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INTRAMOLECULAR ENONE-FURAN PHOTOCYCLOADDITIONS: STUDIES TOWARD THE SYNTHESIS OF GINKGOLIDES A AND B

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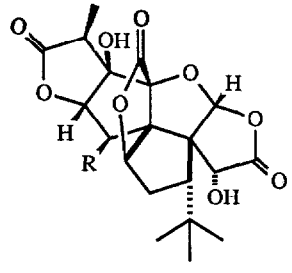
Summary: The synthesis of a pentacyclic model **14** for ginkgolides A and B has been accomplished utilizing an intramolecular furan-enone photochemical cycloaddition as the key transformation.

Ginkgolides A and B **1, 2,** hexacyclic trilactones obtained from extracts of the ancient tree *Ginkgo Biloba*, were isolated and characterized by Nakanishi in 1967.[3] While these compounds are known antagonists of platelet activating factor (PAF) and have already found important medicinal applications in Europe and Asia,[4] there has been relatively little effort directed toward their synthesis until recently.[5-8] In 1988 Corey reported the first synthesis of ginkgolide B[5] and a few other model studies have been disclosed.[6-8] We report here our studies on the synthesis of a pentacyclic analog of ginkgolides A and B which should serve as a model for further development of a new synthetic approach to these complex diterpenes.

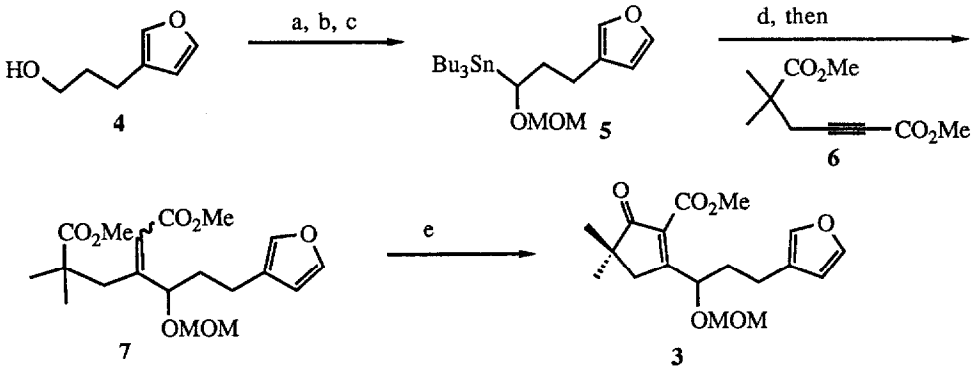


Ginkgolide A : R = H **(1)**
Ginkgolide B : R = OH **(2)**

The basic strategy for the construction of the ginkgolide analog centered around the intramolecular photocycloaddition[9] of furan enone **3** which can be prepared from the known furanpropanol **4**[10] as shown in Scheme 1. Swern oxidation of the alcohol followed by addition of Bu_3SnLi and protection of the alcohol as the MOM ether gave the α-alkoxy tin reagent **5**.[11,12] Preparation of the copper lithium reagent of **5** followed by the addition of acetylenic diester **6** produced the alkenes **7** which were cyclized to the desired enone **3** with LDA at -78°C.[13] Irradiation of enone **3** at >350 nm in hexanes produced a 74% yield of a single diastereomer[14] **8** (Scheme 2). To our knowledge this is the first example of the use of a furan as the olefin partner in an intramolecular enone-olefin photocycloaddition reaction.

Closure of the bridging lactone ring required that the MOM protected hydroxyl be inverted. Hydrolysis of the MOM ether was with MeOH, HCl also resulted in the formation of the methyl acetal from the enol ether to give **9** (3:1 mixture of anomers). Oxidation of the alcohol provided diketone **10** and subsequent reduction with $NaBH_4$ effected spontaneous lactonization. Reoxidation of the ring A hydroxyl produced the pentacyclic lactone **11**. It was found that only the major anomer of **9** proceeded cleanly to **11**, while the minor anomer reverted primarily to the diketone intermediate **10** after the second oxidation.[15]

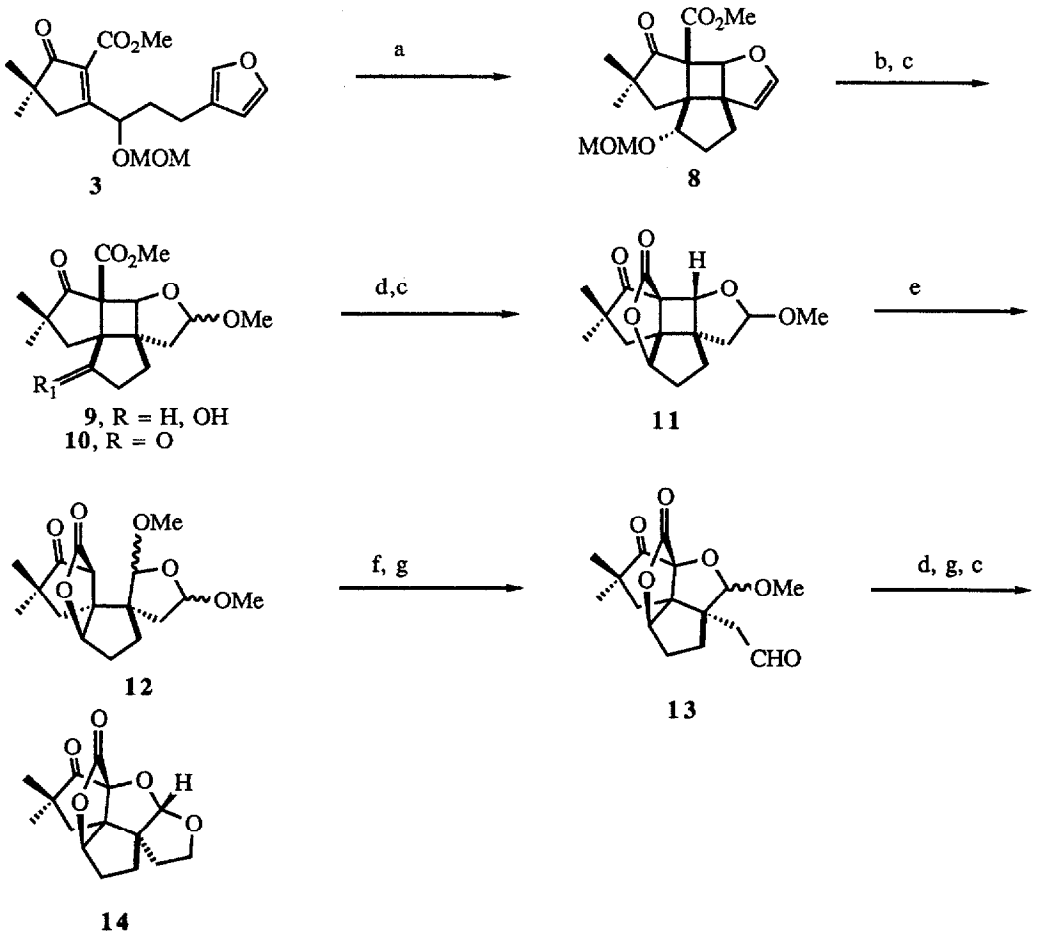
Scheme 1



(a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C; 96%. **(b)** Bu_3SnLi, THF, -78°C, 60%. (c) CH_3OCH_2Cl, CH_2Cl_2, i-Pr_2EtN, 80%. (d) BuLi, THF, then CuBr-Me_2S, i-Pr_2S, -78°C to -50°C, 70%. (e) LDA, THF, -78°C, 50%.

At this point, the main transformation remaining was to ring expand the cyclobutane to a tetrahydrofuran by some fragmentation-oxidation sequence. This was accomplished by treatment of **11** with $BF_3{\cdot}Et_2O$ in methanol to regiospecifically open the cyclobutane and produce a 95% yield of the bisacetal **12**. It is interesting to note that this fragmentation fails in the absence of the bridging lactone ring (e.g. **9**) presumably due to less strain in the four membered ring. Several oxidation methods were tested for the required hydroxylation of the dicarbonyl system. Ultimately, deprotonation of the 1,3-dicarbonyl system with lithium diethylamide followed by treatment of the lithium species with the Davis oxaziridine[16] resulted in α-hydroxylation of the keto-ester and isolation of tetracycle **13** after exposure to p-toluenesulfonic acid. The stereoselectivity of the hydroxylation is controlled by the kinetic and thermodynamic preference for cis ring fusions in bicyclo[3.3.0] ring systems. The fact that ring C of intermediate **12** opens during the cyclization of ring D may be due to the absence of the t-butyl substituent.[17] As a further confirmation of the structure, the aldehyde was reduced to the primary hydroxyl and the final ring was closed by the action of catalytic p-TSA to give **14** which contains the basic elements of five of the six rings of the ginkgolides. The pentacycle **14** is thus stereoselectively produced in 16 steps from the known furanpropanol **4**. Current efforts are directed toward applying this basic strategy to a synthesis of the naturally occurring ginkgolides A and B.

Scheme 2



(a) hν, >350 nm, hexanes, 74%. (b) MeOH, HCl, 95%. (c) PCC, CH_2Cl_2, 95%. (d) $NaBH_4$, DME, 90-95%. (e) BF_3-Et_2O, MeOH, 95%. (f) $LiNEt_2$, THF, -25°C; (E)-2-(phenylsulfonyl)-3-phenyloxaziridine, 0°C. (g) p-TsOH, CH_2Cl_2, 33% of **14** from **12**.

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