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THE GINKGOLIDES. IV[1, 2].

STEREOCHEMISTRY OF THE GINKGOLIDES

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The configurations at seven asymmetric centers, C-1, C-2, C-3, C-7, C-8, C-10 and C-14 have to be considered for GC (1), which contains the largest number of asymmetric carbon atoms. The configurations at the other asymmetric centers are necessarily defined by the rigid cage structure.

1) 3-OH and 2-H are cis: The ease with which the hydroxy acid from the γ-lactone in ring F reforms a lactone[3] requires a cis fusion of ring F to the five-membered ring A.

2) 3-OH and 14-H are trans: This trans arrangement is suggested by the very ready formation of the 3, 14-double bond by treatment of GA, GB and GC under a variety of conditions, e. g., treatment of GA diacetate with NaOAc/MeOH at room temperature gave monoanhydro-GA monoacetate (Fig. 2, Part II[4]), and is established by the following evidence. The monoanhydro triacetate 2 of iso-GC (see below) was hydrogenated to the corresponding dihydro derivative 3 (14-Me at 1.68 ppm), which upon mild base treatment was epimerized at C-14, with concomitant hydrolysis of acetates and translactonization of ring E (see below), to the dihydro derivative 4 (14-Me at 1.47 ppm), which was identical in every respect with GM. That epimerization had occurred at C-14 was evident from a comparison of the sec-Me signals of 3 and 4**. Since hydrogenation must have introduced two hydrogens on the same side of ring

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* from Varian Associates.

**The 14-Me signal appears in the range 1.37 to 1.51 ppm (in TFA) for all ginkgolide derivatives excepting the two 14-epi compounds formed by hydrogenation of the 3, 14-double bond, namely, compound 3 and 14-epi-dihydromonoanhydro-GA monoacetate (1.61 ppm).

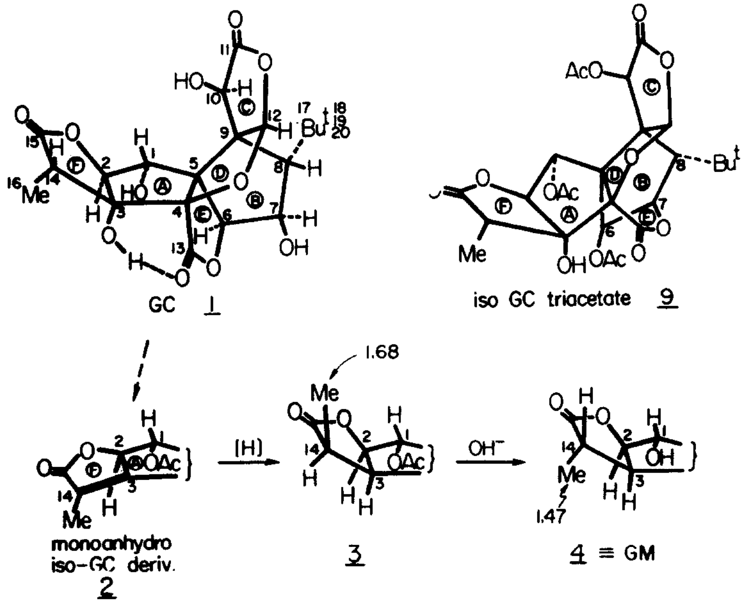
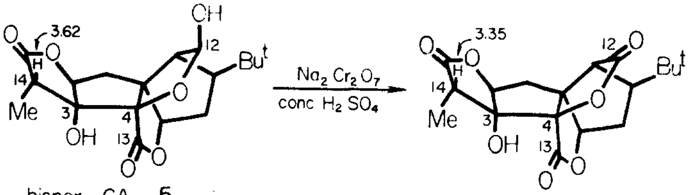


Fig. 1

F in 2, the first dihydro derivative 3 has 3-H and 14-H in a cis relationship, while the thermodynamically more stable compound 4 has them in a trans arrangement. The 14-Me is in the more stable configuration in all ginkgolides since they do not undergo epimerization at C-14 on mild base treatment.

3) <u>3-OH and 4, 13-bond are cis</u>: The C-14 proton signal suffers an 0.27 ppm diamagnetic shift when the 12-OH in bisnor-GA (5) (14-H at 3.62 ppm) is converted to a carbonyl (in dehydrobisnor-GA 6, the 14-H is at 3.35 ppm). This effect of the 12-C=O on the 14-H is only in accord with structure 6 having the 3-OH and 4, 13-bond in a cis relationship; it is also in agreement with the earlier conclusion that the 14-H and 3-OH are trans.



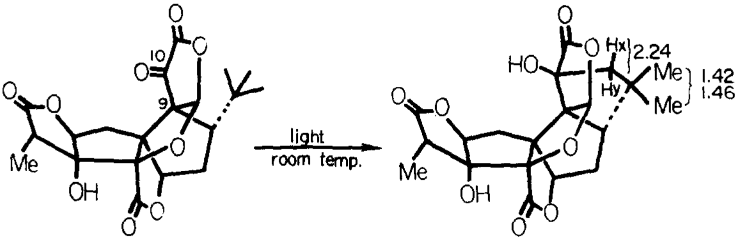
bisnor-GA 5
$C_{18}H_{24}O_7$

dehydrobisnor-GA 6
$C_{18}H_{22}O_7$

Further support for the 3-OH/4, 13-bond stereochemistry is provided by the following observation. Treatment of GA with MeI/K_2CO_3 in acetone results in methylation of the 3- and

10-OH. The ease of methylation of the 10-OH can be attributed to its being contained in an α-hydroxy lactone moiety, whereas that of the 3-hydroxyl can be understood on the basis of an intramolecular H-bonding between the 3-OH and the 13-CO, which would serve to weaken the O-H bond and facilitate methylation.

4) tert-Bu group is cis to the 9, 10-bond: Vigorous oxidation of GA afforded dehydro-GA (7), the UV and RD curves of which established the presence of the α-hydroxylactone group in GA[4). For a long time the sec-OH in GA was considered to be part of a hemiacetal group since the RD curve of the oxidation product was thought to exhibit no Cotton effect above 250 mμ. However, it was later discovered that the RD curve measured actually belonged to the photodehydro-GA (8) which had been formed during storage of 7[5). A model of GA having the tert-Bu group cis with respect to the 9, 10-bond indicates that the tert-Bu and 10-CO are ideally situated for abstraction of a hydrogen from one of the methyls of the tert-Bu group to form a new five-membered ring bearing a pair of non-equivalent (geminal) methyls; photodehydro-GA (8) has a cage structure consisting of seven five-membered rings.



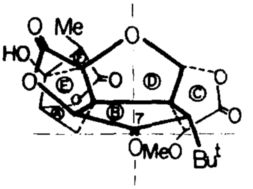
dehydro-GA 7
$C_{20}H_{22}O_9$

photodehydro-GA 8
$C_{20}H_{22}C_9$

5) The C-6 and C-7 oxygen functions are cis: Acetylation of GC with Ac_2O/NaOAc at room temperature yields the 1, 3, 7-triacetate, which can be further acetylated to the 1, 3, 7, 10-tetraacetate. In contrast to this, acetylation of GC in boiling Ac_2O/NaOAc affords an isomeric triacetate (iso-GC triacetate) 9 (Fig. 1), which is further acetylated to iso-GC tetraacetate. The iso-GC acetates are formed by translactonization of lactone E from C-6 to C-7, which is consistent with the coupling constants: $J_{6,7}$ 4 cps and $J_{7,8}$ 13 cps in GC tri- and tetra-acetate, and $J_{6,7}$ ca. 4 cps and $J_{7,8}$ 0 cps in iso-GC tri and tetra-acetate. The detected nuclear Overhauser effects in the two series of acetates (Fig. 3 and Table 2 in Part V[6)) are

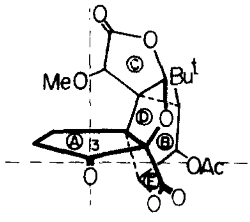
also consistent with the structural change resulting from translactonization.

6) 10-OH is cis to the 9,5-bond: This follows from the large nuclear Overhauser effect exhibited by the 10-H (proton I) in the ginkgolides upon irradiation of the tert-Bu group which requires that proton I and the tert-Bu be closely located in space (Part V[6]).



7-oxo-GC monomethyl ether 10

(+) Cotton



GC F-nor ketone 11

(+) Cotton

7) Absolute configuration: Since 7-oxo-GC monomethyl ether (Part II[4]) and the F-nor ketone derived from monoacetyldianhydro-GC monomethyl ether (Part II[4]) both exhibit a positive Cotton effect in their RD curves, it follows from the octant diagrams 10 and 11 that the ginkgolides must have the absolute stereochemistry depicted in the figures. In the case of 11 it is known empirically that the rotatory contribution of a substituent parallels the magnitude of its atomic refractivity[7] so that to a first approximation the contribution of lactone E is larger than that of the ether linkage (atomic refractivities of COOH and OH are, respectively, 3.38 and 1.52).

The full structures of the four ginkgolides, A, B, C and M (for " minor ") are summarized in Fig. 2. The ginkgolide structure is built up very comfortably from six five-membered rings, the chemical inertness and the rigid cage structure being not unrelated.

It has been gratifying to us to be informed, after completion of our studies, that an independent X-ray study[8] of a heavy atom derivative of GA had arrived at identical conclusions regarding the structure of GA.

Acknowledgements

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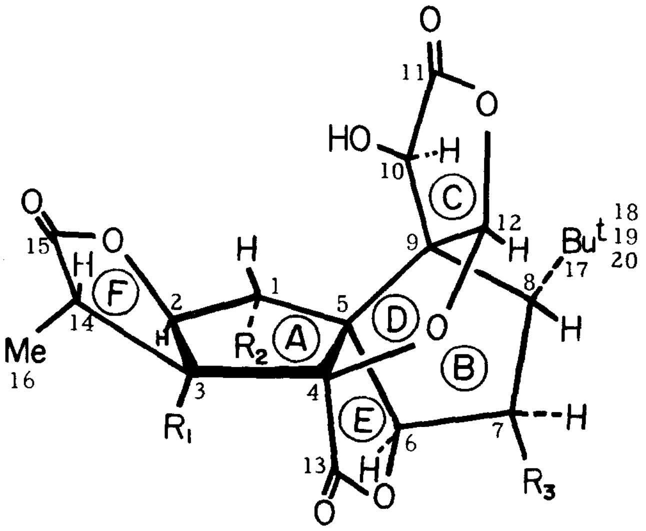
Several ginkgolide derivatives, with and without heavy atoms, had been sent to Professors M. Kakudo and Y. Sasada, Osaka University, and Professor W. N. Lipscomb and Dr. J. W. Moncrief, Harvard University, for X-ray analysis, but none of the crystals sent were suitable, owing to our inappropriate recrystallization techniques or deterioration of crystals in the post; nevertheless, we are grateful to the people mentioned for their interest and preliminary examination of ginkgolide crystals.



	R_1	R_2	R_3
ginkgolide A	OH	H	H
ginkgolide B	OH	OH	H
ginkgolide C	OH	OH	OH
ginkgolide M	H	OH	OH

Fig. 2

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1) Part III. M. Maruyama, A. Terahara, Y. Nakadaira, M. C. Woods and K. Nakanishi, Tetrahedron Letters, this issue.

2) Supported by the National Institutes of Health, Public Health Service Research Grant No. CA08394.

3) Part I. M. Maruyama, A. Terahara, Y. Itagaki and K. Nakanishi, Tetrahedron Letters, this issue.

4) Part II. M. Maruyama, A. Terahara, Y. Itagaki and K. Nakanishi, Tetrahedron Letters, this issue.

5) Dehydro-GA 2 is rapidly transformed into photodehydro-GA 8, by either leaving a solution or a spot on a TLC plate in the light; in the latter case the conversion is complete after 4 hours.

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8) Private communication from Dr. N. Sakabe, Nagoya University: N. Sakabe, et al., submitted for publication to Chem. Comm. We are grateful to Dr. Sakabe for this information prior to publication.