epoxides for fixed allylic alcohols.

In general, the epoxidation data seem consistent with an electrophilic process. The *cis/trans*-dialkylalkene results support a spiro transition state[8] for dioxirane epoxidation. The ρ^+ value obtained for epoxidation of styrenes and the observed rate enhancements vs mole fraction of added water (apparent polar solvent effect) also support an electrophilic mechanism.

Experimental Section

All solvents were of reagent grade. ^{1}H NMR spectra were recorded on a Varian EM-360L NMR spectrometer. UV kinetic experiments were conducted on a Cary 17D spectrometer; cell temperature (±0.3 °C) was maintained via a constant-temperature circulating bath. The alkenes (≥99%, Wiley Organics and Aldrich) and Oxone (Aldrich) were used without further purification. Dimethyldioxirane (1) was prepared in acetone by the general procedure developed by Murray,[4] simplified by slight modification.[5,8] The dioxirane stock solutions were dried twice with anhydrous $MgSO_4$ at −78 °C and at ambient temperature. The concentration (≤0.1 M) of dioxirane 1 was determined by reaction with excess dimethyl sulfide, followed by integration (^{1}H NMR) of the DMSO signal vs that of added internal standard (anisole) and was in good agreement with that determined by UV methods.[5,8] All glassware used in dioxirane preparation had been treated with aqueous $EDTA^{2-}$ followed by acetone wash. Authentic samples of the epoxides were prepared by the reaction of *m*-chloroperbenzoic acid (Aldrich) with 1 equiv of the corresponding alkenes.

Product Studies. Two general procedures were used to determine the yield of epoxide for reaction of 1 with alkenes **2**–**17**. For nonvolatile epoxides, 10.0 μL of the desired alkene were added to 1.1 equiv of 1 in acetone. After complete oxidation, the solvent was removed under reduced pressure (ice bath) to yield the pure epoxides in essentially quantitative yield. The compounds were identified by comparison of physical and spectral properties with those of authentic samples. For volatile epoxides, the epoxidation was carried out as above except that dimethyldioxirane-d_6 in acetone-d_6 was used.[8] Epoxide yield was determined by ^{1}H NMR integration relative to internal standard. Except as noted for alkene **7**, the epoxides were obtained in ≥95% yield. As expected,[2,3,8] the epoxidations were stereospecific in all cases.

Kinetic Studies. Dimethyldioxirane solutions (1.00 mL) of known concentration in *dried* acetone were placed in a 1-cm UV cell at 23 °C. The desired equivalents of alkene were added via syringe and rapidly mixed. Pseudo-first-order conditions with 1:10 and 10:1 alkene to peroxide ratios gave identical values of k_2. The loss of dimethyldioxirane vs time was monitored at 332 nm for all cases except for those of **12**, **13**, and **15e**. For these three exceptions, the kinetics were monitored by following the loss of alkene at longer wavelengths. Excellent correlations were obtained for all cases except **7**. For **7**, normal behavior was obtained for roughly the first 20% reaction, and then the reaction increased in rate before slowing. These characteristics indicate that a competing free-radical-like allylic oxidation may be taking place and are consistent with the low yield (50%) of epoxide for this case. For kinetic runs with added water, the desired quantity of deionized water was added via syringe to 1.00 mL of the stock solution and mixed prior to the addition of the alkene.

Acknowledgment is made to the National Science Foundation (CHE-8506665) and to the GSU Research Fund for support of this work.

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Total Syntheses of (±)-Cephalotaxine and (±)-8-Oxocephalotaxine

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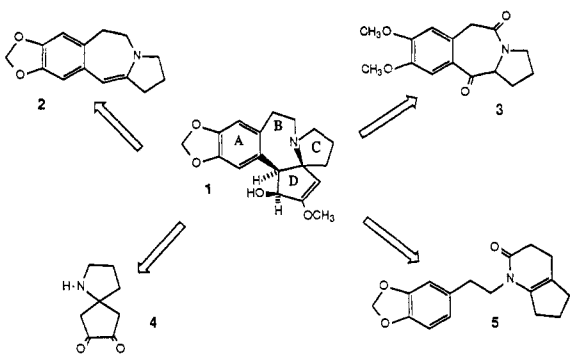
A synthesis of (±)-cephalotaxine (1) was obtained based on a novel oxidative rearrangement of the bicyclic enamide **5** to the spirocyclopentanone lactam **20**. The overall yield from keto ester **6** and amine **7** was 28%, in nine steps, or 41% in ten steps. Double-bond isomerization of minor side product ene lactam **9**, with formation of the key ene lactam intermediate **5**, increased the overall yields of the synthesis to 45% (nine steps) or 66% (ten steps). The racemate of the natural product 8-oxocephalotaxine (**40**) was obtained in an alternative last step by a selective reduction of the keto lactam **39**.

Cephalotaxine (1),[1-12] the major alkaloid constituent of the Chinese plum yew *Cephalotaxus fortunei* and of the Japanese plum yew *Cephalotaxus drupacea* has become an interesting synthetic target, not only because of its unique ring skeleton but also as a result of the anticancer activity found for some of its derivative esters (harringtonine, homoharringtonine, etc.), with leukemia L-1210 and, particularly, P-388 in mice.[13,14] This anticancer activity is currently undergoing clinical evaluation.

Scheme I



The most extensively explored approach to cephalotaxine has focused on use of the ABC tricyclic enamine **2**

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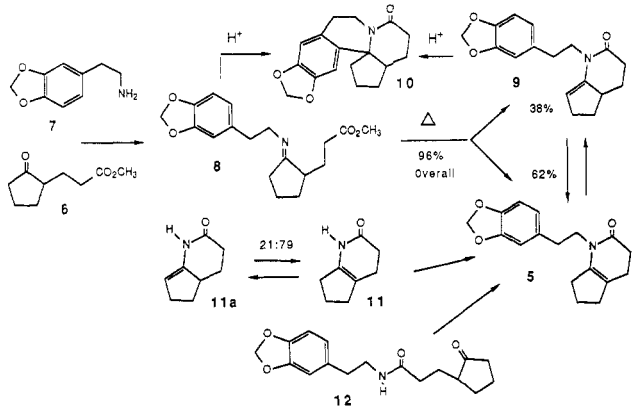
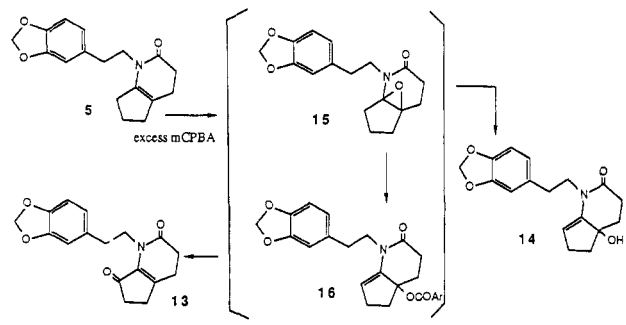
[§] SUNY-Albany. Address where inquiries regarding the X-ray structure of the tetracyclic intermediate **33** should be sent.

0022-3263/88/1953-3439$01.50/0

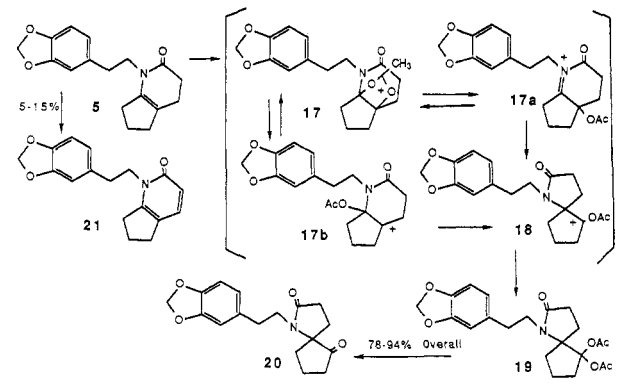
Scheme II



Scheme III



Scheme IV



as a key intermediate (Scheme I). While this compound had originally resisted a variety of further elaborations to cephalotaxine (1),[15-17] it could be carried to its synthetic goal in the Weinreb synthesis.[18,19]

Employing the alternative ABC tricyclic keto lactam **3**, and very different chemistry, Hanaoka recently also obtained cephalotaxine (1).[20] A third synthesis of this target molecule, by Semmelhack,[21,22] was based on generation of the CD bicyclic amino diketone **4**, with a final closure of ring B leading to formation of cephalotaxinone. A number of other approaches have not yet reached their final objective.[23-34]

Our own strategy was based on consideration of the spirocyclopentanopyrrolidine as the most interesting component of the cephalotaxine structure, and on the thought of meeting this challenge through rearrangement of a more commonly accessible fused cyclopentanopiperidine precursor. In order to drive such a rearrangement in the desired direction, we planned to take advantage of the observation that five-membered lactones are generally favored when equilibratable with six-membered lactones,[35,36] and we expected that this five vs six ring relationship should also hold for lactams. With the need for an elevated oxidation level, suitable for a subsequent intramolecular arylation and for an elaboration of the ring D oxygenation pattern of cephalotaxine, we thus directed our attention to the bicyclic ene lactam **5**, with the hope that we would find an oxidative rearrangement reaction for this system.

The required ene lactam was obtained by condensation of 2-(2-carbomethoxyethyl)cyclopentanone (**6**) and 3,4-(methylenedioxy)-β-phenethylamine (**7**) (Scheme II). The two required starting materials for this condensation were readily available from alkylation of the pyrrolidine enamine of cyclopentanone with methyl acrylate (68%)[37] and from reduction of 3,4-(methylenedioxy)nitrostyrene by hydrogenation (81%)[38] or reduction of the corresponding propionitrile with sodium borohydride and trifluoroacetic

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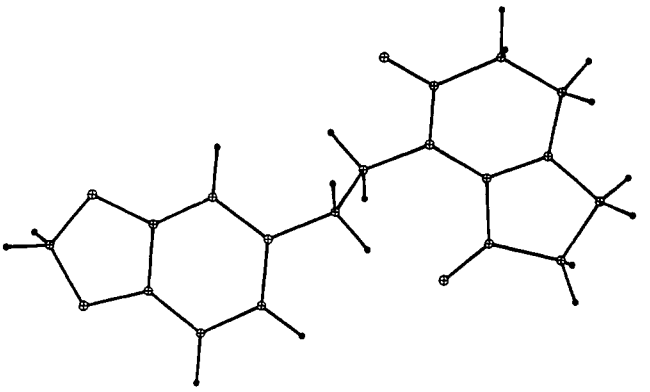
acid in tetrahydrofuran (67%).[39] An intermediate imine **8**, formed on condensation of the keto ester **6** and the amine **7** in refluxing benzene, required prolonged heating at 210 °C, under vacuum, for cyclization to the ene lactam **5**.

While a crystalline product was obtained in 96% yield from this cyclization, this product contained somewhat variable amounts (about 40%) of the alternative ene lactam **9**, in addition to the desired compound **5**. The two double-bond isomers, defined by NMR, could not be separated by fractional crystallization, but HPLC on a reverse-phase column provided the two compounds **5** and **9**. The purified compounds were found to isomerize to a 6:4 isomer mixture under remarkably mild conditions, e.g., almost instantly at 20 °C in dichloromethane with anhydrous $MgSO_4$ (but not with Na_2SO_4), slowly on heating in methanol with a catalytic amount of acid (not without acid), or in dichloromethane under fluorescent light.[40] At 200 °C, with a catalytic amount of acid, or in phosphoric acid at 100 °C, the ene amides **5** and **9** underwent cyclization to the tetracyclic lactam **10**.

Since the corresponding NH cyclopentanodihydropyridone **11**[41] (also equilibratable with its corresponding double-bond isomer **11a**) was more easily obtained as the desired double-bond isomer, we developed alternative preparations of the ene lactam **5** by alkylation of the NH lactam **11**. However this route, or the cyclization of the keto amide **12**, did not result in a significant diminution of the minor product **9**. For optimization of our cephalotaxine synthesis, a chromatographic separation and isomerization of the minor ene lactam **9** is thus required.

In a first attempt at oxidative rearrangement of the ene lactam **5**, the compound was treated with *m*-chloroperoxybenzoic acid (Scheme III). On chromatography of the resulting reaction mixture, we obtained two crystalline products. The spectroscopic properties of one are consistent with the enone structure **13** (UV 243 nm; IR 1694, 1665 cm^{-1}; mass spectrum m/z 299), which could be confirmed by X-ray crystallographic analysis (Figure 1). The other product was assigned the hydroxy ene lactam structure **14** (IR 3347, 1623 cm^{-1}; ^1H NMR δ 4.92 for vinyl hydrogen; ^{13}C NMR δ 77.82 for allylic hydroxy-substituted quaternary carbon; MS, m/z 301). These products presumably arise from alternative openings of intermediate epoxide **15**, with subsequent further epoxidation of a postulated ene lactam benzoate **16**, followed by rearrangement to a ketone and elimination of benzoate leading to the enone **13**. The latter compound was not obtained when the hydroxy ene lactam **14** was subjected to the initial oxidation conditions. Thus under these conditions, or on treatment of the ene lactam **5** with peroxyacetic acid in acetic acid, the desired ring condensation of an intermediate epoxypiperidone **15** did not seem to take place.

For an alternative solution to this oxidation problem we turned to a reaction of the ene lactam **5** with lead tetraacetate (Scheme IV). In this reaction we expected to generate, transiently, the bridging acetal carbocation **17**. This intermediate might be formed either by initial attack of the oxidant on the ene lactam double bond, with formation of an acylimonium group having an α Pb substituent, and its reaction with acetate, or alternatively, by reaction of Pb^{4+} at the lactam oxygen, followed by acetate addition to the double bond with generation of an α-acetoxy *N*-acylimonium product **17a**.



Cartesian coordinates of keto-lactam (13)

	(X)	(Y)	(Z)
O	-4.8995	0.1185	-0.9129
O	-4.9808	-2.1426	-1.4175
O	0.8662	3.1458	0.2852
O	2.2601	-1.2551	-2.2079
N(9)	1.8484	1.4547	-0.8233
C-17	-2.4766	0.1861	-0.4389
C-16	-3.6447	-0.4341	-0.8119
C-15	-3.6905	-1.7717	-1.1069
C-14	-2.5970	-2.5750	-1.0585
C-13	-1.3985	-1.9592	-0.6789
C-12	-1.3283	-0.6152	-0.3729
C-11	0.0000	0.0000	0.0000
C-10	0.5293	0.8754	-1.1355
C-8	1.8904	2.6242	-0.1130
C-7	3.2211	3.2529	0.1528
C-6	4.4706	2.6177	-0.3000
C-5	4.2448	1.3388	-1.0088
C-4	3.0269	0.8276	-1.2299
C-3	3.1351	-0.4908	-1.8851
C-2	4.6032	-0.7509	-2.0985
C-1	5.3339	0.4732	-1.5514
C-18	-5.7145	-0.9447	-1.4197
H-17	-2.4266	1.1968	-0.2302
H-14	-2.6402	-3.5715	-1.3074
H-13	-0.5606	-2.5270	-0.5667
H-11	-0.0781	0.5659	0.8376
H-11	0.6928	-0.7259	0.1670
H-10	0.5833	0.3026	-1.9811
H-10	-0.1521	1.5924	-1.3303
H-7	3.2015	4.1837	-0.2844
H-7	3.2921	3.4042	1.1408
H-6	4.9920	3.2594	-0.9085
H-6	5.0807	2.4566	0.5084
H-2	4.9316	-1.5669	-1.6439
H-2	4.8320	-0.8369	-3.0971
H-1	6.0078	0.2180	-0.8226
H-1	5.8857	0.9675	-2.2705
H-18	-6.0373	-0.7027	-2.3999
H-18	-6.5902	-1.0276	-0.8985

Figure 1. X-ray crystallographic structure of enone lactam **13**.

Lactam ring contraction of the cationic intermediate **17**, followed by hydrolytic removal of acetate groups from initial diacetate **19**, or from an enol acetate equivalent, was anticipated to lead to the spiroketopyrrolidone **20**. This desired reaction result was indeed achieved and the structure of product **20**, formed in 78–94% yield, was confirmed by an X-ray crystallographic analysis of its (2,4-dinitrophenyl)hydrazone derivative.[42] Intermediate diacetate **19** could also be isolated. In addition, the pyridone **21** was obtained as a minor product (5–15% yield)

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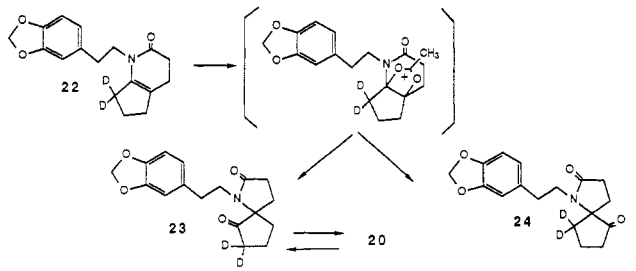
Scheme V



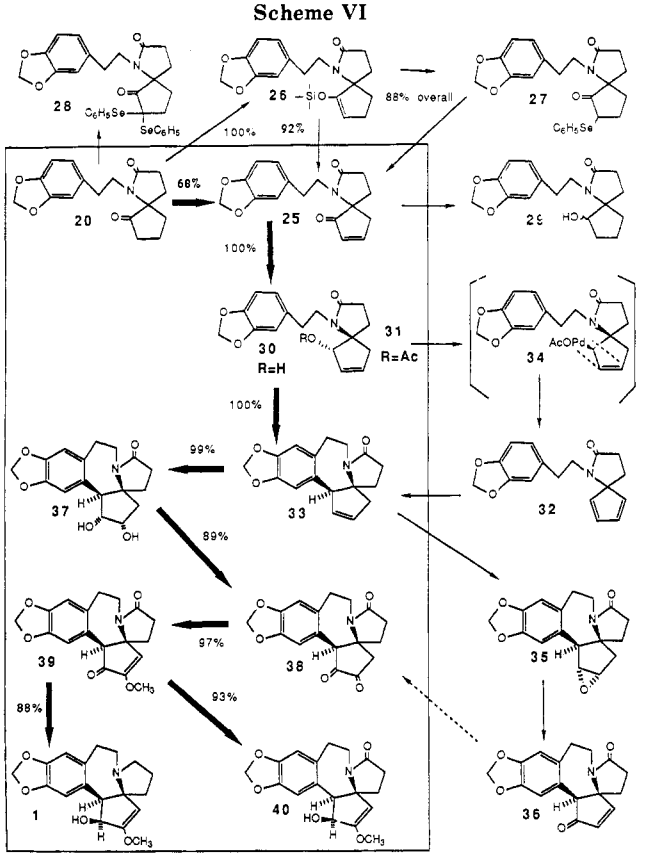
from this oxidation reaction.

Two mechanistic pathways were considered for formation of the observed spiro lactam ring, namely, a shift of the C–N bond (in **17b**) or, alternatively, a shift of the C–C bond (in **17a**). The same acetoxy-substituted carbocation **18** would be obtained in either event. In order to distinguish between these mechanistic alternatives, the deuterio-substituted ene lactam **22** was prepared by H–D exchange on the keto ester **6**, followed by the subsequent reactions for the ene lactam formation. When the deuterio-substituted ene lactam **22** (4.0 D_2:2.2 D_1:1.0 D_0) was subjected to the oxidative rearrangement with lead tetraacetate (Scheme V), it gave a ketone product **23**, **24** from which about $^2/_3$ of the deuterium could not be exchanged with sodium methoxide in methanol (1.0 D_2:1.5 D_1:1.0 D_0). The dideuterio ketone **23**, which allows such an exchange, was readily obtained by reaction of the ketone **20** with sodium methoxide in deuteriomethanol. Consequently, the rearrangement of an intermediate of type **17** must have proceeded by both migration of the C–C bond (i.e. **17a**) and by migration of the C–N bond (i.e. **17b**). An exact relative migratory aptitude cannot be derived from these data because of some H–D exchange of ene lactam **22** with acetic acid, which is likely prior to the actual reaction with lead tetraacetate. This supposition is strengthened by noting the disproportionate amount of nonexchangeable monodeuterio keto lactam in the final reaction product.

Oxidative rearrangement of the ene lactam **5** to the spiro ketone **20** with lead tetraacetate required elevated temperature (although **5** reacted at 20 °C). Since, at 80 °C, $Pb(OAc)_4$ provides oxidations that are recognized as homolytic processes, radical equivalents of intermediates **17**, **17a**, **17b**, and **18** should also be considered. With such diversity of mechanistic paths, it was gratifying to find that this new reaction gave the desired ketone **20** in high yield.

Further functionalization of the spiro ketone **20** was envisioned to require the initial introduction of a double bond, which would not only serve for oxygenation of the cyclopentane moiety, but which would also assist in the more immediate cycloarylation step (Scheme VI). Thus, in order to generate the enone **25**, the ketone **20** was first quantitatively converted to its silyl enol ether **26** with trimethylsilyl iodide and hexamethyldisilazane.[43] A subsequent reaction with benzeneselenenyl chloride gave the selenyl ether **27**.[44] Direct reaction of the ketone **20** with benzeneselenenyl chloride in ethyl acetate and HCl,[45] on the other hand, led predominantly to formation of the diselenyl ether **28**. When the selenyl ether **27** was oxidized with hydrogen peroxide,[46] or with sodium periodate,[45] the desired enone **25** was formed in good yields (88%, overall, from **26**).

Scheme VI



In an alternative method for generation of the unsaturated ketone **25**, the silyl enol ether **26** was oxidized with palladium diacetate and quinone at room temperature[47,48] to provide the enone **25** in 92% yield. For a still more direct oxidation, the ketone **20** was heated with bis(benzonitrile)palladium dichloride at 116 °C,[49,50] resulting in a 68% yield of the enone **25**.

Reduction of the enone **25** with sodium borohydride proceeded by an initial conjugate addition of hydride, followed by reduction of the carbonyl group, and thus led only to a saturated alcohol product **29**. In the presence of $CeCl_3$,[51] however, the reduction could be largely directed to formation of an allylic alcohol product. The cleanest formation of the allylic alcohol **30** was obtained with the classic Meerwein–Pondorff method, using aluminum isopropoxide and 2-propanol (100% yield). The stereochemistry of the product was not established but the following reactions may be interpreted on the basis of a trans orientation of the hydroxyl and lactam functions.

Acetylation of the alcohol **30** and reaction of its acetate **31** with tetrakis(triphenylphosphine)palladium(0)[52] resulted in the generation of the cyclopentadiene **32** and none of the desired cycloarylation product **33**. This result suggests that intermediate (π-allyl)palladium complex **34** in this reaction, with a geometry derived from inversion of the initial allylic acetate **31**,[52] has the (π-allyl)palladium complex unfavorably placed for an intramolecular attack by the (methylenedioxy)benzene ring.

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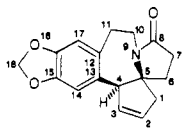
Table I. 250-MHz ^{1}H NMR Chemical Shift Values



	cycloarylation product 33[b]	cephalotaxine (1)[c]
H-1α	2.93[a]	4.92
H-1β	2.60[a]	
H-2	5.61	
H-3	5.86	4.76
H-4	3.80	3.67
H-6, H-7	2.05–2.28	1.68–2.08
H-8α		3.07
H-8β		2.59
H-10α	4.10	2.92
H-10β	3.00	2.62
H-11α	2.43	2.34
H-11β	3.30	3.36
H-14	6.63[a]	6.67[a]
H-17	6.57[a]	6.64[a]
H-18	5.90	5.90
OCH_3		3.72
OH		-1.8

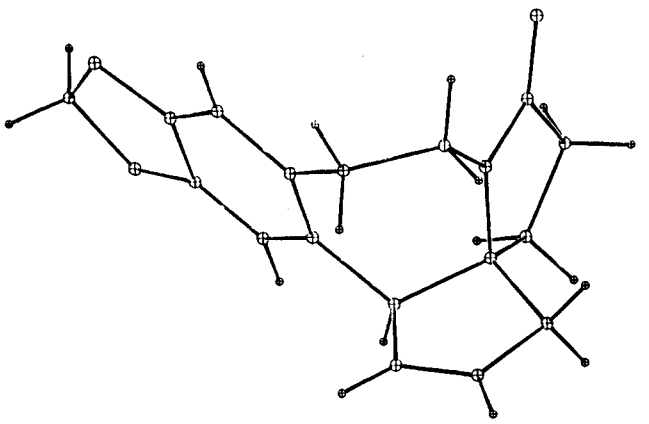
[a] These assignments may be reversed. [b] Compound **33**: $J_{1\alpha-1\beta}$ = 18.2, $J_{1\alpha-2}$ = 2.2, $J_{1\alpha-3}$ = 2.1, $J_{1\alpha-4}$ = 2.4, $J_{1\beta-2}$ = 2.0, $J_{1\beta-3}$ = 2.4, $J_{1\beta-4}$ = 2.3, J_{2-3} = 5.9, J_{2-4} = 2.0, J_{3-4} = 2.9, $J_{10\alpha-10\beta}$ = 12.7, $J_{10\alpha-11\alpha}$ = 7.8, $J_{10\alpha-11\beta}$ = 11.5, $J_{10\beta-11\alpha}$ = <0.5, $J_{10\beta-11\beta}$ = 7.9, $J_{11\alpha-11\beta}$ = 14.3. [c] Cephalotaxine: J_{3-4} = 9.4, $J_{10\alpha-10\beta}$ = 11.2, $J_{10\alpha-11\alpha}$ = 6.8, $J_{10\alpha-11\beta}$ = 12.1, $J_{10\beta-11\alpha}$ = <0.5, $J_{10\beta-11\beta}$ = 7.9, $J_{11\alpha-11\beta}$ = 14.3.

An unshielded allylic carbocation then would avoid this stereochemical barrier. Consequently, the allylic alcohol **30** was treated with stannic chloride in dichloromethane and nitromethane,[53] resulting in a quantitative yield of the tetracyclic lactam **33**. Alternatively, the cyclopentadiene **32**, in trifluoroacetic acid, also cyclized to the same product **33**. The anticipated stereochemistry of this product, which corresponds to that of cephalotaxine, could be confirmed by X-ray crystallographic analysis (Figure 2).

Lactam **33** and cephalotaxine (**1**) were analyzed by ^{1}H NMR spectroscopy. The chemical shift assignments and coupling constants are presented in Table I. Worth noting for both compounds are the coupling constants between hydrogens on C10 and C11. In both cases the observed coupling constants between H10 β and H11 α agree well with those predicted by the Altona equation for a dihedral angle in the range of 80–100°.[54] The observed chemical shifts, particularly those of H10 of both compounds, are also consistent with this conformation. Finally, the ^{1}H NMR derived conformation in solution is in agreement with the structure obtained by X-ray crystallography.

While completion of a cephalotaxine synthesis now seemed close at hand, its realization actually was delayed by inapplicability of general methods for conversion of olefins to α-diketones[55–57] and by failure of initial efforts to adapt common oxidation reactions to an elaboration of the intermediate **33**. Formation of the epoxide **35** with *m*-chloroperoxybenzoic acid proceeded readily, but opening of the epoxide to an α-hydroxy ketone, with dimethyl sulfoxide,[58,59] under a variety of conditions, did not prove fruitful. Only the tetracyclic enone **36** could be obtained in low yield from this reaction. Since the yield of the enone **36** was poor, a further oxidation to an epoxy ketone and its rearrangement to an α-diketone **38** was abandoned.

Oxidation of the olefin **33** with *N*-methylmorpholine *N*-oxide and osmium tetraoxide gave the cis diol **37** almost quantitatively.[60,61] Its relative stereochemistry could be seen from the ^{1}H NMR coupling constant of the angular hydrogen (J = 10 Hz).[62] Numerous attempts at oxidation of the diol **37** to an α-diketone **38**, using pyridinium



Cartesian coordinates of ene-lactam (33)

	(X)	(Y)	(Z)
C-18	-4.5809	-1.4687	-2.9213
C-15	-2.7798	-0.2041	-2.2893
C-14	-1.8122	0.6588	-2.1583
C-13	-1.0374	0.6484	-0.9965
C-12	-1.2752	-0.3115	-0.0121
C-17	-2.2917	-1.2376	-0.1622
C-16	-3.0404	-1.1468	-1.2993
C-11	-0.4322	-0.3469	1.2277
C-10	1.0374	-0.6485	0.9964
C-8	2.1500	-1.2298	-1.1240
C-7	2.5928	-0.5697	-2.3849
C-6	1.9759	0.7629	-2.3672
C-5	1.5301	1.0313	-0.9553
C-4	0.1115	1.6477	-0.8578
C-1	2.3585	1.9818	-0.1051
C-2	1.3704	2.6808	0.7685
C-3	0.1664	2.5073	0.3734
N(9)	1.5391	-0.3026	-0.3555
O	-3.6979	-0.4024	-3.333
O	-4.1192	-1.9776	-1.6755
O	2.3583	-2.4085	-0.7630
H-18	-4.5792	-2.1673	-3.5805
H-18	-5.4730	-1.1288	-2.8190
H-14	-1.6377	1.2970	-2.8538
H-17	-2.4634	-1.9096	0.5018
H-11	-0.4995	0.5056	1.6617
H-11	-0.7829	-1.0297	1.8031
H-10	1.1816	-1.5865	1.1405
H-10	1.5465	-0.1451	1.6373
H-7	2.2649	-1.0611	-3.1401
H-7	3.5498	-0.5145	-2.4302
H-6	2.6330	1.4146	-2.6224
H-6	1.2293	0.8073	-2.9700
H-4	-0.1073	2.1939	-1.6156
H-1	2.8588	2.5728	-0.6230
H-1	2.9665	1.4522	0.4676
H-2	1.6127	3.2252	1.5222
H-3	-0.6074	2.8724	0.8095

Figure 2. X-ray crystallographic structure of cycloarylation product **33**.

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Table II. Equilibration of Ene Lactams 5 and 9[a]

starting isomer	medium	t = 1 min	t = 6 h	t = 24 h
5	CH_2Cl_2, $MgSO_4$ dark	60% 5, 36% 9	61% 5, 38% 9	61% 5, 38% 9
9	CH_2Cl_2, $MgSO_4$ dark	61% 5, 37% 9	60% 5, 38% 9	60% 5, 36% 9
5	CH_2Cl_2–fluorescent light	100% 5	99% 5	72% 5, 26% 9
9	CH_2Cl_2–fluorescent light	99% 9	98% 9	25% 5, 74% 9
5	neat layer on glass, fluorescent light	100% 5	98% 5, trace 9	92% 5, 8% 9
9	neat layer on glass, fluorescent light	100% 9		10% 5, 86% 9
5	4:1 methanol–water reflux	100% 5	100% 5	100% 5
5	4:1 methanol–water cat. benzoic acid, reflux	100% 5		66% 5, 13% 9
5	toluene, reflux	100% 5	4 h: 80% 5, 20% 9	65% 5, 34% 9

[a] The isomer ratio was obtained by HPLC on a reverse-phase 4.6 mm × 25 cm Microsorb-R column, 1 mL/min, 2296 psi, 3:1 methanol–water, detection 285 nm; t_R 11.0 min (5), 12.5 min (9).

Table III. Cyclization of Keto Amide 12

solvent	% keto amide 12 t_R 4.4 min	% ene lactam 5 t_R 11.0 min	% ene lactam 9 t_R 12.6 min	% lactam 10 t_R 8.0 min
none	10.4	58.2	28.6	
1:1 HOAc/MeOH	18.6			35.7
MeOH	48.6	34.6	14.5	
MeOH/cat. TsOH				99.3
toluene/cat. Et_3N	72.3	18.0	7.7	
toluene/cat. py	40.1	40.3	19.1	
toluene/cat. py, TsOH	1.5	44.2	14.8	32.1
toluene	45.3	35.7	17.6	
toluene/cat. TsOH				77.4

chlorochromate, pyridine/SO_3, DMSO/oxalyl chloride, or DMSO/trifluoroacetic anhydride did not give the desired product. However, an oxidation with dimethyl sulfide, *N*-chlorosuccinimide, and triethylamine in dichloromethane at −42 °C,[63,64] finally produced the lactam diketone **38** in 89% yield.

In the Weinreb synthesis of cephalotaxine, a corresponding amino diketone serves as a late stage intermediate. It selective conversion to a methyl enol ether ketone was achieved by methoxy exchange with dimethoxypropane (45% yield). With our lactam diketone **38** a broader range of methylating reagents could be considered. Using trimethylsilyl methyl ether and triflic acid,[65] the sterically more accessible oxygen was selectively alkylated to give the (less conjugated!) enol ether **39** in 97% yield. A reduction of the ketone **39** with sodium borohydride provided the racemic alcohol **40** (93%) corresponding to a naturally occurring cephalotaxine lactam.[66] Reduction of the keto lactam **39** with lithium aluminum hydride, on the other hand, gave cephalotaxine (88%).

Experimental Section

General Methods. All reactions were carried out under nitrogen or argon. Melting points were obtained in a heated oil bath or on a Kofler micro hotstage with thermometers calibrated against a National Bureau of Standards certified set. NMR spectra were recorded on Bruker 250-MHz or 270-MHz instruments. J values are in hertz. Mass spectra were obtained with a Finnegan 4610 quadrupole instrument at 70 eV, calibrated with perfluorotributylamine and bis(pentafluorophenyl)phenylphosphine for compounds below M_r 600 and with tris(perfluorononyl)-*s*-triazine for higher molecular weight compounds. IR spectra were obtained with a Nicolet 6000 F.T. or a Perkin-Elmer 267 grating instrument. UV spectra were recorded on Perkin-Elmer 202 or 402 instruments. TLC data were obtained with E. Merck 60F-254 precoated silica on alumina sheets. For centrifugal chromatography a Harrison Chromatotron was used with E. Merck 60 PF 254 silica with gypsum. For column chromatography 60–200-mesh Baker R3405 silica was used. Microanalyses were provied by Mr. George Robertson, Robertson Laboratories, Florham Park, NJ.

***N*-[2-[3,4-(Methylenedioxy)phenyl]ethyl]-1,2,3,4,6,7-hexahydro-5*H*-1-pyrind-2-one (5) and Its 4a*H* Isomer (9).** (a) A mixture of 6.01 g (35.3 mmol) of methyl 3-(2-oxocyclopentyl)propionate,[36,37] 5.83 g (35.3 mmol) of 3,4-(methylenedioxy)-β-phenethylamine,[37-39] 50 mL of benzene, and a crystal of *p*-toluenesulfonic acid was heated at reflux for 2 h. The solvent was removed under vacuum at 40 °C and the residual oily imine heated at reflux (210 °C bath) under vacuum (15 mm) for 12 h. Kugelrohr distillation of the 6:4 mixture of lactams **5** and **9** at 177 °C/0.5 mm and trituration with ether gave 9.59 g (96%) of a product with mp 93–95 °C after recrystallization from dichloromethane and hexanes. An NMR spectrum of the recrystallized product showed equal amounts of the two double bond isomers **5** and **9**. TLC R_f 0.40 (dichloromethane, UV detection, I_2) or R_f 0.87 (ether).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.70; N, 4.90. Found: C, 71.30; H, 6.82; N, 4.91.

Preparation separation of isomers **5** and **9** was achieved by HPLC on tandem 21.4 mm × 25 cm + 21.4 mm × 5 cm reverse-phase 60A 8-μm C18 Dynamax columns with 4:1 methanol–water at 8 mL/min; t_R 26.5 min (**5**), 29.7 min (**9**).

Equilibration of the Separated Isomers 5 and 9. The two compounds were unchanged after storage in dichloromethane in the dark for 24 h (Table II). Addition of sodium sulfate or silica gel to the solution did not cause isomerization in 1 h. However, addition of magnesium sulfate caused isomerization of each compound within 1 min.

Amorphous ene lactam **5**: UV (ethanol) λ_{max} 202, 236, 284 nm; IR (film) ν_{max} 2948, 2927, 2899, 2847, 1690, 1663, 1503, 1490, 1443, 1406, 1338, 1247, 1188, 1173, 1038, 937, 927, 810 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 1.92 (p, J = 7 Hz, 2 H), 2.18–2.24 (m, 2 H), 2.31–2.41 (m, 4 H), 2.56 (t, J = 8 Hz, 2 H), 2.73 (t, J = 8 Hz, 2 H), 3.63 (t, J = 8 Hz, 2 H), 5.91 (s, 2 H), 6.64 (d,d, J = 8, 1 Hz, 1 H), 6.69 (d, J = 1 Hz, 1 H), 6.72 (d, J = 8 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 169.49, 147.51, 145.96, 136.47, 132.71, 121.62, 115.23, 109.21, 108.07, 100.67, 45.02, 35.11, 33.06, 31.65, 30.81, 21.65, 20.98.

Ene lactam **9**, mp 70–72 °C: UV (ethanol) λ_{max} 200, 236, 289 nm; IR (film) ν_{max} 2948, 2935, 2926, 2900, 2869, 2864, 2849, 1668, 1637, 1503, 1491, 1443, 1396, 1373, 1330, 1287, 1246, 1188, 1172, 1040, 937, 927, 810, 735 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 1.38–1.57 (m, 2 H), 1.94–2.01 (m, 1 H), 2.14–2.29 (m, 1 H), 2.34–2.42 (m, 2 H), 2.47–2.57 (m, 2 H), 2.76 (t, J = 8 Hz, 2 H), 2.79–2.69 (m, 1 H), 3.73–3.82 (m, 2 H), 4.85 (q, J = 2 Hz, 1 H), 5.91 (s, 2 H), 6.66 (dd, J = 8, 1 Hz, 1 H), 6.72 (d, J = 1 Hz, 1 H), 6.73 (d,

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Table IV. Alkylation of Ene Lactam 11

solvent, temp,[a] base	% recovd ene lactam 11 t_R 4.0 min	% recovd tosylate t_R 7.3 min	% 3,4-(methylenedioxy)styrene t_R 8.1 min	% ene lactam 5 t_R 11 min	% ene lactam 9 t_R 12.5 min
DMF, rt, NaH	29		36	22	7
DMSO, rt, NaH	20		25	37	12
THF, 67 °C, NaH	17	16		49	16
(no reaction rt)					
THF, rt, NaH, 18-crown-6			53	26	10
DMSO, rt, LiH	33	34		14	7

[a] rt = room temperature.

J = 8 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 168.67, 147.65, 146.07, 143.72, 132.84, 121.59, 109.21, 108.14, 102.13, 100.72, 44.94, 41.84, 32.83, 32.66, 30.50, 29.95, 27.04.

(b) A solution of the keto amide **12** (0.10 g) in 1.0 mL of the solvent listed in Table III was heated at 200 °C in a sealed tube for 2 h. The concentrated reaction mixture was then examined by HPLC on a C-18 reverse-phase column using the conditions indicated in the footnote of Table II. Material balances to 100% consist of unidentified components.

(c) Alternatively, compounds **5** and **9** were prepared by alkylation of 1,2,3,4,6,7-hexahydro-5*H*-1-pyrind-2-one (**11**)[41] with 2-[(*p*-tolylsulfonyl)oxy]-1-[3,4-(methylenedioxy)phenyl]ethane. The alkylations were carried out by dissolving 0.025 g (0.18 mmol) of the ene lactam **11** in 0.5 mL of the solvent shown in Table IV, followed by addition of 0.22 mmol of the listed base and 0.18 mmol of the arylethyl tosylate in 0.5 mL of the same solvent. After 2 h the mixture was poured into 10 mL of water and extracted with 3 × 10 mL of dichloromethane and subjected to HPLC analysis, using the conditions listed in the footnote of Table II.

***N*-[2-[3,4-(Methylenedioxy)phenyl]ethyl]-3-(2-oxocyclopentyl)propionamide (12).** A mixture of 5.00 g (0.029 mol) of methyl 3-(2-oxocyclopentyl)propionate[37] and 70 mL of 7 N hydrochloric acid was heated under reflux for 6 h. TLC then showed complete consumption of the starting ester (R_f 0.42, 1:1 ether–hexane). After cooling and addition of excess 6 N sodium hydroxide solution and extraction with 3 × 100 mL of ether, the aqueous solution was acidified with 1 N HCl and extracted with 3 × 100 mL of ether. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under vacuum to give 4.20 g (92%) of the parent keto acid. After heating 4.00 g (25.6 mmol) of this acid in 200 mL of acetic anhydride at reflux for 6 h, 0.246 g (1.29 mmol) of *p*-toluenesulfonic acid was added and heating continued for 1 h. The mixture was concentrated under vacuum (14 mm) and the residue partitioned between 100 mL of dichloromethane and 2 × 100 mL of 5% sodium bicarbonate. The organic phase was washed with 100 mL of brine, dried ($MgSO_4$), and concentrated. The residue, dissolved in 20 mL of dichloromethane, was adsorbed on 30 g of silica gel. This mixture was placed on a 4 × 30 cm column of dry silica gel and eluted with 10% ethyl acetate in hexane. After 180 mL of forerun, the following 320 mL of eluate contained 2.41 g (68%) of the corresponding enol lactone 4,5,6,7-tetrahydrocyclopenta[*b*]pyran-2-(3*H*)-one,[67,68] which distilled at 55 °C/15 Torr (Kugelrohr): 270-MHz ^1H NMR ($CDCl_3$) δ 1.92–2.03 (m, 2 H^7), 2.28–2.38 (m, 4 $H^{6,8}$), 2.41–2.50 (m, 2 H^3), 2.68 (t, J = 7 Hz, 2 H^2); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 169.02, 149.39, 111.20, 30.58, 29.75, 28.19, 19.91, 19.86. A solution of 1.00 g (7.24 mmol) of the enol lactone and 1.19 g (7.24 mmol) of 3,4-(methylenedioxy)-β-phenethylamine in 50 mL of dry benzene was heated at reflux for 1 h. Concentration under vacuum and centrifugal chromatography of the residue on a 4-mm silica gel plate, eluting with 5% methanol in dichloromethane at 1.5 mL/min, provided, in the first 72 mL of eluate, 2.16 g (98%) of the title amide, mp 86–87 °C, after drying at 10 Torr: TLC R_f 0.48 (ethyl acetate), 0.43 (5% methanol in dichloromethane); UV (ethanol) λ_{max} 203, 235, 287 nm; IR (KBr) ν_{max} 3304, 3184, 3083, 2970, 2944, 2929, 2871, 1734, 1629, 1552, 1505, 1489, 1455, 1441, 1404, 1243, 1197, 1186, 1118, 1035, 935, 924, 819, 727, 689 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 1.46–1.59 (m, 1 H), 1.62–1.84 (m, 2 H), 1.85–2.45 (m, 8 H), 2.72 (t, J = 7 Hz, 2 H), 3.44 (q, J = 7 Hz, 2 H), 5.91 (s, 2 H), 6.12 (t, J = 6 Hz, 1 H), 6.62 (dd, J = 1, 8 Hz, 1 H), 6.67 (d, J = 1 Hz, 1 H), 6.72 (d, J = 8 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 220.42, 172.28, 147.68, 146.02, 132.60, 121.40, 108.87, 108.11, 100.68, 47.69, 40.55, 37.86, 35.55, 34.01, 29.60, 25.77, 20.40; MS, m/z (relative intensity) 305 (4), 304 (19), 303 (M^+, 28), 156 (15), 149 (10), 148 (100), 147 (8), 139 (23), 136 (6), 135 (27), 119 (3), 111 (16), 91 (9), 83 (13), 77 (14), 65 (6), 55 (46), 51 (9).

1,2,3,4,6,7-Hexahydro-5*H*-1-pyrind-2-one (11) and 1,2,3,4,5,6-Hexahydro-4a*H*-1-pyrind-2-one (11a). A sealed tube containing 5.00 g (36.5 mmol) of 2-(2-cyanoethyl)cyclopentanone[37] and 0.3 mL of 50% aqueous acetic acid was heated at 200 °C for 2 h. The contents were then mixed with 15 mL of dichloromethane and the organic solution was adsorbed on 20 g of silica gel. Addition to a 3 × 30 cm column of dry silica gel and elution with 3% methanol in dichloromethane gave, after 40 mL of eluate, the crude product in the following 200 mL of eluate. Concentration under vacuum and centrifugal chromatography of the residue on a 4-mm silica gel plate, and elution with 4% methanol in dichloromethane in 1.5 mL/min fractions, gave 3.05 g (61%) of the 5*H* isomer **11** in fractions 13–41; mp 117–118 °C (lit.[41,67] mp 103–105 °C, 80–81 °C); TLC R_f 0.52 (5% methanol in dichloromethane); UV (ethanol) λ_{max} 193, 249 nm; IR (KBr) ν_{max} 3819, 3217, 3188, 3179, 3171, 3141, 3106, 2964, 2949, 2909, 2844, 1672, 1497, 1442, 1383, 1308, 1236, 1158, 811, 751, 517, 464, cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 1.91–2.07 (m, 2 H), 2.19–2.40 (m, 4 H), 2.48–2.65 (m, 2 H), 2.54 (t, J = 8 Hz, 2 H), 8.80 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 172.05, 133.75, 112.46, 32.32, 30.72, 30.49, 21.46, 21.15; MS, m/z (relative intensity) 138 (13), 137 (M^+, 100), 136 (65), 109 (58), 108 (47), 96 (16), 94 (30), 86 (15), 84 (24), 83 (13), 82 (38), 81 (43), 80 (23), 79 (13), 68 (13), 67 (29), 65 (10), 55 (23), 54 (29), 53 (27), 52 (17), 51 (40), 49 (17).

Equilibration of the two ene amide isomers **11** and **11a** was achieved by stirring about 20 mg of the more substituted double-bond isomer **11** in 5 mL of dichloromethane, containing about 20 mg of magnesium sulfate, for 24 h. A ratio of 79% 11:21% **11a** was then indicated by ^1H NMR.

2-[(*p*-Tolylsulfonyl)oxy]-1-[3,4-(methylenedioxy)-phenyl]ethane. To a solution of 3.37 g (19.9 mmol) of 2-[3,4-(methylenedioxy)phenyl]ethanol and 3.15 g (39.8 mol) of pyridine in 100 mL of dry chloroform at 0 °C was added, over 1 h, a solution of 5.69 g (29.8 mmol) of *p*-toluenesulfonyl chloride in 50 mL of chloroform. After 5 at 0 °C and 12 h at 20 °C, the mixture was washed with 100 mL of saturated sodium bicarbonate solution and 100 mL of brine and dried ($MgSO_4$). Concentration and chromatography on a 3 × 40 cm column of silica gel, eluting with 1:2 ether–hexanes, gave, in the initial 760 mL off eluate, 5.49 g (86%) of the tosylate; mp 57–58 °C; TLC R_f 0.38 (1:1 ether/hexanes); UV (ethanol) λ_{max} 200, 225, 287 nm; IR (KBr) ν_{max} 3064, 2999, 2971, 2950, 2923, 2898, 1599, 1506, 1494, 1485, 1464, 1445, 1369, 1347, 1245, 1203, 1188, 1174, 1038, 971, 904, 809, 774, 666, 575, 555 cm^{-1}; 270-MHz ^1H NMR ($CDCl_3$) δ 2.42 (s, 3 H), 2.84 (t, J = 7 Hz, 2 H), 4.15 (t, J = 7 Hz, 2 H), 5.90 (s, 2 H), 6.54 (d, J = 8 Hz, 1 H), 6.55 (s, 1 H), 6.67 (d, J = 8 Hz, 1 H), 7.28 (d, J = 8 Hz, 2 H), 7.69 (d, J = 8 Hz, 2 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 21.41, 35.07, 70.60, 100.84, 108.25, 109.15, 121.85, 127.74, 129.65, 129.96, 133.38, 144.52, 146.49, 147.96; MS, m/z (relative intensity) 322 (3), 321 (8), 320 (M^+, 37), 150 (4), 149 (33), 148 (100), 147 (14), 136 (6), 135 (58), 105 (8), 92 (4), 91 (33), 89 (8), 86 (9), 79 (7), 78

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(4), 77 (23), 65 (22), 63 (7), 51 (20).

Tetracyclic Lactam 10. A mixture of 1.06 g (3.73 mmol) of the ene lactam **5**, 1.5 mL of water, 4 mL of methanol, and 2 mL of 85% phosphoric acid was heated at 100 °C for 1 h. The cooled reaction mixture was then poured into 50 mL of saturated sodium bicarbonate solution at 0 °C and extracted with 3 × 30 mL of dichloromethane. The dried ($MgSO_4$) extracts were concentrated under vacuum and the residue was subjected to centrifugal chromatography on a 4-mm silica gel plate, eluting with ethyl acetate at 1.2 mL/min, to provide 0.859 g (81%) of product **10**, mp 128–129 °C, in fractions 6 mL–31 mL: TLC R_f 0.42 (ethyl acetate) 0.62 (5% methanol/dichloromethane); UV (ethanol) λ_{max} 203, 234, 292 nm; 250-MHz ^1H NMR δ 1.66–1.82 (m, 5 H), 1.94–2.02 (m, 1 H), 2.07–2.34 (m, 3 H), 2.41–2.62 (m, 2 H), 2.70–2.75 (m, 1 H), 2.89–3.05 (m, 2 H), 4.78–4.86 (m, 1 H), 5.90 (s, 2 H), 6.52 (s, 1 H), 6.69 (s, 1 H); 67.9-MHz ^{13}C NMR δ 169.81, 146.10, 145.91, 134.96, 128.58, 108.48, 104.52, 100.68, 69.78, 43.89, 43.69, 37.12, 29.78, 28.59, 28.39, 23.73, 22.38; IR (KBr) λ_{max} 3062, 3041, 2970, 2941, 2927, 2912, 2897, 2868, 1630, 1501, 1486, 1460, 1450, 1430, 1403, 1371, 1249, 1226, 1138, 1035, 929, 700, 682 cm^{-1}; MS, m/z (relative intensity) 286 (12), 285 (M^+, 40), 284 (6), 257 (10), 256 (52), 244 (15), 243 (92), 242 (38), 229 (20), 228 (33), 215 (9), 214 (19), 199 (11), 172 (6), 148 (11), 115 (9), 89 (6), 88 (10), 86 (59), 84 (100), 83 (6), 55 (10), 51 (50), 50 (19).

Peracid Oxidation of Ene Lactams 5 and 9. To 1.00 g (3.50 mmol) of a 6:4 mixture of ene lactams **5** and **9** in 10 mL of dry benzene at 0 °C was added 1.40 g (8.10 mmol) of *m*-chloroperoxybenzoic acid in 20 mL of benzene. After 1 h at 0 °C and 50 h at 20 °C, the mixture was partitioned between 100 mL of saturated sodium bicarbonate and 3 × 50 mL of benzene. The dried ($MgSO_4$) extracts were concentrated under vacuum and the residue was subjected to centrifugal chromatography on a 4-mm silica gel plate. Elution with ethyl acetate at 1.2 mL/min gave, in fractions 11–39 mL, a mixture of the oxidation products **13** and **14**. A second centrifugal chromatography, eluting with 4% methanol in dichloromethane, gave 0.610 g of the enone **13** in fractions 7–13 mL and 0.26 g of the alcohol **14**.

Oxidation of 0.060 g of the individual ene lactams **5** and **9** under the same conditions, followed by the initial chromatography, and HPLC analysis of the reaction products, showed that the ene lactam **5** gave a 3:1 mixture of the enone **13** and the alcohol **14** (60%), while only the enone **13** (51%) was obtained from oxidation of the ene lactam **9**. HPLC separation was performed on a 4.6 mm × 25 cm silica gel column, eluting with 5% methanol in dichloromethane.

Enone **13**: TLC R_f 0.48 (ethyl acetate), 0.64 (4% methanol/CH_2Cl_2); UV (ethanol) 203, 231, 285 nm; 250-MHz ^1H NMR ($CDCl_3$) δ 2.45–2.51 (m, 4 H), 2.54–2.63 (m, 4 H), 2.69–2.76 (m, 2 H), 4.13–4.20 (m, 2 H), 5.88 (s, 2 H), 6.69 (s, 2 H), 6.76 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 23.51, 25.58, 30.10, 34.77, 35.15, 41.76, 100.45, 107.74, 109.29, 121.71, 132.65, 138.13, 145.79, 147.31, 152.56, 168.17, 198.59; IR (KBr) ν_{max} 3023, 2964, 2920, 2906, 2858, 2835, 1694, 1665, 1500, 1483, 1428, 1412, 1375, 1362, 1332, 1295, 1245, 1210, 1191, 1128, 1035, 1015, 924, 821 cm^{-1}; MS, m/z (relative intensity) 301 (4), 300 (16), 299 (M^+, 79), 164 (26), 149 (13), 148 (100), 147 (13), 136 (26), 135 (19), 110 (7), 94 (35), 91 (12), 80 (7), 79 (6), 77 (15), 67 (9), 65 (12), 55 (17), 53 (9), 51 (10).

Alcohol **14**: TLC R_f 0.48 (ethyl acetate), 0.23 (4% methanol/CH_2Cl_2); UV (ethanol) λ_{max} 203, 235, 286 nm; 250-MHz ^1H NMR ($CDCl_3$) δ 1.69–1.82 (m, 1 H), 1.86–1.98 (m, 1 H), 2.04–2.19 (m, 2 H), 2.27–2.38 (m, 2 H), 2.42–2.51 (m, 1 H), 2.58–2.94 (m, 1 H), 3.65–3.87 (m, 2 H), 4.92–4.93 (m, 1 H), 5.90 (s, 2 H), 6.65 (dd, J = 1, 8 Hz, 1 H), 6.71 (d J = 1 Hz, 1 H), 6.72 (d, J = 8 Hz, 1 H), 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 27.75, 28.89, 31.65, 32.75, 38.50, 44.85, 76.52, 77.82, 100.73, 104.69, 108.14, 109.27, 121.62, 132.74, 144.84, 147.74, 168.59; IR ν_{max} (film) 3347, 3024, 2985, 2933, 2893, 2851, 1623, 1501, 1489, 1440, 1399, 1383, 1243, 1226, 1182, 1080, 1039, 939, 811 cm^{-1}; MS, m/z (relative intensity) 302 (3), 301 (M^+, 14), 149 (13), 148 (100), 135 (10), 120 (9), 106 (6), 94 (7), 91 (13), 79 (6), 77 (13), 65 (10), 55 (9), 53 (6).

***N*-[2-[3,4-(Methylenedioxy)phenyl]ethyl]-2,6-dioxo-1-azaspiro[4.4]nonane (20).** **(a)** Under an atmosphere or argon, a mixture of 0.442 g (0.997 mmol) of lead tetraacetate and 2 mL of dry benzene was heated at reflux. With rapid stirring, 0.132 g (0.464 mmol) of the ene lactam **5**, in 2 mL of dry benzene, was added in one portion. After 10 min the hot solution was filtered through a 1 × 3 cm plug of Celite 454, followed by elution with 10 mL of benzene. The filtrate was stirred for 30 min with 25 mL of saturated sodium bicarbonate solution and the separated aqueous phase was then extracted with 10 mL of benzene. The combined and dried ($MgSO_4$) organic solutions were concentrated under vacuum at 42 °C to provide 0.127 g of a product mixture, which was subjected to HPLC analysis on a 5-μm Microsorb silica column (4.6 mm × 25 cm), eluting with 5% methanol in dichloromethane. The product mixture contained 35.4% of the diacetate **19**, t_R 4.9 min, 42.7% of the spiro keto lactam **20**, t_R 5.2 min, and 14.9% of the pyridone **21**, t_R 5.5 min. With a 5-μm Microsorb C-18 reverse-phase column (4.6 mm × 25 cm) and 15% aqueous methanol at 2 mL/min, relative retentions were **21** (t_R 4.8 min), **20** (t_R 5.1 min), **19** (t_R 5.5 min).

(b) Repeating the reaction with 1.46 g (5.11 mmol) of the ene lactam **5** and centrifugal chromatography of the resultant product mixture on a 4-mm silica gel plate, eluting 2-mL fractions with ethyl acetate at 2 mL/min, provided a mixture of the diacetate **19** and the spiro keto lactam **20** in fractions 9–22 and 0.21 g (23%) of the latter compound in fractions 23–30. Rechromatography of the mixture from fractions 9–22, under the same conditions, gave 0.287 g (31%) of the diacetate **19** in fractions 10–18 and 0.370 g (40%) of the spiro keto lactam **20**.

Alternatively, the initial mixture of products **19** and **20** from fractions 9–22 was stirred for 2 h in 25 mL of dry methanol containing a catalytic amount of sodium methoxide. This resulted in complete conversion of the diacetate **19** to the spiro keto lactam **20** (total 94%).

Preparative purification of the initial reaction mixture by medium pressure liquid chromatography on tandem 25 mm × 25 cm and two 25 mm × 1 m silica gel 60 (230–400 mesh) columns, eluting with ethyl acetate at 10 mL/min and collecting 11-mL fractions, gave 0.81 g (89%) of the spiro keto lactam **20**.

Spiro keto lactam **20**: mp 101–102 °C; (2,4-dinitrophenyl)-hydroazone mp 225–226 °C. TLC R_f 0.39 (ethyl acetate), 0.49 (5% methanol/CH_2Cl_2); UV (ethanol λ_{max} 204, 233, 286 nm; 250-MHz ^1H NMR ($CDCl_3$) δ 1.68–1.87 (m, 3 H), 1.90–2.17 (m, 4 H), 2.26–2.44 (m, 3 H), 2.57–2.77 (m, 2 H), 3.03 (ddd, J = 14, 10, 7 Hz, 1 H), 3.39 (ddd, J = 14, 9, 5 Hz, 1 H), 5.84 (s, 2 H), 6.55 (d, J = 8 Hz, 1 H), 6.61 (s, 1 H), 6.65 (d, J = 8 Hz, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 17.16, 28.76, 29.59, 33.22, 34.51, 34.83, 43.39, 71.99, 100.72, 108.16, 109.16, 121.57, 132.74, 146.00, 147.58, 175.66, 216.63; IR (KBr) ν_{max} 3066, 3031, 3016, 2974, 2932, 2904, 2864, 2785, 1742, 1684, 1505, 1492, 1439, 1400, 1241, 1185, 1037, 975, 926, 833, 789, 620 cm^{-1}; MS, m/z (relative intensity) 302 (M + 1, 3), 301 (13), 166 (3), 149 (12), 148 (100), 135 (8), 110 (5), 91 (5), 82 (6), 77 (5), 65 (4), 55 (7), 51 (4). Anal. Calcd for $C_{23}H_{23}N_5O_7$: C, 57.38; H, 4.78; N, 14.55. Found: C, 57.15; H, 4.78; N, 14.33.

Diacetate **19**: TLC R_f 0.47 (ethyl acetate), 0.56 (5% methanol/CH_2Cl_2); UV (ethanol) λ_{max} 213, 231, 285 nm; 250-MHz ^1H NMR ($CDCl_3$) δ 1.26–1.36 (m, 1 H), 1.65–1.82 (m, 3 H), 1.93–2.14 (m, 2 H), 2.00 (s, 3 H), 2.03 (s, 3 H), 2.24–2.69 (m, 4 H), 2.78–2.89 (m, 2 H), 3.16–3.87 (m, 1 H), 3.72–3.83 (m, 1 H), 5.92 (s, 2 H), 6.64 (dd, J = 2, 8 Hz, 1 H), 6.70 (d, J = 2 Hz, 1 H) 6.71 (d, J = 8 Hz, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 17.81, 21.78, 22.04, 29.91, 30.92, 32.43, 32.63, 34.38, 44.37, 74.07, 100.85, 108.27, 109.33, 112.45, 121.74, 133.25, 146.09, 147.71, 167.92, 168.09, 176.02; IR (film) ν_{max} 3040, 3020, 2980, 2960, 2800, 1760, 1685, 1600, 1510, 1495, 1450, 1410, 1375, 1350, 1255, 1180, 1045, 1015, 945, 915 cm^{-1}; MS, m/z (relative intensity) 404 (12), 403 (M^+, 25), 360 (9), 318 (14), 302 (19), 301 (5), 258 (7), 166 (24), 150 (5), 149 (46), 148 (100), 147 (10), 135 (9), 119 (8), 91 (16), 77 (5), 65 (6), 55 (10), 51 (5).

Pyridone **21**: TLC R_f 0.32 (ethyl acetate), 0.36 (5% methanol-CH_2Cl_2); UV (ethanol) λ_{max} 220, 240, 285, 325 nm; 250-MHz ^1H NMR ($CDCl_3$) δ 1.99 (p, J = 7 Hz, 2 H), 2.59 (t, J = 7 Hz, 2 H), 2.68 (t, J = 7 Hz, 2 H), 2.93 (t, J = 7 Hz, 2 H), 4.07 (t, J = 7 Hz, 2 H), 5.90 (s, 2 H), 6.42 (d, J = 9 Hz, 1 H), 6.59 (dd, J = 8, 2 Hz), 1 H), 6.64 (d, J = 2 Hz, 1 H, 6.70 (d, J = 8 Hz, 1 H), 7.23 (d, J = 9 Hz, 1 H); 62.9-MHz ^{13}C NMR ($CDCl_3$) δ 22.66, 29.99, 31.67, 33.95, 47.99, 100.64, 108.13, 109.10, 117.24, 118.51, 121.61, 132.08, 136.87, 146.08, 147.52, 149.74, 162.95; IR (KBr) ν_{max} 2945, 2785, 1665, 1585, 1550, 1500, 1445, 1360, 1245, 1215, 1185, 1135, 1030, 1015, 965, 935, 825 cm^{-1}; MS, m/z (relative intensity) 284 (2), 283 (M^+, 6), 149 (15), 148 (100), 147 (20), 135 (7), 120 (4), 118 (4), 91 (8), 89 (4), 77 (8), 65 (6), 51 (6).

Oxidation of the Deuteriated Ene Lactam 22. The keto ester **6** (5.0 g) and the arylethylamine **7** (4.3 g) were each subjected to H–D exchange by stirring for 2 h in 25 mL of CH_3OD, in which 0.1 g of sodium had been dissolved. Formation of the deuteriated ene lactams **5** and **9** (**22** and its double-bond isomer) from these reactants, under conditions described for the formation of **5** and **9**, provided a product mixture which gave the following MS analysis: m/z (relative intensity and approximate assignment) 285 (10, M^+, **5**, **9**), 286 (7, $M + 1^+$, **5**, **9**; **22**, M^+, **5D**, **9D**), 287 (39, M^+, $\mathbf{5D_2}$, $\mathbf{9D_2}$), 288 (26, $M + 1^+$, $\mathbf{5D_2}$, $\mathbf{9D_2}$), 289 (9, M^+, $\mathbf{5D_3}$, $\mathbf{9D_3}$), 290 (1, M^+, $\mathbf{5D_4}$, $\mathbf{9D_4}$). This indicates a ratio of 1 (**5**, **9**):2.2 (**5D**, **9D**):3.9 ($\mathbf{5D_2}$, $\mathbf{9D_2}$).

Oxidation of this ene lactam mixture with lead tetraacetate and workup with sodium bicarbonate provided a mixture of keto lactams with m/z (relative intensity) 301 (11), 302 (19), 303 (20), 304 (13). After this mixture was stirred for 8 h in methanol containing some sodium methoxide, the mixture showed corresponding values of 301 (12), 302 (21), 303 (13), 304 (3). There was no change in the relative intensities after 3 h. This suggests a final ratio of 1 (**20**):1.5 (**20D**):1 (**24**).

***N*-[2-[3,4-(Methylenedioxy)phenyl]ethyl]-2,6-dioxo-1-azaspiro[4.4]non-7-ene (25).** **(a)** A solution of 0.018 g (0.35 mmol) of the spiro keto lactam **20** in 10 mL of dry *tert*-butyl alcohol and 5.00 g (13.0 mmol) of bis(benzonitrile)palladium(II) chloride was stirred under argon at 73 °C for 30 min. No enone **25** was seen by TLC at that point. The mixture was then heated at 116 °C in the presence of air, resulting in the formation of a black precipitate. Heating was continued until all of the ketone **20** had reacted (several hours, monitored by TLC). The reaction mixture was then filtered through a 2 × 6 cm column of Celite 545, eluting with 200 mL of ethyl acetate. Concentration, trituration with 5 mL of cold ethyl acetate, and filtration allowed recovery of some palladium complex. The filtrate was subjected to centrifugal chromatography on a 2-mm silica gel plate, collecting 3 mL/min fractions. Concentration of fractions 45–90 gave 77 mg (66%) of enone **25** as an oil. Some unreacted ketone **20** was obtained in fractions 32–43: TLC (ethyl acetate) R_f 0.41 (CAS, heat); UV (ethanol) λ_{max} 205, 226, 287 (335 weak) nm; 250-MHz ^{1}H NMR ($CDCl_3$) δ 1.81 (ddd, J = 13, 8, 7 Hz, 1 H), 2.21 (ddd, J = 13, 9, 6 Hz, 1 H), 2.45 (ddd, J = 17, 9, 6 Hz, 1 H), 2.56–2.71 (m, 4 H), 2.88 (ddd, J = 17, 9, 7 Hz, 1 H), 3.09–3.19 (m, 2 H), 5.91 (s, 2 H), 6.29 (dt, J = 6, 2 Hz, 1 H), 6.60 (dd, J = 8, 1 Hz, 1 H), 6.65 (d, J = 1 Hz, 1 H), 6.71 (d, J = 8 Hz, 1 H), 7.74 (dt, J = 6, 3 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 207.49, 175.67, 162.10, 147.53, 145.95, 132.72, 132.46, 121.50, 109.08, 108.14, 100.68, 68.38, 43.43, 40.54, 33.98, 31.11, 29.36; IR (film) ν_{max} 3066, 3031, 2967, 2935, 2892, 1715, 1689, 1503, 1491, 1444, 1399, 1346, 1246, 1038, 926, 831 cm^{-1}; MS, m/z (relative intensity) 300 (M + 1, 4), 299 (20), 164 (8), 149 (15), 148 (100), 147 (10), 136 (5), 135 (9), 91 (8), 86 (7), 84 (9), 77 (7), 65 (6), 56 (9). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22, H, 5.72, N, 4.68. Found: C, 67.95; H, 6.00; N, 4.60.

(b) The silyl enol ether **26** was prepared by addition of 91 μL (0.43 mmol) of 1,1,1,3,3,3-hexamethyldisilazane to 0.100 g (0.332 mmol) of the spiro keto lactam **20** in 8 mL of dichloromethane. After 30 min the rapidly stirred solution was cooled to 0 °C and 52 μL (0.36 mmol) of iodotrimethylsilane added over 5 min. After 1 h at 0 °C and 12 h at 20 °C the mixture was poured into 100 mL of ice-cold saturated sodium bicarbonate solution and extracted with 3 × 30 mL of dichloromethane. The combined extracts were washed with 100 mL of saturated brine, dried ($MgSO_4$), and concentrated at 40 °C under vacuum. IR spectra indicated complete absence of the ketone carbonyl function of **20**. Integration of NMR signals for the vinyl H at δ 4.72 and the methylenedioxy signal at 5.85 showed a 1:2 ratio. Alternative reactions with trimethylsilyl acetate and tetrabutylammonium fluoride[69] or with trimethylsilyl trifluoromethanesulfonate and triethylamine[70] gave 74% and 88% conversions of the ketone **20** to the silyl enol ether, based on the above NMR signal criterion.

250-MHz ^{1}H NMR ($CDCl_3$) δ 0.15 (s, 9 H), 1.73–1.87 (m, 3 H), 2.06–2.24 (m, 3 H), 2.25–2.47 (m, 2 H), 2.66–2.87 (m, 2 H), 3.06–3.16 (m, 2 H), 4.72 (t, J = 2 Hz, 1 H), 5.85 (s, 2 H), 6.61 (d, J = 8 Hz, 1 H), 6.66 (s, 1 H), 6.67 (d, J = 8 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 175.03, 154.02, 147.68, 145.99, 133.67, 121.53, 109.18, 108.14, 103.00, 100.64, 73.54, 42.58, 34.63, 33.53, 30.95, 30.25, 25.17, –0.37; IR (NaCl, film) ν_{max} 3067, 2960, 2902, 2859, 1687, 1647, 1503, 1491, 1403, 1253, 1177, 1078, 1038, 870, 849; MS, m/z (relative intensity) 374 (M + 1, 9), 373 (33), 239 (7), 238 (38), 226 (7), 225 (14), 209 (11), 181 (7), 167 (24), 149 (16), 148 (100), 131 (15), 91 (10), 77 (6), 75 (11), 73 (64), 65 (5), 55 (11).

A solution of 0.121 g (0.323 mmol) of the silyl enol ether **26** in 4 mL of dry acetonitrile was added to 72 mg (0.32 mmol) of palladium(II) acetate and 34 mg (0.32 mmol) of *p*-benzoquinone. After being stirred for 24 h at 20 °C the mixture was adsorbed on 5 g of silica gel and the solvent evaporated under vacuum. Addition to a 30-g dry column of silica gel, elution with ethyl acetate, and concentration under vacuum gave the crude enone **25** as a yellow oil. This oil was subjected to centrifugal chromatography on a 1.5-mm silica gel plate. Elution with ethyl acetate provided 89 mg (92%) of the enone **25**.

(c) A solution of 0.123 g (0.332 mmol) of the silyl enol ether **26** in 4 mL of dichloromethane was cooled to –78 °C and 66 mg (0.35 mmol) of phenylbenzeneselenenyl chloride in 1 mL of dichloromethane was added dropwise over 5 min. After 1 h at –78 °C and 1 h at 20 °C the mixture was poured into 100 mL of ice-cold 10% aqueous sodium bicarbonate and extracted with 3 × 3 mL of dichloromethane. The combined extracts were washed with 100 mL of cold saturated brine, dried ($MgSO_4$), and concentrated at 40 °C under vacuum. The residue was subjected to centrifugal chromatography on a 1-mm silica gel plate, collecting 0.5-mL fractions from elution with ethyl acetate at 1 mL/min. Fractions 23–35 provided 0.133 g (91%) of the α-phenylselenyl ketone **27** on concentration and drying at 5 Torr. Dropwise addition of 67 μL (0.60 mmol) of 30% hydrogen peroxide to 0.133 g (0.298 mmol) of the phenyl selenide **20** in 6 mL of dichloromethane, over 1 min, with rapid stirring, resulted in an exothermic reaction. After 30 min the mixture was poured into 40 mL of ice-cold 7% aqueous sodium bicarbonate and extracted with 3 × 20 mL of dichloromethane. The combined extracts were washed with 50 mL of cold saturated brine, dried ($MgSO_4$), and concentrated at 40 °C under vacuum. Centrifugal chromatography on silica gel, eluting with ethyl acetate, as in section (**a**), gave 87 mg (97%) of the enone **25**.

Alternatively, oxidation of 0.120 g (0.289 mmol) of phenyl selenide **27** in 4 mL of tetrahydrofuran with 0.114 g (0.537 mmol) of sodium periodate in 2 mL of water, stirring for 4 h at 20 °C, and workup with sodium bicarbonate gave a comparable yield of the enone **25**.

***N*-[2-[(3,4-(Methylenedioxy)phenyl]ethyl]-6α-hydroxy-2-oxo-1β-azaspiro[4.4]non-7-ene (30).** Aluminum isopropoxide (2.04 g, 10.0 mmol) was added to 0.98 g (0.33 mmol) of *N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]-2,6-dioxo-1-azaspiro[4.4]-non-7-ene (**25**) in 25 mL of dry 2-propanol. The solvents (and acetone) were distilled until 40 mL had been collected. The cooled residue was then added slowly, with rapid stirring, to 50 mL of 1 N HCl at –15 °C. Extraction with 5 × 30 mL of dichloromethane and concentration of the dried ($MgSO_4$) extracts at 40 °C under vacuum gave a residue which was subjected to centrifugal chromatography on a 1-mm silica gel plate. Elution with ethyl acetate and collection of 2 mL/min fractions gave, in fractions 48–98, 98 mg (100%) of product **30**, mp 103–104 °C, after crystallization from ether: TLC (ethyl acetate) R_f 0.16 (CAS, heat); HPLC (μ-Porasil, ethyl acetate, 1.9 mL/min) t_R 13.4 min; UV (ethanol) λ_{max} 206, 234, 287 nm; 250-MHz ^{1}H NMR ($CDCl_3$) δ 1.89 (ddd, J = 12, 12, 9 Hz, 1 H), 2.06 (ddd, J = 13, 6, 2 Hz, 1 H), 2.11 (dt, J = 18, 2 Hz, 1 H), 2.28 (ddd, J = 17, 9, 1 Hz, 1 H), 2.53 (ddd, J = 17, 11, 8 Hz, 1 H), 2.57 (ddd, J = 17, 2, 1 Hz, 1 H), 2.68 (ddd, J = 13, 9, 7 Hz, 1 H), 2.84 (ddd, J = 11, 11, 4 Hz, 1 H), 3.20 (ddd, J = 14, 9, 7 Hz, 1 H), 3.71 (ddd, J = 12, 12, 5 Hz, 1 H), 5.81 (dd, J = 6, 2 Hz, 1 H), 5.91 (s, 2 H), 5.91 (d, J = 6 Hz, 1 H), 6.61 (dd, J = 8, 1 Hz, 1 H), 6.67 (d, J = 1 Hz, 1 H), 6.71 (d, J = 8 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 176.36, 147.48, 145.85, 132.58, 121.83, 120.78, 109.45, 108.25, 100.79, 81.54, 71.33, 44.94, 41.72, 34.92, 33.64, 29.88; IR (KBr) ν_{max} 3025, 3008, 2941, 2896, 1671, 1504, 1491, 1444, 1412, 1356, 1342, 1250, 1188, 1135, 1122, 1108, 1042, 938, 812, 784, 766, 757, 746, 730, 668 cm^{-1}; MS, m/z (relative intensity) 303 (M^+, 5), 302 (26), 301 (41), 166 (6), 149 (16), 148 (100), 147 (10), 138 (8), 136 (30), 135 (16), 134 (7), 119 (6), 108 (6), 91 (26), 82 (6), 79 (1), 77 (16), 65 (14), 55 (16), 53 (6), 51 (9).

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Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.60; H, 6.50; N, 4.48.

***N*-[2-[3,4-(Methylenedioxy)phenyl]ethyl]-1-azaspiro[4.4]nona-6,8-diene (32).** Acetylation of 0.100 g (0.332 mmol) of the allylic alcohol **30** with 3 mL of acetic anhydride and 1.5 mL of pyridine, with stirring for 15 h at 20 °C, followed by addition to 50 mL of ice-cold water and extraction with 5 × 25 ml of dichloromethane gave, after concentration and centrifugal chromatography on a 1-mm silica gel plate, collecting 1.8 mL/min fractions, the acetate **31** in fraction 4–10. Crystallization from ether provided a sample with mp 120–121 °C: TLC (ethyl acetate) R_f 0.77 (CAS, heat), (ether) R_f 0.35. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.47; H, 6.16; N, 4.08. Found: C, 66.37; H, 6.54, N, 3.88.

A solution of 93 mg (0.27 mmol) of the allylic acetate **31** in 9 mL of tetrahydrofuran was added to 313 mg (0.271 mmol) of tetrakis(triphenylphosphine) palladium(0) complex, resulting in formation of a yellow heterogeneous mixture. Stirring of the reaction mixture for 24 h in a heating bath at 100 °C led to precipitation of Pd black. The cooled mixture was concentrated under vacuum and the residue subjected to centrifugal chromatography on a 1-mm silica gel plate. Elution with ethyl acetate and rechromatography with ethyl ether, eluting at 1.5 mL/min and collecting 0.5-mL fractions, gave the diene **32** in fractions 16–33, contaminated by some triphenylphosphine. Rechromatography provided a sample which was homogeneous by HPLC on a μ-Porasil column (25 × 0.46 cm), eluted with ethyl acetate at 0.8 mL/min (t_R 6.1 min): 250-MHz ^{1}H NMR ($CDCl_3$) δ 2.11 (t, J = 8 Hz, 2 H), 2.54 (t, J = 8 Hz, 2 H), 2.68 (d, J = 7 Hz, 1 H), 2.71 (d, J = 5.4 Hz, 1 H), 2.96 (d, J = 5 Hz, 1 H), 3.00 (d, J = 8 Hz, 1 H), 6.26–6.63 (m, 2 H), 6.02–6.05 (m, 2 H, 5.91 (s, 2 H), 6.59 (dd, J = 8, 2 Hz, 1 H), 6.63 (d, J = 1 Hz, 1 H), 6.71 (d, J = 8 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 24.69, 30.89, 35.95, 42.77, 75.07, 100.79, 108.17, 109.39, 121.78, 131.43, 132.93, 139.47, 145.98, 147.55, 175.32; UV (ethanol) λ_{max} 211, 222, 285 nm; IR ($CHCl_3$) ν_{max} 3067, 3009, 2937, 2891, 1673, 1504, 1492, 1410, 1362, 1250, 1215, 1130, 1042, 940, 929, 813, 766 cm^{-1}; MS, m/z (relative intensity) 284 (M + 1, 10), 283 (35), 149 (14), 148 (100), 147 (9), 135 (15), 120 (9), 119 (7), 106 (8), 94 (10), 91 (23), 86 (19), 84 (29), 77 (23), 65 (17), 55 (12), 51 (32).

2,3-Dehydrocephalotaxan-8-one (33). (a) A solution of 52 mg (0.17 mmol) of *N*-[2-[3,4-(methylenedioxy)phenyl]ethyl]-6α-hydroxy-2-oxo-1β-azaspiro[4.4]non-7-ene (**30**) in 2.5 mL of dichloromethane and 2.5 mL of nitromethane was cooled to −78 °C. With rapid stirring 200 μL (1.72 mmol) of stannic chloride was added in one portion. After 1 h at −78 °C the bright yellow reaction mixture was warmed slowly to 20 °C, stirred for 2 h, and then added to 50 mL of 1 N aqueous HCl, chilled to 0 °C. After being stirred for 15 min, the mixture was extracted with 3 × 50 mL of dichloromethane. The combined extracts were washed with 50 mL of saturated aqueous sodium bicarbonate and 50 mL of saturated brine, dried ($MgSO_4$), and concentrated at 40 °C under vacuum. Centrifugal chromatography on a 1-mm silica gel plate, eluting with ethyl acetate at 1.8 mL/min and collection of 0.9-mL fractions, gave, in fractions 60–70, 49 mg (100% yield) of tetracyclic lactam **33** with mp 142–143 °C, after crystallization from ether: TLC (SiO_2, ethyl acetate) R_f 0.42 (CAS, heat); HPLC (μ-Poracil, ethyl acetate, 1.1 mL/min) t_R 9.3 min; UV (ethanol) λ_{max} 207, 240, 290 nm; 250-MHz ^{1}H NMR ($CDCl_3$) δ [6,7] 2.12–2.29 (m, 4 H) [11α] 2.43 (dd, J = 14, 7 Hz, 1 H), [1α] 2.60 (dq, J = 18, 2 Hz, 1 H), [1β] 2.94 (dq, J = 18, 2 Hz, 1 H), [10β] 3.00 (dd, J = 13, 8 Hz, 1 H), [11β] 3.30 (ddd, J = 14, 11, 8 Hz, 1 H), [4] 3.80 (m, 1 H), [10α] 4.10 (ddd, J = 13, 11, 9 Hz, 1 H), [2] 5.61 (dt, J = 6, 2 Hz, 1 H), [3] 5.85 (dt, J = 7, 3 Hz, 1 H), [18] 5.89 (d, J = 1.5 Hz, 1 H), [18] 5.91 (d, J = 1.5 Hz, 1 H), 6.57 (s, 1 H), 6.63 (s, 1 H); (DMSO-d_6) δ 1.96–2.22 (m, 4 H), 2.45 (dd, J = 14, 7 Hz, 1 H), 2.54 (dq, J = 18, 2 Hz, 1 H), 2.95 (dq, J = 18, 2 Hz, 1 H), 2.98 (dd, J = 13, 7 Hz, 1 H), 3.13 (ddd, J = 14, 11, 8 Hz, 1 H), 3.84 (ddd, J = 12, 12, 7 Hz, 1 H), 3.93 (m, 1 H), 5.55 (dt, J = 7, 2 Hz, 1 H), 5.86 (dt, J = 6, 2 Hz, 1 H), 5.93 (d, J = 1 Hz, 1 H), 5.96 (d, J = 1 Hz, 1 H), 6.69 (s, 1 H), 6.86 (s, 1 H); 67.9-MHz ^{13}C NMR in $CDCl_3$ or (DMSO-d_6) δ [8] 174.66 (173.13), [15] 146.80 (145.84), [16] 146.21 (145.39), [3] 131.93 (131.24), [13] 131.01 (130.88), [2] 129.90 (130.42), [12] 128.02 (127.89), [14] 110.64 (110.47), [17] 110.54 (109.73), [18] 100.84 (100.35), [5] 69.22 (68.11), [4] 63.61 (62.22), [10] 43.80 (42.90), [7] 37.38 (36.88), [1] 35.48 (34.98), [11] 30.07 (29.33), [6] 29.61 (28.63); IR (KBr) ν_{max} 3045, 2968, 2935, 2905, 2869, 2846, 1664, 1623, 1504, 1488, 1396, 1225, 1040, 934, 743, 676, 658 cm^{-1}; MS, m/z (relative intensity) 284 (M + 1, 64), 283 (82), 282 (11), 268 (7), 242 (14), 231 (8), 230 (58), 228 (8), 200 (7), 187 (17), 186 (100), 185 (10), 174 (12), 173 (24), 172 (22), 160 (17), 148 (8), 141 (12), 139 (7), 134 (12), 129 (11), 128 (24), 127 (11), 115 (38), 111 (46), 103 (12), 102 (12), 98 (16), 89 (10), 77 (16), 63 (11), 55 (19), 54 (11). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.04; N, 4.94. Found: C, 72.13; H, 6.26; N, 4.71.

(b) Alternatively, a sample of the cyclopentadiene **32** was dissolved in dichloromethane and 1 equiv of trifluoroacetic acid was added. After 0.5 h the mixture was neutralized with sodium bicarbonate and the organic solution concentrated. The residue gave TLC and ^{1}H NMR data matching those of the product of procedure (**a**) above.

2α,3α-Epoxycephalotaxan-8-one (35). To a stirred solution of 0.04 g (0.14 mmol) of the tetracyclic ene lactam **33** in 1 mL of dichloromethane was added 0.036 g (0.21 mmol) of *m*-chloroperoxybenzoic acid in 1 mL of dichloromethane. After 14 h the mixture was poured into 25 mL of cold saturated sodium bicarbonate solution and extracted with 4 × 20 mL of dichloromethane. The extracts were washed with 25 mL of saturated brine, dried ($MgSO_4$), and concentrated at 40 °C under vacuum. Centrifugal chromatography on a 1-mm silica gel plate and elution with ethyl acetate at 2.2 mL/min and collection of 1.1-mL fractions gave the product in fractions 5–29. Concentration and recrystallization from ether provided 0.042 g (100%) of the epoxide **35**, mp 171–172 °C: TLC (ethyl acetate, CAS-heat) R_f 0.33; HPLC (μ-Porasil 25 cm × 4.6 mm, ethyl acetate, 1.1 mL/min) t_R 12.9 min; UV (ethanol) λ_{max} 211, 241, 291 nm; 250-MHz ^{1}H NMR ($CDCl_3$) δ 2.01–2.25 (m, 5 H), 2.56 (dd, J = 15, 5 Hz, 1 H), 2.64 (dd, J = 16, 2 Hz, 1 H), 2.89 (ddd, J = 14, 14, 6 Hz, 1 H), 3.12 (dd, J = 14, 5 Hz, 1 H), 3.31 (s, 1 H), 3.46 (d, J = 2 Hz, 1 H), 3.75 (t, J = 2 Hz, 1 H), 4.08 (ddd, J = 13, 13, 6 Hz, 1 H), 5.91 (d, J = 1 Hz, 1 H), 5.94 (d, J = 1 Hz, 1 H), 6.63 (s, 1 H), 6.66 (s, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 30.10, 30.85, 37.98, 38.77, 39.67, 59.47, 59.74, 62.38, 72.84, 101.21, 110.12, 111.24, 129.52, 129.86, 146.84, 147.58, 174.43; IR (KBr) ν_{max} 3040, 2980, 2955, 2915, 2895, 1680, 1500, 1485, 1400, 1380, 1275, 1226, 1060, 1040, 935, 865, 840, 815 cm^{-1}; MS, m/z (relative intensity) 300 (M + 1, 24), 299 (100, 281 (8), 256 (33), 255 (7), 244 (8), 243 (49), 242 (12), 230 (9), 228 (9), 203 (8), 202 (56), 189 (11), 186 (8), 185 (32), 176 (9), 175 (65), 174 (35), 173 (69), 172 (17), 161 (11), 160 (11), 159 (16), 158 (15), 156 (41), 149 (7), 148 (12), 144 (11), 143 (16), 141 (13), 139 (40), 131 (23), 130 (9), 128 (13), 127 (7), 117 (8), 116 (19), 115 (47), 113 (8), 111 (41), 110 (47), 104 (7), 103 (21), 102 (15), 101 (7), 91 (9), 89 (9), 83 (7), 82 (36), 78 (7), 77 (25), 76 (12), 75 (20), 74 (9), 67 (7), 65 (12), 63 (15), 59 (8), 55 (16), 54 (10), 53 (12), 51 (20), 50 (15). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 67.98; H, 5.71; N, 4.48.

3,8-Dioxocephalotax-1-ene (36). To 0.025 g (0.083 mmol) of the epoxy lactam **35** was added 1 mL of dry dimethyl sulfoxide followed, with rapid stirring, by 10 μL (0.083 mmol) of boron trifluoride etherate. The mixture was heated at 92 °C for 10 h, with addition of a second portion of 10 μL of boron trifluoride etherate during this time. The reaction mixture was poured into 20 mL of cold water and extracted with 3 × 15 mL of chloroform. The extracts were washed with 50 mL of cold saturated sodium bicarbonate solution and 50 mL of cold saturated brine, dried ($MgSO_4$), and concentrated at 40 °C under vacuum. Centrifugal chromatography on a 1-mm silica gel plate, eluting with ethyl acetate at 1.8 mL/min and collecting 0.9-mL fractions, gave the enone **36** in fractions 15–36. Trituration with anhydrous ether provided 8 mg (32%) of product **36**. No further products could be eluted with methanol. TLC (ethyl acetate, CAS-heat) R_f 0.23; HPLC (μ-Poracil 25 cm × 4.6 mm, ethyl acetate, 1.1 mL/min) t_R 14.0 min; UV (ethanol) λ_{max} 217, 240, 291 nm; 250-MHz ^{1}H NMR ($CDCl_3$) δ 2.15–2.41 (m, 4 H), 2.46–2.52 (m, 2 H), 2.91 (dt, J = 12, 4 Hz, 1 H), 3.41 (s, 1 H), 4.14 (ddd, J = 13, 11, 9 Hz, 1 H), 5.93 (d, J = 1 Hz, 1 H), 5.94 (d, J = 1 Hz, 1 H), 6.56 (d, J = 6 Hz, 1 H), 6.62 (s, 1 H), 6.69 (s, 1 H), 7.42 (d, J = 6 Hz, 1 H); 67.9-MHz ^{13}C NMR ($CDCl_3$) δ 29.48, 30.86, 33.39, 38.67, 63.19, 70.16, 101.30, 110.81, 112.30, 127.25, 129.53, 137.07, 147.88, 160.66, 174.49, 205.76, 224.60; IR ($CHCl_3$) ν_{max} 3012, 2967, 2945, 2927, 2882, 1720, 1686, 1504, 1488, 1456, 1430, 1405, 1371, 1332, 1271, 1222, 1196, 1156, 1135, 1104, 1072, 1044, 938, 858, 813, 788, 768, 745

cm^{-1}; MS, m/z (relative intensity) 298 (M + 1, 22), 297 (100), 282 (28), 280 (8), 269 (8), 268 (9), 243 (11), 228 (15), 212 (7), 198 (8), 172 (9), 160 (17), 150 (12), 148 (6), 115 (7), 102 (6), 84 (5), 77 (10), 63 (8), 55 (10), 53 (6), 51 (9).

2α,3α-Dihydroxycephalotaxan-8-one (37). To a solution of 0.200 g (0.706 mmol) of 2,3-dehydrocephalotaxan-8-one (**33**) and 0.099 g (0.85 mmol) of *N*-methylmorpholine *N*-oxide in 2 mL of tetrahydrofuran, under argon, was added 0.25 mL of water. The resulting heterogeneous mixture was stirred rapidly and 200 μL of a 4% (w/w) solution of osmium tetraoxide in water was added. After stirring for 24 h at 20 °C, the reaction mixture was poured into 25 mL of 10% HCl and 10 mL of 15% sodium bisulfite. The resulting dark brown mixture was extracted with five 15-mL portions of dichloromethane, and the dried ($MgSO_4$) extracts were concentrated under vacuum at 42 °C. The residual foam was dissolved in 5 mL of dichloromethane and subjected to centrifugal chromatography on a 2-mm silica gel plate, eluting with 2:1 ethyl acetate–ethanol, collecting 1.2 mL/min fractions. Concentration of fractions 10–28 under vacuum gave 0.220 g (99% yield) of amorphous product, which crystallized from toluene, mp 250–251 °C: TLC (4:1 ethyl acetate: ethanol) R_f 0.38; (10% methanol in dichloromethane) R_f 0.21; UV (ethanol) λ_{max} 205, 241, 289nm; 250-MHz ^1H NMR (DMSO-d_6) δ 1.73 (d, J = 14 Hz, 1 H), 2.04–1.86 (m, 2 H), 2.16–2.10 (m, 3 H), 2.35 (dd, J = 14, 4 Hz, 1 H), 2.63–2.55 (m, 2 H), 3.10–2.94 (m, 3 H), 3.87–3.74 (m, 1 H), 3.97 (t, J = 3 Hz, 1 H), 4.21–4.13 (m, 1 H), 4.72–4.67 (m, 1 H), 5.93 (d, J = 5 Hz, 2 H), 6.68 (s, 1 H), 6.76 (s, 1 H); 67.9-MHz ^{13}C NMR (DMSO-d_6) δ 173.69, 145.61, 145.22, 131.94, 129.83, 111.81, 109.95, 100.26, 77.29, 70.92, 66.49, 60.87, 54.40, 39.04, 37.42, 29.07, 28.94; IR (KBr) ν_{max} 3389, 2968, 2906, 2881, 1663, 1646, 1501, 1486, 1421, 1369, 1255, 1226, 1038, 934, 859 cm^{-1}; MS, m/z (relative intensity) 318 (M + 1, 29), 317 (100), 302 (33), 300 (47), 272 (14), 244 (14), 243 (42), 242 (38), 230 (37), 228 (17), 214 (11), 200 (10), 174 (12), 173 (11), 162 (13), 161 (25), 156 (14), 149 (14), 147 (10), 138 (14), 131 (15), 130 (10), 128 (10), 115 (23), 110 (11), 103 (20), 102 (11), 98 (16), 91 (19), 82 (10), 77 (20), 65 (13), 55 (24), 51 (10). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.28; H, 6.18; N, 4.20. A diacetate of **37**, mp 256–257 °C, was prepared with acetic anhydride in pyridine: 250-MHz ^1H NMR ($CDCl_3$) δ 1.96 (s, 3 H), 2.11–1.98 (m, 1 H), 2.16 (s, 3 H), 2.21–2.36 (m, 4 H), 2.58 (dd, J = 15, 4 Hz, 1 H), 2.69 (dd, J = 14, 7 Hz, 1 H), 3.02–3.16 (m, 2 H), 3.31 (d, J = 10 Hz, 1 H), 4.13 (ddd, J = 15, 11, 6 Hz, 1 H), 5.47–5.56 (m, 2 H), 5.94 (d, J = 1 Hz, 1 H), 5.91 (d, J = 1 Hz, 1 H), 6.59 (s, 1 H), 6.64 (s, 1 H); IR (KBr) ν_{max} 3046, 3022, 2982, 2948, 2931, 2873, 1746, 1683, 1512, 1493, 1460, 1433, 1400, 1370, 1326, 1250, 1227, 1174, 1140, 1079, 1041, 974, 933, 910, 891, 880, 865, 733, 605, 521 cm^{-1}; MS, m/z (relative intensity) 402 (M + 1, 15), 401 (58), 343 (17), 342 (100), 300 (18), 282 (14), 281 (22), 244 (16), 243 (17), 242 (15), 161 (11), 115 (11), 86 (33), 55 (11), 51 (29).

2,3,8-Trioxocephalotaxane (38). At 0 °C, 0.297 g (4.49 mmol) of methyl sulfide was added dropwise to 0.599 g (4.49 mmol) of *N*-chlorosuccinimide in 5 mL of dry dichloromethane. After stirring for 30 min at 0 °C, the mixture was cooled to −42 °C and then a solution of 0.285 g (0.898 mmol) of 2α,3α-dihydroxycephalotaxan-8-one (**37**) in 20 mL of dry dichloromethane was added dropwise over 5 min. After stirring at −40 °C for 1 h, 1.0 mL of triethylamine was added in one portion, and the reaction mixture brought to 20 °C over 1.5 h. The mixture was poured onto 50 mL of saturated brine and extracted with three 50-mL portions of dichloromethane. The dried ($MgSO_4$) extracts were concentrated under vacuum at 42 °C (and the residue triturated with dry toluene) to provide 0.251 g (89%) of the diketone **38** which, after recrystallization from toluene, had mp 325 °C dec: TLC (4:1 ethyl acetate: ethanol) R_f 0.64; (10% methanol in dichloromethane) R_f 0.47. UV (ethanol) λ_{max} 206, 235, 288, 313 nm; 250-MHz ^1H NMR (DMSO-d_6) δ 1.73–1.93 (m, 2 H), 2.04 (dd, J = 16, 8 Hz, 1 H), 2.38–2.53 (m, 1 H), 2.60 (d, J = 18 Hz, 1 H), 2.78 (d, J = 18 Hz, 1 H), 2.84–3.19 (m, 3 H), 3.66–3.78 (m, 1 H), 6.01 (s, 1 H), 6.03 (s, 1 H), 6.78 (s, 1 H), 6.82 (s, 1 H), 9.99 (br s, 1 H); 67.9-MHz ^{13}C NMR (DMSO-d_6) δ 198.10, 172.48, 149.32, 147.30, 145.05, 141.60, 130.14, 122.76, 109.87, 108.99, 100.83, 66.46, 44.13, 34.58, 33.01, 32.65, 29.22; IR (KBr) ν_{max} 3082, 3062, 3020, 3013, 2994, 2966, 2939, 2906, 1703, 1660, 1504, 1486, 1380, 1260, 1231, 1127, 1048, 1036, 936, 874, 792 cm^{-1}; MS, m/z (relative intensity) 314 (M + 1, 22), 313 (100), 296 (27), 284 (10), 270 (10), 257 (9). 255 (11), 254 (11), 242 (16), 188 (27), 160 (13), 141 (7), 128 (15), 127 (10), 115 (20), 107 (13), 103 (11), 102 (11), 98 (15), 89 (8), 77 (11), 57 (10), 56 (7), 55 (19). Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.17;, H, 4.82; N, 4.47. Found: C, 64.88; H, 4.73; N, 4.27.

2-Methoxy-3,8-dioxocephalotax-1-ene (39). To a mixture of 0.40 mL (2.9 mmol) of methoxytrimethylsilane, 10 mL of dry dichloromethane, and 0.100 g (0.319 mmol) of 2,3,8-trioxocephalotaxane (**38**) was added, in one portion, 0.070 mL (0.791 mmol) of trifluoromethanesulfonic acid. The now homogeneous yellow solution was, after 24 h, poured into 25 mL of saturated sodium bicarbonate solution and extracted with 3 × 30 mL of dichloromethane. The dried ($MgSO_4$) extracts were concentrated under vacuum at 42 °C and the residue was subjected to centrifugal chromatography on a 2-mm silica gel plate. Elution with dichloromethane containing 5% methanol and 1% triethylamine and collection of 1 mL/min fractions gave, from fractions 9–20, on concentration under vacuum and trituration with toluene, 0.101 g (97% yield) of the enol ether (**39**). A sample crystallized from toluene had mp 335 °C dec. TLC (5% methanol, 1% triethylamine in dichloromethane) R_f 0.40; UV (ethanol) λ_{max} 204, 242, 289 nm; 250-MHz ^1H NMR ($CDCl_3$) δ 2.21–2.59 (m, 6 H), 2.97 (dd, J = 13, 6 Hz, 1 H), 3.57 (s, 1 H), 3.88 (s, 3 H), 4.08 (ddd, J = 13, 12, 8 Hz, 1 H), 5.94 (s, 2 H), 6.15 (s, 1 H), 6.64 (s, 1 H), 6.71 (s, 1 H); (DMSO-d_6) δ 1.97–2.10 (m, 1 H), 2.14–2.27 (m, 4 H), 2.53 (dd, J = 16, 7 Hz, 1 H), 2.89 (dd, J = 13, 7 Hz, 1 H), 3.78 (s, 3 H), 3.83 (ddd, J = 16, 13, 8 Hz, 1 H), 3.94 (s, 1 H), 5.97 (s, 1 H), 5.99 (s, 1 H), 6.51 (s, 1 H), 6.76 (s, 1 H), 6.91 (s, 1 H); 67.9-MHz ^{13}C NMR (DMSO-d_6) δ 198.72, 173.18, 158.31, 146.43, 145.56, 129.69, 128.57, 125.17, 111.98, 109.74, 100.63, 65.17, 60.95, 57.16, 37.14, 32.85, 29.65, 28.97; IR (KBr) ν_{max} 3072, 3057, 2985, 2959, 2940, 2914, 2866, 2843, 2802, 1718, 1688, 1624, 1506, 1491, 1396, 1229, 1031, 934, 871 cm^{-1}; MS, m/z (relative intensity) 328 (M + 1, 21), 327 (100), 312 (77), 256 (16), 242 (25), 241 (21), 240 (12), 228 (22), 185 (31), 180 (17), 179 (54), 178 (16), 172 (14), 161 (17), 160 (25), 150 (20), 149 (15), 148 (33), 147 (20), 141 (15), 131 (18), 130 (20), 128 (19), 127 (16), 124 (34), 115 (33), 103 (37), 102 (22), 89 (15), 86 (36), 84 (58), 77 (24), 68 (16), 55 (27), 51 (34). Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 66.06; H, 4.97; N, 4.22.

(±)-8-Oxocephalotaxine (40). To a solution of 0.040 g (0.122 mmol) of 2-methoxy-3,8-dioxocephalotax-1-ene (**39**) in 5 mL of dry methanol and 5 mL of dry dichloromethane was added 0.010 g (0.264 mmol) of sodium borohydride in small portions, over 15 min, at 20 °C. After being stirred for 1 h at room temperature the mixture was poured into 25 mL of saturated brine. Extraction with 4 × 20 mL of dichloromethane, concentration of the dried ($MgSO_4$) extracts under vacuum at 42 °C, and centrifugal chromatography on a 1-mm silica gel plate, eluting with 5% methanol and 1% triethylamine in dichloromethane, with collection of 0.8 mL/min fractions, gave 0.037 g (93% yield) of the alcohol **40**, eluted in fractions 7–15: mp 230 °C dec; UV (ethanol) λ_{max} 209, 239, 290 nm; 250-MHz ^1H NMR ($CDCl_3$) δ 1.86 (d, J = 3 Hz, 1 H), 2.03–1.94 (m, 1 H), 2.09 (dd, J = 10, 8 Hz, 1 H), 2.27–2.15 (m, 2 H), 2.48 (ddd, J = 15, 7, 2 Hz, 1 H), 3.10 (dd, J = 13, 7 Hz, 1 H), 3.43 (ddd, J = 15, 12, 7 Hz, 1 H), 3.62 (d, J = 9 Hz, 1 H), 3.78 (s, 3 H), 4.02 (ddd, J = 12, 12, 7 Hz, 1 H), 4.67 (s, 1 H), 4.77 (dd, J = 9, 3 Hz, 1 H), 5.91 (s, 2 H), 6.06 (s, 1 H), 6.64 (s, 1 H); (DMSO-d_6) δ 1.89–2.08 (m, 4 H), 2.35 (dd, J = 14, 5 Hz, 1 H), 2.97 (dd, J = 12, 6 Hz, 1 H), 3.36 (ddd, J = 14, 12, 7 Hz, 1 H), 3.66 (s, 3 H), 3.66 (d, J = 9 Hz, 1 H), 3.75 (ddd, J = 12, 12, 7 Hz, 1 H), 4.48 (dd, J = 9, 6 Hz, 1 H), 4.73 (s, 1 H), 5.12 (d, J = 6 Hz, 1 H), 5.90 (s, 1 H), 5.93 (s, 1 H), 6.66 (s, 1 H), 6.74 (s, 1 H); 67.9-MHz ^{13}C NMR (DMSO-d_6) δ 172.35, 163.13, 145.53, 144.79, 133.03, 129.64, 111.97, 109.47, 100.15, 99.05, 72.15, 70.12, 57.88, 56.59, 36.91, 36.54, 30.31, 29.14; IR (KBr ν_{max} 3448, 2972, 2935, 2910, 2879, 1679, 1654, 1492, 1432, 1273, 1222, 1087, 1031, 930, 817, 804, 655 cm^{-1}; MS, m/z (relative intensity) 330 (M + 1, 20), 329 (90), 315 (15), 314 (84), 312 (10), 298 (8), 280 (16), 268 (6), 243 (10), 242 (33), 241 (5), 230 (18), 228 (14), 214 (5), 200 (10), 199 (6), 178 (6), 173 (7), 164 (18), 161 (7), 149 (10), 148 (7), 135 (5), 131 (6), 124 (8), 115 (12), 103 (8), 88 (11), 86 (73), 84 (100), 77 (9), 55 (31), 51 (48).

(±)-Cephalotaxine (1). A 1 N solution of lithium aluminum hydride (0.360 mL, 0.360 mmol) in tetrahydrofuran was added to 0.059 g (0.180 mmol) of 2-methoxy-3,8-dioxocephalotax-1-ene (**39**) in 10 mL of tetrahydrofuran. The homogeneous solution was

heated at reflux for 1 h, cooled, and poured into 40 mL of 10% ammonium chloride saturated with sodium chloride. Extraction with 3 × 20 mL of dichloromethane and concentration of the dried ($MgSO_4$) extracts under vacuum at 42 °C gave a crude product which was subjected to centrifugal chromatography on a 1-mm alumina plate. Elution with dichloromethane–methanol (99:1) at 0.6 mL/min and concentration of fractions 6–23 gave 0.050 mg (88% yield) of (±)-cephalotaxine, mp 122–124 °C (lit.[19,20] mp 115–117, 116–118 °C), which gave IR, NMR and mass spectra that matched those of a sample of natural cephalotaxine.

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Registry No. (±)-**1**, 38848-21-4; **5**, 13838-23-8; (±)-**6**, 58712-01-9; (±)-**6** (acid), 114942-61-9; **7**, 1484-85-1; (±)-**8**, 114942-62-0; (±)-**9**, 114942-63-1; **10**, 6612-99-3; **11**, 10333-13-8; (±)-**11a**, 114942-67-5; (±)-**12**, 114942-64-2; **13**, 114942-65-3; (±)-**14**, 114942-66-4; (±)-**19**, 114942-68-6; (±)-**20**, 114942-69-7; **21**, 114942-70-0; **22**, 114942-71-1; (±)-**22** (4a D-isomer), 114942-72-2; (±)-**24**, 114942-73-3; (±)-**25**, 114942-74-4; (±)-**26**, 114942-75-5; **27**, 114942-76-6; (±)-**30**, 114942-77-7; (±)-**31**, 114942-78-8; (±)-**32**, 114942-79-9; (±)-**33**, 114942-80-2; (±)-**35**, 114942-81-3; (±)-**36**, 114942-82-4; (±)-**37**, 114978-16-4; (±)-**37** (diacetate), 114978-17-5; (±)-**38**, 114956-74-0; (±)-**39**, 114942-83-5; (±)-**40**, 114942-84-6; 2-[(*p*-tolylsulfonyl)oxy]-1-[3,4-(methylenedioxy)phenyl]ethane, 57587-09-4; 4,5,6,7-tetrahydrocyclopenta[*b*]pyran-2(3*H*)-one, 5587-71-3; (±)-2-(2-cyanoethyl)cyclopentanone, 58734-78-4; 2-[3,4-(methylenedioxy)phenyl]ethanol, 6006-82-2.

Supplementary Material Available: X-ray crystallographic data for compounds **13** and **33** (17 pages). Ordering information is given on any current masthead page.

Novel Convergent Synthesis of Side-Chain-Modified Analogues of 1α,25-Dihydroxycholecalciferol and 1α,25-Dihydroxyergocalciferol[1]

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A novel synthetic strategy for the preparation of side-chain-modified analogues of 1α,25-dihydroxycholecalciferol and 1α,25-dihydroxyergocalciferol was developed as a part of the extensive synthetic search for vitamin D analogues of potential anticancer activity. In the methodology developed, the preparation of both series of analogues proceeds conveniently through the partially protected 1α-hydroxyvitamin D C-22 alcohol **5** as the common key intermediate. The 24-dihomo and 25-cyclopentane analogues **1** and **2** of 1α,25-dihydroxycholecalciferol were obtained by alkylation of sulfones **22** and **31**, respectively, with tosylate **6**. Swern oxidation of alcohol **5** afforded 1α-hydroxyvitamin D C-22 aldehyde **7** as a novel useful precursor for side-chain-modified analogues of 1α,25-dihydroxyergocalciferol. As a representative example of this series, the 24*R* analogue **3** was obtained by the condensation of aldehyde **7** with the chiral sulfone **39**. Preliminary studies from this laboratory on human leukemia HL-60 cells reveal **1** as the most active vitamin D analogue to induce the differentiation of human leukemia HL-60 cells with markedly diminished calcemic activity.

Recent discoveries from this[3] and other laboratories[4] of valuable biological activity of 1α-hydroxy analogues of vitamin D modified in the aliphatic side chain have further stimulated our interest in this area. Our extensive studies[5] on the effect of various analogues of 1α,25-dihydroxyvitamin D on differentiation of human leukemia HL-60 cells led us to the conclusion that the elongation of the side chain of (5*Z*,7*E*)-1α-hydroxyvitamin D improves significantly its activity. To further investigate this effect we designed two C-29 homologues with two additional carbon atoms added to the side chain in both aliphatic and alicyclic manner. The novel synthetic strategy developed for the preparation of 24-dihomo analogue **1** (Chart I) and 25-cyclopentane analogue **2** allows also for the more efficient preparation of analogue **3**[6] as well as for further variations of the side chain part of the vitamin D molecule. In our strategy the key vitamin D synthons for the preparation of all side-chain analogues are C-22 vitamin D like compounds **4**–**7**. These, in turn, can be obtained from commercially available steroid **8** by the classical approach.

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