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Total Synthesis of (±)-Ginkgolide B

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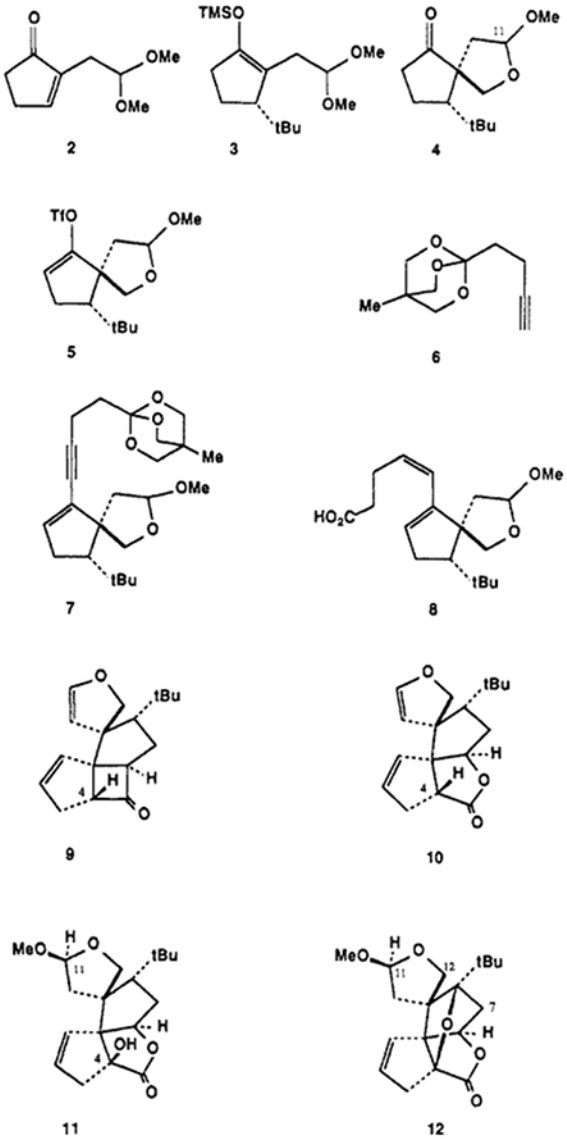
Extracts of the ginkgo tree, *Ginkgo biloba*, now widely recommended in Asian and European medicine (annual sales ca. $500 000 000 per annum), have been found to antagonize platelet activating factor (PAF),[1] a very fundamental mammalian regulator.[2] Ginkgo extracts increasingly find therapeutic use in the treatment of cerebrovascular and peripheral circulatory problems of the elderly and asthma. The most active anti-PAF agent in the ginkgo extract is the hexacyclic C_{20} trilactone ginkgolide B (**1**)[3] (IC_{50} 10^{-7}–10^{-8} M in various tests),[1] which appears to antagonize all known PAF-induced membrane events. The first total synthesis of ginkgolide B (racemic form) is described herein. A recent paper from these laboratories[4] has reported the total synthesis of the related C_{15} ginkgolide, (±)-bilobalide,[5] by a totally different approach.

Reaction of 1-morpholinocyclopentene with dimethoxyacetaldehyde in benzene at 23 °C for 18 h, stirring of the resulting solution with 6 N hydrochloric acid at 0 °C for 30 min, extractive isolation and distillation (145–146 °C at 15 Torr) provided enone **2** in 70% yield.[6–8] Enone **2** was converted into the end silyl ether **3** (93% yield) by reaction in ether with the cuprate reagent *t*-$Bu_2CuCNLi_2$ (1.5 equiv relative to **2**; prepared from reaction of cuprous cyanide and *tert*-butyllithium in a 1:2 ratio at −78 °C for 50 min and then at −45 °C for 30 min) at −78 °C for 10 min and then at −45 °C for 30 min, followed by silylation of the resulting enolate with 5 equiv each of trimethylchlorosilane and triethylamine (−45 °C for 45 min, then −10 °C for 5 min) and extractive isolation. Addition of **3** in methylene chloride to a solution of 1,3,5-trioxane (1.2 mol equiv) and titanium tetrachloride (3.6 equiv) in methylene chloride at −78 °C (over 20 min), further reaction (−78 °C for 2 h and −45 °C for 1 h), and finally treatment with one-half volume of methanol (0 °C initially then 23 °C for 12 h) produced stereoselectively[9] cyclopentanone **4**, mp 25–27 °C, as a 2:1 mixture of two C(11) anomeric methyl acetals (ginkgolide numbering) in 65% yield. Deprotonation of **4** with 1.25 equiv of lithium diisopropylamide (LDA) in dimethoxyethane (−78 °C for 1 h, 0 °C for 20 min) and subsequent reaction with *N*-phenyltriflimide[10] (0 °C for 1.5 h, 23 °C for 1 h) afforded after isolation and silica gel chromatography (SGC) an 80% yield of enol triflate **5**. A solution of **5** and $Pd(PPh_3)_4$ (5.7 mol%) in benzene was stirred at 16 °C for 15 min and then treated successively with a benzene solution of acetylenic OBO ester **6**[11] (1 equiv), *n*-propylamine (2.3 equiv), and 0.5 equiv of cuprous iodide, all at 16 °C to give after 4 h at 16 °C, extractive isolation and SGC 76–84% of the coupling product **7** (2:1 mixture of anomers), mp 44–47 °C.[12] The triple bond of **7** was reduced by reaction with 1.5 equiv of dicyclohexylborane in tetrahydrofuran (THF) (0 °C for 2 h, 23 °C for 0.5 h), followed by

Supplementary Material **Available:** Spectral data for compounds **1**–**23** (6 pages). Ordering information is given on any current masthead page.

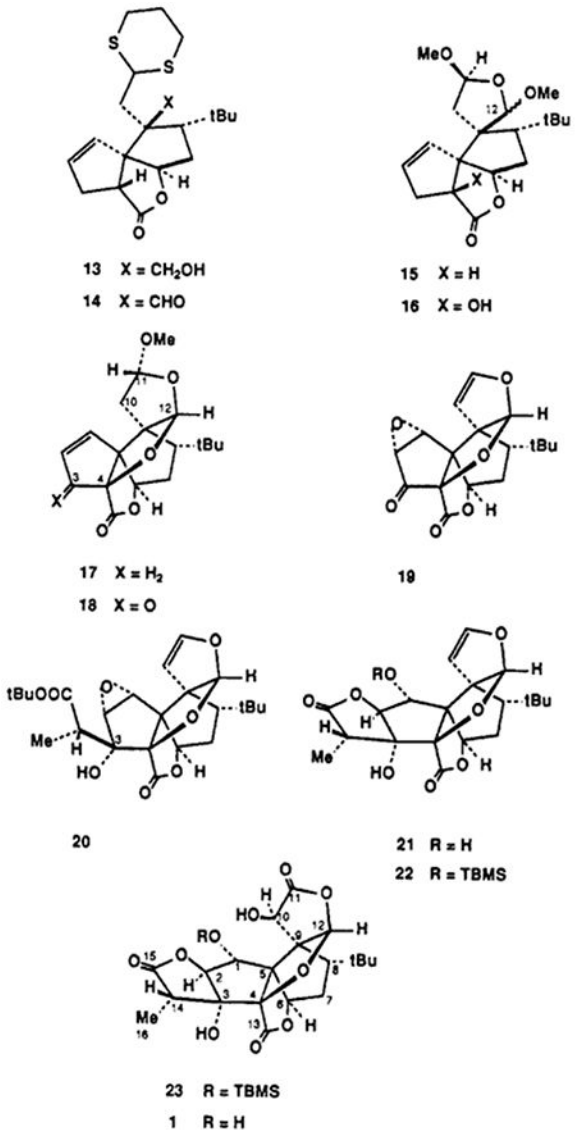
protonolysis (acetic acid 23 °C for 16 h), and decomposition of residual boranes (H_2O_2, 23 °C, pH 10). The resulting solution was acidified to pH 3 with 1 N hydrochloric acid, brought to pH 11 (vigorous stirring, 4 h) and reacidified to pH 3 to cleave the OBO ester unit,[13] and the (*Z*)-olefinic acid **8** was isolated by extraction and removal of solvent (70% yield, colorless oil). Conversion of **8** to the corresponding acid chloride (5 equiv of oxalyl chloride in benzene at 23 °C for 2 h) and addition of the acid chloride in toluene solution (0.2 M) over 2 h to a stirred solution of tri-*n*-butyiamine (10 equiv) in toluene at reflux, followed by further reaction at reflux for 1 h, furnished stereospecifically (71–87% yield) the tetracyclic ketone **9**, mp 59 °C. Structure **9**, which results from internal ketene–olefin cycloaddition[14] and elimination of the anomeric methoxy group (under tri-*n*-butylammonium chloride catalysis), follows from spectroscopic data and the transformation **11** → **12** described below.[15]



Addition of **9** in acetone (at −30 °C) to a stirred solution of triphenylmethyl hydroperoxide in 8:1 acetone–1 N aqueous sodium hydroxide at −30 °C over 10 min and a further reaction time of 2 h at −30 °C produced a single Baeyer–Villiger product **10**, mp 163 °C, in 86% yield.[15] Lactone **10** was transformed into 4-hydroxylactone **11** (ginkgolide numbering as in **1**) by a two-step sequence: (1) deprotonation (1.5 equiv of sodium bis(trimethylsilyl)amide in THF at −50 °C for 20 min) followed by reaction of the resulting anion with 2 equiv of (*E*)-2-(phenylsulfonyl)-3-phenyloxaziridine[16] (at −50 °C for 5 min and then at −50 °C to 0 °C over 10 min) to afford the corresponding α-hydroxylactone (73% after SGC) and (2) exposure to a 1% solution of camphorsulfonic acid (CSA) in methanol at 23 °C for 48 h to give **11**, mp 155 °C (75%).[17] Reaction of **11** with lead tetraacetate (4.5 equiv) and iodine (3 equiv) in pyridine-1,2-dichloroethane at 5 °C under sunlamp irradiation for 10 min resulted in complete conversion to a single product, determined by 500-MHz ^{1}H NMR analysis to be the cyclic ether **12**,[18] rather than the hoped for product of functionalization at C(12). Although this result was not useful as a synthetic step, it did provide conformation of the stereochemistry of intermediates **9**, **10**, and **11**.

The required oxygen bridge between C(4) and C(12) was established by an alternative route starting from **10**. Reaction of **10** with 1.2 equiv of propane-1,3-dithiol and excess titanium tetrachloride in methylene chloride at 0 °C for 10 min and then at 23 °C for 40 min produced the thioacetal–primary alcohol **13**, mp 230 °C (98%), which was transformed into the aldehyde **14**, mp 165–166 °C (75% yield), by treatment with pyridinium dichromate (PDC, 1 mol equiv), powdered 3-Å molecular sieves and acetic acid in methylene chloride at 0 °C for 1 h. The aldehyde **14** was converted into the bis-acetal **15** (80% overall yield as a 2:1 mixture of C(12) anomers) (major anomer from SGC, mp 107 °C) by the following process: (1) oxidative dithiane cleavage by reaction of **14** with 0.5 mol equiv of periodic acid in 1:1 methanol–methylene chloride containing ca. 1% water at −30 °C initially then at 0 °C for 20 min and 23 °C for 40 min and (2) stirring of the resulting product with methanolic CSA at 23 °C. The C(4)–C(12) oxygen bridge was generated by the following sequence: (1) deprotonation of bis-acetal **15** with use of 1.9 equiv of lithium diethylamide initially at −25 °C and then at 0 °C for 15 min and subsequent oxygenation with (*E*)-2-(phenylsulfonyl)-3-phenyloxaziridine[16] (2 equiv, 0 °C for 30 min) to form the α-hydroxylacetone **16**, mp 115–116 °C, and (2) reaction with a solution of CSA in methylene chloride (20 mg/100 mL) at 23 °C for 24 h to afford **17**, mp 151–153 °C (75%).[20] The introduction of an oxo function at C(3) was accomplished in 50% overall yield by the following transformations: (1) allylic bromination with 1.3 equiv of *N*-bromosuccinimide in carbon tetrachloride (0.02 M) under external tungsten lamp irradiation at 10 °C for 2–3 h (monitored by SG TLC) to give a mixture of 60% of the C(3) brominated product (Br^3), 30% of the C(l) brominated product (Br^1), and 10% of the 3,3-dibrominated product ($Br^{3,3}$); (2) reaction of the mixture with 10 M silver nitrate in acetonitrile at 23 °C for 15 min which generates a mixture of the enone **18**, mp 267–268 °C (from $Br^{3,3}$), the 1-nitrate ester (from Br^3), and the 3-nitrate ester (from Br^1), easily separated by SGC; (3) conversion of the 3-nitrate ester to **18** by nitrate cleavage with zinc–acetic acid followed by oxidation of the resulting C(3) alcohol with PDC in methylene chloride at 23 °C for 5 h; (4) conversion of the 1-nitrate ester to **18** by exposure to 20 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene and

20 equiv of water in 10:1 benzene–methanol at 23 °C for 30 h followed by oxidation of the resulting C(3) alcohol (from overall S_N2' reaction) by PDC.



The final γ-lactone ring was affixed starting with epoxy ketone **19** which was obtained from **18** in the following two steps: (1) elimination of methanol from C(10)–C(11) by heating **18** under argon with 5 equiv of pyridinium tosylate and 2.5 equiv of dry pyridine in chlorobenzene at 135 °C for 16 h (80% yield)[21,22] and (2) enone epoxidation with triphenylmethyl hydroperoxide (5 equiv) and benzyltrimethylammonium isopropoxide (0.5 equiv) in THF at −10 °C for 3 h to give after reduction of excess hydroperoxide by trimethyl phosphite (10 equiv) and SGC 72% of **19**. Reaction of **19** with 7 equiv of the lithium enolate of *tert*-butyl propionate (from LDA) in 4:1 THF–hexamethylphosphorictriamide, at −78 °C to −30 °C for 2 h and then at −30 °C for 10 h, furnished the desired aldol adduct **20** in 60% yield after SGC.[23] Exposure of **20** to 4 equiv of CSA in methylene chloride (23 °C for 15 h) afforded bis-lactone **21** (82%) which was converted to the *tert*-butyldimethylsilyl (TBMS)

ether **22** upon treatment with 2.5 equiv of TBMS triflate and 5 equiv of 2,6-lutidine in acetonitrile at **23** °C for 1 h (89%). Hydroxylation of **22** using osmium tetroxide in pyridine followed by oxidation of the resulting product with excess iodine in methanol in the presence of $CaCO_3$ (23 °C for 12 h) produced trilactone **23** (ca. 40% from **22**)[21] along with a small amount of the C(10) epimer. Desilylation of **23** (5 equiv of $BF_3{\cdot}Et_2O$ in methylene chloride at 23 °C for 14 h) gave 89% yield of (±)-ginkgolide B (**1**), identical with an authentic sample by 500-MHz ^{1}H NMR, FT-IR, SG-TLC analysis in several solvent systems, and mass spectral comparison.[24]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(5). Nakanishi K; Habaguchi K; Nakadaira Y; Woods MC; Maruyama M; Major RT; Alauddin M; Patel AR; Weinges K; Bähr W J. Am. Chem. Soc 1971, 93, 3544–3546, and references contained therein.

(6). See: Barco A; Benetti S Synthesis 1981, 199–200.

(7). All reaction products were liquids unless otherwise noted. Satisfactory high resolution mass spectra were obtained for all stable products.

(8). Dimethoxyacetaldehyde was prepared in 72% yield by ozonolysis of acrolein dimethyl acetal (CH_2Cl_2 at −78 °C). See: Bestmann H; Ermann P Chem. Ber 1983, 116, 3264–3266.

(9). The trans arrangement of the vicinal β-tert-butyl and α-oxymethyl substituents in **4** was demonstrated by ^{1}H NOE experiments involving irradiation of the *tert*-butyl group of **4** and the isomer of **4** with the cis arrangment of these substituents (available to us by an alternative synthetic route but not produced under the conditions indicated for **4**).

(10). McMurray JE; Scott WJ Tetrahedron Lett. 1983, 24, 979–983.

(11). The preparation of **6** was carried out as follows. 4-Pentynoic acid was converted to the acid chloride (oxalyl chloride, benzene, 23 °C) which was treated with 3-methyl-3-hydroxymethyloxetane to form the corresponding ester (85% overall) and in turn rearranged with boron trifluoride in methylene chloride at −20 °C to form **6** (92%). See: Corey EJ; Raju N Tetrahedron Lett. 1983, 24, 5571–5574.4-Pentynoic acid was obtained in 25% overall yield by the following sequence: (1) alkylation of diethyl sodiomalonate in ethanol with propargyl chloride; (2) saponification with potassium hydroxide in aqueous ethanol at 23 °C; and (3) thermal decarboxylation of propargyl malonic acid at 150–170 °C over 45 min.

(12). (a)Sonogashira K; Tohda Y; Hagihara N Tetrahedron Lett. 1975, 4467–4471.(b)Ratevelomana V; Linstrumelle G Synth. Commun 1981, 11, 917–923.

(13). Corey EJ; De BJ Am. Chem. Soc 1984, 106, 2735–2736.

(14). (a)See: Corey EJ; Desai MC; Engler TA J. Am. Chem. Soe 1985,107, 4339–4340.(b)Corey EJ; Desai MC Tetrahedron Lett. 1985, 26, 3535–3538.The stereospecificity of the internal cycloaddition to form **9** was predicted from mechanistic considerations[14b] and the lesser degree of steric screening for the pathway leading to **9**.

(15). The structure of **10** was confirmed by the conversion of **11** → **12**. Use of *tert*-butyl hydroperoxide as oxidant or higher reaction temperatures led to the appearance of the position isomeric lactone as a byproduct.

(16). (a)Davis FA; Stringer OD J. Org. Chem 1982, 47, 1774–1775.(b)Davis FA; Vishwakarma LC; Billmers JM; Finn J J. Org. Chem 1984, 49, 3241–3243.

(17). Methyl acetal lactone **11** was obtained as a single kinetically controlled stereoisomer (from 500-MHz ^{1}H NMR analysis). The orientation of methoxy at C(11) follows from the strong steric shielding by *tert*-butyl at the opposite face of the tetrahydrofuran subunit. The orientation of the hydroxyl group at C(4) follows from the strong preference for formation of a cis 5,5-fusion in the hydroxylation reaction and is further confirmed by the conversion to **12**.

(18). The ^{1}H NMR spectrum of **12** (with spin decoupling) provides unambiguous support for this structure and the following key assignments: H_{12a}, d, 4.33 δ, $J_{12a,12b}$ = 9.6 Hz; H_{12b}, d, 3.45 δ, $J_{12a,12b}$ = 9.6 Hz; H_{7a}, dd, 2.40 δ, $J_{7a,7b}$ = 15.1 Hz, $J_{6,7a}$ = 7.7 Hz; H_{7b} d, 1.98 δ, $J_{7a,7b}$ = 15.1 Hz; *t*-Bu, s, 1.07 δ. In all intermediates in the synthesis which have H attached to C(8) a coupling $J_{7b,8}$ of 5–6 Hz is observed; the doublet for H_{7b} then shows there is no H attached to C(8).

(19). The observed course of the functionalization to give **12** suggests that steric repulsion between the *tert*-butyl substituent at C(8) and the hydrogens at C(10) and C(11) causes puckering of the C(5)–C(9) ring so as to bring H–C(8) into proximity to O–C(4).

(20). The configuration at C(11) of **17** follows clearly from chemical and NOE studies not reported herein.

(21). The yields given for this and remaining steps in the synthesis are probably not optimum since these reactions have been conducted only a few times without systematic attempts at further improvement.

(22). This product and also **21** and **1** are solids which decompose before melting; **22** and **23** are colorless oils.

(23). A small amount of C(3) epimer (ca. 7%) was also obtained; the C(3) epimer became the major product from reaction in THF alone at −78 °C.

(24). We are grateful to Dr. P. Braquet, Institute Henri Beaufour, Paris and Dr. K. Yamada of Kagoya University for samples of ginkgolide B, to Dr. Ashvinikumar V. Gavai and Dr. Yi Bin Xiang for valuable experimental assistance, and to Francis J. Hannon for determination of mass spectra. This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation.