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Synthesis of Eupolauramine via an Intramolecular Kondrat'eva Pyridine Synthesis

Jeremy I. Levin and Steven M. Weinreb*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

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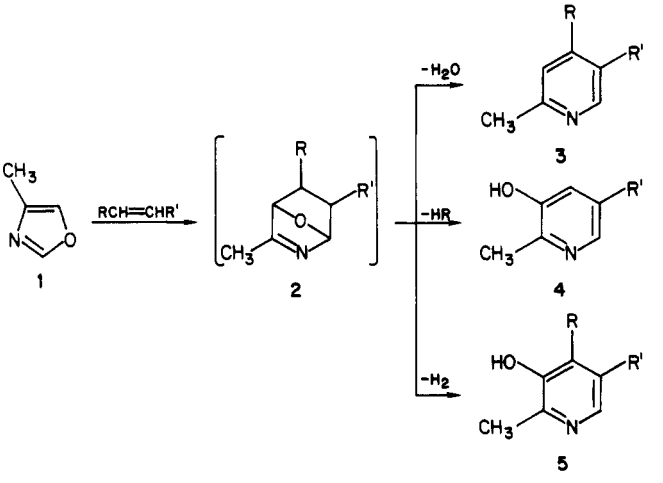
A strategy has been tested for synthesis of annulated pyridines which involves the intramolecular Diels–Alder cycloaddition of an oxazole with an alkene. Oxazole **21** was prepared in four steps from (*o*-methoxyphenyl)oxazoline **16**. Upon heating, **21** produced mixtures of two tricyclic hydroxypyridines **23** and **24** in good total yield. Thermolysis of **21** in the presence of DBN changed the course of the reaction, leading to the desired tricyclic pyridine **25**. Two short routes have been developed for conversion of **25** to the structurally unique azaphenanthrene alkaloid eupolauramine (**6a**). The first sequence involved intermediate azaphenanthrene-*o*-quinone **30** and hydroxy lactam **31** (Scheme IV). A more efficient route from **25** utilized the azaarene epoxide **33**, which was converted via lactam alcohol **34a** to eupolauramine.

In 1957 Kondrat'eva described the first example of a Diels–Alder cycloaddition of an oxazole with an alkene to produce a pyridine.[1,2] Thus, a ring-substituted oxazole such as **1** will react with both electron-rich and electron-deficient alkenes to afford an intermediate bicyclic adduct **2** which is usually not detected (Scheme I).[3] Adduct **2** can decompose via the three different routes shown in the scheme.[4] Loss of water from **2** affords the substituted pyridine **3**. Alternatively, depending upon the nature of the substituents on the alkene used in the cycloaddition, an elimination to give a pyridinol **4** may occur. Finally, a curious oxidative fission to yield pyridinol **5** has also been observed upon occasion. This methodology has been used extensively in synthesis of pyridoxol and derivatives[2] but has found little use in preparation of other pyridine-containing natural products. This may be due in part to the fact that only certain substituted oxazoles undergo the [4 + 2] cycloaddition.[2a] It was our hope that this sensitivity to oxazole substitution pattern could be overcome by effecting the cycloaddition intramolecularly. At the outset of this work, no example had been reported of an intramolecular Kondrat'eva pyridine synthesis although Jacobi et al. had elegantly applied a related intramolecular cycloaddition of acetylenes with oxazoles in preparation of some annulated furans.[5]

Scheme I



As a target to test the feasibility of the proposed intramolecular Diels–Alder cycloaddition we chose the un-

(1) Kondrat'eva, G. Y. *Khim. Nauka Prom.* **1957**, *2*, 666. Kondrat'eva, G. Y. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1959**, 484.

(2) For reviews of Diels–Alder reactions of oxazoles, see: (a) Karpeiskii, M. Y.; Florent'ev, V. L. *Russ. Chem. Rev. (Engl. Transl.)* **1969**, *38*, 540. (b) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389. (c) Lakhan, R.; Ternai, B. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1974; Vol. 17. (d) Turchi, I. J. *Ind. Eng. Chem. Prod. Res. Dev.* **1981**, *20*, 58.

(3) For exceptions, see: Matsuo, T.; Miki, T. *Chem. Pharm. Bull.* **1972**, *20*, 669. Naito, T.; Ueno, K.; Sano, M.; Omura, Y.; Itoh, I.; Ishikawa, F. *Tetrahedron Lett.* **1968**, 5767.

(4) (a) Naito, T.; Yoshikawa, T.; Ishikawa, F.; Isoda, S.; Omura, Y.; Takamura, I. *Chem. Pharm. Bull.* **1965**, *13*, 869. (b) Yoshikawa, T.; Ishikawa, F.; Omura, Y.; Naito, T. *Ibid.* **1965**, *13*, 873. (c) Yoshikawa, T.; Ishkawa, F.; Naito, T. *Ibid.* **1965**, *13*, 878. (d) Naito, T.; Yoshikawa, T. *Ibid.* **1966**, *14*, 918.

(5) (a) Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* **1978**, *100*, 7748. Jacobi, P. A.; Walker, D. G.; Odeh, I. M. A. *J. Org. Chem.* **1981**, *46*, 2065. (b) Recently some examples of intramolecular alkene–oxazole cycloadditions to give pyridines have appeared: Shimada, S.; Tojo, T. *Chem. Pharm. Bull.* **1983**, *31*, 4247.

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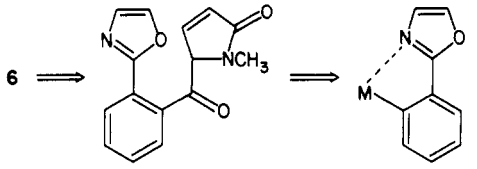
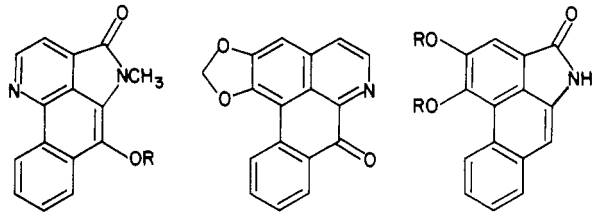
Scheme II



9 10

usual azaphenanthrene alkaloid eupolauramine (**6a**).[6] This compound was first isolated in 1972 by Taylor et al. from the bark of *Eupomatia laurina*, a small tree found along the eastern coasts of Australia and New Guinea.[7,8] The structure of the alkaloid proved sufficiently unique that it could not be solved by chemical and spectral methods on the very small quantity of material available. However, structure **6a** was finally established unambiguously by X-ray crystallography.[9] The biosynthesis of eupolauramine has not been investigated, but it is possible that the alkaloid arises from liriodenine (**7**) with which it co-occurs and would seem to have a close biogenetic relationship to the aristolactams **8**.[10]

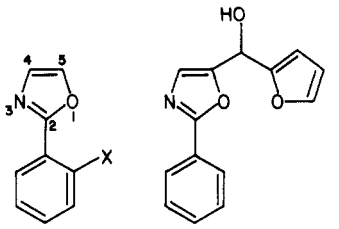


6a, R=CH_3
6b, R=H
6c, R=Ac

7 8

Our initial synthetic strategy for the production of eupolauramine (**6**) required the synthesis of a complex ortho-acylated 2-phenyloxazole such as **9** (Scheme II). Upon examination of the literature it became apparent that very few methods exist for making 4,5-unsubstituted 2-aryloxazoles. Furthermore, those methods that are available did not seem to be compatible with a 2-aryl group substituted with a sensitive side chain, since oxazole ring formation generally requires high temperatures and strongly acidic conditions.[2] However, 2-phenyloxazole (**11**)[11] and 2-(*o*-aminophenyl)oxazole (**12**)[12] are readily available compounds and appeared potentially useful for preparing the desired ortho-acylated aryloxazole via a metalated species **10**. The *o*-amino compound **12** was readily converted into the (*o*-bromophenyl)oxazole **13** via the diazonium tetrafluoroborate salt **14** in a Sandmeyer reaction.[13]

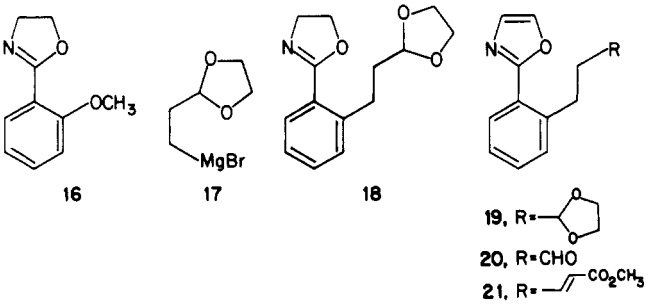
Several attempts were made to metalate 2-phenyloxazole (**11**) in the ortho position of the phenyl ring using *n*-butyllithium but the desired aryllithium compound **10** (M = Li) was not formed. ^1H NMR analysis of the product obtained upon D_2O quench of the reaction mixture indicated that the 5-position of the oxazole ring had actually been cleanly metalated in preference to the phenyl ring. The *same* deuterated compound was obtained by lithium–halogen exchange on 2-(*o*-bromophenyl)oxazole (**13**). Also, addition of compound **13** to a suspension of activated magnesium[14a] (generated from anhydrous magnesium chloride and sodium naphthenide[14b]) followed by addition of furfural did not provide the desired ortho-substituted 2-phenyloxazole but rather gave the 5-alkylated oxazole **15**. Thus, the C-5 proton of an oxazole is apparently thermodynamically more acidic than the ortho proton of the phenyl ring,[15] and the high degree of stabilization observed in structurally related ortho-metalated aryl oxazolines[16,17] does not apply here as we had hoped.



11, X=H
12, X=NH_2
13, X=Br
14, X=$N_2^+BF_4^-$

15

Since we were unable to functionalize an intact 2-aryloxazole in the desired manner, we next turned to synthesis of a considerably simpler Diels–Alder precursor via oxazoline chemistry developed by Meyers et al.[17,18] (Methoxyphenyl)oxazoline **16**, prepared from *o*-anisic acid and ethanolamine (75% yield), was treated with excess Grignard reagent **17**[18] to afford the alkylated oxazoline **18** (95%).[19]



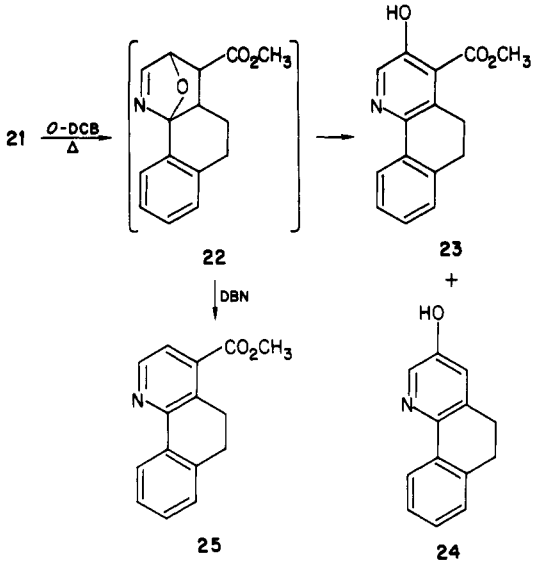
16 17 18

19, R=
20, R=CHO
21, R=

The dehydrogenation of oxazoline **18** to the oxazole **19** proved to be a relatively difficult transformation to effect cleanly. Manganese dioxide, *o*-chloranil, barium manganate, and trityl tetrafluoroborate each failed to react with the oxazoline. DDQ did accomplish the desired transformation but afforded the desired oxazole **19** in only 36% yield. Nickel peroxide was found to be the most efficient means of accomplishing the conversion to the oxazole.[20]

(6) (a) For a preliminary account of this research, see: Levin, J. I.; Weinreb, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 1397. (b) Levin, J. I. Ph.D. Thesis, The Pennsylvania State University, 1983.
(7) Bowden, B. F.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1972**, *25*, 2659.
(8) Bowden, B. F.; Picker, K.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1975**, *28*, 2681.
(9) Bowden, B. F.; Freeman, H. C.; Jones, R. D. G. *J. Chem. Soc. Perkin Trans. 2* **1976**, 658.
(10) Shamma, M.; Moniot, J. L. "Isoquinoline Alkaloids Research 1972–1977"; Plenum Press: New York, 1978; pp 189–196. Mix, D. B.; Guinaudeau, H.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 657.
(11) Cass, W. E. *J. Am. Chem. Soc.* **1942**, *64*, 785. Ferrini, P. G.; Marxer, A. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 99.
(12) Brown, E. V. *J. Org. Chem.* **1977**, *42*, 3208.
(13) Kobayashi, M.; Yamada, E.; Matsui, M.; Kobori, N. *Org. Prep. Proced. Int.* **1969**, *1*, 221.
(14) (a) Rieke, R. D. *Acc. Chem. Res.* **1977**, *10*, 301. (b) Arnold, R. T.; Kulenovic, S. T. *Synth. Commun.* **1977**, *7*, 223.
(15) Cf: Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1981**, *22*, 3163.
(16) Gschwend, H. W.; Hamdan, A. *J. Org. Chem.* **1975**, *40*, 2008.
(17) Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787. Meyers, A. I.; Temple, D. L. *J. Am. Chem. Soc.* **1970**, *92*, 6646.
(18) Buchi, G.; Wuest, H. *J. Org. Chem.* **1969**, *34*, 1122. Marfat, A.; Bal, S. A.; Helquist, P. *Ibid.* **1982**, *47*, 5045.
(19) Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383.
(20) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497.

Scheme III



Thus, upon refluxing a suspension of 15 equiv of nickel peroxide in a dry benzene solution of the oxazoline for 18 h, the oxazole **19** and the starting oxazoline **18** were the only compounds detectable by TLC. The oxazole **19** was obtained in 56% isolated yield based on starting material recovered, which was approximately 50% of the original quantity used. Longer reaction times or the addition of fresh reagent failed to increase either the yield of oxazole or the percent conversion.

Hydrolysis of the acetal functionality of **19** to afford aldehyde **20** was performed with 3 N HCl at room temperature (90%). Reaction of this aldehyde with the carbanion derived from trimethyl phosphonoacetate gave exclusively the trans unsaturated ester **21** (90%) as evidenced by ^{1}H NMR (J = 15 Hz).

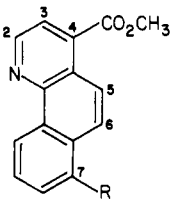
When a 0.014 M *o*-dichlorobenzene solution of unsaturated ester **21** was heated at reflux under nitrogen for 3 h, two tricyclic hydroxypyridines **23** and **24** were obtained in a 1:1.7 ratio in 76% total yield (Scheme III). The ^{1}H NMR spectrum of each compound showed a singlet at approximately 8.5 ppm, corresponding to the C-2 proton of a 3-substituted pyridine.

Compounds **23** and **24** probably arise via Diels–Alder adduct **22** which undergoes oxidative fragmentation through the "hydride elimination" pathway mentioned above. Although this general type of cycloadduct decomposition has been observed several times before in intermolecular cases,[4] this would appear to be the first case in which an excellent yield of such pyridinol products has been obtained when no hydride accepter (i.e., H_2O_2) was used to "direct" decomposition through this pathway. Normally, yields of this type of fragmentation product have not exceeded 25%.

It was our initial assumption that either traces of oxygen which where present during the Diels–Alder reaction and/or the solvent itself was responsible for the oxidative fragmentation of the tetrahydroepoxypyridine cycloadduct **22**. Thus, cycloaddition reactions were performed using ethylbenzene, bromobenzene, and *o*-dichlorobenzene as solvent after thoroughly degassing each with argon. In every case, however, the 3-hydroxypyridines **23** and **24** were the sole products of the Diels–Alder reactions. The only affect of changing solvent appeared to be a decrease in the relative amount of the decarboxylated pyridinol **24** obtained when the reaction was run at a lower reflux temperature. For example, the ratio of **23** to **24** changed to 4.4:1 (70% total yield) when bromobenzene was used as the reaction solvent. In fact, even when a solution of the Diels–Alder precursor **21** in *o*-dichlorobenzene was thoroughly deoxygenated and heated in a sealed tube at 185 °C the 3-hydroxypyridine **23** was still obtained. However, in this case compound **24** was not detected and the yield of **23** had decreased to only 20%. Thus, it would appear that oxygen is at least partly responsible for the oxidative decomposition of cycloadduct **22**. In the absence of oxygen the Diels–Alder adduct must follow other degradative pathways, possibly involving disproportionation. It is not clear why the loss of water from the bridged Diels–Alder adduct **22** is so unfavorable that the desired 3-unsubstituted pyridine **25** was not observed.

In 1968 Colin patented a synthesis of isonicotinic acid esters and isonicotinonitriles via the Diels–Alder reaction of oxazole with acrylic esters or acrylonitrile in the presence of triethylamine.[21] It seemed reasonable that the triethylamine might function here by accelerating the elimination of water from the initially formed Diels–Alder cycloadduct. If that were in fact the case, we reasoned that the use of a nonnucleophilic base in the Diels–Alder reaction of compound **21** might increase the rate of the loss of water from cycloadduct **22** relative to that of the oxidative fragmentation, thereby providing the desired annulated pyridine **25** instead of the 3-hydroxypyridines. Indeed, when Diels–Alder precursor **21** was refluxed in *o*-dichlorobenzene for 16 h with 0.75 equiv of DBN only the desired tricyclic pyridine ester **25** was produced (76%). Interestingly, tlc analysis during the course of the cycloaddition indicated that the use of DBN slowed the overall rate of formation of pyridine products. It is possible that DBN is acting as a scavenger of adventitious acid, and it is known that acids can catalyze both the initial cycloaddition of oxazoles and olefins and the subsequent decomposition of the epoxytetrahydropyridine cycloadducts.[22] In any case, the formation in good yield of the dihydrobenzoquinoline **25** clearly demonstrated that, contrary to their reported lack of reactivity in *inter*molecular cycloadditions,[2a] 2-phenyloxazoles are useful azadienes for *intra*molecular Diels–Alder reactions.

Although tricyclic pyridine **25** was somewhat less functionalized than the adduct toward which we had initially aimed, we decided to explore routes for its conversion to eupolauramine (**6a**). Dehydrogenation of **25** with NBS gave the azaphenanthrene **26** (90%). By analogy with

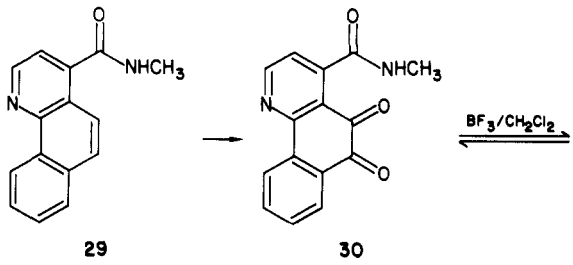


26, R=H
27, R=NO_2
28, R=NH_2

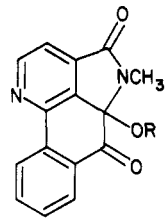
reported nitrations of some carboxyl-substituted phenanthrenes used in synthesis of aristolactams, we hoped that azaphenanthrene **26** could be functionalized at C-5.[23] However, treatment of **26** with H_2SO_4/HNO_3 (−20 °C) gave only one nitro compound eventually assigned structure **27**

(21) Colin, P. French Patent 1 550 352, 1968; *Chem. Abstr.* **1970**, *72*, 31629.
(22) Firestone, R. A.; Harris, E. E.; Reuter, W. *Tetrahedron* **1967**, *23*, 943. Florentlev, V. L.; Drobinskaya, N. A.; Ionova, L. V. *Tetrahedron Lett.* **1967**, 1747.
(23) Gorecki, P.; Otta, H. *Pharmazie* **1975**, *30*, 337. Gorecki, P. *Monatsh. Chem.* **1982**, *113*, 201.

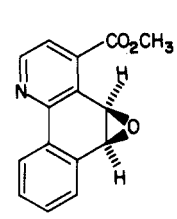
Scheme IV



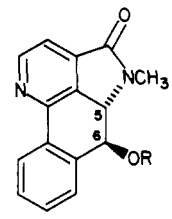
29 30



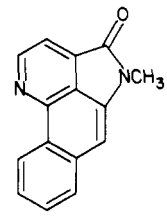
31, R=H
32, R=Ac



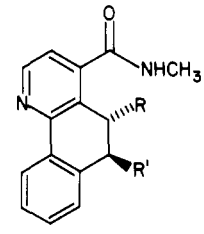
33



34a, R=H
34b, R=Ac



35



36a, R'=OH, R'=NHCH3
36b, R=NHCH3, R'=OH

(39%). Reduction of **27** gave an amine which could not be cyclized to a lactam, and careful analysis of its 360-MHz ^{1}H NMR spectrum indicated that it was in fact substituted at C-7 (i.e., **28**).[24] We were thus forced to investigate other methods for functionalizing the C-5,6 double bond of **26**.

Treatment of ester **26** with the reagent prepared from methylamine hydrochloride and trimethyl aluminum[25] yielded amide **29** (92%). The next step of the proposed synthesis proved to be difficult. Our plan was to oxidize the azaphenanthrene system **29** to the corresponding 5,6-azaphenanthrene quinone **30**. The quinone, we believed, could then be converted into hydroxylactam **31** (Scheme IV). This strategy did turn out to be partially successful. It was found that both chromium trioxide in acetic acid and iodic acid in acetic acid[26] were capable of converting the arene into *o*-quinone **30**. Moreover, in both experiments a separable mixture of the quinone and the hydroxy lactam **31** was isolated. Furthermore, if the pure quinone **30** was treated with boron trifluoride etherate, approximately a 1:1 mixture of the starting *o*-quinone and lactam **31** was obtained. Unfortunately the yield in the oxidation of azaphenanthrene **29** could never be improved over about 33% of **30** and **31** combined. However, since **31** was so close to the target alkaloid, we decided to complete a synthesis via this route.

Acetylation of **31** with acetic anhydride/DMAP afforded acetate **32**, which upon reduction with chromous chloride[27] provided demethyleupolauramine (**6b**) in 77% yield as a bright orange solid. Methylation of **6b** afforded eupolauramine (**6a**), identical with authentic material.[28]

We have also investigated a more efficient approach to eupolauramine from azaphenanthrene ester **26**. Oxidation of **26** with sodium hypochlorite under phase-transfer conditions as described by Hamilton and co-workers[29] gave azaarene epoxide **33** (69%). In order to introduce the methylamino group needed to form the lactam ring of eupolauramine, epoxide **33** was treated with dimethylaluminum *N*-methylamide.[30,31] Different ratios of products could be obtained in this step depending on reaction temperature and time. Thus, if the aminolysis was performed in methylene chloride at room temperature for 4 h, the desired lactam alcohol **34a** could be isolated in 49% yield based on recovered starting material (39%). On the other hand, if the reaction was run in refluxing benzene for 3 h the azaphenanthrene lactam **35** was obtained in 44% yield as the major isolable product. Analysis of the ^{1}H NMR spectrum of **34a** revealed a doublet with a coupling constant of 11 Hz at δ 4.6, which was assigned to the C-5 methine proton, indicating a trans relationship between the protons at carbons 5 and 6. A molecular model of **34a** shows that the dihedral angle for these protons is approximately 175°, whereas a cis relationship between the protons would provide a compound having a dihedral angle of approximately 45° and therefore an expected coupling constant of about 5 Hz.

It should be noted that lactam alcohol **34a** could be readily converted into azaphenanthrene lactam **35** by mild treatment with either mineral acid or base. The base-promoted elimination of water from **34a** to form **35** was surprisingly facile considering the fact that a syn β-elimination is required.

One other compound was also produced in 18% yield in the room-temperature aminolysis of epoxide **33**. Two structures, **36a** and **36b**, are possible for this compound which is an amide amino alcohol. At present it is not clear which of these regioisomeric structures is in fact the correct one.

Much to our surprise, oxidation of the benzylic hydroxyl group of **34a** to produce demethyleupolauramine (**6a**) could not be effected, although many reagents were tried. Those oxidation methods which required basic reaction conditions such as an Oppenauer oxidation, activated Me_2SO oxidation, and CrO_3/pyridine generally provided only mixtures of the starting alcohol and the dehydration product **35**. Reagents such as MnO_2, $BaMnO_4$, DDQ, chloranil, and sodium hypochlorite did not react at all with the alcohol. However, it was possible to convert alcohol **34a** into acetate **34b** with acetic anhydride and pyridine in 76% yield. Acetate **34b** was then readily oxidized with *N*-bromosuccinimide[32] to provide acetyl demethyleupolauramine (**6c**) in 73% yield. Curiously, all attempts to methylate alcohol **34a** failed to afford the corresponding methyl ether

(24) Cf: Haid, R. *Monatsh. Chem.* **1906**, *27*, 318.
(25) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
(26) Fuson, R. C.; Tomboulian, P. *J. Am. Chem. Soc.* **1957**, *79*, 956. Williams, A. G. *Ibid.* **1921**, *43*, 1911.
(27) House, H. O.; Carlson, R. G. *J. Org. Chem.* **1964**, *29*, 74.
(28) We are grateful to Dr. W. C. Taylor for a sample of authentic eupolauramine.
(29) Krishnan, S.; Kuhn, D. G.; Hamilton, G. A. *J. Am. Chem. Soc.* **1977**, *99*, 8121.
(30) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171. Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1979**, *59*, 49.
(31) Overman, L. E.; Flippin, L. A. *Tetrahedron Lett.* **1981**, *22*, 195.
(32) Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317.

which might have been directly converted into eupolauramine. Again, the dehydration product **35** was the major product of these methylation attempts.

The aromatic acetate **34b** could be cleanly hydrolyzed with aqueous KOH to form the bright red potassium phenoxide which could be directly O-methylated with dimethyl sulfate to give eupolauramine (**6a**) (82%) identical with an authentic sample.[28]

Thus, this work has demonstrated that it is possible to efficiently generate annulated pyridines via an intramolecular Diels–Alder reaction of an oxazole acting as an azadiene. We hope to use this basic strategy in synthesis of other polycyclic pyridine-containing natural products.[6b]

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 197 instrument. ^{1}H Nuclear magnetic resonance spectra (60 MHz) were recorded on a Varian EM-360 NMR spectrometer. ^{1}H NMR spectra at 200 MHz were obtained on a Bruker WP-200 spectrometer and at 360 MHz on a Bruker WM-360 spectrometer. All ^{1}H NMR spectra were recorded at 60 MHz unless otherwise noted. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, IL. Low and high resolution mass spectra were obtained at 50–70 eV by electron impact on an Associated Electrical Industries, Ltd. MS-9/50 double focusing instrument. Analytical and preparative thin-layer chromatography were performed using E. M. Merck silica gel 60 PF-254 and column chromatography was done using 70–230-mesh silica gel 60 (E. M. Merck) as the stationary phase. Methylene chloride was freshly distilled from P_2O_5, benzene from CaH_2, and THF from sodium/benzophenone ketyl.

2-(*o*-Bromophenyl)oxazole (13). To a solution of 0.075 g (0.470 mmol) of (aminophenyl)oxazole **12**[12] in 5 mL of 50% aqueous fluoroboric acid cooled to 0 °C was slowly added 0.042 g (0.607 mmol) of sodium nitrite dissolved in 0.2 mL of water. After 20 min the yellow precipitate was filtered and was washed successively with water, methanol, and ether. The solid was dried in vacuo to yield 0.096 g (79%) of diazonium salt **14**.

To a rapidly stirred solution of 0.248 g (1.11 mmol) of cupric bromide in 3 mL of Me_2SO was added 0.200 g (0.722 mmol) of diazonium salt **14** in 1 mL of Me_2SO. After 5 min the reaction mixture was diluted with water and was extracted 3 times with benzene. The combined organic extract was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified on two 20 × 20 cm silica gel preparative TLC plates eluting with 1:3 ethyl acetate/hexane to provide 0.150 g (87%) of (bromophenyl)oxazole **13** as a colorless oil: IR (film) 3130, 3060, 1600, 1570, 1360, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.21 (1 H, s), 7.23 (2 H, m), 7.68 (1 H, s), 7.70 (2 H, m); mass spectrum, m/z (relative intensity) 225 (31.8), 223 (33.0), 197 (11.9), 195 (11.7), 116 (29.9), 89 (31.2).

2-(*o*-Methoxyphenyl)oxazoline (16). To a solution of 26.0 g (0.43 mol) of ethanolamine in 100 mL of methylene chloride at 0 °C was added dropwise a solution of 30.0 g (0.18 mol) of anisoyl chloride in 100 mL of methylene chloride. The reaction mixture was stirred at room temperature for 2 h and was diluted with 300 mL of water. The aqueous layer was extracted 3 times with ethyl acetate and the combined organic extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to provide 31.1 g (90%) of crude amide alcohol.

To a solution of 27.0 g (0.16 mol) of the above material in 100 mL of methylene chloride was added dropwise 63.5 g (0.53 mol) of thionyl chloride. When the vigorous evolution of gas had subsided, the reaction mixture was poured into 300 mL of diethyl ether, and the resulting white precipitate was collected and washed with ether. The hydrochloride salt was neutralized with 10% aqueous sodium hydroxide and was extracted with methylene chloride. The organic extract was dried over $MgSO_4$ and concentrated in vacuo, and the residue was distilled (bp 109 °C (5 torr)) to provide 18.0 g (75%) of oxazoline **16**: IR (film) 2950, 1645, 1600, 1490, 1460, 1360, 1260, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.90 (3 H, s), 4.15 (4 H, m), 6.90 (2 H, m), 7.30 (1 H, m), 7.75 (1 H, m); mass spectrum, m/z (relative intensity) 177 (74.3), 148 (72.2), 132 (28.6), 117 (100), 105 (55.5), 91 (50.2), 77 (47.0); exact mass calcd for $C_{10}H_{11}NO_2$ 177.0790, found 177.0798.

2-[2-[2-(1,3-Dioxolan-2-yl)ethyl]phenyl]-4,5-dihydrooxazole (18). To a vigorously stirred mixture of 1.74 g (0.072 mol) of magnesium turnings in 30 mL of THF containing one crystal of iodine was added 5 mL of a solution of 10.86 g (0.060 mol) of β-bromopropionaldehyde ethylene acetal in 50 mL of THF.[18] The mixture was heated until the iodine color disappeared and was cooled to 0 °C. The remainder of the bromide was added slowly, and the mixture was stirred at room temperature for 1 h after the addition was complete.

The cloudy, brown Grignard reagent **17** was added slowly to a solution of 3.52 g (0.020 mol) of oxazoline **16** in 30 mL of THF. The reaction mixture was stirred overnight at room temperature, was quenched with saturated NH_4Cl solution, and was extracted 3 times with dichloromethane. The combined organic extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on 75 g of silica gel eluting with ethyl acetate to provide 4.69 g (95%) of the product **18** as a colorless oil: IR (film) 2950, 1640, 1400, 1350, 1240, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.95 (2 H, m), 3.10 (2 H, m), 3.80 (4 H, m), 4.15 (4 H, m), 4.82 (1 H, t, J = 4.5 Hz), 7.18 (3 H, m), 7.65 (1 H, m); mass spectrum, m/z (relative intensity) 247 (35.0), 202 (21.5), 174 (100), 161 (18.2), 158 (8.9), 131 (61.1), 103 (33.3), 73 (76.4); exact mass calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1215.

2-[2-[2-(1,3-Dioxolan-2-yl)ethyl]phenyl]oxazole (19). Method A. To a solution of 0.050 g (0.20 mmol) of oxazoline **18** in 10 mL of freshly distilled dry benzene was added 0.356 g (3.03 mmol) of nickel peroxide.[20] The reaction mixture was refluxed for 18 h, cooled to room temperature, and filtered through Celite. The filtrate was concentrated in vacuo and the residue was chromatographed on one 20 × 20 cm silica gel preparative TLC plate eluting with 1:1 ethyl acetate/hexane to afford 0.023 g (46%) of starting oxazoline **18** and 0.015 g (56% based on recovered starting material) of oxazole **19** as a colorless oil: IR (film) 2975, 2950, 1550, 1400, 1140, 1360 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00 (2 H, m), 3.15 (2 H, m), 3.85 (4 H, m), 4.87 (1 H, t, J = 4.5 Hz), 7.20 (3 H, m), 7.22 (1 H, s), 7.80 (1 H, s), 7.84 (1 H, m); mass spectrum, m/z (relative intensity) 245 (4.3), 200 (12.0), 172 (21.0), 73 (100); exact mass calcd for $C_{14}H_{15}NO_3$ 245.1052, found 245.1046.

Method B. To a solution of 0.050 g (0.202 mmol) of oxazoline **18** in 10 mL of freshly distilled benzene was added 0.050 g (0.222 mmol) of DDQ. The solution was refluxed for 20 h, cooled to room temperature, and diluted with 30 mL of benzene. The organic phase was washed with 5% NaOH, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on one 20 × 20 cm silica gel preparative TLC plate eluting with 1:1 ethyl acetate/hexane to afford 0.018 g (36%) of oxazole **19**, identical with material prepared by method A.

2-(2-Oxazolyl)benzenepropanal (20). To a solution of 0.538 g (2.196 mmol) of dioxolane **19** in 10 mL of THF was slowly added 7.0 mL of 3 N HCl. The reaction mixture was stirred at room temperature for 12 h and was neutralized with saturated $NaHCO_3$ solution. The aqueous layer was extracted 3 times with dichloromethane. The combined organic extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on 15 g of silica gel eluting with 1:1 ethyl acetate/hexane to provide 0.406 g (92%) of aldehyde **20** as a colorless oil: IR (film) 3150, 2900, 1720, 1550, 1485, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.75 (2 H, m), 3.38 (2 H, m), 7.15 (3 H, m), 7.17 (1 H, s), 7.60 (1 H, s), 7.82 (1 H, m), 9.72 (1 H, t, J = 1.0 Hz); mass spectrum, m/z (relative intensity) 201 (3.2), 172 (40.7), 144 (3.9), 130 (2.5), 115 (13.9), 103 (4.2), 89 (3.5), 77 (5.5); exact mass calcd for $C_{12}H_{11}NO_2$ 201.0790, found 201.0800.

Methyl (*E*)-5-(*o*-2-Oxazolylphenyl)-2-pentenoate (21). To a solution of 0.062 g (1.15 mmol) of sodium methoxide in 4 mL of dry methanol was added 0.208 g (1.15 mmol) of trimethyl phosphonoacetate in 2 mL of methanol. After stirring the reaction mixture for 30 min at room temperature, a solution of 0.177 g (0.88 mmol) of aldehyde **20** in 2 mL of methanol was added dropwise over 15 min. The reaction mixture was stirred for 5 h at room temperature, was diluted with NH_4Cl solution, and was extracted 3 times with dichloromethane. The combined organic extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on 15 g of silica gel eluting with 1:1.5 ethyl acetate/hexane to provide 0.203 g (90%)

of *trans*-olefin **21** as a colorless oil: IR (film) 2950, 1720, 1660, 1430, 1270, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (2 H, m), 3.21 (2 H, m), 3.68 (3 H, 3), 5.76 (1 H, dt, J = 1.0, 15.0 Hz), 7.18 (4 H, m), 7.26 (1 H, s), 7.62 (1 H, m); mass spectrum, m/z (relative intensity) 257 (19.1), 228 (98.4), 198 (22.6), 170 (100), 158 (63.1), 130 (25.7), 103 (24.1), 90 (17.1), 77 (21.2); exact mass calcd for $C_{15}H_{15}NO_3$ 257.1052, found 257.1044.

3-Hydroxy-5,6-dihydrobenzo[*h*]quinoline (24) and 3-Hydroxy-4-carbomethoxy-5,6-dihydrobenzo[*h*]quinoline (23). To 0.030 g (0.117 mmol) of oxazole olefin **21** was added 10 mL of freshly distilled *o*-dichlorobenzene. The solution was refluxed under nitrogen for 4 h, cooled to room temperature, and concentrated in vacuo. The residue was chromatographed on one 20 × 20 cm silica gel preparative TLC plate eluting with 1:1 ethyl acetate/hexane to afford 0.012 g (52%) of 3-hydroxypyridine **24** and 0.007 g (24%) of 3-hydroxy-4-carbomethoxypyridine **23** as colorless oils.

3-Hydroxypyridine 24: IR (film) 3300–3000, 2950, 1600, 1460, 1300 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85 (4 H, br s), 7.22 (4 H, m), 8.13 (1 H, m), 8.70 (1 H, br s); mass spectrum, m/z (relative intensity) 197 (45.0), 167 (7.8), 139 (5.0), 115 (4.3), 84 (7.9).

3-Hydroxy-4-carbomethoxypyridine 23: IR (film) 3400–3000, 2950, 1730, 1555, 1440, 1255, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.82 (2 H, m), 3.20 (2 H, m), 4.00 (3 H, s), 7.22 (4 H, m), 8.14 (1 H, m), 8.40 (1 H, br s); mass spectrum, m/z (relative intensity) 255 (52.0), 223 (100.0), 195 (15.7), 167 (35.1), 139 (18.0), 115 (4.4), 97 (3.7).

4-Carbomethoxy-5,6-dihydrobenzo[*h*]quinoline (25). To a solution of 0.024 g (0.093 mmol) of oxazole **21** in 8 mL of freshly distilled (CaH_2) *o*-dichlorobenzene was added 0.75 equiv of DBN. The solution was refluxed under nitrogen for 16 h and was cooled to room temperature. The solvent was removed in vacuo and the residue was purified on one 20 × 20 cm silica gel preparative TLC plate eluting with 1:1 ethyl acetate/hexane to afford 0.017 g (76%) of pyridine **25** as a colorless oil: IR (film) 2950, 1730, 1560, 1435, 1390, 1270, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85 (2 H, m), 3.30 (2 H, m), 3.93 (3 H, s), 7.22 (3 H, m), 7.52 (1 H, d, J = 5.0 Hz), 8.30 (1 H, m), 8.60 (1 H, d, J = 5.0 Hz); mass spectrum, m/z (relative intensity) 239 (97.7), 224 (51.3), 179 (48.0), 152 (16.4), 127 (3.4), 89 (9.4), 76 (12.2); exact mass calcd for $C_{15}H_{13}NO_2$ 239.0946, found 239.0935.

4-Carbomethoxybenzo[*h*]quinoline (26). To a solution of 0.120 g (0.502 mmol) of ester **25** dissolved in 15 mL of carbon tetrachloride was added 0.197 g (1.505 mmol) of *N*-bromosuccinimide. The suspension was refluxed for 12 h, cooled to room temperature, and filtered. The filtrate was washed 3 times with saturated $NaHSO_3$ solution, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on one 20 × 20 cm silica gel preparative TLC plate eluting with 1:3 ethyl acetate/hexane to afford 0.107 g (90%) of azaphenanthrene **26** as a white solid. A sample recrystallized from hexane had mp 92–93 °C: IR (film) 3040, 2950, 1730, 1525, 1435, 1350, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.08 (3 H, s), 7.85 (4 H, m), 7.94 (1 H, d, J = 5.0 Hz), 8.65 (1 H, d, J = 9.0 Hz), 9.13 (1 H, d, J = 5.0 Hz), 9.32 (1 H, m); mass spectrum, m/z (relative intensity) 237 (100.0), 206 (24.9), 178 (51.8), 151 (16.9), 103 (2.8), 89 (3.1), 75 (7.0). Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67. Found: C, 75.83; H, 4.66.

Nitration of Azaphenanthrene 26. To a solution of 0.015 g (0.063 mmol) of azaphenanthrene **26** in 0.5 mL of concentrated H_2SO_4 at −20 °C was added 0.5 mL of a 1:1 H_2SO_4/HNO_3 solution. The reaction mixture was stirred at −20 °C for 2.5 min and was neutralized with saturated $NaHCO_3$ solution. The aqueous layer was extracted with methylene chloride. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on one 10 × 20 cm silica gel preparative TLC plate eluting with 1:1 ethyl acetate/hexane to provide 0.007 g (39%) of nitroazaphenanthrene **27**: IR ($CHCl_3$) 3000, 1727, 1520, 1340, 1270 cm^{-1}.

The nitroazaphenanthrene **27** (0.007 g, 0.025 mmol) was dissolved in 10 mL of benzene and 0.002 g of 10% Pd/C catalyst was added. The reaction mixture was stirred at room temperature under 1 atm of hydrogen for 3 h and was filtered through Celite. The filtrate was concentrated in vacuo and the residue was purified on one 10 × 20 cm silica gel preparative TLC plate eluting with 1:1 ethyl acetate/hexane to provide 0.005 g (80%) of amine **28** as a yellow solid: IR ($CHCl_3$) 3460, 3400, 3000, 1727, 1625, 1436, 1265, 1128 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.07 (3 H, s), 7.05 (1 H, dd, J = 0.9, 7.5 Hz), 7.56 (1 H, dd, J = 7.5, 8.2 Hz), 7.95 (1 H, dd, J = 0.9, 9.8 Hz), 7.97 (1 H, d, J = 4.5 Hz), 8.59 (1 H, d, J = 9.8 Hz), 8.78 (1 H, dt, J = 0.9, 8.2 Hz), 9.07 (1 H, d, J = 4.6 Hz); mass spectrum, m/z (relative intensity) 252 (100.0), 221 (2.6), 193 (32.0), 166 (4.0), 139 (10.9), 84 (14.2).

Synthesis of *N*-Methylamide 29. To a solution of 0.050 g (0.211 mmol) of ester **26** in 2 mL of dry benzene was added 1.58 mL (0.633 mmol) of a 0.4 M benzene solution of methylchloroaluminum *N*-methylamide reagent.[25] The solution was refluxed under nitrogen for 12 h, cooled to room temperature, and carefully diluted with 5% HCl solution. The organic layer was separated and the aqueous layer was extracted 3 times with ethyl acetate. The combined organic extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on one 20 × 20 cm silica gel preparative TLC plate eluting with ethyl acetate to afford 0.046 g (92%) of amide **29** as a white solid, mp 167–168 °C, upon recrystallization from ethyl acetate: IR (film) 3450, 3000, 1670, 1530, 1510, 1420, 1290 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.00 (5 H, m), 8.76 (1 H, d, J = 4.8 Hz), 9.7 (1 H, m); mass spectrum, m/z (relative intensity) 236 (100), 206 (35.4), 178 (69.0), 151 (25.9), 118 (6.4), 84 (8.1), 75 (4.4). Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12. Found: C, 76.05; H, 5.25.

Conversion of Azaphenanthrene 29 to Hydroxy Lactam 31 and Quinone 30. To a solution of 0.010 g (0.042 mmol) of azaphenanthrene **29** in 2 mL of acetic acid was added a solution of 0.022 g (0.127 mmol) of iodic acid in 2 mL of H_2O. The reaction mixture was refluxed overnight and was cooled to room temperature. The solvent was removed in vacuo, and the residue was dissolved in methylene chloride. The organic layer was washed with $NaHCO_3$ solution, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on one 20 × 20 cm silica gel preparative TLC plate eluting with ethyl acetate to afford 0.002 g (18%) of *o*-quinone **30**, 0.001 g (9%) of lactam **31**, and 0.002 g (20%) of starting azaphenanthrene **29**. The quinone was obtained as a yellow solid, mp 206–207 °C dec; the lactam was obtained as a colorless solid, mp 182–182.5 °C dec, upon recrystallization from ethanol.

Lactam 31: IR (film) 3300, 3000, 1720, 1695, 1610, 1420, 1380, 1010 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.32 (3 H, s), 7.39 (1 H, d, J = 4.9 Hz), 7.58 (1 H, m), 7.75 (1 H, m), 7.95 (1 H, m), 8.24 (1 H, m), 8.75 (1 H, d, J = 4.9 Hz); mass spectrum, m/z (relative intensity) 266 (5.7), 251 (3.4), 237 (6.8), 207 (3.0), 162 (49.7), 147 (13.9), 105 (100), 77 (40.8).

***o*-Quinone 30**: IR ($CHCl_3$) 3010, 2940, 1690, 1520, 1420, 1180 cm^{-1}; ^1H NMR (360 MHz, Me_2SO-d_6) δ 2.78 (3 H, d, J = 4.9 Hz), 7.40 (1 H, d, J = 4.9 Hz), 7.68 (1 H, m), 7.87 (1 H, m), 8.08 (1 H, m), 8.66 (1 H, m), 8.90 (1 H, d, J = 4.9 Hz); mass spectrum, m/z (relative intensity) 266 (32.1), 252 (46.9), 237 (32.5), 221 (35.5), 182 (19.1), 153 (36.9), 125 (15.6), 84 (21.4), 73 (34.1).

Equilibration of Quinone 30 and Hydroxy Lactam 31. To a solution of 3.0 mg (0.011 mmol) of quinone **30** in 2.5 mL of dry methylene chloride was added dropwise 0.05 mL of boron trifluoride etherate. The reaction mixture was stirred overnight at room temperature, was diluted with aqueous $NaHCO_3$ solution, and was extracted 3 times with methylene chloride. The combined organic extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on one 10 × 20 cm silica gel preparative TLC plate eluting with 1:1 ethyl acetate/hexane to afford 1.2 mg (40%) of hydroxy lactam **31** and 1.0 mg (33%) of the starting *o*-quinone **30**.

Acetylation of Hydroxy Lactam 31 to Acetoxy Lactam 32. To a solution of 0.005 g (0.019 mmol) of hydroxy lactam **31** in 0.5 mL of acetic anhydride was added a catalytic amount of 4-(dimethylamino)pyridine. The reaction mixture was stirred at room temperature for 0.5 h and the solvent was removed in vacuo. The residue was chromatographed on one 10 × 20 cm silica gel preparative TLC plate eluting with ethyl acetate to provide 1.75 mg (30%) of acetoxy lactam **32** as a pale yellow oil: IR (film) 3000, 1760, 1727, 1630, 1600, 1420, 1360, 1190, 1005, 990 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.97 (3 H, s), 3.31 (3 H, s), 7.53 (1 H, d, J = 4.9 Hz), 7.58 (1 H, m), 7.76 (1 H, m), 7.90 (1 H, m), 8.30 (1 H, m), 8.86 (1 H, d, J = 4.9 Hz); mass spectrum, m/z (relative intensity) 265 (76.0), 255 (47.0), 249 (23.3), 224 (23.4), 207 (14.0), 180 (21.5), 166 (27.0), 139 (24.4), 69 (10.6).

Reduction of Acetoxy Lactam 32 to Demethyleupolauramine (6b). To a solution of 2.8 mg (0.009 mmol) of acetoxy lactam **32** in 1 mL of acetone was added 10.0 mg (0.081 mmol) of chromous chloride in 1 mL of water. The solution turned yellow-brown immediately upon addition of the chromium(II) reagent. After 0.5 h the solution was diluted with water and methylene chloride. The organic layer was washed with saturated $NaHCO_3$ solution, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified on one 10 × 20 cm silica gel preparative TLC plate eluting with ethyl acetate to provide 2.0 mg (77%) of demethyleupolauramine (**6b**) as an orange solid, mp 300–301 °C, upon recrystallization from chloroform–ether: IR ($CHCl_3$) 3000, 2940, 1720, 1600, 1380, 1100 cm^{-1}; ^1H NMR (360 MHz, Me_2SO-d_6) δ 3.80 (3 H, s), 7.29 (1 H, m), 7.73 (1 H, m), 8.00 (1 H, d, J = 4.5 Hz), 8.38 (1 H, m), 8.93 (1 H, m), 9.08 (1 H, d, J = 4.5 Hz); mass spectrum, m/z (relative intensity) 250 (10.6), 207 (7.5), 105 (4.1), 89 (18.8), 84 (71.2), 66 (100), 59 (35.8).

Synthesis of Eupolauramine (6a) from Demethyleupolauramine (6b). To a solution of 2.0 mg (0.008 mmol) of **6b** in 2 mL of acetone was added excess solid potassium carbonate. The solution turned deep red after 2 min. Excess dimethyl sulfate was added and the mixture was stirred for 2 h at room temperature. The excess dimethyl sulfate was destroyed with diethylamine and the solution was diluted with methylene chloride. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on one 10 × 20 cm silica gel preparative TLC plate eluting with 1:1 ethyl acetate/hexane to provide 1.0 mg (50%) of solid, bright yellow eupolauramine (**6a**) which was identical with an authentic sample in IR, MS, ^1H NMR, and TLC behavior: IR ($CHCl_3$) 2950, 1703, 1650, 1600, 1220, 1100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.77 (3 H, s), 4.09 (3 H, s), 7.73 (2 H, m), 7.95 (1 H, d, J = 4.9 Hz), 8.16 (1 H, m), 9.05 (1 H, m), 9.19 (1 H, d, J = 4.9 Hz); mass spectrum, m/z (relative intensity) 264 (57.9), 249 (100), 221 (7.87), 194 (3.8), 166 (12.2), 140 (3.2), 125 (4.8), 91 (2.1), 75 (2.73).

4-Carbomethoxy-5,6-epoxybenzo[*h*]quinoline (33). To a solution of 0.181 g (0.764 mmol) of azaphenanthrene **26** in 5 mL of methylene chloride was added 10 mL (7.06 mmol) of 5.25% NaOCl solution which had been adjusted to pH 9 with concentrated HCl and 0.120 g (0.353 mmol) of tetrabutylammonium hydrogen sulfate.[29] The mixture was stirred vigorously at room temperature for 4 h, and the two layers were separated. The organic phase was washed with cold water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on two 20 × 20 cm silica gel preparative TLC plates eluting with 1:1 ethyl acetate/hexane to provide 0.133 g (69%) of epoxide **33** as a white solid, mp 104 °C, on recrystallization from hexane: IR (film) 3050, 2950, 1730, 1560, 1440, 1400, 1280, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93 (3 H, s), 4.43 (1 H, d, J = 4.0 Hz), 5.34 (1 H, d, J = 4.0 Hz), 7.45 (4 H, m), 8.54 (1 H, m), 8.67 (1 H, d, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$) δ 51.92, 52.87, 56.10, 122.16, 122.29, 125.92, 126.45, 129.44, 129.98, 131.87, 132.68, 139.69, 149.35, 166.19; mass spectrum, m/z (relative intensity) 253 (92.3), 238 (100), 221 (34.5), 195 (42.9), 167 (70.1), 139 (38.7), 127 (13.3), 89 (11.0), 63 (17.0); exact mass calcd for $C_{15}H_{11}NO_3$ 253.0738, found 253.0732.

Reaction of Epoxide 33 with Dimethylaluminum *N*-Methylamide. To a solution of 0.027 g (0.107 mmol) of epoxide **33** in 10 mL of dry methylene chloride was rapidly added 1.50 mL (0.51 mmol) of a 0.34 M solution of dimethylaluminum *N*-methylamide in methylene chloride.[30,31] The mixture was stirred at room temperature for 4 h, was carefully quenched with saturated sodium–potassium tartrate solution, and was extracted 3 times with methylene chloride. The combined organic extract was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified on one 20 × 20 cm silica gel preparative TLC plate eluting with ethyl acetate to provide 10.5 mg (39%) of starting epoxide **33**, 2.5 mg (10%) of azaphenanthrene **35**, 8.1 mg (30%, 49% based on recovered starting material) of lactam alcohol **34a**, and 5.5 mg (18%) of amide amino alcohol **36a/b**, which was characterized as its diacetyl derivative.

Lactam alcohol 34a: White solid, mp 232 °C on recrystallization from ethyl acetate; IR (film) 3000, 1695, 1420, 1380, 1260, 1100 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 2.66 (1 H, d, J = 7.6 Hz), 3.43 (3 H, s), 4.60 (1 H, d, J = 11.3 Hz), 4.81 (1 H, dd, J = 7.6, 11.3 Hz), 7.54 (3 H, m), 7.73 (1 H, m), 8.25 (1 H, m), 8.79 (1 H, d, J = 4.9 Hz); ^{13}C NMR (Me_2SO-d_6) δ 29.55, 62.85, 72.62, 115.29, 123.34, 125.99, 128.19, 130.44, 132.16, 134.76, 138.58, 141.70, 149.29, 150.69, 167.36; mass spectrum, m/z (relative intensity) 252 (100), 224 (59.1), 195 (46.3), 167 (34.6), 139 (8.5), 119 (10.1), 91 (32.5), 77 (10.0); exact mass calcd for $C_{15}H_{12}N_2O_2$ 252.0899, found 252.0891.

Diacetyl derivative of amide amino alcohol 36a/b: IR (film) 3300, 3075, 2950, 1750, 1650, 1560, 1410, 1230, 1020 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.94 (3 H, s), 2.15 (3 H, s), 2.57 (3 H, s), 3.02 (3 H, d, J = 4.8 Hz), 6.20 (1 H, d, J = 5.2 Hz), 6.42 (1 H, d, J = 5.2 Hz), 7.23 (2 H, m), 7.46 (2 H, m), 8.46 (1 H, m), 8.69 (1 H, d, J = 4.8 Hz).

Azaphenanthrene 35: yellow solid, mp 182 °C dec on recrystallization from ethanol; IR ($CHCl_3$) 3000, 2940, 1710, 1650, 1390, 1200, 1020 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.50 (3 H, s), 7.08 (1 H, s), 7.66 (2 H, m), 7.84 (1 H, m), 7.90 (1 H, d, J = 4.9 Hz), 8.98 (1 H, m), 9.22 (1 H, d, J = 4.9 Hz); mass spectrum, m/z (relative intensity) 234 (100), 205 (11.8), 178 (16.6), 151 (11.1), 117 (5.9), 89 (8.4).

***trans*-5a,6-Dihydro-6-(acetyloxy)-5-methylbenzo[*h*]pyrrolo[4,3,2-*de*]quinolin-4(5*H*)-one (34b).** To a suspension of 0.018 g (0.071 mmol) of alcohol **34a** in 2 mL of acetic anhydride was added 2 drops of dry pyridine. The reaction mixture was stirred at room temperature for 2 h, by which time all of the starting alcohol had dissolved, and the solvent was removed in vacuo. The residue was chromatographed on one 20 × 20 cm silica gel preparative TLC plate eluting with 1:1 ethyl acetate/hexane to provide 0.016 g (76%) of acetate **34b** as a white solid: mp 193.5–194 °C upon recrystallization from ethanol: IR (film) 3000, 1755, 1705, 1630, 1420, 1380, 1040 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.41 (3 H, s), 3.24 (3 H, s), 4.81 (1 H, d, J = 11.3 Hz), 6.08 (1 H, d, J = 11.3 Hz), 7.55 (4 H, m), 8.28 (1 H, m), 8.83 (1 H, d, J = 5.2 Hz); mass spectrum, m/z (relative intensity) 294 (100), 252 (46.7), 234 (27.4), 224 (54.5), 195 (21.7), 167 (29.2), 154 (9.0), 127 (8.0), 77 (5.7); exact mass calcd for $C_{17}H_{14}N_2O_3$ 294.1004, found 294.0998.

6-(Acetyloxy)-5-methylbenzo[*h*]pyrrolo[4,3,2-*de*]quinolin-4(5*H*)-one (6c). To a solution of 4.65 mg (0.016 mmol) of acetate **34b** in 2.5 mL of carbon tetrachloride was added 2.80 mg (0.016 mmol) of *N*-bromosuccinimide. The reaction mixture was refluxed for 2 h, cooled to room temperature, and washed with saturated $NaHSO_3$ solution, water, and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified on one 10 × 20 cm silica gel preparative TLC plate eluting with 1:1 ethyl acetate/hexane to provide 3.38 mg (73%) of phenolic acetate **6c** as a bright yellow solid: mp 182–183 °C upon recrystallization from ethanol; IR ($CHCl_3$) 3000, 1775, 1715, 1660, 1600, 1450, 1380, 1300, 1180 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 2.59 (3 H, s), 3.58 (3 H, s), 7.69 (2 H, m), 7.80 (1 H, m), 7.94 (1 H, d, J = 4.6 Hz), 9.04 (1 H, m), 9.22 (1 H, d, J = 4.6 Hz); mass spectrum, m/z (relative intensity) 292 (8.8), 250 (100), 221 (7.9), 207 (25.8), 166 (12.6), 139 (5.5), 84 (11.5); exact mass calcd for $C_{17}H_{12}N_2O_3$ 292.0847, found 292.0855.

Preparation of Eupolauramine (6a) from Acetate 6c. To 3.4 mg (0.02 mmol) of acetate **6c** was added 0.5 mL of 20% aqueous KOH. The reaction mixture was stirred at room temperature for 1 h, and 2 mL of acetone and 0.1 mL of dimethyl sulfate were added. After 2 h at room temperature, the yellow solution was diluted with diethylamine and methylene chloride. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified on one 20 × 20 cm silica gel preparative TLC plate eluting with 1:1 ethyl acetate/hexane to provide 2.5 mg (82%) of synthetic eupolauramine (**6a**) which was identical with an authentic sample in IR, MS, ^1H NMR, and TLC.[28]

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Registry No. **12**, 62882-10-4; **6a**, 58856-98-7; **6b**, 58856-95-4; **13**, 92346-48-0; **14**, 92346-50-4; **16**, 74272-88-1; **17**, 37610-80-3; **18**,

84731-36-2; **19**, 84731-37-3; **20**, 84731-38-4; **21**, 84731-39-5; **23**, 84731-40-8; **24**, 84731-41-9; **25**, 84731-42-0; **26**, 84731-43-1; **27**, 92346-51-5; **28**, 92346-52-6; **29**, 92346-53-7; **30**, 92346-54-8; **31**, 92346-55-9; **32**, 92346-56-0; **33**, 84731-44-2; **34a**, 84731-45-3; **34b**, 92346-59-3; **35**, 84731-48-6; **36a**, 92346-57-1; **36b**, 92346-58-2; *o*-anisoyl chloride, 21615-34-9; *N*-anisoyl-2-aminoethanol, 88105-15-1; β-bromopropionaldehyde ethylene acetal, 18742-02-4; ethanolamine, 141-43-5; trimethyl phosphonoacetate, 5927-18-4.

Synthesis of Verrucarin B[1]

William R. Roush*[2] and Timothy A. Blizzard[3]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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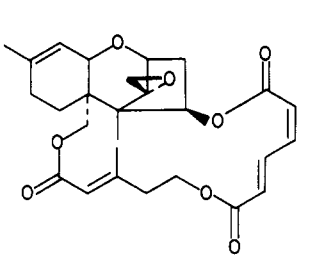
A four-step synthesis of verrucarin B (**3**) from verrucarol (**2**) is described. Coupling of **2** with in situ generated carboxylic acid **5** proceeded with moderate regioselectivity and afforded trichothecene monoester **14** in only 35% yield. It was necessary therefore to block the C(4)-hydroxyl group of verrucarol prior to the coupling reaction with **5**. Selective protection of **2** was accomplished in 54% yield (81% corrected for recovered verrucarol after hydrolysis of the other reaction products) by treatment with [[2-(trimethylsilyl)ethoxy]carbonyl]imidazole (**16**) and DBU in benzene. Esterification of **17** with in situ generated **5** in the presence of BOP-Cl, Et_3N, and catalytic DMAP as the condensing reagents afforded **18** in 64% yield, deprotection of which with KF in wet Me_2SO smoothly afforded seco acid **4** (81%). A number of methods for macrolactonization of **4** via mixed anhydride **21** were examined. Best results were obtained when **21** was treated with stoichiometric 4-pyrrolidinopyridine (4-PP) which afforded verrucarin B in 55% yield along with 34% of the (*E*,*E*)-muconate isomer **19**. Exposure of **19** to I_2 in benzene effected rapid isomerization to verrucarin B (60%) and a new isomer **20** (30%). In this manner the yield of **3** from seco acid **4** was 75% and 35% overall from verrucarol.

The verrucarins, roridins, and baccharinoids are important groups of macrocyclic epoxytrichothecenes which are of considerable interest as a consequence of their potent cytotoxic properties.[4,5] Naturally occurring baccharinoids, for example, typically show T/C values of 160–320 at dose levels of 1–10 mg/kg in the in vivo P388 mouse leukemia assay.[4a] The verrucarins and roridins are generally less active but nonetheless are regarded as promising prototypes for drug development. Indeed, Jarvis has shown that a number of chemically modified verrucarins (e.g., 8β-hydroxy-9β,10β-epoxyverrucarin A) possess very significant activity in the in vivo P388 assay.[6]

For the past several years we have been exploring methodology applicable to the synthesis of a range of macrocyclic epoxytrichothecenes[7,8] and recently described a five-step synthesis of verrucarin J (**1**) from verrucarol (**2**).[7a,b] Although this synthesis was relatively efficient



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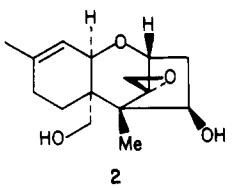

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(22–24% overall yield), we felt that several aspects of our strategy could be improved. Specifically, we wished to develop a more efficient approach in which the intact macrocyclic "ribbon" would be attached to verrucarol. In principle, this would permit the synthesis of any macrocyclic epoxytrichothecene in as few as three steps from the starting trichothecene (usually **2**). In addition, we hoped to find a solution to the problem of olefin isomerization which we encountered in the macrocyclization of the seco acid intermediate.[7a]

We decided to focus on these problems by using verrucarin B (**3**)[9] as a synthetic target. Based on our experience

(1) Taken in part from the Ph.D. Thesis of T. A. Blizzard, Massachusetts Institute of Technology, Cambridge, MA, 1984.

(2) Holder of the Firmenich Career Development Chair in Natural Products Chemistry; Fellow of the Alfred P. Sloan Foundation, 1982–84.

(3) National Science Foundation Predoctoral Fellow, 1979–82; Fellow of the Whitaker Health Sciences Fund, 1982–84.

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