Table I. Yield of Nucleophilic Substitution by Butyllithium at Phosphorus in (+)-$(R)_P$-5 as a Function of Reaction Medium[a]

Medium	*n*-BuLi, yield 7 (%)	*t*-BuLi, yield 9 (%)
THF	39	14
THF–TMEDA	38	16
Et_2O	21	3
Et_2O–TMEDA	50	73
C_6H_{14}	0	2
C_6H_{14}–TMEDA	77	76

[a] The following standard conditions were used: [5] ~0.05 to 0.1 *M*; BuLi introduced as ~1.7 *M* solution in hydrocarbon solvent in nine- to tenfold excess; the reaction was run for 0.50 hr at room temperature, quenched with water, and analyzed by GLPC, using n-$C_{16}H_{34}$ as internal standard; TMEDA:BuLi = 1:1 mole ratio.

TMEDA probably functions as a deag ..ting agent,[18] generating a more nucleophilic anion and a lithium ion more available (than in the aggregates) to participate in the transition state.[9]

When (+)-$(R)_P$-**5** was treated with *n*-BuLi (1.0 g, 4.7 mmol) in THF (conditions as in the footnote of Table I) the lower boiling phosphine **7** was isolated in 18% yield, $[\alpha]D^{25}$ +14.5° (*c* 2.79, C_6H_6), indicating a minimum 66% ee and maximum racemization of 12% (assuming 95% ee in (+)-**5**). The sample contained considerable amounts of low boiling impurities (most of which could be traced back to the BuLi solution), however, as determined by GLPC. A much better indication of optic l purity was obtained from the NMR spectrum of the phosphonium salt of this phosphine and (−)-**8**,[15] which indicated per cent ee at least as great as that of authentic (+)-$(S)_P$-**7** obtained as shown in Scheme I. A similar run using *n*-BuLi in Et_2O–TMEDA with (+)-**5** gave **7** in 28% isolated yield, $[\alpha]D^{25}$ +17.2° (*c* 6.79, C_6H_6) (minimum 78% ee, maximum racemization 8%). Again the NMR spectrum of the phosphonium salt from (−)-**8** indicated ee at least as large as authentic (+)-**7**. Treatment of (+)-$(R)_P$-**5** with *t*-BuLi in Et_2O–TMEDA allowed the isolation of **9** (29%)[17] with a minimum of 71% ee and maximum of 11% racemization. As with **7**, the NMR spectrum of the phosphonium salt from (−)-**8** indicated ≥95% ee.

These data are consistent with S_N^P occurring with complete inversion of configuration at phosphorus, within experimental error. Although the medium and nucleophile have a marked effect on the amount of S_N^P which occurs, these factors apparently do not affect the stereochemical course of the reaction. It is not possible to rule out **2** as an intermediate[19] rather than a transition state; however, it can be concluded that if **2** is an intermediate, the barrier to pseudorotation in this hypervalent anion[7] is high enough that racemization does not occur during its lifetime.

Acknowledgments. I wish to thank Mr. Carl W. Hudson for carrying out some preliminary experiments. Grateful acknowledgement is made to the Robert A. Welch Foundation for support of this research (F-573).

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(14) Bromide **8** had $[\alpha]D^{25}$ −74° (c 2.58, MeOH) (lit.[4b,12] $[\alpha]D$ +73° for (*S*)-**8**. In $CDCl_3$, for the phosphonium salt derived from (+)-**5** and (−)-**8**, δ^{MeO} 2.82 ppm, and for (−)-**5** and (−)-**8** (deduced from (±)-**5** and **8**), δ^{MeO} 3.05 ppm.
(15) In $CDCl_3$ for the phosphonium salt derived from (+)-**7** and (−)-**8**, δ^{MeO} 3.06 ppm, and for (−)-**7** and (−)-**8** (deduced from (±)-**7** and **8**), δ^{MeO} 2.95 ppm.
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(17) $[\alpha]D^{25}$ −34° (*c* 3.59, C_6H_6) (lit.[3b] $[\alpha]D$ +29.5° (C_6H_6) (ca. 62% ee) for the $(R)_P$ enantiomer). Because of the small sample size it was difficult to remove all the low boiling impurities by fractional distillation. Another indication of the optical purity of (−)-**9** was obtained from the NMR spectra ($CDCl_3$) of the phosphonium salts from (±)-**9** + (−)-**8** and (−)-**9** + (−)-**8** which indicated >95% ee (δ^{MeO} 2.97 ppm (from (−)-**9**) and δ^{MeO} 2.73 ppm (from (+)-**9** deduced from (±)-**9**)).
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Biosynthesis of *Cephalotaxus* Alkaloids. I. Novel Mode of Tyrosine Incorporation into Cephalotaxine

Sir:

Conifers of the genus *Cephalotaxus* contain a group of unusual alkaloids, the most abundant of which is cephalotaxine (**1**) whose structure and absolute stereochemistry have been determined by X-ray analysis.[1] In *C. harringtonia*, **1** is accompanied by a number of minor alkaloids, including some cephalotaxine derivatives with potent antileukemic activity,[2] and several alkaloids of the homoerythrina type.[3]

The presence of homoerythrina alkaloids such as 3-epischelhammericine (**2**) in *Cephalotaxus* has led to the proposal[3] that both cephalotaxine and the homoerythrina bases may arise from a 1-phenethyl-1,2,3,4-tetrahydroisoquinoline derivative (**3**) via oxidative phenolic coupling. If **3** were

Scheme I

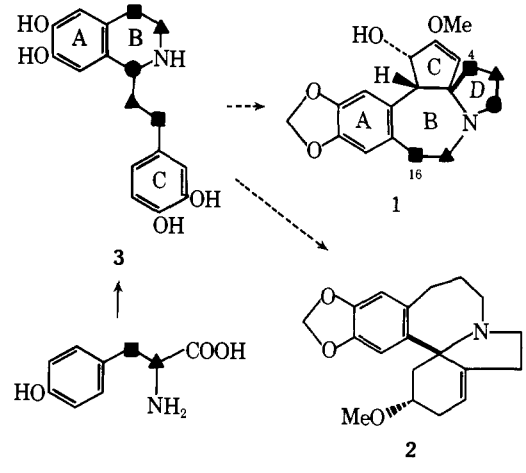


Table I. Incorporation of Tyrosine into Cephalotaxine

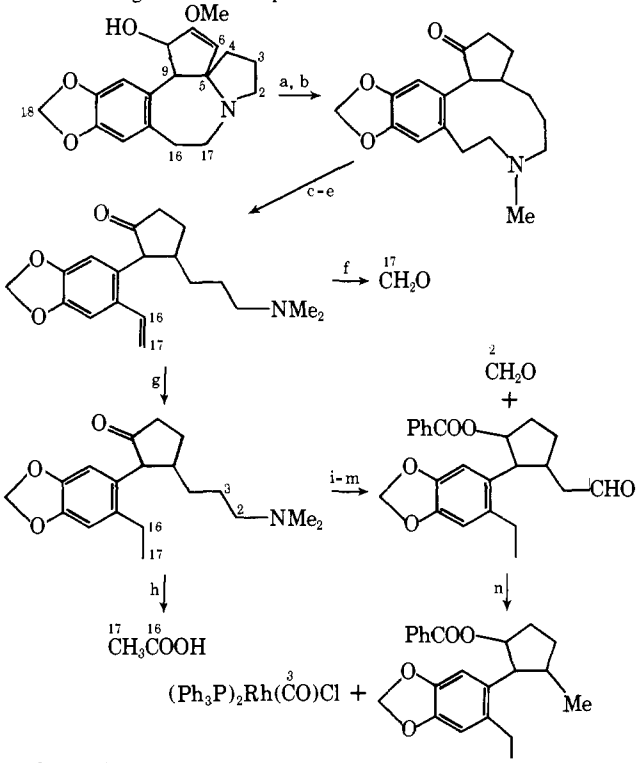
Expt No.	Precursor Fed to *Cephalotaxus*	Distribution of activity in the alkaloid (% carbon no.) 2	3	9, 16	16	17
1	[3-^{14}C]-DL-Tyrosine			100	68	
2	[1-^{14}C]-DL-Tyrosine	7.6				
3	[2-^{14}C]-DL-Tyrosine	0	0			36.9, 37.6[a]

[a] Results of two feeding experiments.

an intermediate in the biosynthesis of cephalotaxine, then two molecules of phenylalanine or tyrosine should be incorporated into the alkaloid to give the labeling pattern shown in Scheme I. This labeling pattern is expected on the basis of a number of tracer experiments on the biosynthesis of tetrahydroisoquinoline alkaloids.[4]

We wish to report the results of experiments which establish that **1** is biosynthesized from two molecules of tyrosine, but in a quite unexpected manner. Administration of [3-^{14}C]-DL-tyrosine to young *C. harringtonia* plants by the cotton-wick method followed by work-up after an 8-week period[5] yielded radioactive cephalotaxine (ca. 0.18% incorporation).[6] The hypothesis outlined in Scheme I predicts that the radioactive alkaloid should be labeled at C-16 and C-4. Degradation of the radioactive alkaloid by permanganate oxidation gave 4,5-methylenedioxyphthalic acid. Surprisingly, all of the radioactivity of the starting alkaloid was found in this diacid (Table I, expt 1). Hofmann degradation[7] of the labeled diacid gave 4,5-methylenedioxyanthranilic acid which carried 53% of the total activity; therefore, all of the radioactivity in the phthalic acid is located in the carboxyl groups. These results suggested that both C-9 and C-16 of cephalotaxine might be derived from C-3 of tyrosine. Proof of this was obtained by degradation of the radioactive alkaloid to isolate C-16 as shown in Scheme II.[8] This carbon atom was found to carry 68% of the total activity (expt 1); the remaining 32% of the label must therefore reside at C-9. These observations are clearly incompatible with the hypothesis for cephalotaxine biosynthesis shown in Scheme I. Additional data indicating that Scheme I cannot be correct have been obtained by administration of [1-^{14}C]- and [3-^{14}C]-DL-tyrosine to *C. harringtonia*.

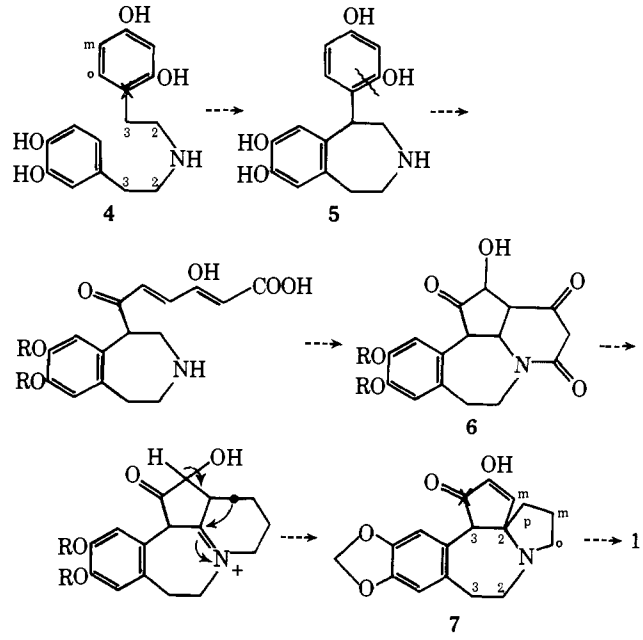
Scheme II. Degradation of Cephalotaxine[a,b]



[a] Key: (a) MeI; (b) Na-Hg, H_2O; (c) MeI; (d) Rexyn 201 (HO^-); (e) Δ, C_6H_6; (f) OSO_4, $NaIO_4$; (g) H_2/Pd; (h) CrO_3, H_2SO_4; (i) $NaBH_4$; (j) H_2O_2; (k) Δ; (l) PhCOCl; (m) OsO_4, $NaIO_4$; (n) $(Ph_3P)_3RhCl$, C_6H_6, Δ.

[b] All the degradation products of cephalotaxine are mixtures of diastereomers.

Scheme III



Radioactive cephalotaxine is produced from [1-^{14}C]-DL-tyrosine, but the level of incorporation (0.008-0.02%) is consistently lower than that obtained with [2-^{14}C]- and [3-^{14}C]-DL-tyrosine fed under identical conditions. Degradation of radioactive **1** obtained from [1-^{14}C]-DL-tyrosine was carried out according to Scheme II to isolate C-2 of the alkaloid. As Table I shows (expt 2), this carbon atom carried a small quantity of radioactivity. We attribute this radioactivity and the low incorporation figures to scatter of the C-1 label via decarboxylation of the tyrosine and reentry of the labeled carbon dioxide into primary metabolism via photosynthesis.

Administration of [2-^{14}C]-DL-tyrosine to *Cephalotaxus* yields radioactive **1** with incorporation levels comparable to those obtained with [3-^{14}C]-DL-tyrosine (ca. 0.16-0.18%). Degradation of the radioactive cephalotaxine to isolate C-2, C-3, and C-17 was carried out as shown in Scheme II. The results of these degradations are summarized in Table I (expt 3). It can be seen that essentially no activity is found at C-2 and C-3 while 37% of the total activity is found at C-17. On the basis of the results obtained by degradation of **1** derived from [3-^{14}C]-DL-tyrosine, one would expect to find ca. 68% of the label at C-17 in cephalotaxine formed from [2-^{14}C]-DL-tyrosine. The observed figure is considerably lower. This appears to be due to some excess, nonspecific incorporation of the C-2 label of tyrosine into **1** as a result of catabolism of the amino acid. Thus, additional degradative experiments[9] have shown that small amounts of radioactivity reside at a number of carbon atoms in **1** derived from [2-^{14}C]-DL-tyrosine. These experiments have also shown that the remaining portion of the activity due to specific C-2 labeling must be present at C-4, C-5, or C-6 of the alkaloid.

Scheme III provides a tentative hypothesis for cephalotaxine biosynthesis which will account for the labeling pattern disclosed by our feeding experiments. This hypothesis suggests that **1** is biosynthesized from a bis(β-phenethylamine), **4**, which is in turn derived from two molecules of tyro-

sine.[10] Cyclization of **4** to a tetrahydrobenzazepine **5** could be followed by oxidative fission of one aromatic ring in a manner analogous to the degradation of aromatic rings observed in a variety of living systems.[11] Two successive cyclizations transform **5** into a tetracyclic compound, **6.** Rearrangement of **6** could then give desmethylcephalotaxinone (**7**), which has been isolated from *Cephalotaxus* plants.[12] This hypothesis predicts that cephalotaxine should be labeled as shown in **7.** Experiments are in progress to determine if this prediction is correct.

Acknowledgment. We wish to thank Dr. R. G. Powell for gifts of alkaloids and Dr. Robert F. Perdue for dried plant material. Financial support from the National Institutes of Health (GM-19220) is gratefully acknowledged as is support from the National Science Foundation (GU 3852, GP 37156) which allowed purchase of a Bruker WH-90 NMR spectrometer used in this work.

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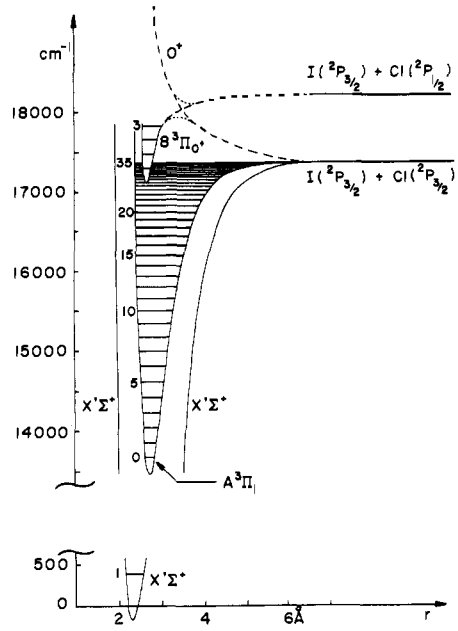

Figure 1. Potential energy curves for the X, A, and B states of ICl, taken from ref 1b with minor modification.

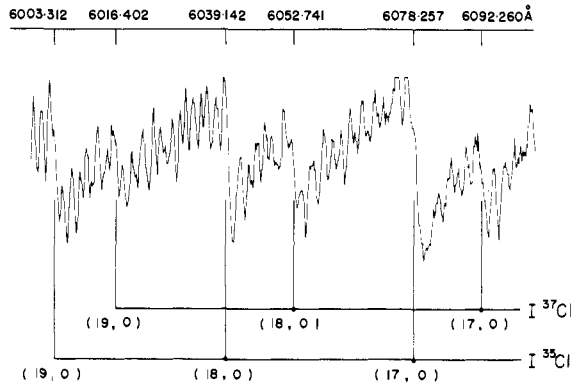

Figure 2. Low-resolution visible absorption spectrum of ICl taken from 6000 to 6100 Å. Note that the separation between the $I^{35}Cl$ and $I^{37}Cl$ bandheads are about 15 Å in this spectral region.

Laser Separation of Chlorine Isotopes. The Photochemical Reaction of Electronically Excited Iodine Monochloride with Halogenated Olefins

Sir:

We report here the photochemical separation of ^{35}Cl and ^{37}Cl when a mixture of ICl and the scavengers *trans*-ClHC=CHCl and 1,2-dibromoethylene (cis, trans mixture) is irradiated by a CW tunable dye laser that selectively excites $I^{37}Cl$. The scavenger has the property that it does not react with ground state ICl but does react with ICl in the excited A $^3\Pi_1$ state. Thus, from *trans*-ClHC=CHCl, both the photoproduct *cis*-ClHC=CHCl and the starting material *trans*-ClHC=CHCl show ^{37}Cl-^{35}Cl exchange. The latter demonstrates for the first time laser-controlled isotope interchange. In the case of BrHC=CHBr, all photoproducts are ^{37}Cl enriched; in particular, the *trans*-ClHC=CHCl photoproduct has a ^{35}Cl:^{37}Cl ratio of 2:1 compared to 3:1 for naturally occurring *trans*-ClHC=CHCl. This technique of selective laser excitation and subsequent isotope labeling provides us with a new means of following organic gas-phase photochemical reactions with state selection of the reactants.

The visible absorption spectrum of $I^{35}Cl$ and $I^{37}Cl$ has been extensively studied,[1] and the relevant potential energy curves are shown in Figure 1. By tuning the CW dye laser to the (18, 0) bandhead of the $I^{37}Cl$ A-X system at 6053 Å (see Figure 2), we can be assured that no photodissociation or photopredissociation occurs because the $v' = 18$ level of the A state lies ~784 cm^{-1} below the X state dissociation limit. Our laser has an average power of 10 mW and a relatively wide band width (3 Å); this permits preferential excitation of the $I^{37}Cl$ molecule, although some $I^{35}Cl$ is also excited.

A 1:1 mixture of ICl and *trans*-ClHC=CHCl (10 Torr each) is placed inside a Pyrex tube 1 m long and 5 cm diameter, and exposed for 3 hr. In the single-pass reaction cell about one-third of the laser beam (5-mm spot size) is absorbed. Then excess C_2H_4 is added to trap unreacted ICl. The products are separated by gas-liquid phase chromatography (GC). The presence of an extra peak in the GC spectrum is analyzed to be the photoproduct *cis*-ClHC=CHCl.

Isotope analysis of the products is accomplished using a Nier-type mass spectrometer having an accuracy in the ratio of the mass peaks, P, of four parts per thousand. For starting material, *trans*-ClHC=CHCl, the ratio $P_{35}:P_{37} = 3.01$, while for exposed *trans*-ClHC=CHCl $P_{35}:P_{37} = 2.73$. A small but significant enrichment of ^{37}Cl in the ex-