Tetrahedron Letters No.4, pp. 303-308, 1967. Pergamon Press Ltd. Printed in Great Britain.

THE GINKGOLIDES. II[1, 2].

DERIVATION OF PARTIAL STRUCTURES

M. Maruyama, A. Terahara, Y. Itagaki and K. Nakanishi

Department of Chemistry, Tohoku University, Sendai, Japan.

(Received 25 October 1966)

The ginkgolides, GA, GB, GC and GM, which have been shown[1] to be hexacyclic $C_{20}H_{24}O_{9-11}$ compounds containing a tert-Bu grouping and three lactone rings and differing only in the position and number of their hydroxyl groups, give rise to relatively uncomplicated NMR spectra[3] (Fig. 1). A straightforward comparison of their spectra suggested the presence of five isolated proton systems (shown in Table 1) connected by intervening quaternary carbon atoms.

From the reactions outlined in the following sections it is possible to extend the arrangements of protons shown in Table 1 to the partial structures 1 (Fig. 2), 8 (Fig. 3), and 16 (Fig. 4)*, and finally to show that in GA the partial structures 8 and 16 must be combined together in either arrangement I or II.

Rings F/A (Fig. 2) The presence of part-structure 1 in GC was established by the following series of reactions. GC is readily converted into monoacetyl dianhydro-GC monomethyl ether, the spectroscopic properties of which are fully consistent with part-structure 2[4]; hydrogenation followed by methylation afforded the hydrogenolysis product with part-structure 3, which upon ozonolysis gave the F-nor ketone (4) with IR absorption at 1745 cm^{-1}, thus establishing

TABLE 1. The isolated proton systems. The various protons are indicated by the letters A-J and M; plus sign denotes presence of the tert-Bu, sec-Me or the proton in question.

	tert-Bu	Me-C—C—C——C						C——C——C				C-OH	C
		Me	H_A	H_M	H_B	H_C	H_D	H_E	H_F	H_G	H_H	H_I	H_J
GA	+	+	+	OH	+	+	+	+	+	+	+	+	+
GB	+	+	+	OH	+	+	OH	+	+	+	+	+	+
GC	+	+	+	OH	+	+	OH	+	+	OH	+	+	+
GM	+	+	+	+	+	+	OH	+	+	OH	+	+	+

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* In Figs. 2 to 5, carbons drawn as ■ are fully substituted.

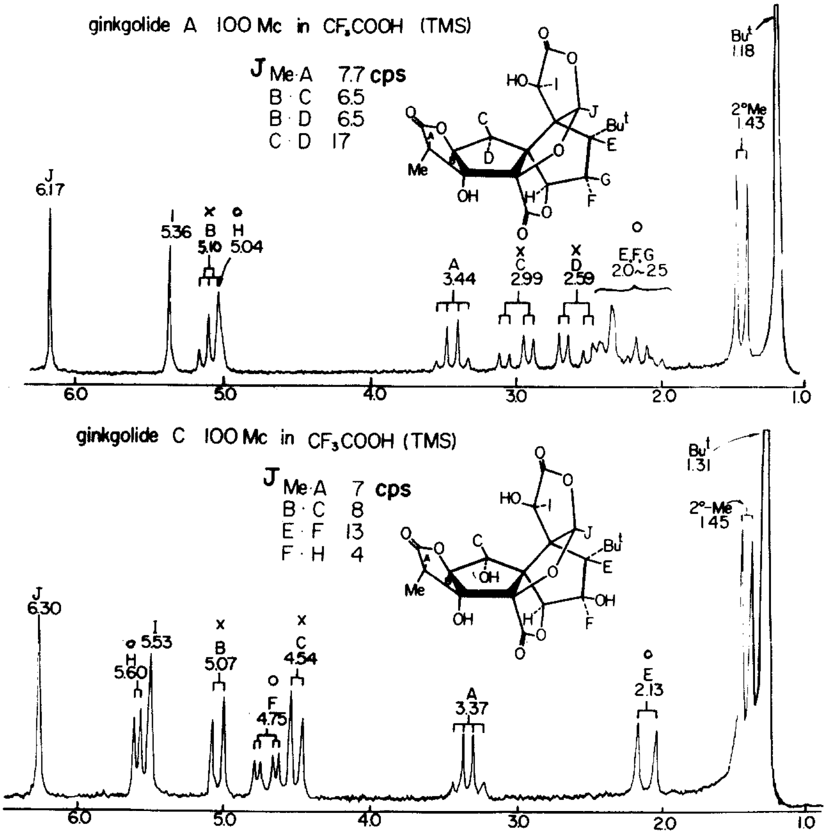


Fig. 1

that ring A is five-membered. GB was also readily converted into a dianhydro derivative. On the other hand, GA (5) which lacks the secondary OH on ring A, afforded monoanhydro-GA monoacetate (6) under similar acetylating conditions.

Lithium aluminum hydride reduction of GA followed by pyrolysis of the product yielded the so-called "GA triether" (in fact a tetraether) a compound which played an extremely important role in the present studies. Its complicated NMR was fully analysed and the assignments were confirmed by comparing the spectrum with that of its deuterated analog (Fig. 1 in Part V[5]). It is clearly shown[5] that the only changes induced by this reaction sequence are straightforward reductions of all three lactone carbonyl groups to methylene groups involving no skeletal rearrangement. Thus, the part-structure 5 (rings F/A of GA) has become the part-structure 7[6] in " GA triether" ; protons f and f' appear as an AB type quartet further split by coupling with proton A.

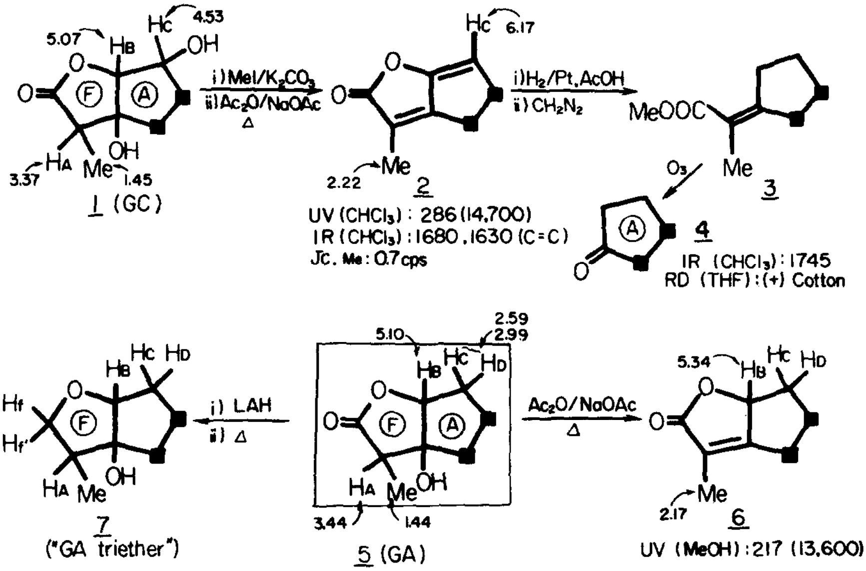


Fig. 2.

Protons E, F, G and H (Ring B) (Fig. 3) The NMR signals due to the isolated four-proton system E-H in GA and GB (both with part-structure 8) could not be fully analysed because of the overlap of signals due to protons E-G; however, proton G is fortunately replaced by a hydroxyl in GC (10), enabling the arrangement $-CH_H-CH_FOH-CH_E-$ to be readily derived from the NMR. Oxidation of GC yielded the ketone with part-structure 11 absorbing at 1770 cm^{-1} and from this it is obvious that ring B is five-membered[7].

The low-field position of the proton H signal (5.04-5.73 ppm) in the four ginkgolides obviously requires this proton to be α to an oxygen atom: it cannot be adjacent to a lactone carbonyl since in "GA triether" (loc. cit.) (9)[5] the proton H signal is not coupled to any of the newly introduced CH_2 groups. Furthermore, in "GA triether" (9) proton H (at 4.09 ppm; $CDCl_3$) shifts 0.55 ppm up-field from its position (4.64 ppm; $CDCl_3$) in GA dimethyl ether, thereby indicating that proton H in the ginkgolides is α to the oxygen end of a lactone, as shown in part-structures 8 and 10.

Protons I and J and the hydroxy-lactone (Ring C) (Fig. 4) Treatment of GA (12) with strong chromic acid resulted only in oxidation of the hydroxyl α to proton I to afford dehydro-GA (13) in more than 70% yield. Dehydro-GA[8] shows complex UV and RD curves which clearly

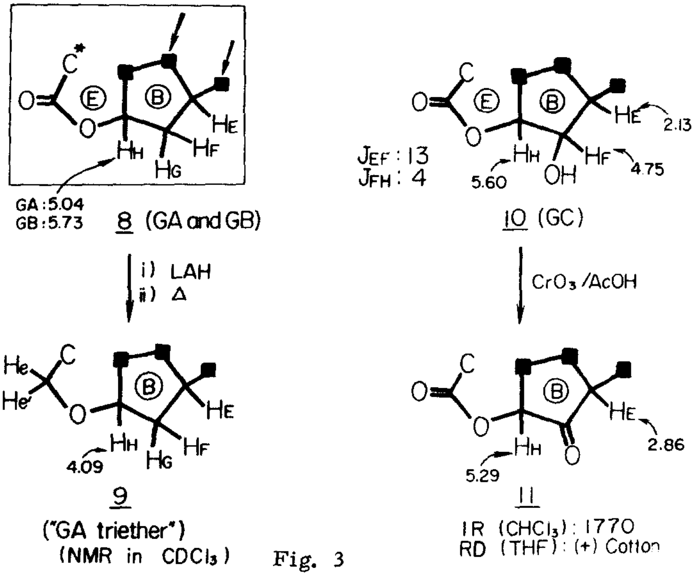


Fig. 3

indicate that an α-dicarbonyl function has been formed; thus GA contains an α-hydroxylactone group which is oxidized to a keto-lactone. This conclusion received further support from the following observations with "GA triether" (loc. cit.) (14): (i) splitting of the NMR signal of H_I in $CDCl_3$ and DMSO-d_6[5]; (ii) a clear M-60 peak in the mass spectrum.

Finally, ring C is five-membered because oxidation of "GA triether" (14) gave dehydro-"GA triether" (15) with an IR band at 1748 cm^{-1}.

Since the substitutents on the carbons marked * attached to the lactones in partial structures 8 (Fig. 3) and 12 (Fig. 4) have not been defined, it is possible that these two lactones are one and the same. That these lactones are in fact not the same can be shown as follows. Alkali fusion of GA (16) gave bisnor-GA[9] (17) through loss of a two carbon unit which was identified in the form of oxalic acid. Bisnor-GA, $C_{18}H_{24}O_7$, which is a hemiacetal oxidizable to a trilactone (18), has only two lactone rings (from titration) and these must be the lactones in rings F and E, since the NMR signals arising from proton A, protons B-D (5, Fig. 2) and protons H-E (8, Fig. 3) are essentially the same in both GA and bisnor-GA. It is therefore apparent that the lactone in ring C is the one destroyed by alkali fusion.

Thus GA has been shown to contain the part-structures 5, 8 and 12, and these define the substituents on all carbons bearing oxygen functions with the exception of the two carbons

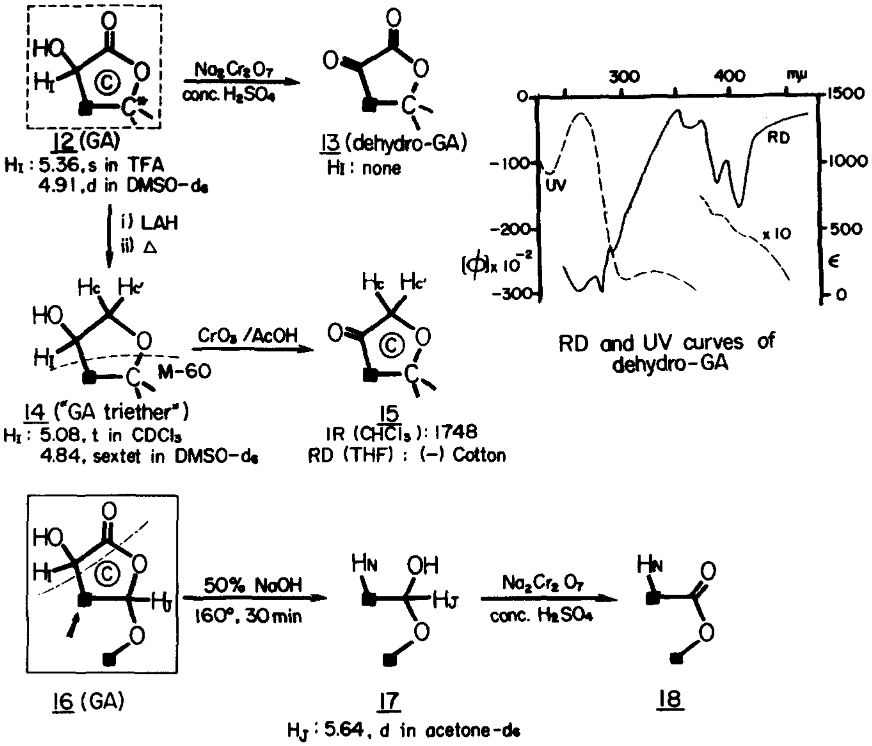
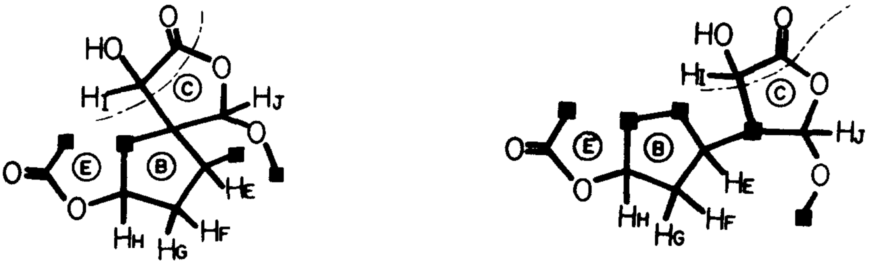


Fig. 4

marked * and those bearing the remaining ether oxygen. The appearance of proton J as a low-field sharp singlet, both in $CDCl_3$ and in DMSO-d_6, at ca. 5.6 ppm in the NMR of "GA triether" [5] (loc. cit.), which contains no carbonyl group, requires H_J to be attached to a carbon bearing two ether oxygens in the triether; since the only change in going from GA to "GA triether" lies in the reduction of lactone carbonyls to methylenes; this conclusion applies to GA as well. Hence the only way in which to accomodate proton J is to attach it to the C^* in 12, and to extend 12 to 16.

The linking of partial structures 8 and 16 (Fig. 5) Bisnor-GA (17) is informative in that it is the only derivative that has a proton (N) strongly coupled to a proton (E) in the hitherto isolated proton system E-H, J_{NE} being ca. 9 cps.

Accordingly, the blocked carbon in ring C (16, marked with an arrow) must be identical with one of the blocked carbons adjacent to proton E (8, marked with arrows), and this leads to the two possibilities I and II depicted in Fig. 5. In further confirmation of these two partial structures, proton N is weakly coupled to proton J.



I

II

Fig. 5

REFERENCES AND FOOTNOTES

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

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

3) Unless otherwise stated, all NMR data refer to trifluoroacetic acid solutions.

4) All derivatives quoted gave satisfactory elemental analyses. The minimum of data with a direct bearing on the derivation of the particular part-structures are given in Figs. 2-5; minor structural variations (e. g. OH to OMe or OAc) which may have occurred in the part of molecule not shown in the part-structures have been ignored since they do not affect the argument.

5) Part V. M. C. Woods, I. Miura, Y. Nakadaira, A. Terahara, M. Maruyama and K. Nakanishi, Tetrahedron Letters, this issue.

6) Protons introduced by reduction of the lactone carbonyls to methylenes by the LAH treatment are indicated by lower case letterings.

7) The relatively high position of the five-membered ketone IR band appears to be due to puckering of ring B induced by the bulky tert-Bu group (Fig. 3 in Part V[5]).

8) The ease with which this compound undergoes photorearrangement, even in sunlight (Part IV[9]), makes it essential to work with freshly prepared samples.

9) Part IV. M. Maruyama, A. Terahara, Y. Nakadaira, M. C. Woods, Y. Takagi and K. Nakanishi, Tetrahedron Letters, this issue.