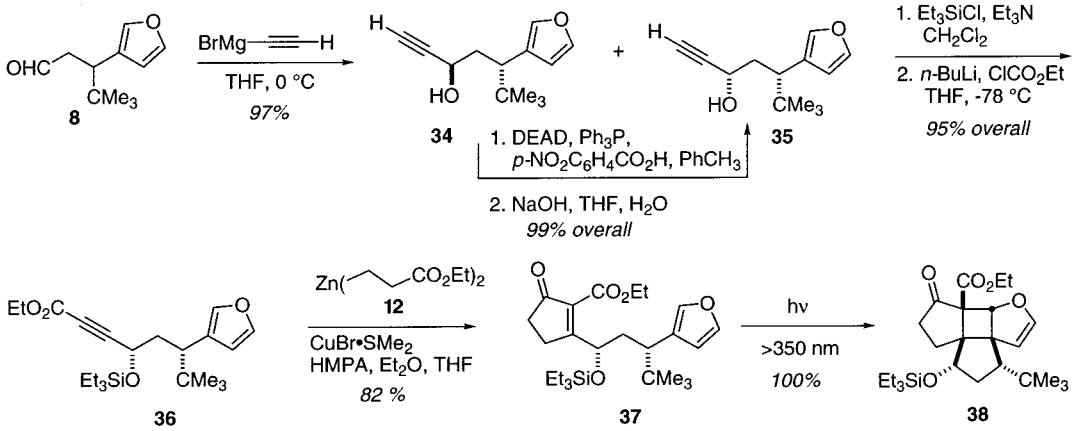
(26) The use of secondary amides was also investigated, and although selectivities in the photocycloaddition were improved (~5:1 desired: undesired), yields were low and the mass balance implied competitive decomposition in the photoreaction.

(27) All attempts to preform the D ring bridged lactone prior to the photoaddition were unsuccessful.

(28) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106−8125

(29) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020.

Scheme 9



Scheme 10

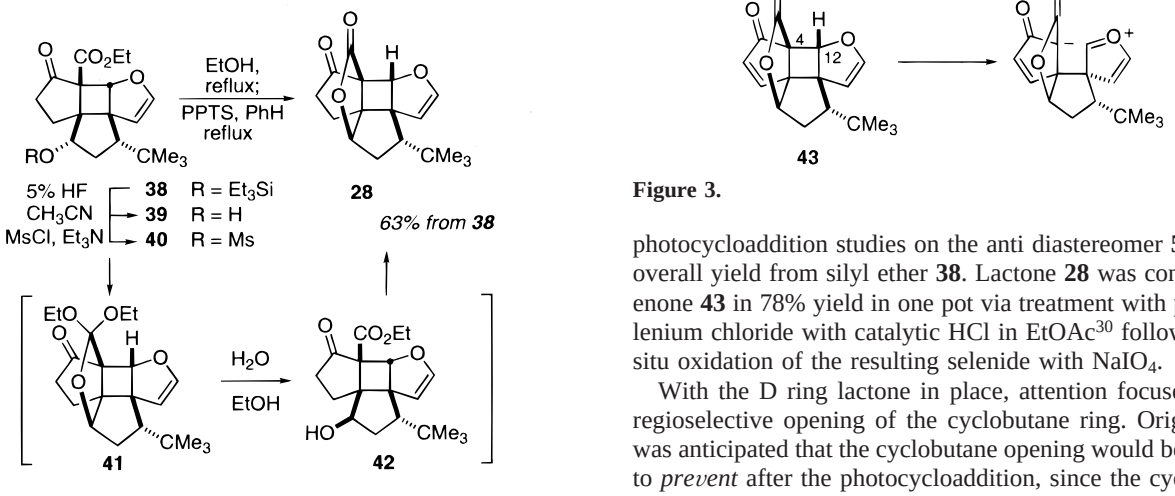


Figure 3.

adopted for scale-up. Alcohol **35** was then protected as its triethylsilyl ether, and the corresponding lithium acetylide was acylated with ethyl chloroformate to provide acetylenic ester **36** in 95% overall yield. Exposure of the acetylenic ester **36** to the previously described conditions for the conjugate addition−cyclization reaction resulted in production of cyclopentenone **37** in 82% yield.[18] As had been anticipated on the basis of the analysis of the substituent effects in the model systems and in the photocycloaddition of enone **5**, irradiation of cyclopentenone **37** in hexanes at >350 nm gave a single diastereomeric photocycloadduct, **38**, in quantitative yield. The remarkable chemical efficiency and stereoselectivity of the photocycloaddition of enone **37** were instrumental in the advancement of the synthesis.

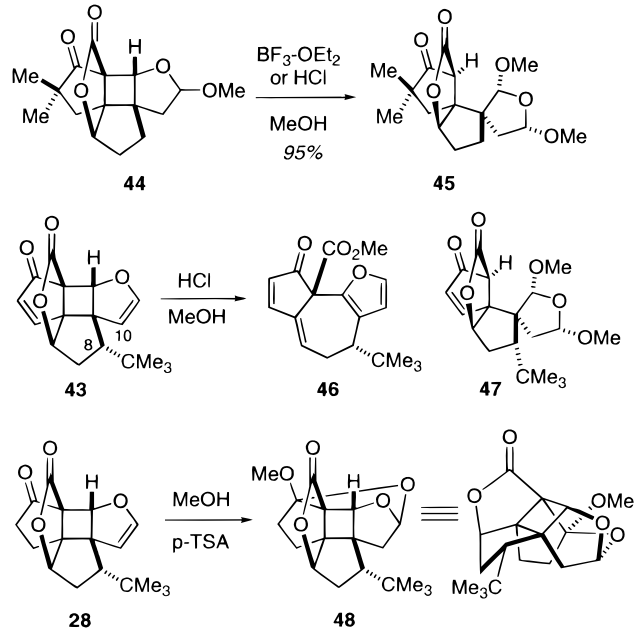
With an efficient and scalable synthesis of the photocycloadduct **38** complete, the next required maneuver was the installation of the D ring bridged lactone with inversion of the C6 stereogenic center. To this end, the triethylsilyl ether **38** was cleaved with 5% HF in acetonitrile, and the resulting free alcohol **39** was treated with methanesulfonyl chloride to give mesylate **40** (Scheme 10). The mesylate **40** was dissolved in ethanol followed by heating of the solution at reflux for 24 h. Water was then added, and the mixture was heated for an additional 8 h. The addition of water was required since early experiments indicated the presence of substantial amounts of ortho ester **41** in the crude product mixture. NMR analysis of the initial product indicated the presence of the desired lactone **28** and the hydroxyester **42**. Subjection of this mixture to pyridinium *p*-toluenesulfonic acid (PPTS) in benzene at reflux furnished the bridged lactone **28**, identical to that produced from the earlier photocycloaddition studies on the anti diastereomer **5**, in 63% overall yield from silyl ether **38**. Lactone **28** was converted to enone **43** in 78% yield in one pot via treatment with phenylselenium chloride with catalytic HCl in EtOAc[30] followed by in situ oxidation of the resulting selenide with $NaIO_4$.

With the D ring lactone in place, attention focused on the regioselective opening of the cyclobutane ring. Originally, it was anticipated that the cyclobutane opening would be difficult to *prevent* after the photocycloaddition, since the cyclobutane bond between C12 and C4 should be substantially weakened by the presence of two strong acceptors at C4 and a good donor at C12 (Figure 3). In fact, the unexpected stability of lactones **28** and **43** necessitated an extensive investigation to ascertain experimental conditions which would lead to selective cleavage of the C4−C12 cyclobutane bond. The π overlap of the enol ether oxygen lone pair with the alkene is believed to diminish its donor ability, thus preventing cyclobutane rupture.

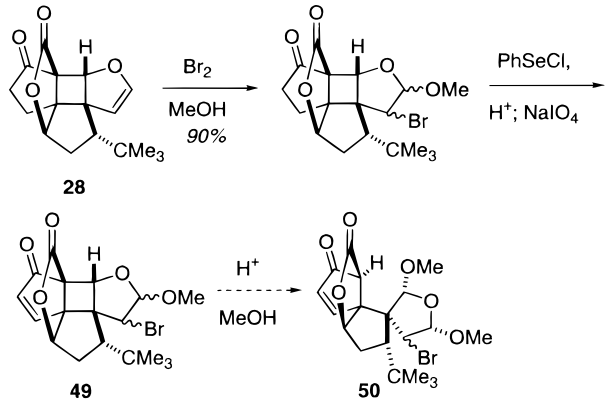
Initial investigations into the feasibility of the selective cleavage of the cyclobutane involving the related system **44** were very encouraging[23] (Scheme 11). Treatment of cyclobutane **44** with BF_3•OEt_2 or HCl in methanol smoothly produced the bis(methyl acetal) **45**. Unfortunately, when this procedure was implemented on the enone **43**, the desired bis(methyl acetal) **47** was not observed. Instead, the furan **46** derived from cleavage of the C3−C9 cyclobutane bond was obtained. Use of the saturated ketone **28** also failed to give the desired product under these conditions. Attempts to execute the cleavage of the cyclobutane bond prior to introduction of the enone to avoid the C3−C11 bond rupture were thwarted by the unexpected formation of the mixed ketal **48**. Several factors appear to contribute to the difference of the behavior of lactones **44** and **28**. The vinyl ether oxygen of **28** is a poorer donor than the ether oxygen of **44**, and the *gem*-dimethyl prevents enolization of the cyclopentanone in **44**, whereas in **28**, the keto−enol tautomerization may decrease the acceptor ability of the cyclopentanone carbonyl. Most importantly, however, is the apparent inability of the enol ether of **28** to undergo acid-

(30) Sharpless, K. B.; Lauer, R. F.; Teranishi, Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137−6139.

Scheme 11



Scheme 12



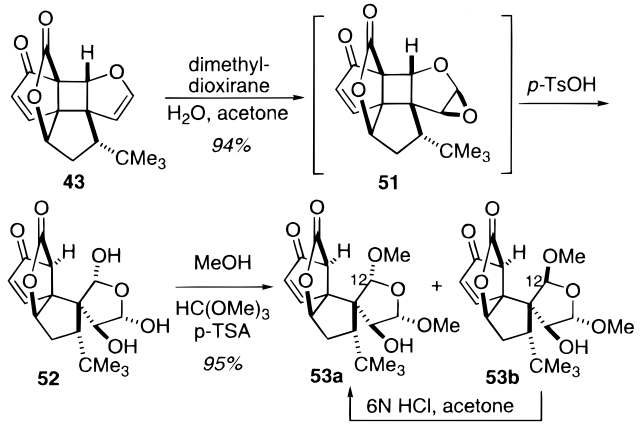
catalyzed addition of methanol. Formation of the methyl acetal of enol ether **28** appears to be both kinetically disfavored because of the highly hindered nature of the vinyl ether and thermodynamically disfavored due to the steric interaction of the C8 *tert*-butyl group and the C10 methylene upon rehybridization of the C10 carbon to sp^3.

More encouraging results were obtained when enol ether **28** was found to undergo electrophilic addition with bromine and methanol (Scheme 12). Subsequent incorporation of the C1−C2 double bond produced the enone **49**; however, all attempts to effect rupture of the cyclobutane to afford enone **50** were unsuccessful.

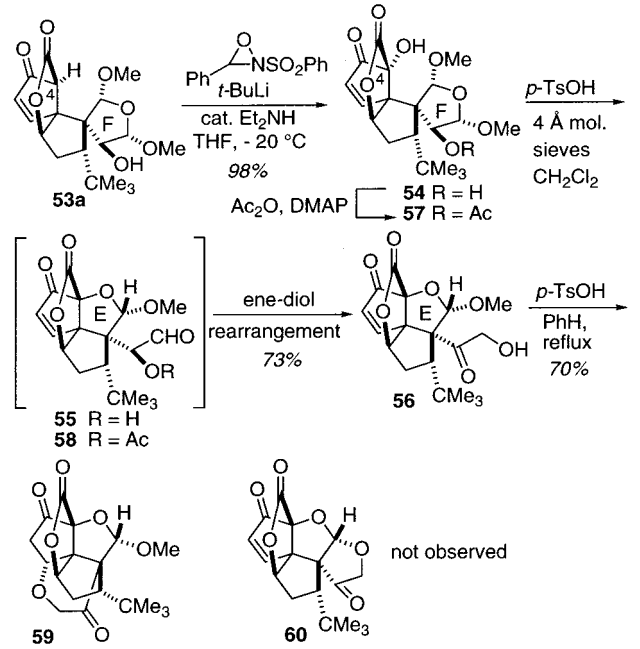
After much experimentation, it was discovered that treatment of vinyl ether **43** with dimethyldioxirane[31] effected selective epoxidation of the vinyl ether to deliver the epoxide **51**, which could be isolated, but was ordinarily processed in situ (Scheme 13). Addition of *p*-toluenesulfonic acid and a small amount of water to the reaction mixture after epoxidation was complete led to the direct formation of dialdehyde hydrate **52** from vinyl ether **43** in excellent yield. Apparently, hydrolysis of the epoxide leads to the hemiacetal which undergoes retroaldol fragmentation of the cyclobutane, leading to a dialdehyde which forms the stable hydrate **52**. It is important to note that epoxidation of

(31) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187−1201.

Scheme 13



Scheme 14

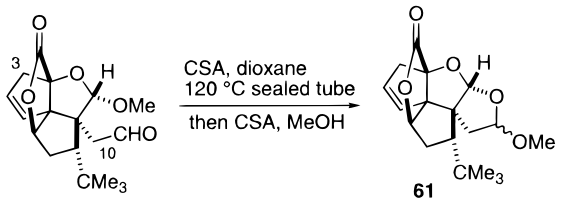


the vinyl ether occurs syn to the *tert*-butyl group, indicating the remarkable steric shielding effected by the cyclopentenone ring. Subjection of triol **52** to *p*-TsOH in methanol and trimethylorthoformate gave 97% of a 5.5:1 mixture of bis(methyl acetal) **53a** and another anomer, **53b**, believed to be the C12 diastereomer. The minor diastereomer **53b** could be readily separated and converted to **53a** in 92% yield upon exposure to 6 N HCl in acetone. Upon successful cleavage of the cyclobutane, a major milestone in the synthesis had been achieved. Four of the six rings had been constructed with appropriately positioned functionality for the installation of the final two rings.

As noted above, the original strategy required closure of the E ring at this juncture of the sequence. Before completion of the central E ring was attempted, oxidation of C4 was required. Hydroxylation of C4 was accomplished under modified Davis conditions (Scheme 14).[32] Treatment of the β-keto ester **53a** with stoichiometric *t*-BuLi and catalytic Et_2NH (20 mol %) followed by addition of the Davis oxaziridine gave high yields of the desired C4 alcohol **54**. When stoichiometric amounts of lithium diethylamide were used, competing oxidation of the dialkylamine by the oxaziridine necessitated the use of excess

(32) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241−3243.

Scheme 15



oxidant, which significantly hampered isolation and purification of the tertiary alcohol **54**.

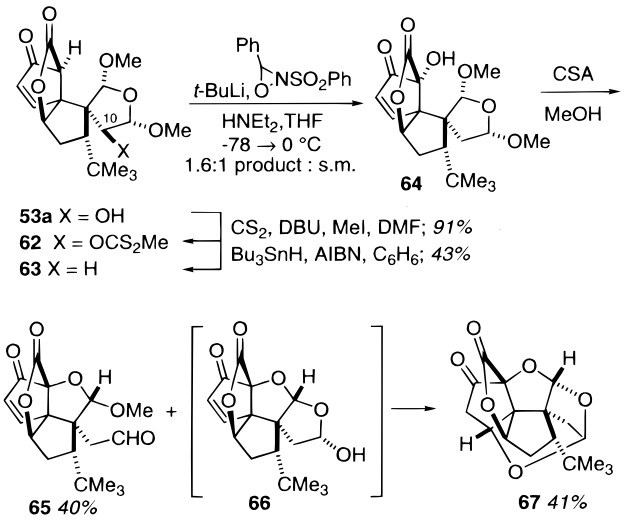
With diol **54** in hand, only acid-catalyzed closure of the E ring obstructed the completion of pentacycle **2**, the proposed precursor of ginkgolide B. While the formation of the E ring acetal from hydroxy acetal **54** appeared uncomplicated, upon treatment of acetal **54** with *p*-toluenesulfonic acid in dichloromethane, an unexpected and devastating sequence of events ensued. The resulting product, hydroxy ketone **56**, is believed to result from the ene−diol rearrangement of intermediate hydroxy aldehyde **55** which originates from S_N2-type E ring closure with concomitant cleavage of the F ring and expulsion of methanol. Further support for this proposal emanates from the observation that acetate **57** results in the production of the acetoxy aldehyde **58** when exposed to identical reaction conditions. An attempt was made to reconstitute the F ring from hydroxy acetal **56** since Corey and co-workers had successfully prepared acetal **61** from the corresponding aldehyde, albeit under fairly extreme conditions (see Scheme 15).[13]

Exposure of hydroxy ketone **56** (or similar intermediates such as the C11 carboxylic acid derived from aldehyde **58**) to more forcing conditions (e.g., *p*-TsOH in benzene at reflux) resulted only in intramolecular conjugate addition to the C1−C2 enone to afford the pentacycle **59** in 70% yield. While the Corey intermediate was similar, the presence of the C3 carbonyl and the C10 hydroxyl in intermediate **56** served to derail all efforts to construct the pentacyclic acetal **2**.

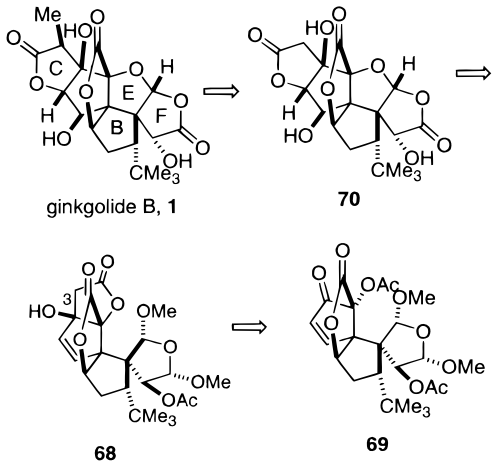
Two major issues with the original synthetic plan were indisputable at this point. First, the unwanted ene−diol rearrangement, which had precluded closure of the F ring, was a result of the hydroxyl at C10. Second, the C1−C2 enone was also interfering with the F ring formation due to its electrophilic nature and its proximity to the C10 and C11 functional groups. The former problem was addressed by attempting to remove the C10 hydroxyl. To obtain reduction product **63**, alcohol **53a** was first converted to the corresponding xanthate in 91% yield upon treatment with CS_2 and MeI in the presence of DBU (Scheme 16).[33] An X-ray crystal structure of xanthate **62** served to confirm the relative stereochemistry shown. When xanthate **62** was treated with tributyltin hydride and AIBN in benzene at reflux for 10 min, 43% of the desired reduction product **63** was obtained.[34] Davis oxidation under unoptimized conditions gave a 1.6:1 mixture of the desired alcohol **64** and recovered starting material **63**. Exposure of the hydroxy acetal **64** to CSA in methanol gave a 1:1 mixture of aldehyde **65** and hexacyclic cage **67**, the latter of which presumably arose from intramolecular hemiacetal attack on the enone in **66**.

Although this approach was temporarily abandoned, it revealed two important clues to the ultimate synthetic solution. First, in the absence of the C10 hydroxyl, the E and F rings could be formed concurrently. Second, to incorporate the E and

Scheme 16



Scheme 17



F rings concomitantly without addition at C1, the electronics of the C1−C2 alkene would have to be modified to reduce its electrophilicity. In this regard, altering the C3 carbonyl offered an attractive option: if an intramolecular aldol addition to the C3 carbonyl could be effected through an enolate attached at the C4 hydroxyl, not only could the C1−C2 alkene electrophilicity be attenuated, but stereoselective addition at the C3 carbonyl could also be accomplished.

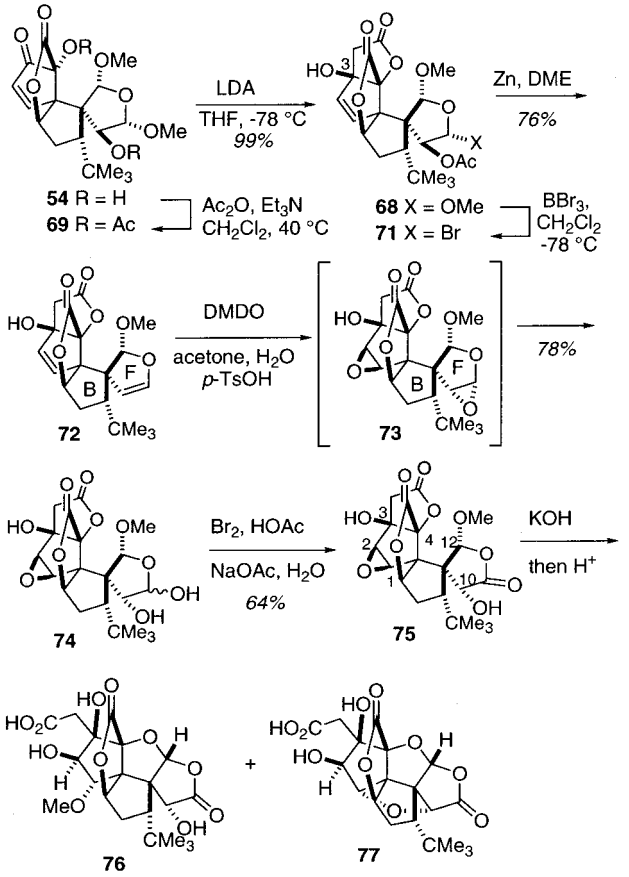
The synthetic plan was revised to incorporate the modified strategy of using an intramolecular aldol reaction to deactivate the A ring enone (Scheme 17). Specifically, ginkgolide B was thought to be accessible from lactone **68** via epoxidation of the C1−C2 alkene, C and E ring formation, and functional modification of the F ring. Lactone **68** would be formed from **69** via an intramolecular aldol reaction which would not only remove the enone as a reactive site, but also set the C3 stereochemistry. Bisacetate **69** would be obtained from the corresponding diol **54**.

The requisite diacetate **69** was readily prepared by treatment of diol **54** with acetic anhydride and triethylamine to give **69** in 48% yield for two steps (hydroxylation and acetylation, Scheme 18). Subjection of bisacetate **69** to lithium diisopropylamide at −78 °C gave high yields of the desired intramolecular aldol product **68**. A fortuitous discovery was made while to selectively hydrolyzing the C11 methyl acetal was attempted. It was determined that treatment of methyl acetal **68** with boron tribromide in dichloromethane resulted in exclusive formation

(33) Paquette, L. A.; Sauer, D. R.; Cleary, D. G.; Kinsella, M. A.; Blackwell, C. M.; Anderson, L. G. *J. Am. Chem. Soc.* **1992**, *114*, 7375−7387.

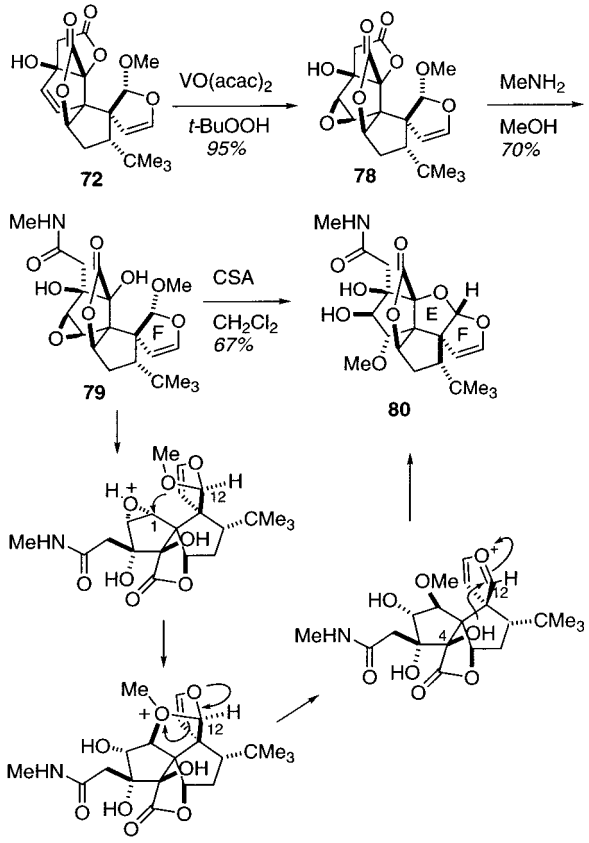
(34) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574−1585.

Scheme 18



of the C11 bromide even in the presence of a large excess of reagent. The low reactivity of the C12 acetal center is presumably related to its extraordinarily hindered nature because of its position in the cavity between the A and F rings. Subsequent treatment of the unstable C11 bromide with activated zinc in 1,2-dimethoxyethane effected reductive elimination to the vinyl ether **72** (76% yield from **68**). The enol ether **72** was subjected to excess dimethyldioxirane in acetone followed by addition of water and *p*-TsOH. The hemiacetal **74** that was produced (78% yield) arose from initial epoxidation of the electron-rich F ring vinyl ether with subsequent epoxidation of the C1−C2 alkene to afford epoxide **73**. The stereoselectivity for this first epoxidation is believed to be the result of steric hindrance by the *tert*-butyl group, which effectively shields one face of the enol ether. The α-epoxide, combined with the F ring methoxy group, then blocks the α-face of the A ring olefin, directing the second epoxidation to the *β*-face of the A ring, giving **73**. Hydrolysis of the more reactive C10−C11 epoxide to the hemiacetal **74** ensued. Selective oxidation of the hemiacetal **74** with Br_2 and acetic acid[35] provided the α-hydroxy lactone **75** in 64% yield. An important confluence in the strategy had been reached. All atoms with the exception of the C14 methyl had been incorporated, and each was in the oxidation state identical to the ultimate objective. Completion of the fully elaborated ginkgolide skeleton required three events: hydrolysis of the lactone derived from the intramolecular aldol, formation of the C ring lactone by attack of the liberated carboxylate (or carboxylic acid) at C2 of the epoxide, and acid-catalyzed closure of the E ring. An aggressive approach to complete the synthesis was envisioned. It was anticipated that basic hydrolysis of lactone **75** and

Scheme 19



subsequent acidification could produce the desired sequence of events in a single synthetic operation. The product of this reaction, trilactone **70** (Scheme 17), would be a methylation (at C14) away from ginkgolide B. Unfortunately, when lactone **75** was treated with aqueous KOH in THF followed by acidification with HCl, none of the desired product was observed. Instead, two acids, **76** and **77**, were isolated: acid **77** was believed to be the result of attack of the C10 hydroxyl at C1 of the epoxide, while acid **76** was the result of epoxide opening at C1 by the C12 methoxy group. A more stepwise approach was clearly indicated.

With this in mind, allylic alcohol **72** underwent a directed epoxidation under Sharpless conditions [$VO(acac)_2$, *t*-BuOOH][36] to give *β*-epoxide **78** in 95% yield (Scheme 19). It was then found that treatment of bislactone **78** with methylamine in methanol resulted in exclusive reaction at the C15 carbonyl to give 70% of amide **79**. It was thought that subjection of the amide **79** to acidic conditions would result in attack of the amide carbonyl on the C2 position of the epoxide which, after aqueous workup, would give the C ring lactone. Furthermore, under the acidic reaction conditions, the liberated C4 tertiary hydroxyl could participate in construction of the E ring, giving desired product **70**. However, yet another unexpected result occurred. Upon exposure of epoxyamide **79** to CSA in dichloromethane, the protonated epoxide was attacked, not by the amide carbonyl, but rather by the C12 methoxy group, which appears to be perfectly oriented with the C1 C−O antibonding orbital of the epoxide. The ensuing oxonium ion is captured by the C4 hydroxyl, resulting in methyl ether **80**.[37]

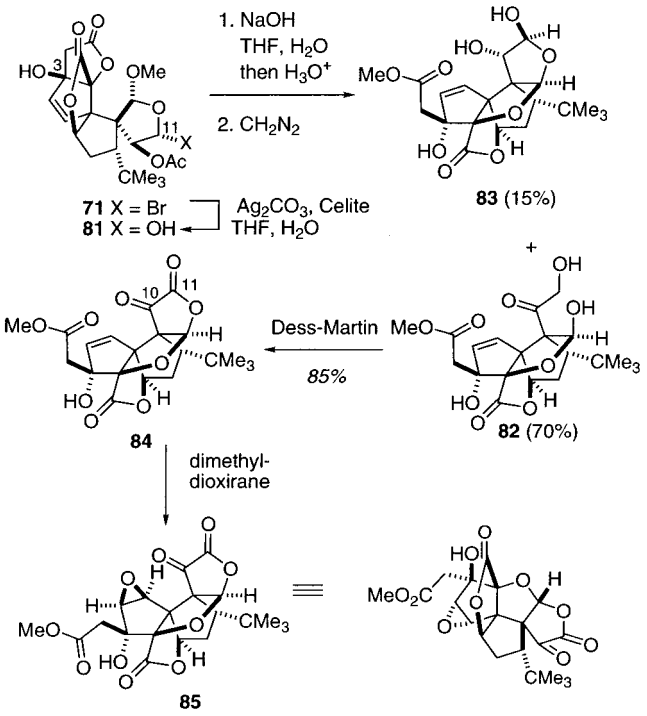
While the desired outcome was not obtained in the reaction of **79** with acid, the product **80** did contain some interesting

(35) Corey, E. J.; Kamiyama, K. *Tetrahedron Lett.* **1990**, *31*, 3995−3998.

(36) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63−74.

(37) The structure of **80** is supported by NOE studies.

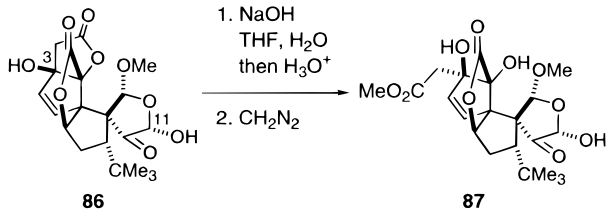
Scheme 20



features. Although **80** had the incorrect stereochemistry at C1 and C2 and also contained an unmanageable methyl ether at C1, the A, B, D, E, and F rings were in place at the same time for the first time in the synthesis. In an effort to capitalize on the observed rearrangement of amide **79** to the pentacycle **80**, extensive efforts to incorporate a different protecting group at C12 other than a methyl ether were undertaken, but none of the attempts were brought to completion.

Due to the serious complications encountered with undesired reactivity of the epoxide with the C12 methoxy and the C10 hydroxyl, it became imperative to complete the E ring prior to incorporation of the C1−C2 epoxide. An attractive option was to exploit the ene−diol rearrangement which had thwarted early attempts at E ring formation, but in a slightly different manner. Bromoacetal **71** was known to be relatively unstable and slowly hydrolyze to the corresponding hemiacetal **81**. The hydrolysis could be accelerated, as shown in Scheme 20, upon exposure of the bromoacetal **71** to Fetizon's reagent.[38] Subjection of hemiacetal **81** to aqueous base followed by an acidic workup gave a mixture of two carboxylic acids which were immediately esterified with diazomethane. The primary alcohol **82** was obtained in 70% yield accompanied by 15% of the hemiacetal **83**. In the absence of the C1−C2 epoxide, the base-induced hydrolysis of the lactone derived from the intramolecular aldol with subsequent closure of the E ring had been realized in the form of pentacyclic intermediate **83**. The major product, hydroxyketone **82**, is the obvious result of an ene−diol rearrangement of the intermediate C11 aldehyde. In an effort to utilize the hydroxyketone **82**, it was treated with 2.5 equiv of the Dess−Martin periodinane[39] to provide excellent yields of the ketolactone **84**. Once again, the ultimate goal seemed imminent. Unfortunately, when the α-ketolactone **84** was epoxidized with dimethyldioxirane, the epoxide **85** was obtained. Apparently, a change in hybridization of the C10 and C11 centers from sp^3 to sp^2 had altered the steric effects of the concave face of the molecule. A similar observation was made during the Corey synthesis in the addition of *tert*-butyl propionate enolate to the C3 carbonyl. A Sharpless-directed epoxidation[36] on the allylic alcohol **84** was attempted, but failed apparently due to the sensitivity of the ketolactone.

Scheme 21



Attention now turned to preventing the ene−diol rearrangement to obtain usable quantities of pentacycle **83** or a similar species. There were three primary paths by which the ene−diol rearrangement might be prevented. First, if the C10 hydroxyl of **54** were oxidized to the corresponding ketone or, second, if the C10 hydroxyl were protected with a base-stable protecting group, ene−diol rearrangement would not be possible. This latter solution is complicated by the hindered nature of the C10 hydroxyl which severely limits the protecting groups that can be incorporated. The third option to prevent the ene−diol rearrangement was to remove the C10 hydroxyl altogether.

Ketone **86** (Scheme 21) was treated with NaOH followed by acidification and esterification of the carboxylic acid with diazomethane, but ester **87** was the only isolated product. Upon exposure to acid, alcohol **87** was converted back to **86**.

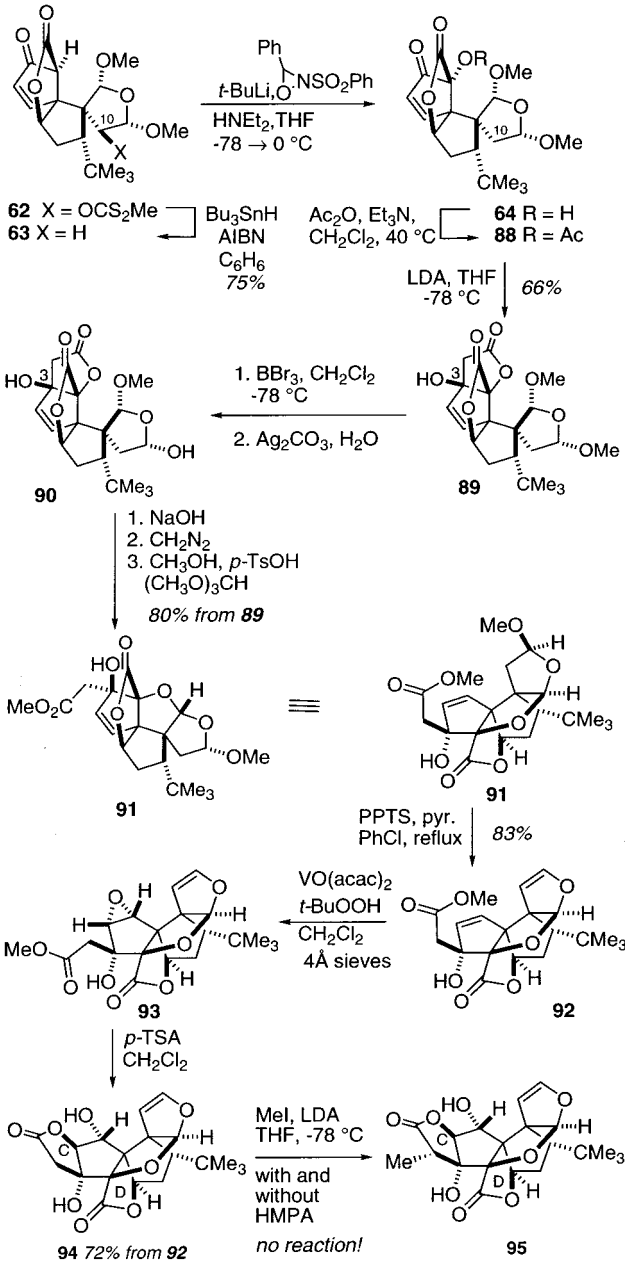
All attempts to protect the C10 hydroxyl as the benzyl ether, mesylate, or methyl ether at various stages all failed, and once again efforts focused on excision of the C10 hydroxyl. Deoxygenation of alcohol **53a** had been previously accomplished in modest yield by reduction of xanthate **62** with tributyltin hydride and AIBN in benzene at reflux, but this reaction was somewhat capricious. An extensive survey of solvents, hydrogen atom donors, initiators, and reaction temperatures was conducted. The most consistent results and highest yields (70−75%) were obtained when the reaction was carried out with tributyltin hydride and AIBN in benzene at 60 °C (Scheme 22).[40] The reduction product **63** was oxidized under modified Davis conditions as described earlier and the resulting C4 hydroxyl converted to the corresponding acetate **88** (Scheme 22). Intramolecular aldol addition gave lactone **89** which was then converted to hemiacetal **90** via treatment with boron tribromide followed by Ag_2CO_3. Exposure of **90** to NaOH effected the base-induced lactone hydrolysis and subsequent cyclization of the E and F rings. After acidic workup, esterification of the carboxylic acid with diazomethane, and exposure to methanol, *p*-TsOH, and trimethylorthoformate, the methyl acetal **91** was obtained in good overall yield from **89**. A significant milestone had been achieved: rings A, B, D, E, and F were in place with suitable functionality to complete the synthesis. Only completion of the C ring and adjustment of the oxidation states of C10 and C11 remained. To this end, exposure of acetal **91** to PPTS and pyridine in chlorobenzene at reflux effected elimination of methanol to give vinyl ether **92** in 83% yield. Subjection of allylic alcohol **92** to the Sharpless-directed epoxidation protocol delivered the epoxide **93** in good yield. Exposure of epoxide **93** to *p*-TsOH in CH_2Cl_2 completed the final ring of ginkgolide B, the C ring, to give lactone **94** (72% for two steps). All that remained was to methylate the C14 position and oxidize the F

(38) McKillop, A.; Young, D. W. *Synthesis* **1979**, 401. Fétizon, M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 1995; Vol. 6, pp 4448−4454.

(39) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(40) Curran, D. P. *Synthesis* **1988**, 417−439.

Scheme 22

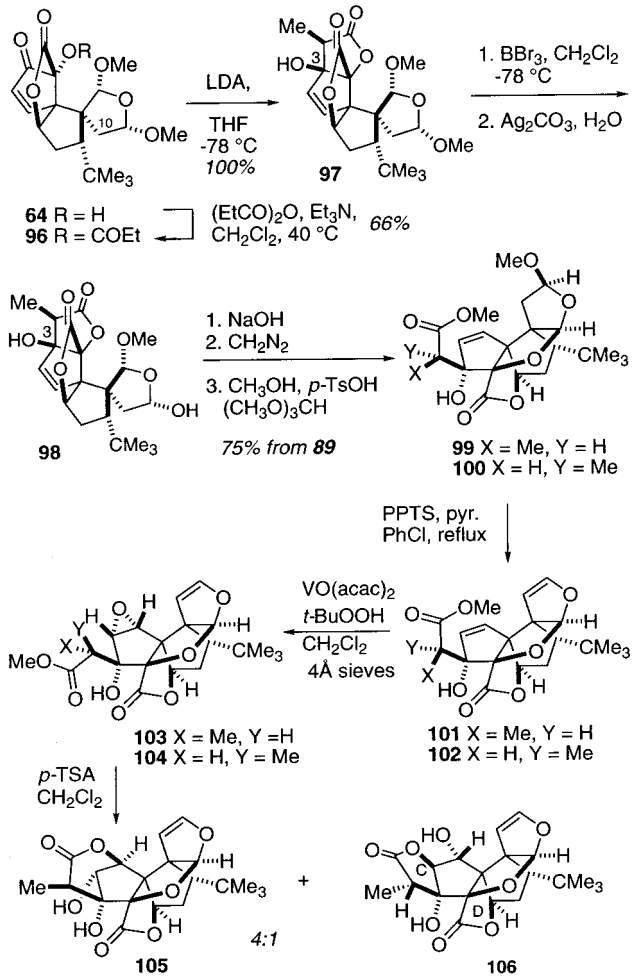


ring. The alkylation of **94** with MeI was attempted under a variety of conditions with no indication of success; instead, only recovered starting material was observed. Methylation of the intramolecular aldol product **89** was also attempted, but again, no alkylation product was observed.

An obvious alternative to methylation at the final stage was to incorporate the additional carbon prior to the intramolecular aldol, that is, utilize the propionate instead of the acetate in the intramolecular aldol reaction. Propionate **96** was obtained from alcohol **64** via treatment with propionic anhydride and triethylamine (Scheme 23). Intramolecular aldol addition of the propionate to the A ring carbonyl gave the lactone **97** with the undesired C14 stereochemistry (Scheme 23). When the enolate geometry was reversed through addition of HMPA,[41] the same diastereomer was obtained. It is postulated that, in the absence of HMPA, the Li is coordinated to the enolate as well as the F ring oxygens, thus orienting the enolate to give the undesired

(41) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868−2877.

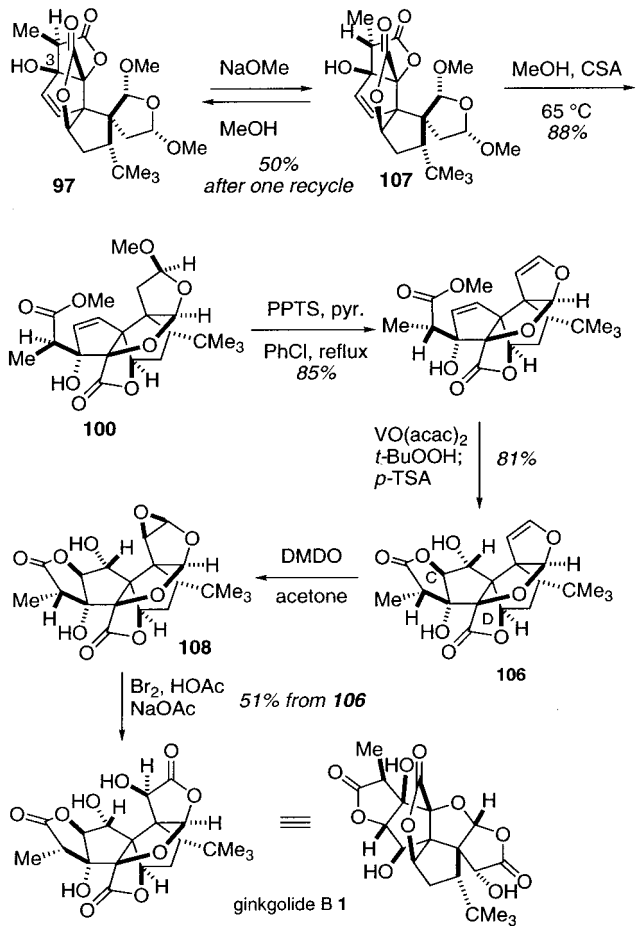
Scheme 23



methyl epimer. When the HMPA is added and coordination of the lithium is minimized, the enolate is free to rotate away from the F ring, and the new orientation is such that the same, undesired methyl epimer is obtained. The inability to control the C14 stereogenicity at this stage was not overly troublesome since there was ample opportunity to correct this stereocenter via epimerization at a later stage, especially after the hemispheric parent ginkgolide skeleton was in place. The C14 methyl group would be positioned on the more sterically compressed concave face of the hemisphere and therefore would be expected to epimerize readily.

In this regard, acetal **97** was converted as before with the normethyl derivative to hemiacetal **98** followed by base-induced rearrangement, esterification, and methyl acetal formation. At the end of this sequence, which was performed in rapid succession, a 4:1 mixture of methyl epimers **99:100** was obtained. Apparently, some epimerization had occurred during the base-induced reorganization of the skeleton. Nonetheless, the mixture was carried forward whereupon treatment with PPTS and pyridine in chlorobenzene at reflux gave vinyl ethers **101** and **102**. Epoxidation with $VO(acac)_2$ and *t*-BuOOH resulted in epoxides **103** and **104**. Finally, treatment of the mixture of **103** and **104** with *p*-TsOH yielded a 4:1 mixture of six-membered ring, lactone **105** and five-membered ring lactone **106**. The undesired C14 methyl epimer **103** had undergone cyclization at C1 to form the six-membered ring while the desired C14 methyl epimer **104** cyclized at the C2 position to form the requisite five-membered ring. As discussed above, in the undesired C14 methyl epimer **103**, the transition state for

Scheme 24



epoxide opening places the methyl group in the concave, sterically congested cavity of the molecule. It had been hoped to exploit this unfavorable interaction to effect epimerization of the C14 center after lactonization. Unfortunately, this same steric interference resulted in the cyclization of ester **103** in an unanticipated manner to form lactone **105**. On the positive side, the cyclization of ester **104**, containing the natural configuration at C14, proceeded to give the desired product **106**. It was clear that epimerization would have to be accomplished prior to the epoxy lactonization.

Fortunately, it was soon discovered that exposure of lactone **97** to NaOMe in MeOH resulted in a 1.4:1 separable mixture of starting lactone **97** and its C14 methyl epimer **107**. Prolonged exposure to base improved the ratio to 1:1, but the yield suffered due to competitive β-elimination. After the diastereomers were separated via flash chromatography, lactone **97** could be resubjected to the NaOMe/MeOH reaction conditions to provide the required diastereomer **107** in 50% yield after one recycle. Additional recycles allowed access to higher yields.

With the C14 stereogenic center corrected, the final resolution to the seemingly endless conundrum had been identified. In the course of the late stages of the investigation, an additional important observation was made. It was also discovered that rather than forming the C11 hemiacetal and effecting a base-catalyzed cyclization as in the conversion of acetal **97** to **99**, simple subjection of lactone **107** to CSA in methanol at reflux produced the rearranged acetal **100** in high yield, thus obviating four synthetic steps. The acid-catalyzed reorganization was only possible in the absence of the C10 hydroxyl since there was no possibility for the derailment by the ene−diol rearrangement. Methyl acetal **100** then underwent elimination with PPTS and pyridine to provide enol ether **102** in 85% yield. Directed epoxidation under Sharpless conditions gave the desired epoxide which, upon in situ exposure to *p*-TsOH, cyclized to form the C ring lactone **106**. Treament of vinyl ether **106** with dimethyldioxirane resulted in exclusive formation of the epoxide **108** (Scheme 24). The selectivity in this reaction is believed to result from the fact that the *tert*-butyl group guards the α-face of the vinyl ether. Finally, treatment of epoxide **108** with bromine and acetic acid[35] resulted in epoxide opening to the corresponding hemiacetal, which was followed by an in situ oxidation to complete the F ring lactone in 52% yield from **106**. The synthesis of ginkgolide B was complete as evidenced by comparison of the synthetic material to an authentic sample. The samples provided identical ^{1}H and ^{13}C NMR, infrared spectroscopic data, and chromatographic properties (TLC). The final synthetic route required 25 linear steps from 3-furaldehyde.

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Supporting Information Available: Experimental procedures and spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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