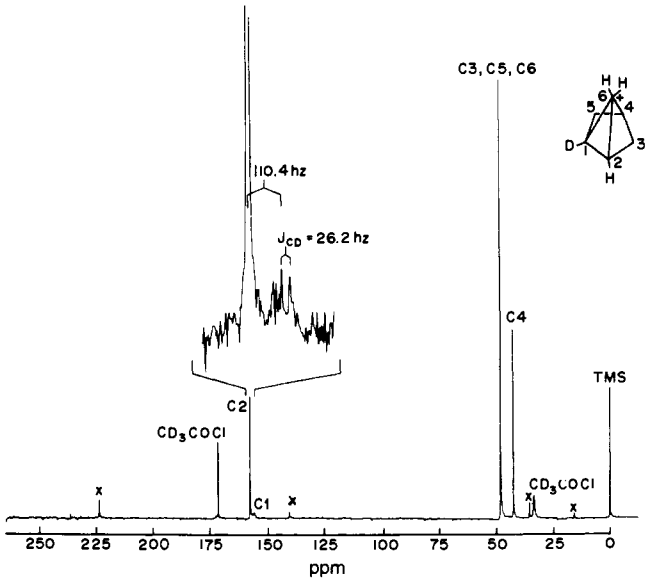


**Figure 1.** 67.9-MHz $^{13}C$ NMR spectrum of II at 115 °C. Cyclohexenyl cation peaks are marked x.

**Table I.** Relative Isotopic Splittings ($\delta/\Delta$)

| Compd | $T$, °C | $\delta$ per D, ppm | $\Delta$, ppm | $\delta/\Delta$ per D |
|---|---|---|---|---|
| III[a] | 109 | 46.9 | 261 | 0.18 |
| IV[a] | 110 | 22.1 | 261 | 0.085 |
| VII[b] | 111 | 11 | 261 | 0.042 |
| V[a] | 119 | 6.4 | 202 | 0.032 |
| II | 115 | 1.18 | 200 | 0.0058 |
| VI[c] | 110 | 0.33 | 94 | 0.0035 |

[a] Reference 2. [b] Unpublished results. [c] Reference 1.

equilibrium (double minimum energy surface), while small values are characteristic of isotopic perturbation of resonance (single minimum or intrinsically symmetric cases).

We have prepared 2-deuterio-2-bicyclo[2.1.1]hexyl cation as previously described.[3,8] In the 67.9-MHz $^{13}C$ NMR spectrum[9] (Figure 1), $C_1$ and $C_2$ appear as a singlet and triplet ($J_{C-D}$ = 26.2 Hz) separated by 110 Hz (1.63 ppm). In the $^{13}C$ NMR spectrum of a 1:5 mixture of I and II, the triplet of the deuterio carbon is not visible, but the $C_1$ singlet appears 33 Hz downfield from the averaged absorption of $C_1$ and $C_2$ in I. The resonance of I is not exactly between the peaks of the deuterated species, because of intrinsic $\alpha$- and $\beta$-deuterium isotope shifts.[1] $\beta$-Deuterium shifts are typically 0.1 ppm upfield;[10] thus the splitting can be corrected by adding 0.1 ppm (7 Hz); so we obtain $\delta = 2(33 + 7) = 80$ Hz, or 1.18 ppm. $\Delta$ can be estimated by taking the value estimated for the dimethylnorbornyl cation, 202 ppm;[1] so $\delta/\Delta = 0.0058$.

When I was prepared with a dideuteriomethylene, the undeuterated methylene carbon was shifted 0.94 ppm downfield from the methylene peak of undeuterated I. The methine carbons gave, as expected, a single peak. The observed shift necessarily reflects an equilibrium isotope effect for *either* the classical or the bridged structure, but we cannot tell which structure is consistent with the observed shift, because we are unable to estimate $\Delta$. For the bridged ion, we have no adequate model for chemical shifts; for the classical structure, 2-methylbicyclo[2.1.1]hexyl cation would be an acceptable model but the two types of methylenes are reported to have the same $^{13}C$ NMR shift.[6] If we *could* estimate $\Delta$, then $K = (\Delta + 3\delta)/(\Delta - 6\delta)$.

In Table I are values of $\delta/\Delta$ for several systems. The largest value is for III; IV and VII have progressively smaller values because of preferential hyperconjugation with the methylene protons in these two systems;[2] hence the effect of methyl deuteration is reduced relative to methylene deuteration. The still smaller $\delta/\Delta$ obtained for V is explained similarly, but here delocalization[1,11,12] probably decreases $\Delta$ *as well.*

The relative splitting for V, though the smallest value observed for an unequivocal equilibrium isotope effect, is still a factor of 10 larger than that for VI where the splitting reflects perturbation of resonance. That $\delta/\Delta$ for II is also an order of magnitude smaller than the values for III–V and VII is strong evidence that we are observing, not an equilibrium isotope effect, but isotopic perturbation of resonance in the $^{13}C$ NMR spectrum of II.[13] In other words, *the relative splitting indicates that the structure of II is extensively $\sigma$-delocalized.*

Even if our estimate of $\Delta$ is incorrect, the relative splitting for II remains considerably smaller than that of VI, unless one sets $\Delta$ to less <50 ppm ($\delta/\Delta = 0.024$). This is equivalent to concluding that I is highly $\sigma$-delocalized.

**Acknowledgment.** We should like to thank the NSF for the support of this work through grants to M.S. and K.B.W. (CHE-7519380). The NMR spectra were obtained using the Southern New England High Field NMR facility supported by a grant from the Biotechnology Resources Program of the National Institutes of Health (RR0798).

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(13) While the deuterium in II cannot participate in hyperconjugation, as can those in III–V and VII, we nevertheless feel that there would be a substantial isotope effect in the $^{13}C$ NMR of II were it an equilibrating pair of ions. See note 11, ref 1.

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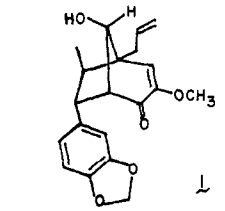
*Received May 25, 1977*

## Biomimetic Syntheses of the Neolignans Guianin, Burchellin, 2-Epi,3a-epiburchellin and Futoenone

*Sir:*

Neolignans[1] are a group of secondary plant metabolites structurally characterized by the presence of two arylpropanoid units. In contradistinction to the related lignans the $\beta$ position of one arylpropane moiety is linked to one of three additional positions in the other. Within the class of neolignans substances with bicyclo[1.2.3]octane, hydrobenzofuran and spiro[5.5]-undecane skeleton are encountered. Guianin (**1**)[2] (from *Aniba guianensis* Aubl.), burchellin (**2**)[3] (from *Aniba burchellii* Kosterm.), and futoenone (**4**)[4] (from *Piper futokadzura* Sieb.



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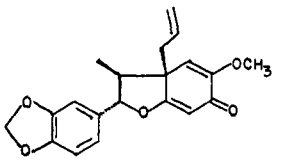

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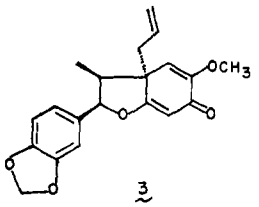

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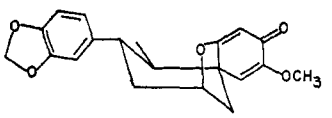

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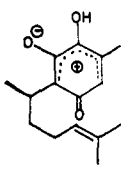
et Zucc.) are representative and their occurrence in nature has been attributed to oxidative coupling of propenyl- and allylphenols either by combination of radicals or ionic intermediates.[1]

Our original plan to synthesize guianin (**1**) by an ionic cycloaddition was based on the remarkable thermolysis of perezone (**5**) to the isomeric pipitzols (**6**)[5] which was postulated[6] and then shown[7] to be a concerted [2 + 4] cycloaddition. Ef-



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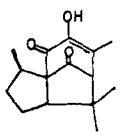

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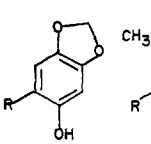
forts to obtain a guianin intermediate by intermolecular addition of 2-hydroxy-, 2-methoxy-, and 2-*N*,*N*-dimethylamino-5-allyl-1,4-benzoquinone to isosafrole failed.[8] Similarly, of the many hydroxyquinone olefin combinations investigated previously elsewhere, only 2-hydroxy-3,6-dimethyl-1,4-benzoquinone combined with *p*-methoxystyrene to give the anticipated adduct in 36% yield.[9]

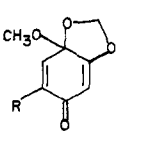
We found cations A derived from the quinone ketals **9, 10** (mp <30 °C), and **11** (mp 70–71 °C) by treatment with Meerwein salts, acids, or silver fluoroborate, respectively, to be much more electrophilic than the corresponding hydroxyquinones and used them for the synthesis of all three types of neolignans.

Oxidation of the phenol **7**[10] with 1 equiv of DDQ in methanol in the presence of a catalytic amount of *p*-nitrophenol (20 °C, 30 min) or with excess $FeCl_3 \cdot 6H_2O$ in methanol containing an equivalent amount of potassium carbonate (20 °C, 1 h) gave the ketal **9** in 88 and 84% yield, respectively: mp 49–50 °C; IR ($CHCl_3$) 1690, 1655, 1630 $cm^{-1}$; UV (95% EtOH) 237 nm ($\epsilon$ 9350), 285 (3200); $^{13}C$ NMR ($CDCl_3$) $\delta$ 187 (s), 168 (s), 99 (t), 51 (q); $^1H$ NMR ($CDCl_3$) $\delta$ 5.63 (s, 2, ketal protons).[11] Condensation of ketal **9** with commercial isosafrole (**12**) (90% *E*, 10% *Z* isomer) in acetonitrile containing 1 equiv of 2,4,6-trinitrobenzenesulfonic acid (0 °C, 75 min) afforded 20% **13** (mp 147–149 °C; IR ($CHCl_3$) 3490, 1765, 1680 $cm^{-1}$) and 27% a mixture of ketone **16** (IR ($CHCl_3$) 1735, 1660 $cm^{-1}$) and its enol **18** (IR ($CHCl_3$) 3480, 1630 $cm^{-1}$). Methyl ether **14** (mp 117–118 °C; IR ($CHCl_3$) 1765, 1695, 1615 $cm^{-1}$) prepared with trimethyloxonium fluoroborate and diisopropyl ethylamine ($CH_2Cl_2$, 20 °C) (90%) on reduction with sodium borohydride ($CH_3OH$, −20 °C) gave racemic guianin (**1**, 83%), mp 162–164 °C. Ultraviolet, infrared, mass, and 270-MHz $^1H$ NMR spectra were indistinguishable from those of natural material.

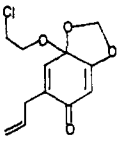
The most efficient preparation of **16**/**18** involved exposure of a mixture of ketal **9** and (*E*)-isosafrole (**12**) to 1 equiv of trifluoromethanesulfonic acid ($CH_2Cl_2$, −70 °C). The resulting mixture of **16** and **18** (33%) was accompanied by the



7 R = allyl
8 R = n-propyl



9 R = allyl
10 R = n-propyl



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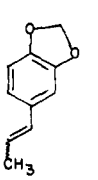

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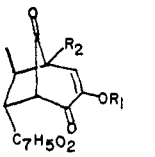
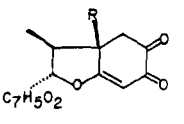
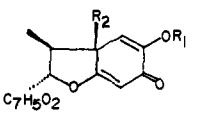


13 $R_1$ = H; $R_2$ = $C_3H_5$
14 $R_1$ = $CH_3$; $R_2$ = $C_3H_5$
15 $R_1$ = H; $R_2$ = $C_3H_7$



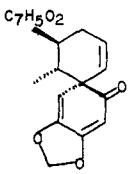
16 R = $C_3H_5$
17 R = $C_3H_7$



18 $R_1$ = H; $R_2$ = $C_3H_5$
19 $R_1$ = $CH_3$; $R_2$ = $C_3H_5$
20 $R_1$ = H; $R_2$ = $C_3H_7$

spiro derivative **21** (18%), mp 168–170 °C $^1H$ NMR $\delta$ 0.61 (d, 3, $J$ = 7 Hz). To complete the synthesis of burchellin (**2**) the mixture of ketone **16** and enol **18** was methylated with methyl iodide and silver(I) oxide (DMF, 20 °C, 20 h) (70%). Infrared and NMR spectra of racemic burchellin (**2**), mp 135 °C were identical with those of natural material and identity was confirmed by chromatographic comparison.

In addition to **21** two other spiro[5,5]undecanes were prepared. A mixture of probably epimeric chlorides **22**, mp 210–212 °C, one isomer sublimes at 170 °C, was formed in 47% yield when **9** and **12** was condensed with diethyloxonium



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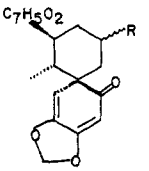
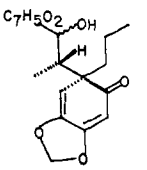


22 R = Cl
23 R = F



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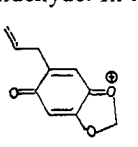
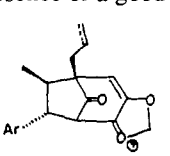
hexachloroantimonate[12] ($CH_2Cl_2$, 0 °C, 2 min) and trimethyloxonium fluoborate ($CH_2Cl_2$, 20 °C, 6 h) caused condensation to a mixture of fluorides **23** (60%), mp 177–200 °C. Significantly, neither olefin **21** nor the halides **22** and **23** could be cyclized further to substances with futoenone (**4**) skeleton and they all seem to have incorrect configurations at the spiro carbon atom.

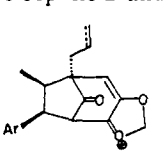
To account for the formation of the three types of condensation products we assume that all reactions are initiated by a concerted cycloaddition of ion A to olefin leading to bicyclooctanes with endo-oriented aryl groups. Intermediate B results from (*E*)-isosafrole (**12**) and its isomer C from (*Z*)-isosafrole. In the presence of water B could afford **13** or **15** and formaldehyde. In the absence of a good nucleophile B and C



A



B



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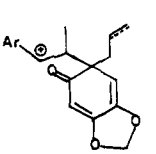

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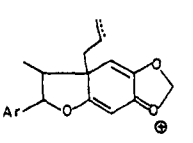

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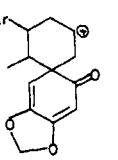

F

could rearrange to their more extensively delocalized isomers *E*, which on hydrolysis would lead to **16/18** or **17/20.** Cation D, probably an intermediate between B and E, might also cyclize further to F, and, provided that (*E*)-isosafrole is the starting olefin, afforded **21, 22,** or **23** with the stereochemistry indicated.

Several observations support this hypothesis. Condensation of ketal **10** with (*E*)-**12** (TsOH, $CH_3CN$, 20 °C, 1 h) gave a mixture of **17,** mp 169–172 °C, **20,** mp 150–154 °C (combined yield 25%), **15,** mp 130–131 °C (28%), and **24,** mp 151–152 °C (7%). The bicyclooctane **15** was stable under the conditions used for its generation but the secondary alcohol **24** was slowly, but quantitatively, converted to **17/20.** The latter mixture on the other hand was stable to trifluoromethanesulfonic acid in acetonitrile, conditions which caused nearly quantitative conversion of **15** to **17/20** showing that "burchellins" are more stable than "guianins". Secondly, isosafrole (**12**) recovered from condensations was found to be enriched in *Z* isomer because cycloadditions leading to C with two endo substituents are slower than those resulting in B with only one such destabilizing substituent. Finally, and most significantly, methanesulfonic acid promoted condensation (1 equiv, $CH_3CN$, 0 °C, 65 min) of pure (*Z*)-isosafrole (**12**) with ketal **9** followed by methylation of the crude mixture with methyl iodide (DMF, $Ag_2O$, 20 °C, 20 h) afforded racemic 2-epi,3a-epiburchellin (**3,** 10%), mp 140–142 °C, $^1H$ NMR $\delta$ 0.52 (d, 3, $J$ = 7 Hz) identical with natural material ex *Aniba terminalis* as judged by spectral comparison[13] and 20% racemic futoenone (**4**), mp 242–246 °C. Identity with natural material rests on comparison of infrared, mass, ultraviolet, and 90-MHz NMR spectra as well as chromatographic behavior.

**Acknowledgments.** The research was supported by the National Institutes of Health (GM 09868). We are indebted to Professor O. R. Gottlieb, University of Sao Paulo, for spectra of guianin and burchellin as well as for a sample of the latter. Dr. A.Ogiso, Sankyo Co., Tokyo, kindly provided futoenone and its NMR and IR spectra.

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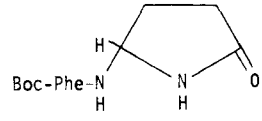
## A General Approach to Retro-Isomeric Linear Peptide Synthesis

*Sir:*

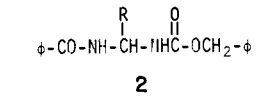
The topochemical approach for studying structure-activity relationships in linear peptides is still relatively new. A retro-isomer of a linear peptide is obtained through formal reversal of all the peptide bonds in the backbone, thus conserving the side-chain topology.[1] Synthesis of an absolute linear retro-isomer also requires solution of the "end-group" problem.[2] An absolute retro-isomer incorporates amino acids of the opposite chirality while preserving the same residues at each end of the peptide. The carboxyl end group problem can be solved by replacement of the C-terminal amino acid with an $\alpha$-substituted malonic acid. However, conservation of the N-terminal amino acid is difficult, since an $\alpha,\alpha$-diamino residue is involved[3] (Figure 1).

Only a single case is known in the literature in which an $\alpha,\alpha$-diamino residue has been used to obtain the correct N terminus in a retro linear peptide. Morley replaced the pyroglutamyl residue by the 2-keto-5-pyrrolidinylamino residue (**1**), the $\alpha,\alpha$-diamino analogue. The synthesis of **1** was accomplished by a nonstereospecific hydrogenation of the 5-imino-2-pyrrolidinone precursor.[3]




**1**

In this paper we introduce a new application for a sequence of reactions, related to work carried out by Bergmann and Zervas[4] who dealt with stepwise degradation of polypeptides. They prepared doubly aminated aldehydes (*gem*-diamino compounds) of the general structure **2** through Curtius rearrangement of *N*-benzoylamino acids or *N*-benzoyl peptide hydrazides. The thermal rearrangement of the corresponding azides in the presence of benzyl alcohol yielded the appropriate benzylurethanes (structure **2**). The removal of the *N*-benzyloxycarbonyl group was accomplished by catalytic hydrogenation in the presence of hydrochloric acid followed by boiling in water which resulted in the corresponding aldehyde. The




**2**

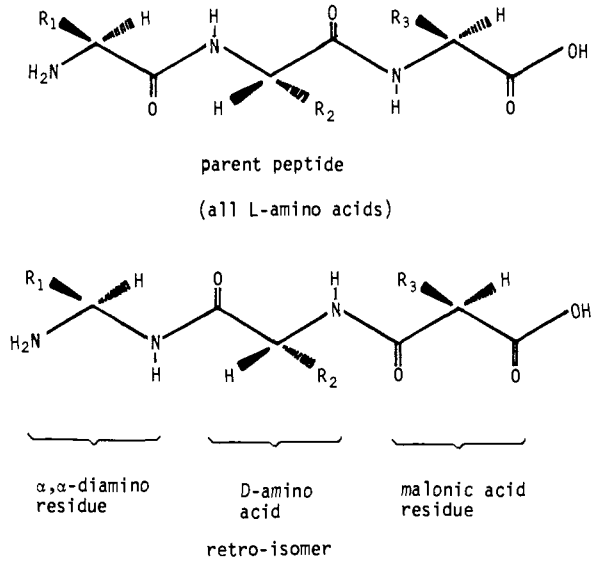



**Figure 1.**