was influenced by the stability for the mixed valence complex. While the half-lives for the decomposition of the $[3, L^-, 3]^{5+}$ and $[2, L, 2]^{4+}$ ions are several hours and days, respectively, the mixed valence complexes of several related malononitrile derivatives decompose rapidly in aqueous solutions. Among the reactions contributing to the instability of the mixed valence ion are: -CN hydrolysis in the protonated mixed valence ion, disproportionation, and, apparently isomerization and internal reduction for some of the bridging ligands used. Some of these reactions are avoided by using the *tert*-butyl derivative. The mixed valence complex derived from it also decomposes rather rapidly—on the time scale of minutes at 25 °C in water but much less rapidly in nonaqueous solvents.

Whereas in the Ru(II)-Ru(III) species heretofore studied, the coupling between the metal centers involves mainly πd-π^* delocalization, in the present system the principal mechanism is almost certainly delocalization from a π level on the ligand (π electrons becoming available on deprotonation) to vacancies in the πd orbitals on the metal ion. The enormous increase in the acidity of the ligand on one-electron oxidation of the [2, L, 2] form speaks directly to this point as does the fact that the coupling becomes strong only on deprotonation (π^* levels will become less stable on deprotonation thus decreasing πd-π^* delocalization). The very large value of ϵ for the IT transition, the largest so far recorded for the bisruthenium series, also supports the conclusion about the coupling mechanism. In the μ-cyanogen bis(pentaammineruthenium) case,[9] where coupling is so strong that the system is valence delocalized, the value of ϵ is only 4.1×10^2 M^{-1} cm^{-1}. In this ion, the yz and zx orbitals, where z is the metal ligand axis, are stabilized by back-donation. As a result, the electron hole in the 5+ ion is expected to develop in an xy orbital, and the low extinction coefficient is ascribable to weak overlap between xy orbitals on separate ions. In consequence, the energy required to make the metal centers equivalent is probably gained largely from the delocalization of the yz and zx electrons, while that from delocalization of the electron hole may make a relatively small contribution. In the present system, where $p\pi$ delocalization from ligand into metal ions is postulated, the electron hole lies in an orbital along the axis of the molecule, and a higher transition probability is expected. Finally, the strong interaction between the Ru(III) ions in the fully oxidized state, as shown by the low value of the magnetic moment, also is in line with the coupling mechanism suggested.

It is of interest to note that an intervalence transition is observed also for the mixed valence species with dialkylated malononitrile as the bridging group. In this case, however, the extinction coefficient is smaller (ϵ 180 M^{-1} cm^{-1}) and the band is at higher energy (925 nm in Me_2SO). Moreover, it is more nearly of normal width (5.86 kK, compared to a calculated value of 4.99 kK).

The large value of the conproportionation constant for reaction 1, the large value of ϵ for the intervalence band and the narrowness of the near-ir band[12] indicate substantial valence delocalization for the species $[3, L^-, 2]$. The fact that the energy of the near-ir band does depend on the solvent is not at variance with this conclusion. The molecule is not linear, and if, as is likely, on excitation there is a change in the distribution of electron density between bridging ligand and metal ions, the dipole moment will change and as a result the energy of the transition is expected to depend on solvent properties. The solvent dependency, it should be noted, does not follow the function $(1/n^2 - 1/D)$ as is the case for linear, trapped valence systems. The decision as to whether the two CN frequencies are averaged for the mixed valence species under present consideration, as they are in the μ-cyanogen case, will have to wait on the outcome of experiments which will be very difficult to perform. The criterion based on averaging or nonaveraging of valence trapping vibrational modes seems the most appropriate of any to apply in deciding when it is useful to regard a species as being valence trapped or valence averaged.

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(3) At pH 5.0, the conproportionation constant, K_c, equals 1.0 and at higher pH values, it increases. In this pH range, two stages in the oxidation of the [2, 2] can be seen. Below pH 5, $K_c < 1.0$ and the oxidation of [2, 2] proceeds with no significant accumulation of [2, 3] in an equilibrium measurement, but in cyclic voltammetry, the oxidation wave for the 2,2 form is discernible. This is invariant with pH over a wide range, including low pH where the reduction wave in relation to oxidation wave approaches reversible behavior. The value of E_f for:

$$[2, L, 3]^{5+} + e^- = [2, L, 2]^{4+}$$

so determined, 0.50 V, is identical (±0.01 V) with that for the acetonitrile complex, and to that for both the mononuclear and binuclear forms of the succinonitrile complex. The value of E_f in question together with the results of potentiometric titration define pK_a for the 2,3 complex.
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Biosynthesis of *Cephalotaxus* Alkaloids. 2. Biosynthesis of the Acyl Portion of Deoxyharringtonine[1]

Sir:

There is currently great interest in the alkaloids produced by conifers of the genus *Cephalotaxus*.[2] This interest is due in large measure to the potent antitumor activity exhibited by several alkaloids which occur in *C. harringtonia*.[3] The active alkaloids are esters of cephalotaxine (**1**) and include deoxyharringtonine (**2**), harringtonine (**3**), isoharringtonine (**4**), and homoharringtonine (**5**).[4] We wish to report experiments which clarify the mode of biosynthesis of the acyl portion of deoxyharringtonine.

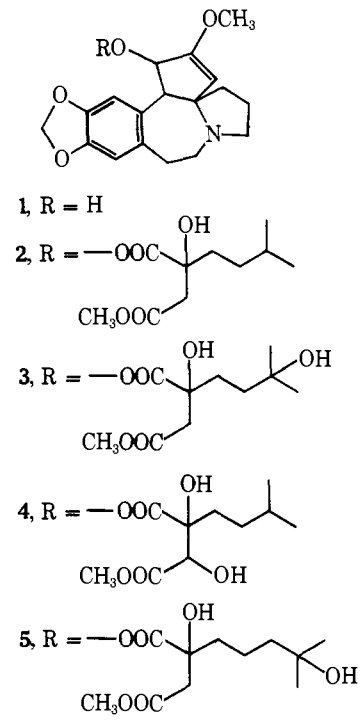
In deoxyharringtonine, cephalotaxine is linked to 3-carboxy-3-hydroxy-6-methylheptanoic acid (**6**). The resemblance of this compound to 3-carboxy-3-hydroxy-4-methylpentanoic acid which is an intermediate in the biosynthesis of L-leucine (**7**) from L-valine[5] suggests that the biosynthesis of **6** may proceed in a manner analogous to the mode of formation of the pentanoic acid derivative. If this hypothesis is correct, then the biosynthesis of **6** should involve the steps outlined in Scheme I.[5] Evidence in support of the biosynthetic pathway shown in this scheme was obtained from the experiments discussed below.

The hypothesis predicts that 3-hydroxy-3-carboxy-5-methylhexanoic acid (**8**) should be an intermediate in the biosynthesis of **6** and that carbon atoms 3-8 of **8** should be

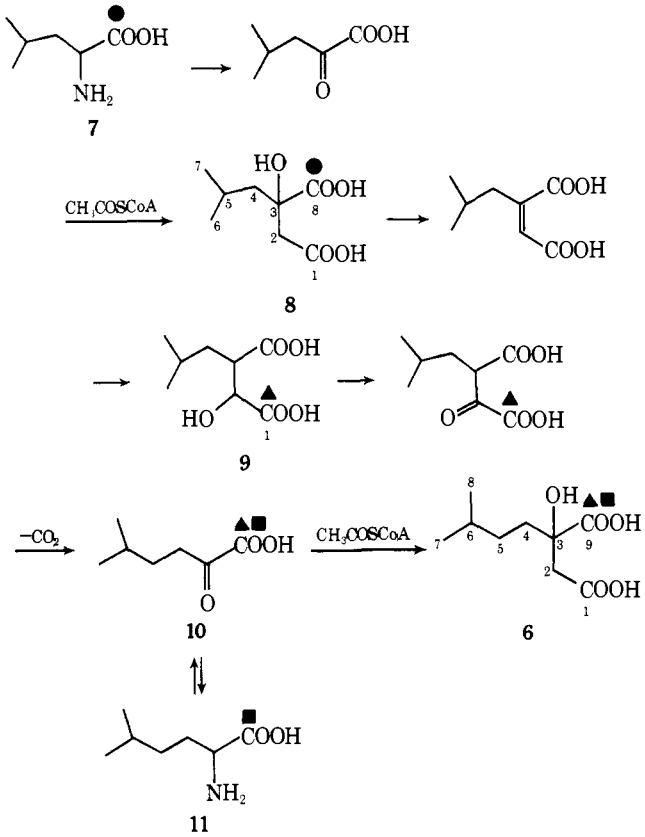
Table I. Feeding Experiments with *Cephalotaxus harringtonia*

Expt no.	Precursor Fed to *Cephalotaxus*	Product isolated	% incorporation	Dist of activity in product
1	[1-^{14}C]-L-Leucine	Diacid **8**	0.03	84% at C-8
2	[1-^{14}C]-**9**[a]	Diacid **6**	0.21[b]	89% at C-9
3	[1-^{14}C]-DL-Homoleucine	Diacid **6**	6.5[c]	94% at C-9

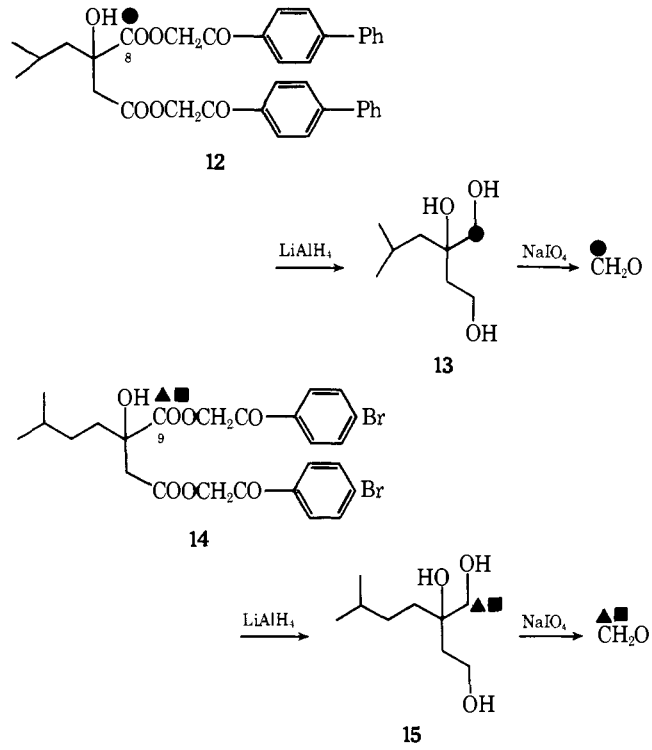
[a] Precursor a mixture of diastereomers. [b] Based on total amount of radioactivity fed. [c] Based on amount of L-homoleucine fed.



Scheme I



Scheme II



derived from L-leucine (**7**). Since the presence of **8** or its derivatives in *Cephalotaxus* plants has never been reported, its presence was sought by isotopic trapping. A synthetic sample of **8** was prepared from 4-methyl-2-pentanone using methods developed for the synthesis of **6** from 5-methyl-2-hexanone.[3d,6] [1-^{14}C]-L-Leucine was administered to rapidly growing *C. harringtonia* plants[7] by the cottonwick method, and the plants were harvested after 14 days. The plant material was worked up by ethanol extraction with addition of radioinactive **8** as carrier. The crude extract was subjected to alkaline saponification to convert any esters of **8** into the free diacid and the crude mixture of acids was derivatized with *p*-phenylphenacyl bromide using the crown ether method.[8] The bis(*p*-phenylphenacyl) ester **12** (Scheme II) was purified by repeated thin-layer chromatography followed by crystallization to constant radioactivity to give the incorporation level shown in Table I (expt 1). The incorporation of L-leucine into **8** was shown to be specific by degradation to isolate C-8 of the diacid. Reduction of **12** with lithium aluminum hydride gave 3-hydroxy-3-hydroxymethyl-5-methyl-1-hexanol (**13**) which was purified by chromatography, distilled, and cleaved with periodate to yield radioactive formaldehyde, trapped as its dimedone adduct. The results (Table I, expt 1) show that most of the radioactivity resides in the expected position of the diacid. Therefore, it appears that the diacid **8** is present in *Cephalotaxus* plants and that it is formed from leucine in the expected fashion.

The hypothesis shown in Scheme I also predicts that 2-hydroxy-3-carboxyl-5-methylhexanoic acid (**9**) lies on the

biosynthetic pathway to **6**. In order to test this prediction, a synthesis of **9** was devised. Formylation of ethyl 4-methylpentanoate with ethyl formate and ethoxide gave ethyl 2-formyl-4-methylpentanoate.[6] Conversion of the formyl ester to its cyanohydrin[5d,6] followed by acid hydrolysis[3d] yielded **9** as a mixture of diastereomers.[6] When carbon-14 labeled cyanide was employed in the synthesis, [1-^{14}C]-**9** was obtained. The labeled sample of **9** was administered to *C. harringtonia* plants and the plants were harvested after 7 days. Radioinactive diacid **6** was added to the crude, alcoholic plant extract which was then subjected to acidic saponification.[9] The crude mixture of acids resulting from the saponification was converted into methyl esters and the dimethyl ester of **6** was purified by repeated thin-layer chromatography using a system in which the dimethyl ester of the precursor **9** exhibited an R_f value considerably smaller than that for the dimethyl ester of **6**.[10] The purified dimethyl ester of **6** was then hydrolyzed to the free diacid and converted to the bis(*p*-bromophenacyl) ester **14** (Scheme II) in the usual way. The bis(*p*-bromophenacyl) ester **14** was purified by repeated thin-layer chromatography using a system in which the bis(*p*-bromophenacyl) ester of the precursor **9** exhibited a lower R_f value than **14**.[10] The labeled diester **14** was then recrystallized to constant activity to give the incorporation figure shown in Table I (expt 2). The specific incorporation of the diacid **9** into **6** was demonstrated by means of the degradative sequence outlined in Scheme II. The bis(*p*-bromophenacyl) ester **14** was reduced with lithium aluminum hydride and the resulting labeled 3-hydroxy-3-hydroxymethyl-6-methyl-1-heptanol (**15**) cleaved with periodate. The results of the degradation (Table I, expt 2) clearly show that **9** is incorporated into **6** with very little randomization of the label.

On the basis of the hypothesis suggested in Scheme I, 2-oxo-5-methylhexanoic acid (**10**) would be expected to be the immediate precursor of **6**. If this is the case, then homoleucine (**11**) should be specifically incorporated into **6** due to the facile interconversion between α-amino acids and the corresponding α-keto acids. DL-Homoleucine was conveniently prepared from 4-methylpentanal by condensation with potassium cyanide and ammonium carbonate followed by hydrolysis of the intermediate hydantoin. The resulting amino acid exhibited properties identical with those previously reported.[11] [1-^{14}C]-DL-Homoleucine was then synthesized using ^{14}C-labeled potassium cyanide. Administration of the labeled homoleucine to *Cephalotaxus* was followed by workup after 7 days in the usual way to give radioactive **6** as its bis(*p*-bromophenacyl) ester **14**. After purification by chromatography, and crystallization to constant activity, the incorporation figure shown in Table I (expt 3) was obtained. The incorporation level is considerably higher than is usually observed in biosynthetic experiments with higher plants and it demonstrates that homoleucine is a highly efficient precursor of **6**. The specific incorporation of **11** into **6** was verified by reduction of the labeled diester **14** and cleavage of the labeled triol **15** with periodate (Scheme II); the results of this degradation are shown in Table I (expt 3).

The experiments presented here provide compelling evidence that the acyl moiety of deoxyharringtonine (**2**) is biosynthesized via the pathway delineated in Scheme I. Similar pathways appear to be involved in the biogenesis of the so called mustard oil glycosides[12] and may prove to be widespread in higher plants. The operation of the pathway shown in Scheme I can also account for the biosynthesis of the acyl portions of the remaining antitumor alkaloids found in *Cephalotaxus*, including homoharringtonine (**5**). The acyl moiety of the latter alkaloid would be expected to arise from the diacid **6** by a series of steps closely analogous to the formation of **6** from the diacid **8**. Experiments are in progress to examine this possibility and to provide additional details concerning the biosynthesis of each of the four antitumor alkaloids **2**–**5**.

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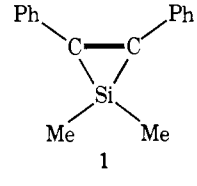
1,1-Dimethyl-2,3-bis(trimethylsilyl)-1-silirene, a Stable Silacyclopropene

Sir:

Some years ago, Vol'pin et al. predicted that silacyclopropenes should be a stable class of organosilicon compounds on the basis of analogies to the cyclopropenium cation.[1] However, the initial claim by these workers that they had prepared 1,1-dimethyl-2,3-diphenyl-1-silirene (**1**) by addition of dimethylsilylene to diphenylacetylene did not stand up to subsequent experimental scrutiny. The highly stable product of their reaction, which was claimed to be **1**, was shown to be the dimer, **2** (R = Ph).[2] At that time there had been no report of any three-membered ring compound containing only silicon and carbon atoms in the ring. Nevertheless, the concept of Vol'pin was an intriguing one and a residual interest in the possible existence of silirenes remained. Recently, Atwell and Weyenberg reported that the generation of dimethylsilylene by 1,2-dimethoxytetramethyldisilane pyrolysis in the presence of 2-butyne and methanol gave *cis*-MeCH=C(Me)Si-



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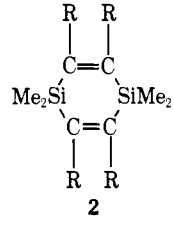

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