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# INTRAMOLECULAR AND INTERMOLECULAR HYDROXYL REACTIVITY DIFFERENCES IN GINKGOLIDES A, B AND C AND THEIR CHEMICAL APPLICATIONS

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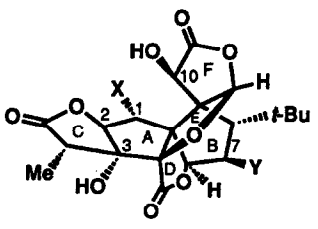
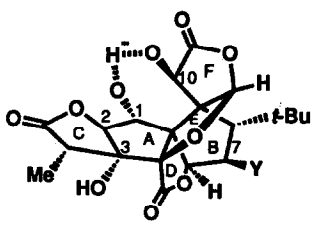
***Summary:*** *An investigation of the chemistry of ginkgolides A, B and C (1) has revealed an unusual interaction between the hydroxyl groups at C(1) and C(10) which activates their deprotonation to give 2 and provides a method for the interconversion of 1C and 1B. The ginkgolide 7-enol system 7 is more stable than the corresponding 7-keto form 6, which is easily made by selective Jones oxidation of ginkgolide C.*

In connection with our studies on the total synthesis,[1] chemistry and biological activities[2] of ginkgolides A, B and C (**1A**, **1B**, and **1C**), and their structural analogs, we have discovered a number of interesting and useful aspects of the relative reactivity of the various hydroxyl functions in these compounds. In this note we describe some of these unusual hydroxyl group reactivity trends and their application to the separation of the ginkgolides and to the conversion of ginkgolide C to ginkgolide B by a route that allows the introduction of a non-labile tritium marker.

The C(1) and C(10) hydroxyls of ginkgolides B and C are much more readily deprotonated than the C(10) hydroxyl of ginkgolide A probably because the resulting alkoxides are stabilized by hydrogen bonding between the oxygens on C(1) and C(10), as shown in **2**. The oxygens at C(1) and C(10) in ginkgolides B and C are only 2.4 Å apart, a distance readily spanned by the hydrogen bridge in **2**. These reactivity differences are clearly revealed by the following experiment. Treatment of a mixture of ginkgolides A, B and C (ratio *ca.* 2 : 2 : 1) with 3.5 equiv of chloromethylbenzyl ether (per equiv of ginkgolide in the mixture) and 4 equiv of diisopropylethylamine in acetonitrile at 23 °C for 72 h gave a mixture which was readily separated by column chromatography on silica gel using 2 : 1 hexane–ethyl acetate for elution. The following products were isolated (amounts per gram of original mixture and silica gel tlc $R_f$ values for 1 : 1 hexane ethyl acetate as indicated):




**1A, X = Y = H**
**1B, X = OH, Y = H**
**1C, X = Y = OH**



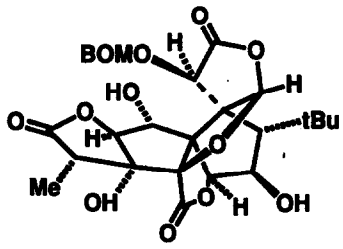

**2**

**1B**–C(10) benzyloxymethyl ether (280 mg, $R_f$ 0.65); **1B**–C(1) benzyloxymethyl ether (187 mg, $R_f$ 0.59), **1C**–C(10) benzyloxymethyl ether (119 mg, $R_f$ 0.47), **1C**–C(1) benzyloxymethyl ether (85 mg, $R_f$ 0.43), **1A** (372 mg, $R_f$ 0.33). Catalytic hydrogenation of the benzyloxymethyl ethers (Pd–C, 1 atm $H_2$, methanol, 23 °C, 5 h) effected quantitative replacement of benzyloxymethyl by hydrogen. The three-step process, benzyloxymethyl ether formation, chromatography on silica gel and benzyloxymethyl cleavage, provides a superior procedure for the separation of the naturally occurring mixture of ginkgolides A, B and C. It is much simpler and more convenient than the 10-15 step fractional recrystallization method which is published.[3,4] Direct chromatographic separation of these ginkgolides is extremely difficult.

Pure ginkgolide A is unreactive toward chloromethylbenzyl ether under the conditions described above and consequently it is clear that the reactivity of the C(10) hydroxyl group of ginkgolide A is lower than that of the C(10) hydroxyl of ginkgolide B or ginkgolide C and that the C(1) hydroxyl is responsible for the higher reactivity. The intervention of the hydrogen bonded mono anion **2** explains these observations and also the fact that a *mixture* of C(1) and C(10) mono benzyloxymethyl ethers invariably results from etherification of ginkgolide B or ginkgolide C. Once either the C(1) hydroxyl or the C(10) hydroxyl of ginkgolide B or ginkgolide C has been etherified, the other hydroxyl is essentially inert toward further reaction, in part because formation of a stabilized mono-hydrogen bonded alkoxide is not possible and in part because the newly introduced benzyloxymethyl group sterically obstructs the attachment of a second such group at either C(1) or C(10).

One consequence of this interesting selectivity for monoetherification at either C(1) or C(10) of ginkgolide C (**1C**) is to make available other selective hydroxyl group reactions of this substance. Thus, reaction of the C(10) benzyloxymethyl (BOM) ether of **1C** (**3**)[5] with pentafluorophenoxythiocarbonyl chloride (2 equiv) and 4-N,N-dimethylaminopyridine (6 equiv) in acetonitrile at 5 °C for 12 h produced selectivity the C(7) pentafluorophenoxythiocarbonyl derivative **4** (63%, 83% based on recovered **3**). Treatment of **4** with 3 equiv of tri-*n*-butyltin hydride and a 0.05 equiv of bisazoisobutyronitrile in benzene at reflux for 12 h gave the C(10) BOM ether of ginkgolide B (**5**) which upon hydrogenation (1 atm $H_2$, Pd–C, MeOH, 23 °C, 5 h) afforded ginkgolide B (**1B**) in 90% yield. This conversion of ginkgolide C into ginkgolide B is of interest for two reasons: (1) ginkgolide B is several orders of magnitude more potent than ginkgolide C as an antagonist of platelet activating factor[6] and (2) it provides a methodology for the introduction of tritium at C(7) in ginkgolide B. Tritium-labeling of ginkgolide B at a chemically stable position has not previously been accomplished.[7]

Despite the greater reactivity of the C(1), C(10) hydroxyl diad of **1C** in base-catalyzed etherification, it appears that the C(7) hydroxyl group is the most readily oxidized by Cr(VI) reagents. Thus, treatment of ginkgolide C with $CrO_3$–acetone (Jones' reagent) at 0 °C for 3 h produces the 7-ketone (**6**) selectivity in 90% yield. It is of interest that this ketone is converted completely to the more stable enol form (**7**) upon treatment with a trace of hydrogen chloride in chloroform.[8] Treatment of **7** with 1 equiv of chloromethylbenzyl ether and diisopropylethylamine in acetonitrile converts it selectively into the corresponding enol BOM ether **8**. This highly unusual situation in which the enol tautomer is more stable than the keto tautomer is probably the result of a difference in steric repulsions involving the *t*-butyl group. In the keto form **6**, the *t*-butyl group is involved in serious steric repulsions with C(10)–H and C(12)–H groups which are somewhat relieved in the enol form **7**.

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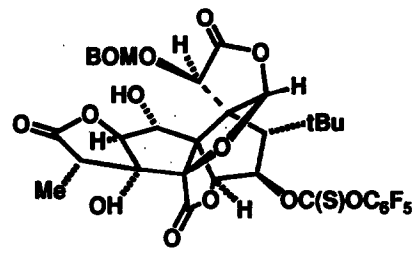


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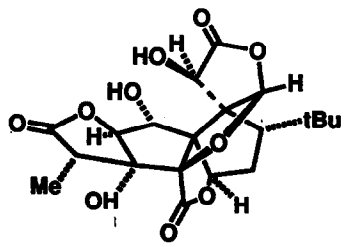
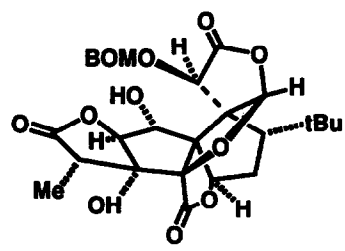



1B

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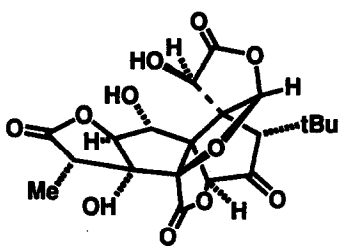


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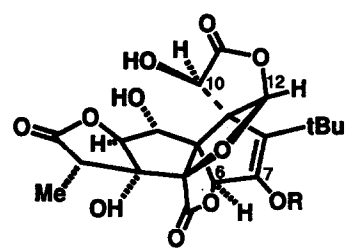


7, R = H
8, R = BOM

BOM = $CH_2OCH_2C_6H_5$

In summary the experimental results reported above demonstrate a number of new and unique aspects of ginkgolide chemistry which lead to useful transformations. These include (1) an interesting interaction of the C(1) and C(10) hydroxyls of ginkgolides B and C which provides an activation mechanism for deprotonation to give 2; (2) a simple new chromatographic process which allows a much improved separation of ginkgolides A, B and C; (3) a selective oxidation of ginkgolide C at the C(7) hydroxyl; and (4) an unusual reversal of ketone-enol stability for the 7-keto and 7-enol ginkgolides.[9]

***References and Notes:***


1. For a review see Corey, E. J. *Chem. Soc. Rev.* **1988**, *17*, 111-133.
2. (a) Corey, E. J.; Gavai, A. V. *Tetrahedron Letters* **1989**, *30*, 6959-6962; (b) Corey, E. J.; Rao, K. S. *Tetrahedron Letters* **1991**, *32*, 4623-4626.
3. See Nakanishi, K. *Pure Appl. Chem.* **1967**, *14*, 89-113.
4. For purposes of separating ginkgolides A, B and C from the naturally occurring mixture, it is clearly not necessary to separate the mixture of C(1) and C(7) benzyloxymethyl ethers either of ginkgolide B or ginkgolide C.
5. The C(10) BOM ether **3** predominates over the C(1) isomer by a ratio of 2 : 1 if the benzyloxy methylation of ginkgolide C is conducted at 0 °C in acetonitrile for 5 h; a ratio of *ca.* 1.4 : 1 is observed for the corresponding reaction at 23 °C.
6. Braquet, P. *Drugs of the Future* **1987**, *12*, 643-699.
7. The following spectral data were obtained for compounds **3**, **4**, **5**, and **6**:
   Compound **3**: IR: 3521, 1791, 1731, 1097, 1087 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 7.4 - 7.25 (m, 5H, Ph), 6.43 (s, 1H, $-OH_3$), 6.15 (s, 1H, $H_{12}$), 5.68 (d, 1H, J=6.1Hz, $-OH_7$), 5.48 (d, 1H, J=5.2Hz, $-OH_1$), 5.3 (s, 1H, $H_{10}$), 5.28 (d, 1H, J=6.6Hz, $-O-CH_2-O-$), 5.15 (d, 1H, J=6.6Hz, $-O-CH_2-O-$), 5.03 (d, 1H, J=4.1Hz, $H_6$), 4.68 (d, 1H, J=12Hz, Ph-$CH_2$-O-), 4.59 (d, 1H, J=6.7Hz, $H_2$), 4.6 (d, 1H, J=12Hz, Ph-$CH_2$-O-), 4.1 - 4.0 (m, 2H, $H_7$&$H_1$), 2.82 (q, 1H, J=12.6Hz, $H_8$), 1.1 (d, 3H, J=7.1Hz, Me), 1.1 (s, 9H, *t*-Bu). Compound **4**: IR: 3447, 1794, 1521, 1169, 1070 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 7.35 - 7.2 (m, 5H, Ph), 6.58 (s, 1H, $-OH_3$), 6.3 (s, 1H, $H_{12}$), 6.0 (d, 1H, 5.7Hz, $-OH_1$), 5.65 - 5.55 (m, 2H, $H_6$&$H_7$), 5.45 (s, 1H, $H_{10}$), 5.27 (d, 1H, J=6.7Hz, $-O-CH_2-O-$), 5.2 (d, 1H, J=6.7Hz, $-O-CH_2-O-$), 4.71 (d, 1H, J=11.9Hz, Ph-$CH_2$-O-), 4.69 (d, 1H, J=5.8Hz, $H_2$), 4.56 (d, 1H, J=11.9Hz, Ph-$CH_2$-), 4.2 (t, 1H, J=5.8Hz, $H_1$), 2.84 (q, 1H, J=7.0Hz, $H_{14}$), 2.2 (d, 1H, J=12.4Hz, $H_8$), 1.14 (d, 3H, J=7.2Hz, Me), 1.11 (s, 9H, *t*-Bu). Compound **5**: IR: 3450, 1789 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.45 - 7.3 (m, 5H, Ph), 6.0 (s, 1H, $H_{12}$), 5.43 (d, 1H, J=3.1Hz, $H_6$), 5.35 (d, 1H, J=6.1Hz, $-O-CH_2-O-$), 5.23 (d, 1H, J=6.1Hz, $-O-CH_2-O-$), 5.0 (s, 1H, $H_{10}$), 4.74 (d, 1H, J=11.9Hz, Ph-$CH_2$-O-), 4.68 (d, 1H, J=11.9Hz, Ph-$CH_2$-O-), 4.64 (d, 1H, J=8.0Hz, $H_2$), 4.28 (dd, 1H, J=3.3Hz, 7.9Hz, $H_1$), 3.22 (d, 1H, J=3.3Hz, $-OH_1$), 3.03 (q, 1H, J=7.0Hz, $H_{14}$), 2.75 (s, 1H), 2.35 - 2.25 (m, 1H), 1.95 - 1.85 (m, 2H), 1.3 (d, 3H, J=7.0Hz, Me), 1.08 (s, 9H, *t*-Bu). Compound **6**: IR: 3450, 1793, 1734, 1138, 1069, 1049 $cm^{-1}$; $^1H$ NMR (500MHz, DMSO-$d_6$): δ 7.52 (d, 1H, J=5.5Hz, $-OH_{10}$), 6.66 (s, 1H, $-OH_3$), 6.18 (s, 1H, $H_{12}$), 5.27 (d, 1H, J=4.1Hz, $-OH_1$), 5.08 (d, 1H, J=5.4Hz, $H_{10}$), 4.98 (s, 1H, $H_6$), 4.68 (d, 1H, J=6.6Hz, $H_2$), 4.25 (dd, 1H, J=4.2Hz, 6.4Hz, $H_1$), 2.9 (q, 1H, J=7.3Hz, $H_{14}$), 2.68 (s, 1H, $H_8$), 1.2 (d, 3H, J=7.4Hz, Me), 1.12 (s, 9H, *t*-Bu).
8. The infrared spectrum of enol **7** shows carbonyl absorption only at 1791 $cm^{-1}$ (lactones) whereas the keto form **8** shows carbonyl bonds at 1793 $cm^{-1}$ (lactones) and 1734 $cm^{-1}$ (ketone). The $^1H$ NMR spectrum of enol **7** in DMSO-$d_6$ shows the enol OH proton at (δ) 9.86 (s), H(12) at 6.30 (s); H(6) at 5.46 (s) and *t*-Bu at 1.20 (s).
9. This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.


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