

Table I. ^{31}P Nmr Data of ML_3 and ML_4 Complexes

Complex	Chemical shift, ^a ppm	$J_{^{31}\text{P}-^{195}\text{Pt}}$, Hz
$\text{Pt}[\text{P}(\text{C}_2\text{H}_5)_3]_3$	-42	4220
$\text{Pt}[\text{P}(p\text{-C}_6\text{H}_4)_3]_3$	-51	4340
$\text{Pt}[\text{P}(\text{C}_2\text{H}_5)_3]_4$	+17	3740
$\text{Pt}[\text{P}(p\text{-C}_6\text{H}_4)_3]_4$	-11	3780
$\text{Ni}[\text{P}(\text{C}_2\text{H}_5)_3]_4$	-3	

^a Relative to external 85% H_3PO_4 .

change is rapid in solutions of PtL_4 at room temperature, and no Pt-P coupling is observed.

Tris(triethylphosphine)platinum(0) is an extraordinarily strong nucleophile and undergoes a wide range of oxidative-addition reactions. For example, addition of benzonitrile to a refluxing toluene solution of the tris complex gives within 15 min a high yield of *trans*- $\text{C}_6\text{H}_5\text{Pt}(\text{CN})[\text{P}(\text{C}_2\text{H}_5)_3]_2$. Under similar conditions, the carbon-chlorine bond in chlorobenzene is cleaved with concomitant formation of *trans*- $\text{C}_6\text{H}_5\text{PtCl}[\text{P}(\text{C}_2\text{H}_5)_3]_2$. In contrast, the tris-triphenylphosphine complex does not react with benzonitrile or chlorobenzene under these conditions.⁸ These comparisons demonstrate the qualitatively different reactivities of aryl- and alkylphosphine complexes of platinum(0). Like the arylphosphine complexes, the alkyl analogs react with alkyl and allyl halides. We found that tris(triethylphosphine)platinum(0) reacts vigorously with allyl chloride at 25° to give $\{(\pi\text{-C}_3\text{H}_5)\text{Pt}[\text{P}(\text{C}_2\text{H}_5)_3]_2\}^+$, which was isolated as the tetrafluoroborate salt.

Hydrogen adds readily to the alkylphosphine-platinum complexes to give five-coordinate hydrides. For example, the tris(triethylphosphine)platinum complex, in hydrocarbon solution, absorbed hydrogen at 25° to give $\text{H}_2\text{Pt}[\text{P}(\text{C}_2\text{H}_5)_3]_3$. This novel hydride is thermally unstable and decomposes within several days on standing in hydrocarbon solvent at -40°. In solution this hydride shows a single platinum-hydrogen infrared stretching frequency at 1766 cm^{-1} . The 220-MHz proton nmr spectrum of the hydride region at -50° consists of a quartet at τ 23.37 ($J_{\text{PtH}} = 18$ Hz) with ^{195}Pt satellites ($J_{\text{PtH}} = 635$ Hz). The spectrum is temperature dependent. On warming, the platinum-hydrogen coupling is lost above $\sim -30^\circ$, and the spectrum consists of three broad resonances with chemical shifts and platinum-hydrogen coupling constants substantially unchanged from those found at -50°. With increasing temperature, the three lines sharpen and remain sharp to 80°. The ligand-proton-decoupled ^{31}P nmr spectrum at -60° consists of a triplet ($J_{\text{PH}} = 18$ Hz) with ^{195}Pt satellites ($J_{\text{PtP}} = 3060$ Hz). These spectral data are consistent with, but do not define, a trigonal-bipyramidal structure with the hydrogen nuclei at axial positions. The temperature dependence of the hydride spectrum indicates that above -30° ligand dissociation is rapid through a four-coordinate complex, $\text{H}_2\text{Pt}[\text{P}(\text{C}_2\text{H}_5)_3]_3$, present at very low concentrations.

species.⁷ In the silver system, the ratio of metal-phosphorus coupling constants in the tris and tetrakis complexes was about 3:4. This ratio in the platinum series is substantially larger.

(7) E. L. Muetterties and C. W. Alegranti, *J. Amer. Chem. Soc.*, **92**, 4114 (1970).

(8) Only very reactive organohalides oxidatively add to $\text{Pt}(\text{C}_6\text{H}_5)_3$.⁹

(9) J. P. Birk, J. Halpern, and A. L. Pickard, *J. Amer. Chem. Soc.*, **90**, 4491 (1968); *Inorg. Chem.*, **7**, 2672 (1968).

For this dissociation process, the free energy of activation is ~ 12 kcal/mol.

The marked basicity of $\text{Pt}[\text{P}(\text{C}_2\text{H}_5)_3]_3$ is well delineated by its interaction with ethanol and water. The tris complex dissolves in both solvents to form the previously reported^{10,11} cationic hydride, $\text{HPt}[\text{P}(\text{C}_2\text{H}_5)_3]_3^+$ which was isolated as the hexafluorophosphate salt by addition of ammonium hexafluorophosphate to the aqueous reaction mixture. The reaction of the tris complex with water is reversible; the tris complex was recovered by simple evaporation of the water.

We find some parallel to the reactivity of $\text{Pt}[\text{P}(\text{C}_2\text{H}_5)_3]_4$ in the chemistry of $\text{Ni}[\text{P}(\text{C}_2\text{H}_5)_3]_4$.¹² This complex, an off-white crystalline compound, was formed almost quantitatively by reaction of bis(1,5-cyclooctadiene)nickel(0) with triethylphosphine. It dissolved in hydrocarbon solvents with ligand dissociation to give intensely purple solutions of $\text{Ni}[\text{P}(\text{C}_2\text{H}_5)_3]_3$. This tris complex reacted smoothly with chlorobenzene and with benzonitrile at room temperature to give the corresponding *trans*- $\text{C}_6\text{H}_5\text{NiX}[\text{P}(\text{C}_2\text{H}_5)_3]_2$ compounds.¹³ Work is in progress to examine other aspects of reactive d^{10} complexes of Ni, Pd, and Pt.

(10) M. J. Church and M. J. Mays, *J. Chem. Soc. A*, 3074 (1968).

(11) The proton nmr data are in accord with the previously reported data.¹⁰ The noise-decoupled ^{31}P spectrum of the ethanol solution of the tris complex was found to consist of a doublet ($\delta - 18$ ppm, $J_{\text{PP}} = 19$ Hz, $J_{\text{P,P}} = 2476$ Hz) and a triplet ($\delta - 14$ ppm, $J_{\text{P,P}} = 2003$ Hz) with relative intensities of 2:1.

(12) C. S. Cundy, Ph.D. Thesis 1969, University of Bristol.

(13) Similar oxidative additions of chlorobenzenes have been reported for $\text{Ni}(\text{C}_2\text{H}_4)[\text{P}(\text{C}_2\text{H}_5)_3]_2$.¹⁴

(14) D. H. Fahey, *J. Amer. Chem. Soc.*, **92**, 402 (1970); J. E. Dobson, R. G. Miller, and J. P. Wiggins, *ibid.*, **93**, 554 (1971).

(15) Contribution No. 1807.

D. H. Gerlach, A. R. Kane, G. W. Parshall
J. P. Jesson, E. L. Muetterties*

Central Research Department¹⁵

E. I. du Pont de Nemours and Company
Experimental Station, Wilmington, Delaware 19898

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Structure of Bilobalide, a Rare *tert*-Butyl Containing Sesquiterpenoid Related to the C_{20} -Ginkgolides

Sir:

Extraction of a sesquiterpene closely related to the diterpenoid ginkgolides^{1,2} from leaves of *Ginkgo biloba* ("fossil tree") was first reported in 1967³ and then in 1969 (bilobalide).⁴ Structure **1** deduced for this bilobalide shows that it is a unique trilactone sesquiterpene having a *tert*-Bu group, which so far has been encountered only in the ginkgolides (*cf.* **10**).

(1) (a) K. Nakanishi, *Pure Appl. Chem.*, **14**, 89 (1967); (b) M. Maruyama, A. Terahara, Y. Itagaki, and K. Nakanishi, *Tetrahedron Lett.*, 299 (1967); (c) M. Maruyama, A. Terahara, Y. Itagaki, and K. Nakanishi, *ibid.*, 303 (1967); (d) M. Maruyama, A. Terahara, Y. Nakadaira, M. C. Woods, and K. Nakanishi, *ibid.*, 309 (1967); (e) M. Maruyama, A. Terahara, Y. Nakadaira, M. C. Woods, Y. Takagi, and K. Nakanishi, *ibid.*, 315 (1967); (f) M. C. Woods, I. Miura, Y. Nakadaira, A. Terahara, M. Maruyama, and K. Nakanishi, *ibid.*, 321 (1967); (g) M. Maruyama and A. Terahara, *Sci. Rep. Tohoku Univ., Ser. 1*, **50**, 92 (1967); (h) Y. Nakadaira, Y. Hirota, and K. Nakanishi, *Chem. Commun.*, 1467 (1969); (i) *ibid.*, 1469 (1969); (j) see also N. Sakabe, S. Tadada, and K. Okabe, *ibid.*, 259 (1967).

(2) K. Nakanishi, and K. Habaguchi *J. Amer. Chem. Soc.*, **93**, 3546 (1971).

(3) R. T. Major, *Science*, **157**, 1270 (1967).

(4) K. Weinges and W. Bähr, *Justus Liebig's Ann. Chem.*, **724**, 214 (1969).

Table I. Nmr Data of Pertinent Compounds^a

	<i>tert</i> -Bu	H _C	H _D	H _F	H _G	H _H	H _I	OH _X	OH _Y	H _J
1	1.19 s	2.78 d (CD 18)	3.12 d	2.30 dd (FG 13.5, FH = GH = 7.0)	2.72 dd	4.98 t	5.33 d (IX 4)	6.43 d	4.55 s	6.32 s
2 ^b	1.19 s	2.76 d (CD 18)	3.12 d	2.17 dd (FG 14.0, FH = GH = 7.0)	2.85 dd	5.12 t	6.38 s		4.76 s	6.57 s
3 ^c	1.19 s	3.25 s	3.25 s	2.92 dd (FG 15.5, FH 7, GH 5)	2.83 dd	4.70 dd	5.89 s (IJ 0.4)			6.92 s (IJ 0.4)
4 ^d	1.35 s	3.19 d (CD 18)	2.84 d	6.31 d (FH 2.8)		5.25 d	6.91 s			6.61 s

^a In acetone-*d*₆, parts per million from TMS, *J* values in parentheses. ^b OAc at 2.17. ^c OAc at 2.11 and 2.24. ^d OAc at 2.03.

Bilobalide (1)⁵ [mp above 300°; C₁₅H₁₈O₈ (M⁺ 326, after deuteration M⁺ 328); [α]_D²⁰₅₇₈ -64.3° (*c* 2, acetone); ir (KBr) 3400–3500, 1810, 1745, 1780 cm⁻¹] titrates for a trilactone (2.64) under conditions developed during the ginkgolide studies.^{1b} Acetylation with acetic anhydride and pyridine gave the monoacetate 2, mp 274–278°, [α]_D²⁰₅₇₈ -66.6° (*c* 2, acetone), and diacetate 3, mp 235–238° (an uncharacterized isomeric diacetate, mp 255° dec, was also formed). Acetylation with acetic anhydride and a trace of concentrated sulfuric acid gave the anhydro monoacetate 4, oil. Some nmr data are given in Tables I and II.

Table II. NOE Measurements^a

	1	3	4
[<i>tert</i> -Bu] I	30	33	24
[<i>tert</i> -Bu] J	24	19	24
[<i>tert</i> -Bu] OH _Y	20		
[<i>tert</i> -Bu] F			14
[H _F] H	11		
[H _I] OH _X	20		

^a Reference 1f; in acetone-*d*₆; given in per cent increase in intensity of observed proton when signal in parentheses is saturated.

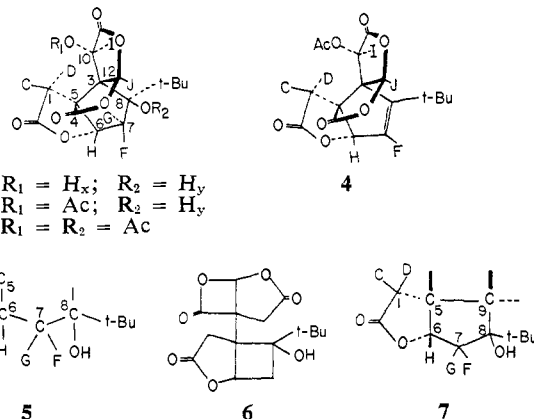
The *sec*- and *tert*-hydroxyls (Table I, OH_X and OH_Y) and three lactones account for all eight oxygens, while the sharp nine-proton singlet (*W*_{1/2} less than 1 Hz) and intense *m/e* 57 peaks in all mass spectra establish the existence of *tert*-Bu.^{1b} The molecular formula requires the presence of one carbocyclic ring or double bond in addition to the three lactones.

Part structure 5 is based on the following reasoning. (i) Protons F, G, and H (attached to C-7 and C-6)⁶ comprise an AMX system. (ii) In the anhydro derivative 4, the *tert*-Bu and proton H are shifted downfield, and moreover, a 14% NOE^{1f} is observed between the *tert*-Bu and proton F. Hence, the adjacent C-8 bears *tert*-OH and *tert*-Bu groups. (iii) Proton H is joined to the oxygen terminal of a lactone as judged from its chemical shift (*cf.* proton H in similar environments in ginkgolides absorbs around 5 ppm).^{1c,g} Also the carbon to which it is bonded, C-5, is most likely quaternary since H_H is only spin coupled to H_F and H_G.

Part structure 5 can next be expanded to 7 in the following manner. There are nine carbons in 5, while the two remaining lactones and the three carbons bearing protons C/D (C-1), J (C-12), and the *sec*-OH (C-10) account for five additional carbons. As there

(5) Elementary analyses of compounds quoted, excepting 4 which was an oil and not analyzed, checked with their compositions.

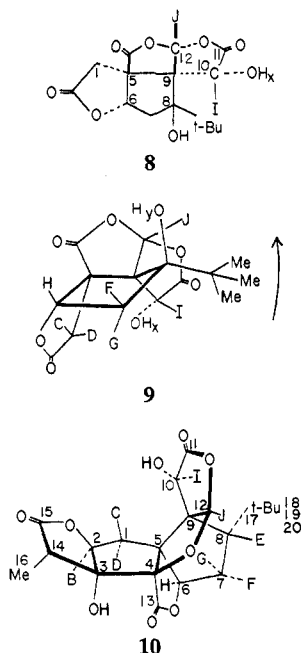
(6) For the sake of convenience, the alphabetical notation of protons and numbering of carbons employed in the text and structures correspond to those in the ginkgolides 10.¹



is only one more carbon to be identified, the presence of a double bond is ruled out and a carbocyclic ring must be present; furthermore, this last carbon (C-9) is quaternary because all protons in the nmr have been characterized. It is readily shown that the ring is five membered and that it incorporates C-5 to C-8 in 5. Namely, if C-5 were linked to C-8 to form a cyclobutane, the resulting skeletons would all have a strained β-lactone, *e.g.*, 6, which is not compatible with the ir. The ring is therefore a cyclopentane. Moreover, the fifth carbon bonded to C-5 and C-8 in 5 should be the remaining quaternary carbon, C-9; if this was not the case and the fifth carbon were any of the remaining carbons, C-1, C-10, or C-12, the derived structures all have highly strained β-lactones or more impossible skeletons.

A most crucial finding was the fact that the *tert*-Bu is responsible for relaxations of H_I and H_J in both bilobalide (1) and in the anhydro derivative 4, in which flexibility of the cyclopentane ring is severely restricted. Molecular models showed that this simply required H_I and H_J to flank the *tert*-Bu and that all rigid bilobalide structures containing bridged to trans-fused lactones could be eliminated; *i.e.*, the lactones are all five membered and *cis* fused.

The large *J*_{CD} of 18 Hz suggests that this methylene group (C-1) is connected to a carbonyl group. In addition, the NOE's of H_I and H_J resulting from *tert*-Bu irradiation require both these protons to be close to the *tert*-Bu and hence they cannot be linked to the lactone carbon in 5. Namely, only C-1 can be linked to this lactone, and this leads to partial structure 7. The H_J singlet, which characteristically appears at a very low field, shows that similar to the ginkgolides (H_J at *ca.* 6.3 ppm^{1a,c,g}), H_J is flanked between the oxygen terminals of the two remaining lactones; structure 7 therefore becomes 8, which is complete except for the C-8 configuration.



In order for the *tert*-Bu group to be sufficiently close to both H_I and H_J in **1** and diacetate **3** (to account for NOE's), the cyclopentane ring must be puckered so that the *tert*-Bu is quasiequatorial,^{1f} and of the two possible arrangements, *tert*-Bu cis or trans to H_H , only the trans arrangement can account for the observed J_{HF} and J_{HG} (ca. 7 Hz) (see **9**; in the opposite configuration, the cyclopentane would be puckered downward^{1f} and adopt a conformation in which these J values cannot be both large). The structure thus derived bears a striking resemblance to the diterpenoid ginkgolides, e.g., ginkgolide A, **10**.^{1,2} The absolute configuration is based on that of the latter.^{1a,e}

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(7) Address correspondence to this author at: Department of Chemistry, Columbia University, New York, N. Y. 10027.

K. Nakanishi,*⁷ K. Habaguchi, Y. Nakadaira
M. C. Woods, M. Maruyama

Department of Chemistry, Tohoku University
Sendai, Japan

R. T. Major, M. Alauddin, A. R. Patel
Department of Chemistry, University of Virginia
Charlottesville, Virginia 22901

K. Weinges, W. Bähr
Institute of Organic Chemistry, University of Heidelberg
69 Heidelberg, West Germany

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Biosynthesis of Ginkgolide B, Its Diterpenoid Nature, and Origin of the *tert*-Butyl Group

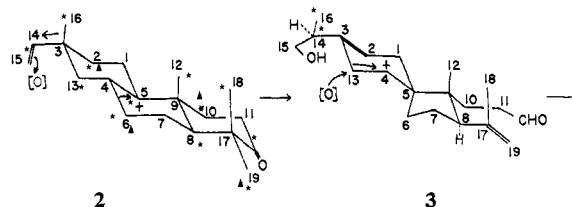
Sir:

Ginkgo biloba ("icho" in Japanese), an extraordinary plant which has remained unchanged during the past several million years, is the only living species of the order Ginkgoales (ancestry traced back to Jurassic

period). The ginkgolides¹ and bilobalide² isolated from the root bark and leaves of this tree are not only very unique cage molecules containing three lactone rings, but are still the only natural products having a *tert*-Bu group.³ Because of their complex framework, it is not immediately obvious to which category of compounds they belong, and ginkgolides have even been classified as being carbohydrates.

In the following we present biosynthetic evidence for their terpenoid origin, the formation of the *tert*-Bu group, and the general biosynthetic route (Scheme I)

Scheme I. Biosynthesis of Ginkgolide B (**1**)^a



^a The origins of carbon atoms are denoted as follows: acetate, *; mevalonate, \blacktriangle ; methionine, \bullet . The numbering system in **2** corresponds to that in **1**.

which is in accord with the stereochemistry of pertinent chiral centers.

Biosynthetic studies were attempted by tissue culture techniques first developed for *G. biloba* by Tulecke.⁴ A total of 11 different media were tested under a variety of growth periods, and although we succeeded in inducing callus growth⁵ from both root and shoot tissues, there was no biosynthesis of ginkgolides. On the other hand, usage of embryos⁶ was partially successful. Namely, embryos from 5-month old seeds were inoculated in agar medium containing suitable nutrients⁵ and [2-¹⁴C]mevalonate; several days later the short roots and shoots were separately processed after addition of cold ginkgolide. Although radioactive ginkgolides could indeed be isolated from young roots, the incorporation yield was only 0.01% at the highest (4–10 days after inoculation), and moreover, the method was far too tedious for practical purposes.

Accordingly, the cotton wick method was finally employed (Table I). After suitable incorporation periods, cold ginkgolide B (**1**) (GB, the only detectable ginkgolide under the experimental conditions) was added, and the GB was purified by column chromatography, tlc, and repeated recrystallizations until constant specific activity was attained. In the case of sodium [2-¹⁴C]acetate (indicated in Scheme I by *) the final GB obtained had 8.90×10^3 dpm/mmol (40 mg).

(1) (a) K. Nakanishi, *Pure Appl. Chem.*, **14**, 89 (1967); (b) M. Maruyama, A. Terahara, Y. Itagaki, and K. Nakanishi, *Tetrahedron Lett.*, 299 (1967); (c) M. Maruyama, A. Terahara, Y. Itagaki, and K. Nakanishi, *ibid.*, 303 (1967); (d) M. Maruyama, A. Terahara, Y. Nakadaira, M. C. Woods, and K. Nakanishi, *ibid.*, 309 (1967); (e) M. Maruyama, A. Terahara, Y. Nakadaira, M. C. Woods, Y. Takagi, and K. Nakanishi, *ibid.*, 315 (1967); (f) M. C. Woods, I. Miura, Y. Nakadaira, A. Terahara, M. Maruyama, and K. Nakanishi, *ibid.*, 321 (1967); (g) M. Maruyama and A. Terahara, *Sci. Rep. Tohoku Univ., Ser. 1*, **50**, 92 (1967); (h) Y. Nakadaira, Y. Hirota, and K. Nakanishi, *Chem. Commun.*, 1467 (1969); (i) *ibid.*, 1469 (1969); (j) see also N. Sakabe, S. Tadada, and K. Okabe, *ibid.*, 259 (1967).

(2) K. Nakanishi, K. Habaguchi, Y. Nakadaira, M. C. Woods, M. Maruyama, R. T. Major, M. Alauddin, A. R. Patel, K. Weinges, and W. Bähr, *J. Amer. Chem. Soc.*, **93**, 3544 (1971).

(3) See the following for a general description of insect repellent properties of *G. biloba*: R. T. Major, *Science*, **157**, 1270 (1967).

(4) W. Tulecke, *Phytomorphology*, **17**, 381 (1967), and earlier papers.

(5) K. Habaguchi, to be published elsewhere.

(6) E. Ball, *Amer. J. Bot.*, **46**, 130 (1959).