Total Synthesis of (±)-Ginkgolide B

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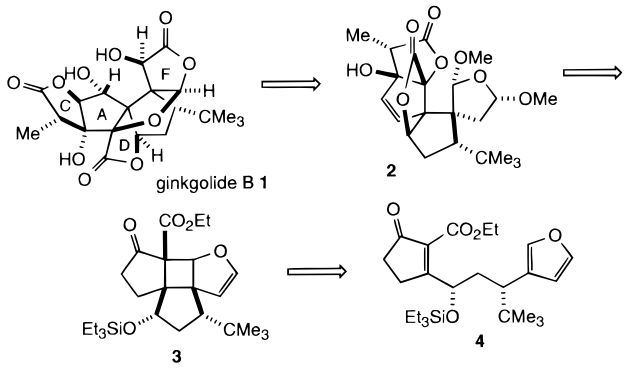
Received August 19, 1999

Ginkgo biloba, termed the "living fossil" by Darwin, has ancestors dating to 230 million B.C.[1] Extracts of *Ginkgo biloba*, which have been used as herbal medicines for 5000 years to treat a variety of conditions such as coughs, asthma, and circulatory disorders, are currently undergoing clinical evaluation for treatment of dementia.[2] Ginkgolide B is the most potent platelet activating factor (PAF) antagonist of the ginkgo extracts, with an IC_{50} of 0.6 μM.[3] The complex molecular 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 diabolical disposition of functionality dictates that introduction of functional groups be judiciously orchestrated. The ginkgolides were first characterized in 1967,[4] and the syntheses of ginkgolides A[5] and B[6] were reported by Corey and co-workers in 1988. The synthesis of the related compound, bilobalide, was also achieved by the Corey group[7] as well as by our laboratory.[8] Reported herein is the total synthesis of ginkgolide B utilizing the zinc−copper homoenolate[9] and double diastereoselective intramolecular [2+2] photocycloaddition methodologies developed in our laboratories.[10]

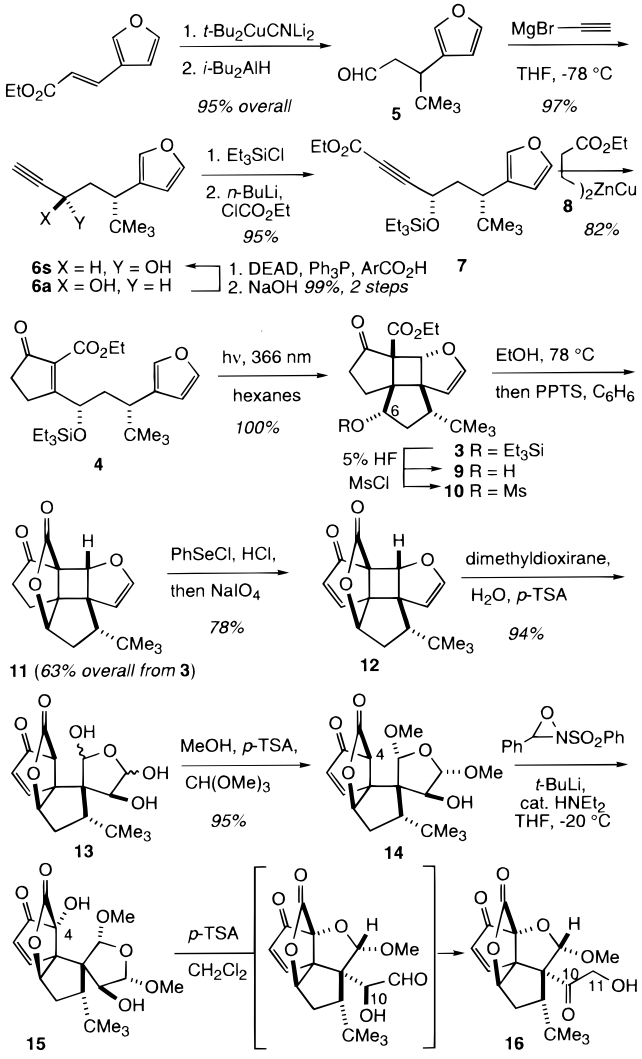
Strategically, the synthesis of ginkgolide B was thought to be achievable from the pentacyclic precursor **2** which was to be derived from **3** by a regioselective cyclobutane fragmentation and further functionalization. A stereoselective intramolecular photocycloaddition of the enone-furan **4** to produce cycloadduct **3** was anticipated to provide the stereochemical control required to construct the congested core of the molecule. Preparation of the photocycloaddition substrate **4** was to be accomplished through our homoenolate technology for the construction of carboalkoxycyclopentenones.[9]

The synthesis of the photocycloadduct **3** is illustrated in Scheme 2. Ethyl 3-(3-furyl)acrylate[8] was subjected to the higher order cuprate [*t*-$Bu_2CuCNLi_2$, TMSCl, Et_2O] to incorporate the critical *tert*-butyl group. The resultant ester was reduced with *i*-Bu_2AlH to provide the corresponding aldehyde **5** in 95% overall yield. Addition of ethynylmagnesium bromide to aldehyde **5** gave a 1.2:1 mixture of the syn and anti acetylenic alcohols **6a**:**6s**. After separation, the undesired anti **6a** was efficiently converted to syn **6s** by a Mitsunobu inversion.[11] The alcohol **6s** was protected as its TES ether and the acetylene was carboxylated to produce acetylenic ester **7** in 95% overall yield in anticipation of the first critical step of the synthesis. Exposure of **7** to the zinc−copper homoenolate **8** [HMPA, THF, Et_2O] resulted in the formation of

Scheme 1



Scheme 2



(1) van Beek, T. A.; Bombardelli, E.; Morazzoni, P.; Peterlongo, F. *Fitoterapia* **1998**, *69*, 195−244. Major, R. T. *Science* **1967**, *157*, 1270.

(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 Investigation* **1999**, *17*, 301−308.

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

(4) Nakanishi, K. *Pure Appl. Chem.* **1967**, *14*, 89−113. Sakabe, N.; Takada, S.; Okabe, K. *J. Chem. Soc., Chem. Commun.* **1967**, 259−261. Okabe, K.; Yamada, K.; Yamamura, S.; Takada, S. *J. Chem. Soc. C* **1967**, 2201−2206.

(5) Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1988**, *29*, 3205−3206.

(6) Corey, E. J.; Kang, M.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 649−651. Corey, E. J. *Chem. Soc. Rev.* **1988**, *17*, 111−133.

(7) Corey, E. J.; Su, W. *J. Am. Chem. Soc.* **1987**, *109*, 7534−7536. Corey, E. J.; Su, W. *Tetrahedron Lett.* **1988**, *29*, 3423−3426.

(8) Crimmins, M. T.; Jung, D. K.; Gray, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 5445−5547. Crimmins, M. T.; Gray, J. L.; Jung, D. K. *J. Am. Chem. Soc.* **1993**, *115*, 3146−3155.

(9) Crimmins, M. T.; Nantermet, P. G. *J. Org. Chem.* **1990**, *55*, 4235−4236. Crimmins, M. T.; Nantermet, P. G.; Trotter, B. W.; Vallin, I. M.; Watson, P. S.; McKerlie, L. A.; Reinhold, T. L.; Cheung, A. W. H.; Stetson, K. A.; Dedopoulou, D.; Gray, J. L. *J. Org. Chem.* **1993**, *58*, 1038−1047.

(10) Crimmins, M. T.; Thomas, J. B. *Tetrahedron Lett.* **1989**, *30*, 5997−6000.

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

10.1021/ja993013p CCC: $18.00
Published on Web 10/16/1999

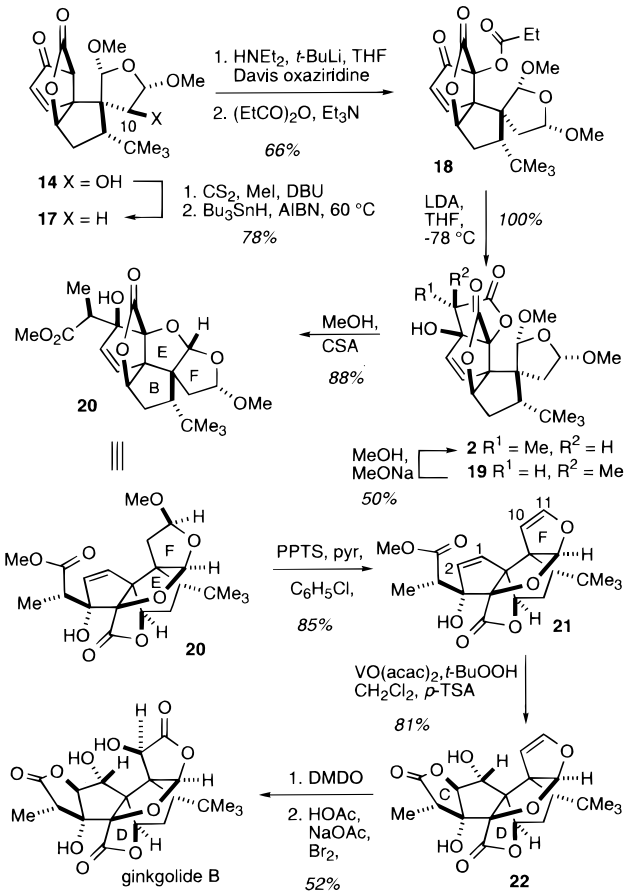
photosubstrate **4** in 82% yield.[9] Irradiation of the enone **4** in hexanes solution at 366 nm (uranium glass filter) produced the photocycloadduct **3** in quantitative yield and >98:2 diastereoselectivity establishing the two contiguous quaternary carbon centers of the core skeleton.[10]

The closure of the D ring lactone was accomplished (Scheme 2) by hydrolysis of the C6 TES ether **3**, mesylation of the resultant alcohol **9,** and solvolysis of the mesylate **10** in ethanol at reflux to provide a mixture of the lactone **11** and the corresponding hydroxy-ester. Treatment of the mixture with PPTS in benzene at 80 °C completed the conversion to the crystalline bridged lactone **11** in 63% overall yield from **3**. The stereochemistry of the lactone **11** was confirmed by single crystal X-ray crystallography. Lactone **11** was transformed in one pot to the enone **12** by selenation of the ketone with PhSeCl and catalytic HCl in EtOAc[12] followed by in situ oxidation with sodium periodate. The enol ether of **12** was selectively oxidized by exposure to dimethyldioxirane in wet acetone.[13] Addition of catalytic *p*-TSA to the reaction mixture resulted in hydrolysis of the epoxide to the hemiacetal and subsequent fragmentation of the cyclobutane producing the triol **13** in 94% yield directly from **12**. Treatment of the bis-hemiacetal **13** with *p*-TSA in methanol provided 82% of the bis-methyl acetal **14** accompanied by 15% of another diastereomer that could be converted to **14** by exposure to 6 N HCl in acetone in 92% yield. Hydroxylation of C4 was achieved using a modified Davis procedure.[14] Exposure of **14** to stoichiometric *t*-BuLi and 20 mol % Et_2NH followed by the Davis oxaziridine gave excellent yields of the tertiary alcohol **15**. The use of sub-stoichiometric amounts of amine obviated the use of excess oxidant and significantly simplified the purification of **15**.

Attempted closure of the central E ring by treatment of acetal **15** with catalytic acid produced hydroxy ketone **16** in high yield. Apparently, an acid-catalyzed closure of the E ring results in the formation of an intermediate hydroxy aldehyde that is converted to **16** by an ene−diol rearrangement. Attempts to close the F ring by more vigorous conditions led to addition to the enone by either the C10 or C11 functional group in a variety of substrates. This and other related failures to close both the E and F rings led to the decision to remove the C10 hydroxyl group in an effort to suppress the ene−diol rearrangement.

Alcohol **14** was converted to the corresponding xanthate[15] and subsequent Barton deoxygenation[16] provided **17** in 78% overall yield (Scheme 3). Hydroxylation of C4, as described above, followed by DMAP catalyzed acylation of the alcohol with propionic anhydride gave the propionate **18** in good overall yield. Exposure of the ester **18** to LDA in THF gave 90% of the lactone **19** which was isomerized to a 1:1 mixture of **2**:**19** by exposure to sodium methoxide in methanol. The diastereomers were separated and **19** was isomerized to the same 1:1 mixture of **2:19** by further exposure to the isomerization conditions. Treatment of **2** with camphorsulfonic acid in methanol at 65 °C resulted in methanolysis of the lactone and closure of the E ring ether to provide the pentacyclic lactone **20** in 88% yield. Only closure of

Scheme 3



C ring lactone and refunctionalization of the F ring remained. To this end, elimination of methanol from the F ring was accomplished in 85% yield by heating the acetal **20** in chlorobenzene (PPTS, pyridine)[6] to give the enol ether **21**. Selective epoxidation of the C1−C2 alkene under Sharpless conditions[17] and subsequent addition of *p*-TSA to the reaction mixture led to the hexacyclic enol ether **22**. Treatment of enol ether **22** with dimethyldioxirane resulted in stereoselective formation of the C10−C11 β-epoxide as a result of steric shielding by the *tert*-butyl group. Opening of the epoxide and in situ oxidation (Br_2, NaOAc, HOAc)[18] of the resulting hemiacetals led to the exclusive formation of (±)-ginkgolide B. Ginkgolide B was obtained in 52% purified yield for the final two steps. Synthetic (±)-ginkgolide B was identical in all respects with a natural sample (^{1}H, ^{13}C NMR, IR, TLC).

Acknowledgment. Financial support of our programs by the NIH, the NSF, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is acknowledged with thanks. Thanks also go to Glaxo-Wellcome for help with mass-spectral data.

Supporting Information Available: Experimental procedures and spectral data (^{1}H, ^{13}C, IR) for compounds **1**−**7** and **9**−**22** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA993013P

(12) Sharpless, K. B.; Lauer, R. F.; Teranishi, Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137−6139.
(13) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187−1201.
(14) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241−3243.
(15) 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.
(16) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574−1585.
(17) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63−74.
(18) Corey, E. J.; Kamiyama, K. *Tetrahedron Lett.* **1990**, *31*, 3995−3998.