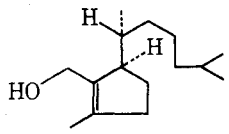

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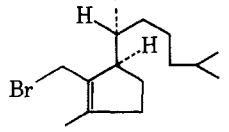

73

tive coupling sequence similar to ones already described.[15,20] Attachment of the terminal epoxide unit, as above with **55a,b**, completed the synthesis of the **50a,b** mixture.

As with **55a,b**, cyclization of epoxide **50a,b**, followed by TLC separation of products, yielded a tetracycle fraction comprising isoeuphenol (**51**; 3.5%), 24,25-dihydro-$\Delta^{13(17)}$-protolanosterol (**52**; 2%), and 24,25-dihydroparkeol (**53**; 3.5%), all from epoxide **50a**, and (−)-isotirucallenol (**54**; 43%) from epimer **50b**. Since $SnCl_4$–CH_3NO_2 or $BF_3 \cdot Et_2O$–CH_3NO_2 treatment of authentic dihydro-$\Delta^{13(17)}$-protolanosterol (**52**) (or its acetate) resulted in formation of dihydroparkeol (**53**) (or acetate), the latter may well be generated from the former during the original cyclization conditions. In that dihydroparkeol (**53**)has been previously converted[12] to 24,25-dihydrolanosterol, the present work also constitutes a direct total synthesis of the latter natural product.

Although generation of either the 9,10-trans or -cis arrangement in the hydronaphthalene framework arising from polycyclization of terpenoid terminal epoxides has been previously observed (vide supra), the formation of tetracycles **52, 53,** and **56** from epoxides **50a** and **55a** represents the first *tri*cyclization featuring the 9,10-cis outcome and thus emerges as a close simulation of the biosynthetic conversion of squalene oxide to the presterol, and thence to the lanosterol level. The results described herein thus not only constitute total syntheses of tetracycles **51, 52, 53, 54, 56,** and **57,** but also suggest that biological chair–boat–chair construction rests on a palpable, purely chemical foundation, the function of the lanosterol cyclase enzyme being in part to optimize this particular folding–cyclization process. As revealed by examination of Dreiding models, a distinct steric interaction between the C-10 (vinyl) methyl and the side chain exists in epoxides **50a** and **55a,** but not in epoxides **50b** and **55b.** As a consequence, formation of the isotirucallol system from **50b** or **55b** proceeds in much higher yield than does that of the isoeuphol type from **50a** or **55a,** where the aforementioned steric interference inhibits the all-trans folding which must preceed cyclization to the all-trans tetracycle. This C-10 methyl–side chain interaction in compounds **50a** and **55a** can be alleviated by chair–boat–chair folding, which permits then competitive cyclization to A–B–C chair–boat–chair tetracyclic carbonium ion, the requisite precursor of protosterol (**52**), dihydroparkeol (**53**), and parkeol (**56**), all observed products from the epimer-b series of epoxides. These results and considerations suggest that, during enzymic formation of lanosterol from squalene oxide, steric crowding between the C-10 methyl and some portion of the enzyme on the β-side of the substrate could inhibit all-chair folding and force the epoxide to assume the chair–boat conformation required for lanosterol production.

Synthesis of the *Cephalotaxus* Alkaloids

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Cephalotaxus is a plant genus in the family *Taxacae,*[1] which includes several species and varieties such as *Cephalotaxus harringtonia* var. *drupacae* (Japanese plumyew), native to Japan and China. This genus is the sole known source of the cephalotaxine family of alkaloids, some members of which are promising for leukemia chemotherapy.

Clinical testing will require larger quantities of the interesting constituents than are now available from natural sources because the biologically active alkaloids such as harringtonine and isoharringtonine are only minor constituents and the trees appear only in small numbers for ornamental purposes in the United States. The problem of supplying the active compounds in sufficient quantities for clinical testing therefore falls to organic chemists to solve via chemi-

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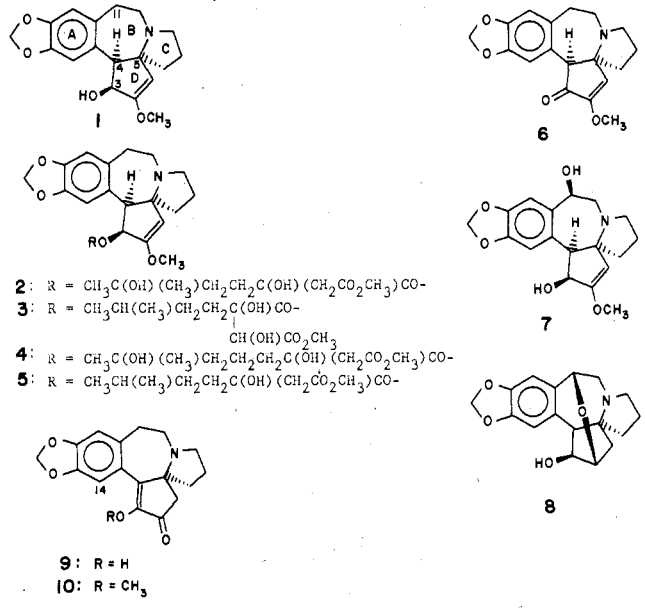
Martin F. Semmelhack received his B.S. degree from the University of Wisconsin and (in 1967) his Ph.D. from Harvard University. After a year at Stanford as an NIH Postdoctoral Fellow, he joined the chemistry staff at Cornell, where he is now Associate Professor and a Fellow of the Alfred P. Sloan Foundation and the Camille and Henry Dreyfus Foundation. His research interests are in synthesis of natural products and of molecules of theoretical interest, and in the development of novel synthetic methods.

(1) Some workers have placed *Cephalotaxus* in a separate family, the *Cephalotaxacea:* W. Dallimore and A. B. Jackson, revised by S. G. Harrison, "A Handbook of Coniferae and Ginkgoaceae", St. Martin's Press, New York, N.Y., 1967, pp 146–152.

cal synthesis. This Account considers strategies for total synthesis of the *Cephalotaxus* alkaloids with special attention to two which have been successful.

The presence of alkaloids in several *Cephalotaxus* species has been known for many years,[2] but separation of the constituents was first achieved in the early 1960's.[3] The basic fraction of an alcohol extract of the stems and leaves was comprised mainly of a new alkaloid, cephalotaxine, and several minor components. Structural elucidation along classical lines yielded a partial structure for cephalotaxine,[3] and parallel studies of the physiological properties of minor constituents of the same fraction gave evidence of powerful activity against experimental leukemia in mice.[4]

This significant antileukemia activity prompted a vigorous program by the National Cancer Institute and the U.S. Department of Agriculture to further define the variety and the structures of the *Cephalotaxus* alkaloids. This effort has produced the detailed structure and absolute stereochemistry for cephalotaxine (**1**)[5] and characterization of the minor components as five esters of cephalotaxine, harringtonine (**2**),[6a] isoharringtonine (**3**),[6a] homoharringtonine (**4**),[6a] deoxyharringtonine (**5**),[6b] and acetylcephalotaxine.[3b,7] Also, the minor alkaloids cephalotaxinone (**6**),[7] 11-hydroxycephalotaxine (**7**),[6,8] drupacine (**8**),[6,8] demethylcephalotaxinone (**9**),[9,10] and five homoerythrina alkaloids[7] have been isolated from various *Cephalotaxus* species. While cephalotaxine (**1**) is inactive toward lymphoid leukemia systems L1210 and P388, small doses of the esters **2–5** produce up to fourfold extension in lifetime of leukemic mice.[4]



The scarcity, biological activity, and unique structures of the cephalotaxine alkaloids have led to strong interest in total synthesis. The goal is an efficient, versatile pathway which can be followed to produce all of the active natural esters (**2–5**) as well as closely related structures not available from Nature.

The problems and opportunities are not unlike those encountered with β-lactam antibiotics, where a relatively complex polycyclic ring structure (i.e., cephalotaxine) is joined to simple aliphatic side chains by an easily reversible process (esterification) in order to produce a series of biologically active analogs. The strategy for the synthesis of harringtonine (**2**) and related esters then involves construction of cephalotaxine (**1**), construction of the alkyl malic acid side chain, and joining of the two parts through esterification. The first two stages have been completed in several ways; the last step has not been accomplished efficiently for any of the esters of interest (**2–5**). An alternative sequence which has seen some success involves esterification of cephalotaxine with a simple carboxylic acid followed by elaboration of the side chain to the proper natural structures of the harringtonines.

Synthesis of Cephalotaxine

Two spiro-fused five-membered rings (C and D in **1**), both of which are annular to a benzazepine system (rings A and B), are a unique feature in the structure of **1**. Five-membered ring D holds the key to the synthesis, as it contains the three contiguous chiral carbon atoms (C-3, 4, 5 in **1**) and the sensitive enol ether and allylic alcohol functional groups.

An important simplification for introduction of the proper chirality derives from early work on the structure proof of **1**. Oxidation produced a ketone (cephalotaxinone, **6**) and hydride reduction returned it to cephalotaxine with very high specificity for the natural configuration at C-3. Cephalotaxinone (**6**) offers an additional lever for stereochemical control via easy epimerization at C-4 through base-catalyzed exchange of the activated proton. Inspection of molecular models allows some confidence in predicting that the natural configuration at C-3 is also the thermodynamically more stable arrangement. No definitive experimental evidence is available to support this point, but the results below are consistent with this assumption. All approaches to cephalotaxine which have been reported rely on these stereochemical control features natural to cephalotaxinone.

The first successful total synthesis of cephalotaxine was reported by Weinreb and Auerbach at Fordham,[11] and a second successful approach followed from Semmelhack, Chong, and Jones at Cornell.[12]

In the strategy used at Cornell, cephalotaxinone (**6**) is visualized as the combination of two much simpler pieces, the aromatic portion **11** and an azaspiro[4.4]nonene derivative **12**. The key elements of

(2) (a) T. Kariyono, M. Takahashi, A. Nitta, and Y. Tsunehisa, *J. Pharm. Soc. Jpn.*, **76**, 611 (1950); (b) I. H. Y. Hsu, *J. Taiwan Pharm. Assoc.*, **9**, 7 (1957); (c) M. E. Wall, *J. Am. Pharm. Assoc.*, **43**, 505 (1954).

(3) (a) W. W. Paudler, G. I. Kerley, and J. McKay, *J. Org. Chem.*, **28**, 2194 (1963); (b) W. W. Paudler and J. McKay, *ibid.*, **38**, 2110 (1973).

(4) Cf. R. G. Powell, D. Weisleder, and C. R. Smith, Jr., *J. Pharm. Sci.*, **61**, 1227 (1972).

(5) (a) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and J. A. Wolff, *Tetrahedron Lett.*, 4081 (1969); (b) D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *ibid.*, 4085 (1969); (c) S. K. Arora, R. B. Bates, R. A. Grady, and R. G. Powell, *J. Org. Chem.*, **39**, 1269 (1974).

(6) (a) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and W. K. Rohwedder, *Tetrahedron Lett.*, 815 (1970); (b) K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., *Tetrahedron*, **28**, 1995 (1972).

(7) R. G. Powell, *Phytochemistry*, **11**, 1467 (1972).

(8) R. G. Powell, R. V. Madrigal, C. R. Smith, Jr., and K. L. Mikolajczak, *J. Org. Chem.*, **39**, 676 (1974).

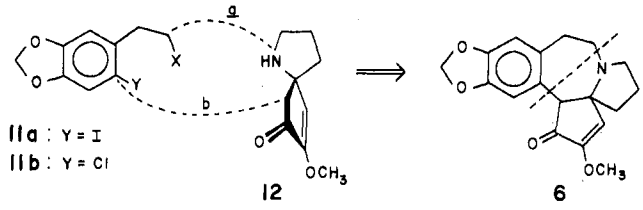
(9) R. G. Powell and K. L. Mikolajczak, *Phytochemistry*, **12**, 2987 (1973).

(10) S. Asada, *Yakugaku Zasshi*, **93**, 916 (1973).

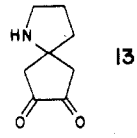
(11) J. Auerbach and S. M. Weinreb, *J. Am. Chem. Soc.*, **94**, 7172 (1972).

(12) M. F. Semmelhack, B. C. Chong, and L. D. Jones, *J. Am. Chem. Soc.*, **94**, 8629 (1972).

this strategy involve connecting bond a between **11** and **12** by SN2 displacement of a suitable leaving group (X in **11**) and formation of the final bond (b)



to complete the construction of the cephalotaxinone structure. An important aspect of this strategy is that the α-methoxycyclopentenone unit can be obtained by methylation of the symmetrical α-diketone **13** where the carbonyl groups are equivalent. The

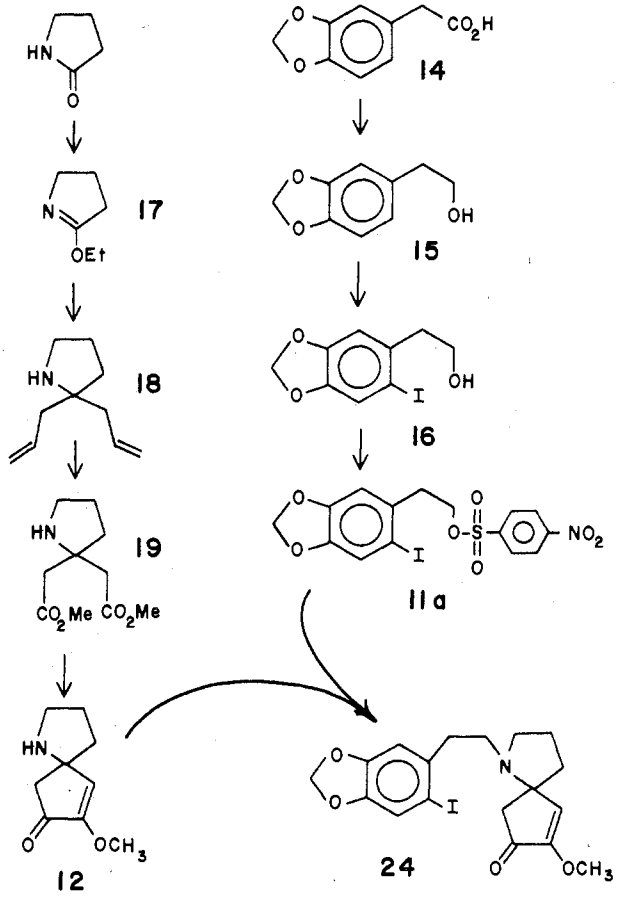


13

aromatic portion, **11a** (X = *p*-nitrobenzenesulfonate, Y = iodide), was prepared by reduction of piperonylformic acid (**14**) to piperonylcarbinol (**15**) using lithium aluminum hydride, direct iodination with iodine and silver trifluoroacetate in chloroform to give iodo alcohol **16**, and then treatment with *p*-nitrobenzenesulfonyl chloride in ether containing pyridine. The yellow, crystalline sulfonate ester **11a** was obtained in 51% yield overall (Scheme I).

The azaspiro[4.4]nonene derivative **12** is obtained through three isolated intermediates from pyrrolidone and allyl bromide (Scheme I). Treatment of

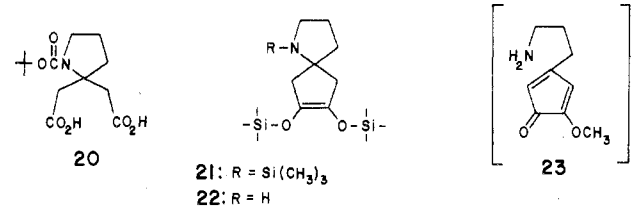
Scheme I



pyrrolidone with triethyloxonium fluoroborate produces the ethyl imidate ester (**17**), which reacts with excess allylmagnesium bromide (3 mol equiv) to afford 2,2-diallylpyrrolidine (**18**).[13] The latent carboxymethyl units are exposed to give **19** via an ozonolysis sequence after protection of the amine function as the *tert*-butoxycarbonyl derivative. The dialdehyde from ozonolysis is oxidized with basic silver hydroxide to the diacid **20** which, in turn, is esterified and the amino group liberated by heating in methanol containing HCl.

The amino diester **19** is converted to the desired spirocycle by means of several operations without isolation of the intermediates. Reaction of **19** with sodium–potassium alloy in the presence of excess chlorotrimethylsilane[15] produces a single product tentatively identified as the tris(trimethylsilyl) derivative **21**. It reacts rapidly with wet ether to give the enediol bis(trimethylsilyl) ether **22**. Reaction with bromine at −78° gives an adduct, which spontaneously fragments[16] at about −30° in dichloromethane to give bromotrimethylsilane and **13**. Consistent with the cyclopentane-1,2-dione unit, **13** exhibits acidity like that of a carboxylic acid, in this case an amino acid.

The amino α-diketone **13** polymerizes readily and is best utilized without purification or storage. Diazomethane in dichloromethane reacts with crude **13** in ethanol to give the desired spirocycle **12**, which cannot be stored neat, even at low temperatures, perhaps due to polymerization *via* elimination to the reactive cyclopentadienone derivative **23**.



The crude spirocycle **12** is mixed with the iodo-*p*-nitrobenzenesulfonate ester **11a** in acetonitrile containing several equivalents of diisopropylethylamine. After 15–20 hr at 25°, the alkylation product **24** is isolated as a colorless solid by column chromatography and recrystallization. The yield of purified material is 30–40% overall from amino diester **19**. An additional amount of **24** of somewhat lower purity is obtained as a second crop of crystals, bringing the yield of usable samples of **24** to 51% overall from **19**.

The ring closure of **24** to produce cephalotaxinone (**6**) is the pivotal step in the Cornell strategy. The iodo ketone **24** is arranged to undergo proton abstraction to form the enolate anion **25a** which must then undergo intramolecular nucleophilic substitution at the aromatic ring halogen. However, in the absence of powerful electron-withdrawing substituents on the aryl ring, the nucleophilic substitution is expected to be an unfavorable process.[17] The anion

(13) This procedure is based on the preparation of 2,2-diallylpiperidine.[14]

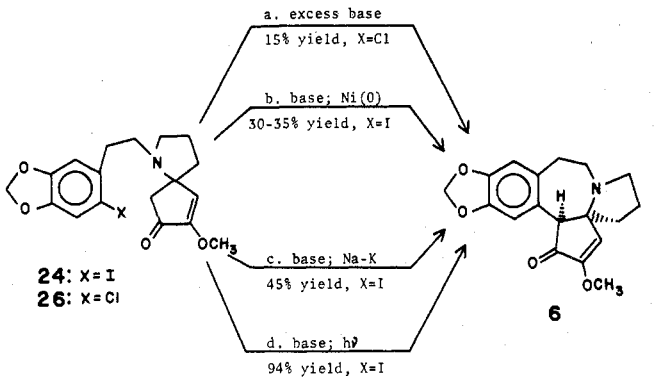
(14) R. Lukes and M. Cerny, *Collect. Czech. Chem. Commun.*, **26**, 2886 (1961).

(15) (a) K. Ruhlmann and S. Paredda, *J. Prakt. Chem.*, **12**, 18 (1960); (b) U. Schrapler and K. Ruhlmann, *Chem. Ber.*, **97**, 1383 (1964).

(16) (a) K. Ruhlmann, *Synthesis*, **2**, 236 (1971); (b) H. G. Heine, *Chem. Ber.*, **104**, 2869 (1971).

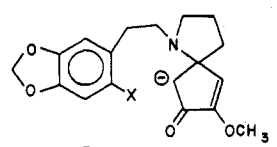
(17) Cf. J. F. Bunnett, *Q. Rev., Chem. Soc.*, **12**, 1 (1958).

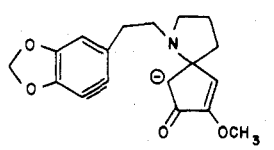
Scheme II



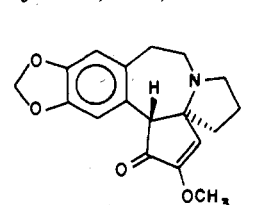
25a (generated from 1 mol equiv of lithium diisopropylamide or potassium triphenylmethide) is stable for hours at 0° and decomposes on heating without forming significant amounts of cephalotaxinone.

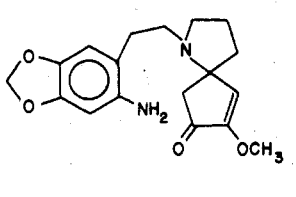
A well-established alternate pathway that is formally equivalent to nucleophilic aromatic substitution is nucleophilic addition to a transient benzyne intermediate.[18] Many intramolecular examples are known, including the key step in a synthesis of lysergic acid.[19] In application of this general method, chloro ketone **26** (prepared in a manner analogous to that used for **24**) reacted with a twofold excess of potassium triphenylmethide in 1,2-dimethoxyethane at 50° to produce a complex mixture of products from which cephalotaxinone (**6**) was isolated in 13–16% yield (Scheme II). At 0°, the reaction mixture contained only anion **25b** as shown by quenching experiments; at the higher temperatures, many reactions were induced by the excess base, apparently including the formation of the benzyne **27** and ring





closure. The cephalotaxinone was isolated from a very complex reaction mixture by repeated preparative layer chromatography. No other products were characterized; none of the isomer with the unnatural configuration, 4-epicephalotaxinone (**28**), was found. The apparent selectivity in the formation of **6** may be due to stereospecific ring closure or equilibration of the configuration at C-4 under the basic reaction conditions. Efforts to improve the efficiency of the benzyne reaction, including use of other bases (potassium amide, lithium diisopropylamide, potassium hydride, etc.) or substituting iodine on the ring (i.e., the iodo ketone **24**), all failed. Reaction with potassium amide in liquid ammonia leads to a new major product, the aniline derivative **29**. The limitations on this approach probably result from the relatively severe conditions necessary to generate the benzyne intermediate.

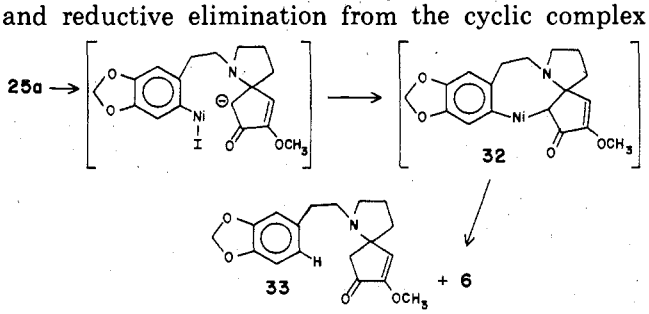




An alternative technique for the activation of aromatic rings toward coupling with anions, involving σ-arylmetal complexes, has been under study at Cornell[20,21] and elsewhere.[22] The opportunity to demonstrate the ease and selectivity of formation of σ-phenylnickel complexes and their high reactivity toward carbon–carbon bond formation was a major impetus in undertaking the total synthesis of cephalotaxine. Direct oxidative addition of aryl halides to zerovalent nickel complexes such as bis(1,5-cyclooctadiene)nickel and tetrakis(triphenylphosphine)nickel proceeds rapidly at 25° to produce σ-phenylnickel(II) halides (e.g., **30**).[23] In simple derivatives, for example with iodobenzene, the intermediate produced with bis(1,5-cyclooctadiene)nickel decomposes rapidly at 25° in solution to give biphenyl in high yield.[23a] Nevertheless, in the presence of carbanions such as enolate anions[20,21] or Grignard reagents,[22] the arylnickel halide is intercepted, probably as the complex with two σ-carbon ligands (as in **31**). Potential advantages to this approach include the compatibility of the oxidative addition step with many functional groups and the catalytic nature of the process with respect to the nickel reagent.

30 **31**

For the specific case of cephalotaxinone, the iodo ketone **24** was added to a solution of lithium diisopropylamide in tetrahydrofuran at −78° in order to generate enolate anion **25a**. Addition of bis(1,5-cyclooctadiene)nickel leads to rapid reaction at 0°, which produces a simple mixture containing equimolar amounts of cephalotaxinone (**6**) (30–35% yield by preparative tlc) and **33**. The latter appears to arise from hydrogen abstraction from the solvent.[21] On the basis of studies with simple aryl halides, the reaction is expected to proceed via oxidative addition, intramolecular anion displacement at nickel, and reductive elimination from the cyclic complex



(18) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes", Academic Press, New York, N.Y., 1967.

(19) M. Julia, F. LeGoffic, J. Igolen, and M. Baillarge, *Tetrahedron Lett.*, 1569 (1969).

(20) Unpublished work of Dr. R. Stauffer and Ms. L. Ryono.

(21) M. F. Semmelhack, R. D. Stauffer, and T. D. Rogerson, *Tetrahedron Lett.*, 4519 (1973).

(22) (a) Cf. Y. Kiso, K. Tamco, N. Miyake, K. Yamamoto, and M. Kumada, *Tetrahedron Lett.*, 3 (1974); (b) L. Cassar, S. Ferrara, and M. Foa, 166th National Meting of the American Chemical Society, Chicago, Ill., Aug. 1973, Abstract INDE-24.

(23) (a) M. F. Semmelhack, P. M. Helquist, and L. D. Jones, *J. Am. Chem. Soc.*, **93**, 5908 (1971); (b) M. Hidai, T. Kashiwagi, I. Ikeguchi, and Y. Jchida, *J. Organomet. Chem.*, **30**, 279 (1971); (c) D. H. Gerlach, A. R. Kane, G. W. Parshall, J. P. Jesson, and E. L. Muetterties, *J. Am. Chem. Soc.*, **93**, 3543 (1971); (d) D. R. Fahey, *ibid.*, **92**, 402 (1970).

32. None of the intermediates has been identified; the implied catalytic mechanism has not been tested for this example. Compound **33** can be iodinated to give **24** and then recycled, so the process can be made efficient, although cumbersome.

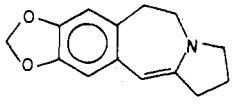
During the course of these studies of techniques for nucleophilic aromatic substitution, Bunnett and Rossi[24] published evidence that aryl radicals can couple with carbanions and showed that alkali metal reduction and photochemical cleavage of aryl halides are effective procedures for producing the required phenyl radicals. For example, reduction of bromobenzene in the presence of the potassium enolate anion of acetone provides phenylacetone in good yield.[24a]

Irradiation of iodobenzene in liquid ammonia containing acetone enolate ion produced the same product.[24b] Both techniques enable the ring closure of **24** to cephalotaxinone (Scheme II) to be achieved with improved efficiency.

With the very vigorous reducing conditions of sodium–potassium alloy in liquid ammonia, the anion **25a** (from potassium amide) produces 65% conversion to a mixture containing principally cephalotaxinone (45% yield based on **24** not recovered) and 28% of the reduction product, **33**. At higher conversion, serious further reduction of cephalotaxinone begins to become important, and no higher absolute yield of **6** is obtained. In general, an excess of sodium–potassium alloy is necessary to achieve substantial conversion, even though the reaction is suggested to proceed by a chain process which would require only catalytic quantities of the reducing agent.[24a]

The photochemical technique provides a much more efficient reaction. With excess (7 mol equiv) potassium *tert*-butoxide present to generate (reversibly) the anion **25a** from iodo ketone **24** in liquid ammonia at −33°, irradiation with medium-pressure mercury arc through Pyrex glass causes rapid disappearance of **25a** and formation of a single product, (±)-cephalotaxinone (**6**, 94% by preparative TLC). The TLC behavior and the ^{1}H NMR, ir, and mass spectra of the synthetic and natural materials were identical.[25] Reduction of **6** according to known procedures[10] gave a single product [(±)-cephalotaxine, **1**] which showed TLC and spectral behavior identical with that of natural (−)-cephalotaxine.[25]

The Fordham synthesis of cephalotaxine (**1**) took an approach conceptually quite different from the Cornell synthesis. Tetracyclic enamine **34**, envisioned as the key intermediate in this approach, would be suitably annelated, giving the pentacyclic *Cephalotaxus* alkaloid ring system.



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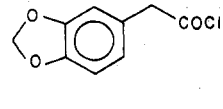

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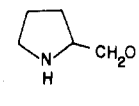
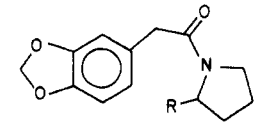


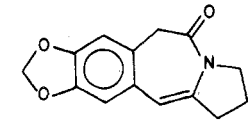
36

The synthetic approach to **1** began with piperonylformic acid (**14**), which on treatment with thionyl chloride gave the acid chloride **35**. Without purification, **35** was combined with 1-prolinol (**36**) in acetonitrile solution at −20° in the presence of anhydrous K_2CO_3, giving alcohol **37**. These particular conditions were needed in order to minimize N,O-diacylation of the prolinol, and **37** could be isolated in 82% yield. Alcohol **37** was then converted to aldehyde **38** by treatment with dimethyl sulfoxide, dicyclohexylcarbodiimide, and dichloroacetic acid to give **38** in



37: R = CH_2OH
38: R = CHO

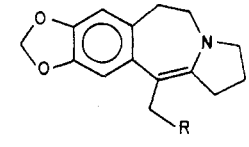
70% yield. Cyclization of **38** was readily effected with boron trifluoride etherate in chloroform at room temperature, giving the crystalline tetracyclic enamide **39** in 85% yield. None of the ortho cyclization prod-

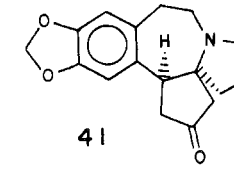


39

uct was observed. Reduction of **39** with $LiAlH_4$ in tetrahydrofuran proceeded smoothly to give enamine **34** in nearly quantitative yield. Compound **34** can be isolated as a white crystalline substance which darkens rapidly, especially in the presence of chlorinated solvents.

Initial approaches at annelation of **34** involved primarily attempted application of the "endocyclic enamine annelation".[26] Alkylation of **34** with propargyl bromide in acetonitrile produced the acetylene **40a**, which on mercury(II)-catalyzed hydration produced ketone **40b**. Treatment of **40b** with a variety of acids gave neither pentacyclic ketone **41** nor any other cy-





41

40a: R = C≡CH
40b: R = $COCH_3$
40c: R = $C(OCH_3)$= $CHCOOCH_3$

clopentanone-containing compound. In a related series of experiments, enamine **34** was combined with methyl 4-bromo-3-methoxycrotonate in acetonitrile, giving **40c**. Again, no cyclopentanone derivative was observed on treatment of **40c** with several acids, and, in general, **40c** was recovered unchanged. These observations may be compared with those reported by Dolby, et al.,[27] for a related system.

These workers also prepared enamine **34**, using a route different from the one just described. Dolby found that on treatment with γ-bromoacetoacetate **34** was converted to the unexpected, rearranged pentacyclic ketone **43a**, presumably *via* the intermediate keto ester **43** (Scheme III). Hydrolysis and decarboxylation of **43a** produced ketone **42**. Dolby also prepared ketone **40b**, which on treatment with pyrroldine, followed by 5% sulfuric acid, produced **42** in

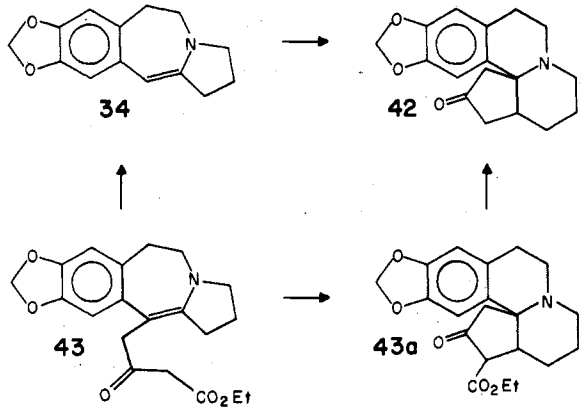
(24) (a) R. A. Rossi and J. F. Bunnett, *J. Am. Chem. Soc.*, **94**, 683, (1972); (b) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 1407 (1973).

(25) Samples of the natural material were kindly supplied by Mr. R. Powell, U.S. Department of Agriculture Laboratories at Peoria, Ill.

(26) (a) R. V. Stevens, R. K. Mehra, and R. L. Zimmerman, *Chem. Commun.*, 877 (1969); (b) F. C. Tahk and S. L. Keely, *J. Am. Chem. Soc.*, **90**, 5584, (1968).

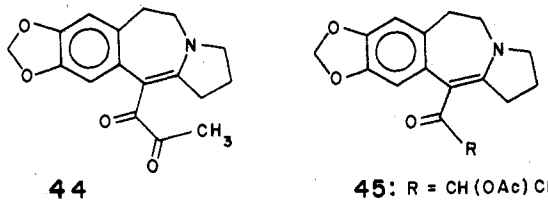
(27) L. J. Dolby, S. J. Nelson, and D. Senkovich, *J. Org. Chem.*, **37**, 3691 (1972).

Scheme III



19% yield. Dolby has suggested mechanisms for these rearrangements.[27]

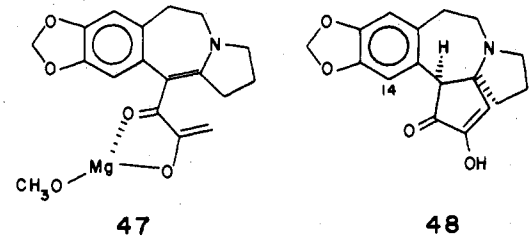
Since these approaches appeared unsuitable for adding the final D ring of cephalotaxine, a new tactic was undertaken, involving preparation of α-dicarbonyl compound 44, synthesized as follows. Acylation of enzyme 34 with 2-acetoxypropionyl chloride in acetonitrile produced 45. Saponification of 45 was effected with aqueous K_2CO_3, giving crystalline alcohol 46. Conversion of 46 to the α-dicarbonyl compound 44 was attempted with a variety of oxidizing agents, of which PbO_2 in refluxing toluene was the most suitable. However, yields were not reproducible, and 44 could not be obtained in crystalline form by this method. In an improved procedure, 44 was prepared as a crystalline solid in a single step by treating enamine 34 with the mixed anhydride prepared from ethyl chloroformate and pyruvic acid in acetonitrile (73% yield).



44

45: R = CH(OAc)CH$_3$
46: R = CH(OH)CH$_3$

Using Muxfeldt's clever solution to the problem of effecting intramolecular Michael reactions,[28] α-dicarbonyl compound 44 was cyclized with magnesium methoxide catalysis to give demethylcephalotaxinone (9) in 58% yield.[25] This cyclization presumably proceeds via the conformationally rigid magnesium enolate 47. Demethylcephalotaxinone was found by nmr to exist exclusively as tautomer 9; none of tautomer 48 appears to be present.



47 48

One might not have predicted this outcome. Molecular models indicate that it is difficult for the aromatic ring of 9 to achieve coplanarity with the cyclopentenone ring; full overlap of π orbitals of the two systems is thus precluded. This distortion from planarity is due both to ring strain and to severe steric interaction between the cyclopentenone hydroxyl group and the aromatic C-14 proton in 9. Tautomer 48 appears to have a far less severe steric interaction between the aromatic C-14 proton and the cyclopentenone carbonyl oxygen and does not appear to be particularly strained.

Despite this analysis, tautomer 9 is far more stable than 48. It did seem, however, that in the methylated product 10 the aforementioned steric interaction would be worse, while in cephalotaxinone (6) there might be only a slight increase in steric strain. It was hoped, therefore, that the relative stabilities of 9 and 48 would be reversed upon methylation, allowing formation of the desired cephalotaxinone (6).

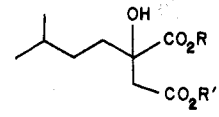
Treatment of 9 with diazomethane produced only the unnatural isomer 10, but this procedure might be a kinetically controlled methylation and not accurately reflect the relative stabilities of 6 and 10.

However, under what are presumably equilibrating conditions (dimethoxypropane, dioxane, *p*-TosOH, 17 hr) a mixture of ethers was obtained. After purification by chromatography the desired (±)-cephalotaxinone (6) could be isolated in 45% yield, along with only 15% of 10. Synthetic cephalotaxinone (6) was found to be identical with natural material.[25]

Sodium borohydride reduction of cephalotaxinone (6) completed the synthesis, producing (±)-cephalotaxine (1)[25] (85% yield), with no detectable amount of epicephalotaxine present.

Synthesis of the Harringtonine Side Chains

The first synthesis of the deoxyharringtonine side chain diacid 49 was reported by workers at the U.S. Department of Agriculture.[5b] They prepared the monoacid 50 by partial methylation of diacid 49.



49: R = R' = H
50: R = H, R' = CH$_3$

The Fordham group has developed a new method for preparation of the deoxyharringtonine side chain which allows easy differentiation of the two carboxyl groups. Epoxidation of readily available benzyl methyl itaconate 51 with *m*-chloroperbenzoic acid in refluxing dichloroethane containing a trace of 2,6-di-*tert*-butyl-4-methylphenol[29] produced 52 in high yield. On coupling[30] of 52 with lithium diisobutylcuprate, 53 was formed in 90% yield. Removal of the benzyl protecting group was effected by catalytic hydrogenation over platinum, giving crystalline acid 50 in nearly quantitative yield.[31]

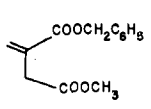
Acid 50 could be resolved into its enantiomers by use of ephedrine. We compared the circular dichroism curve of the (−) isomer (natural enantiom-

(28) H. Muxfeldt, M. Weigele, and V. Van Rheenen, *J. Org. Chem.*, 30, 3573 (1965).

(29) Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and K. Kakoi, *J. Chem. Soc., Chem. Commun.*, 64 (1972).

(30) C. R. Johnson, R. W. Herr, and D. M. Wieland, *J. Org. Chem.*, 38, 4263 (1973).

(31) T. Ipaktchi and S. M. Weinreb, *Tetrahedron Lett.*, 3895 (1973).



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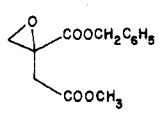

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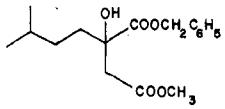

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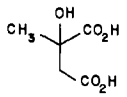
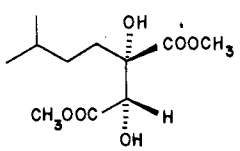


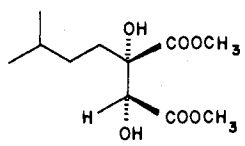
54

er) with citramalic acid (**54**) of known absolute configurations and found that the natural product (**5**) has the *R* configuration in the side chain.[32,33] The diacid side chain of harringtonine (**2**) was synthesized, using a different route, by Kelly, et al.[34]

The side chains of harringtonine, deoxyharringtonine, and homoharringtonine each possess only one asymmetric center, so that no stereochemical problems are associated with their synthesis. The isoharringtonine (**3**) side chain, however, contains two centers of asymmetry. Initial structural work did not determine the relative configuration of these centers. The best approach seemed to be unambiguous synthesis of both possible isomers, **55** (threo) and **56** (erythro).[35]



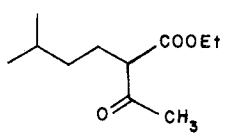
55



56

Synthesis of these esters began with ethyl isoamylacetoacetate (**57**), which was treated with 2 equiv of bromine in refluxing ether, followed by boiling the crude product with aqueous potassium hydroxide[36] to give the alkylfumaric acid **58** in 35% yield. Compound **58** was cleanly esterified with methanolic sulfuric acid, producing **59**. Fumaric acid **58**, on heating with phosphorus pentoxide, produced anhydride **60** which on treatment with methanolic sulfuric acid gave the alkyl maleate **61**. The structures of **59** and **61** were confirmed by examining the NMR spectrum of each. The single vinyl proton of fumarate **59** (δ 6.80) compared favorably with that of dimethyl mesaconate (δ 6.68). Likewise, the vinyl proton of maleate **61** (δ 5.85) was close to that of dimethyl citraconate (δ 5.77).

Cis hydroxylation of **59** and **61** (osmium tetroxide, *tert*-butyl alcohol, hydrogen peroxide, 50°) produced the threo diol **55** and the erythro diol **56**, respectively. Comparison of the dimethyl ester derived by transesterification[5] of isoharringtonine (**3**) with both **55** and **56** showed that the natural material is identical with **56** and thus has the erythro configuration.



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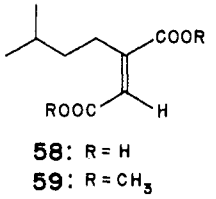
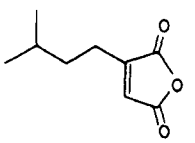
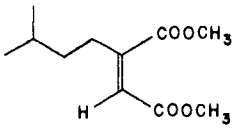


58: R = H
59: R = CH_3

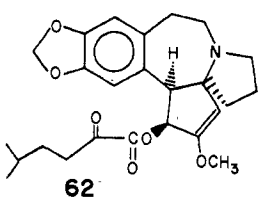


60

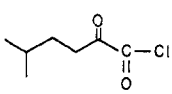


61

Attempts have been made in several laboratories to combine directly the appropriate monoacid with cephalotaxine (**1**) in order to prepare deoxyharringtonine (**5**). All efforts have failed to date.[37] The major reason for this surprising failure appears to be steric problems involved in esterifying a hindered acid such as **50** with the hindered alcohol group of cephalotaxine (**1**). A nonconvergent, low-yield synthesis of deoxyharringtonine has been reported,[38] however. Keto ester **62** was prepared from cephalotaxine (**1**) and acid chloride **63**. Addition of Li-



62



63

$CH_2CO_2CH_3$ to **62** produced deoxyharringtonine (6% yield) and epideoxyharringtonine (9%).

Conclusion

Harringtonine (**2**) and related esters (**3**–**5**), the rare antileukemia agents from *Cephalotaxus*, are the targets of organic total synthesis. This Account has related two successful efforts to generate the central polycyclic ring structure (cephalotaxine) common to each of the esters and the approaches under way to prepare each of the ester side chains. The challenge remains to find efficient techniques for joining cephalotaxine to the side chains. Synthesis of natural (e.g., **7** and **8**) and unnatural analogs of cephalotaxine is also a goal in the search for effective antileukemia agents related to the *Cephalotaxus* alkaloids.

The work at Fordham University was supported by the National Cancer Institute and the Research Corporation. S.M.W. is indebted to his collaborators, Dr. J. Auerbach and Ms. T. Ipaktchi. The effort at Cornell was carried out primarily by Drs. B. P. Chong, R. D. Stauffer, and T. D. Rogerson, with significant assistance from Dr. P. Helquist, Mr. L. D. Jones, and Mr. A. Chong. The work was supported under generous grants from the National Institutes of Health and the Petroleum Research Fund, administered by the American Chemical Society.

(32) We are grateful to Professor W. Klyne, University of London, for his collaboration in obtaining these cd measurements.

(33) Professor S. Brandange has independently determined the absolute configuration of the deoxyharringtonine, harringtonine, and homoharringtonine side chains, and our results agree with his: S. Brandange, S. Josephson, and S. Vallen, *Acta Chem. Scand., Ser. B*, **28**, 153 (1974).

(34) T. R. Kelly, J. C. McKenna, and P. A. Christenson, *Tetrahedron Lett.*, 3501 (1973).

(35) T. Ipaktchi and S. M. Weinreb, *Tetrahedron Lett.*, 3895 (1973).

(36) W. R. Vaughm and K. S. Andersen, *J. Am. Chem. Soc.*, **77**, 6702 (1955).

(37) K. L. Mikolajczak, R. G. Powell, and C. P. Smith, Jr., Abstracts, 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 1973.

(38) K. L. Mikolajczak, C. R. Smith, Jr., D. Weisleder, T. R. Kelly, J. C. McKenna, and P. A. Christenson, *Tetrahedron Lett.*, 283 (1974).