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TREMORGENIC INDOLE ALKALOID STUDIES. 6. PREPARATION OF AN ADVANCED INTERMEDIATE FOR THE SYNTHESIS OF PENITREM D. SYNTHESIS OF AN INDOLE-OXOCANE[1]

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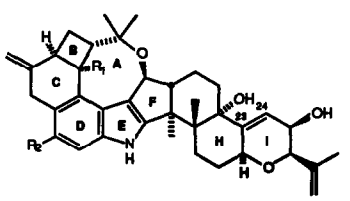
Abstract We describe here an efficient synthesis of tricyclic aniline **9**, an advanced synthetic intermediate which embodies the **B-C-D** rings of the penitrems (A-F), a small family of tremorgenic mycotoxins produced by the ergot fungus *Penicillium crustosum* In addition, we demonstrate the feasibility of a general synthetic tactic for the sequential generation of the **E**, **F**, and **A** rings by construction of a diminutive version of the natural products, specifically indole-oxocane **23** Central to our approach to aniline **9** was a photochemical [2+2]-cycloaddition of methyl acrylate to enone **16**, followed successively by a Robinson annulation and Semmler-Wolff aromatization Assembly of **23** entailed a modified Madelung indole synthesis combined with a novel acid-promoted bis-cyclization (**47** → **46**) to install the oxocane ring system

Introduction and Background

In 1981 Steyn et al published the first of a series of papers on the penitrems (A - F), a small family of tremorgenic mycotoxins, isolated from the ergot fungus *Penicillium crustosum*[2,3] The connectivity and relative stereochemistry of these complex metabolites were secured primarily by means of high-field NMR experiments, the 'partial resolution' method of Horeau[4] served to establish their absolute configuration At the time, several studies had already implicated the penitrems in livestock syndromes characterized by acute neurologic dysfunction[3a,5a-f] Intrigued both by their novel architecture as well as the behavioral effects, we initiated a program directed at their total synthesis[6] The long term goal of this program was to provide further insight into their mode of biological action[5g,h] A total synthesis would also serve to confirm the structures of the penitrems[2]

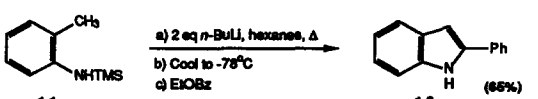


Penitrems

A (1) R_1 = OH, R_2 = Cl; 23,24 α-epoxide
B (2) R_1 = R_2 = H, 23,24 α-epoxide
C (3) R_1 = H R_2 = Cl
D (4) R_1 = R_2 = H
E (5) R_1 = OH R_2 = H 23,24 α-epoxide
F (6) R_1 = H, R_2 = Cl 23,24 α-epoxide

A General Strategy for Construction of the Penitrems

From the retrosynthetic perspective, we envisoned that the synthesis of penitrem D (**4**), structurally the simplest member of the family, would be contingent to a significant extent upon two transformations (Scheme I) Given the size and complexity of the target, a convergent approach that would unite aniline **9** with a functionalized lactone (**10**), representing the western and eastern hemispheres respectively, seemed most appropriate We were of course cognizant of the implications that such a convergent strategy would have vis a vis the required absolute stereochemistry of the two hemispheres For the actual union, we planned to exploit a 2-substituted indole synthesis developed previously in our laboratory (Eq 1)[6b,c]



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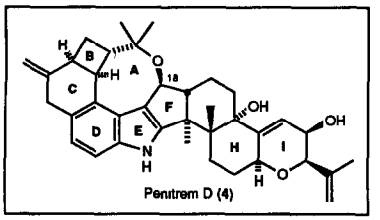
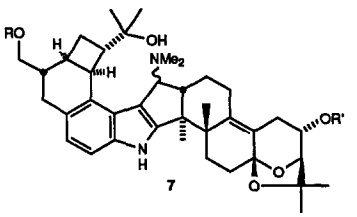
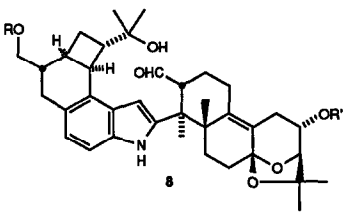
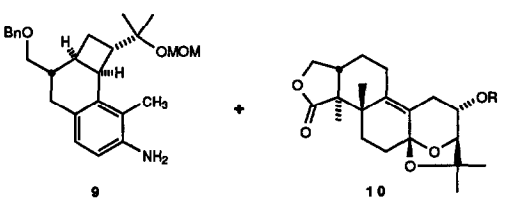
Scheme I

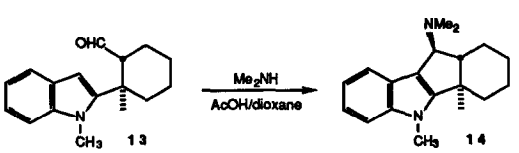








The second strategy-level operation was envisioned to entail formation of the oxocane ring fused to the indole nucleus [7] Analysis of the local connectivity in **4** led us to conjecture that this structural feature might be conveniently installed via a tandem Mannich cyclization-gramine fragmentation, refunctionalization of the H and I rings would then complete the synthesis (e g , **8** → **7** → **4**) Precedent for the proposed Mannich cyclization was established through the conversion of **13** to **14** also developed in our laboratory [6c] The appeal of this general scenario derived in part from the circumstance that both the Mannich and gramine reactions could proceed in a single step (*vide infra*) Furthermore,



(2)

generic versions of both cyclizations are known to occur under mild conditions [8]

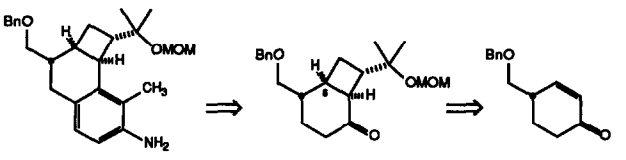
Concerning the requisite β-ether linkage at C(18), we anticipated that the ultimate cation generated in the gramine fragmentation would be captured stereoselectively by the proximal hydroxyl group Support for this outcome can be found in both molecular model studies and molecular mechanics calculations Molecular models suggested that the

tertiary alcohol in **7** is well positioned to trap the incipient α,β-unsaturated iminium ion from the β-face Molecular mechanics calculations employing Macromodel[9] supported this hypothesis, projecting a relative enthalpy difference of approximately 14 kcal/mol between the two possible diastereomers

Continuing with this analysis, we anticipated that aniline **9** would arise from ketone **15** through a Robinson annulation/Semmler-Wolff aromatization sequence [10,11] Construction of the [4 2 0] bicyclic skeleton of **15** in turn would be accomplished via an intermolecular [2+2]-photocycloaddition, in this case between enone **16** and an electron-deficient olefin (e g , methyl acrylate) [12] Although three new stereocenters would be created in this reaction, literature precedent led us to predict that the absolute stereochemistry at C(4) of **16** would induce the correct absolute stereochemistry at C(6) vis a vis the penitrems (*vide infra*) [13]

In this, a full account, we describe an efficient synthesis of aniline **9**, an advanced tricyclic intermediate which embodies the **B-C-D** rings of the western hemisphere of the penitrems We will also demonstrate the feasibility of the Mannich cyclization-gramine fragmentation tactic for the sequential generation of the **E**, **F**, and **A** rings of this class of tremorgens [14]

Scheme II

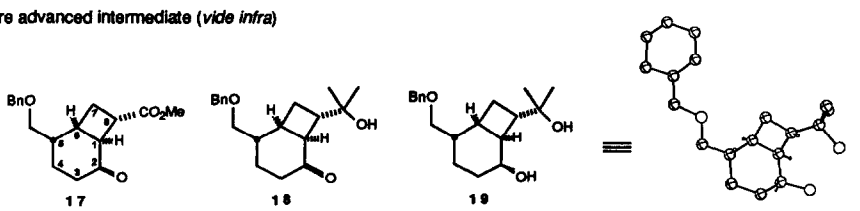


Results and Discussion

(I) Preparation of Ketone 15. Starting Material for the Western Hemisphere The synthesis of **15** begins with the preparation of enone **16**, obtained by the method of Stork and Danheiser [15] Specifically, 3-ethoxy-2-cyclohexenone was alkylated with LDA and benzyl chloromethyl ether and then reduced with lithium aluminum hydride Brief treatment with dilute hydrochloric acid completed the reductive enone transposition, the overall yield for this two step process was 77 %

Attention turned next to the projected intermolecular [2+2]-photocycloaddition Two considerations were important First, a "head to head" addition of the enone and olefin (e g , methyl acrylate) was required Literature precedent here indicates that such a regiochemical outcome occurs in the cycloaddition of enones with electron deficient olefins [16] Second, the cycloaddition would have to take place with the requisite stereoselectivity at C(6), since this center could not be modified subsequently through epimerization In this regard, Cargill reported that a substituent in the γ-position of a monocyclic enone directs β-bond formation with modest anti selectivity (ca 85 15) [17] For the Western Hemisphere of the penitrems, the S configuration at the C(4)-center in **16** would be required [18] The remaining stereochemical aspects of the cycloaddition [i e , stereocenters at C(1) and C(8)] were expected to be favorable or at the very least correctable through epimerization

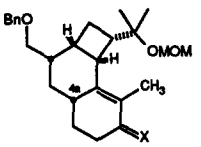
In the event, irradiation of enone **16** with excess methyl acrylate (ca 11 equiv) produced a complex mixture, consisting of a major adduct, in conjunction with no less than twelve additional products, as determined by HPLC and ^{1}H NMR analysis Variation of solvent polarity had little effect on the product ratio, but lower temperatures did increase the relative amount of the major adduct Best results (ca 59% of **17**) were obtained at 4°C Interestingly, base-sponsored equilibration of the mixture did not improve the situation The structure and stereochemistry of **17**, initially based on literature analogy, was subsequently confirmed through aegis of a single crystal X-ray analysis, performed on a derivative of a more advanced intermediate (*vide infra*)



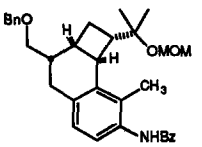
(II) Execution of the Robinson Annulation-Semmler Wolff Aromatization Sequence Completion of the Western Hemisphere (9) With **17** readily available, the remaining synthetic challenge to complete construction

of **9** was attachment of the aromatic ring Here we planned to exploit a Robinson annulation, followed by a Semmler-Wolff aromatization [10,11] However before this sequence could be attempted, some refunctionalization of **17** was required This proved to be most conveniently carried out on the photochemical mixture Specifically, ketalization with trimethylorthoformate and Amberlyst-15,[19] followed by treatment with excess methylmagnesium bromide, and then deketalization with PPTS in acetone[20] afforded ketoalcohol **18**, after chromatographic removal of the undesired isomers, the yield from enone **16** was 49% Protection of **18** as the MOM ether (80-84% yield)[21] then led to **15** At this point, the structure of **18** and thereby **17** was secured More precisely, the major product obtained by hydrogenation of **18** proved to be a crystalline compound (**19**, m p 112 5-115°C) suitable for X-ray analysis [22]

Turning next to construction of the aromatic ring, Robinson annulation as modified by Woodward[10,23] led to enone **20**, which was shown by ^{13}C NMR to be a single diastereomer, the yield from ketone **15** was 86% Although inconsequential vis a vis the penitrem strategy, the C(4a)-hydrogen at the newly generated stereocenter in **20** was assumed to be pseudoaxial [24]



20 X=O
21 X=N-OH



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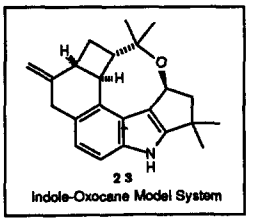
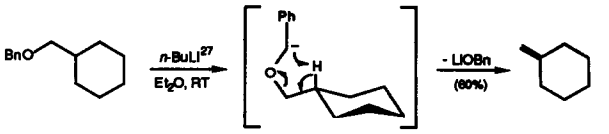
The oxime of **20** was next prepared in 87% yield in anticipation of the Semmler-Wolff reaction [11] Unfortunately, the standard Semmler-Wolff conditions (e g , acetic anhydride at reflux, or acetyl chloride and pyridine in hot acetic anhydride)[11b,25] produced little or no aromatization Even the improved procedure reported by Tamura[26] proved unsatisfactory Fortunately, we discovered that treatment of **21** with benzoic anhydride in xylenes at 130-160°C effected the desired aromatization in 56-65% yield Hydrolysis of the resultant benzamide (**22**) employing strongly basic conditions then delivered free amine **9** The overall yield for the thirteen-step sequence was 12% Equally important, the sequence is amenable to large-scale work.

(III) Indole-Oxocane 23. A Suitable Test of Our Penitrem Synthetic Strategy With a viable route to aniline **9** secure, we next addressed the two critical questions raised by our general penitrem synthetic strategy First, would **9** successfully participate in our indole protocol? Second, would the proposed tandem Mannich cyclization/gramine fragmentation sequence serve to establish the **A** and **F** rings of the penitrem skeleton? To assess the feasibility of these transformations, we set as our goal construction of a diminutive version of the natural product, specifically the indole-oxocane **23** This model system, which subsumes the **A-E-F** ring system of the penitrem skeleton, was seen as a critical test of our basic synthetic strategy



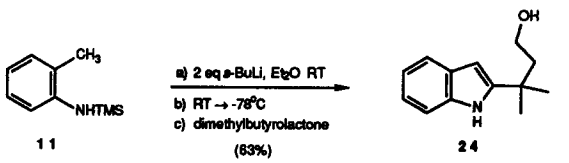
23
Indole-Oxocane Model System

(iv) Union of the Western Hemisphere with Dimethylbutyrolactone Development of an Improved Indole Protocol Turning first to construction of the indole ring, we quickly discovered that the benzyl ether was far too labile to the metallating conditions normally employed to generate the required lithium dianion [6b,c] Instead, **9** underwent a facile fragmentation, not unlike that reported by Harrison and Lythgoe (Eq 3) [27] A search for a more robust substrate led us to TBS ether **26**, readily available via hydrogenation of **9**, using palladium on carbon in the presence of camphorsulfonic acid to suppress catalyst poisoning,[28] followed by silylation with TBS chloride [29] The overall yield for this two-step operation was 71%



(3)

By this time, we had also developed an improved indole protocol In particular, we discovered that *s*-BuLi *at room temperature* was equally effective at metallation For example, when the dianion derived from *N*-TMS-*o*-toluidine[6c] and *s*-BuLi was quenched with dimethylbutyrolactone[30] at -78°C, a 63% yield of indole **24** resulted (Eq 4) Importantly, our advanced *o*-toluidine **26** also behaved more agreeably to the *s*-BuLi/dimethylbutyrolactone protocol, affording a 20-30% yield of the corresponding 2-substituted indole (**27**), in addition to 40-50% of recovered amine (Eq 5) In some trials a trace of the corresponding amide was also observed Additives designed to improve further the metallation process (e g , TMEDA[31] or LDA[32]) however did not increase the product yield, nor did varying the duration of metallation [33]



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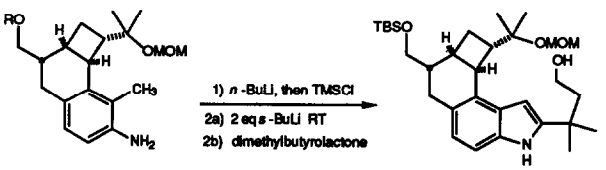


(5)

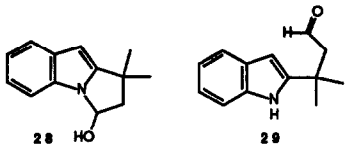
Although a major improvement in indole construction would clearly be necessary before we embarked on the synthesis of penitrem D, we elected to investigate the feasibility of the equally crucial Mannich cyclization-gramine fragmentation scenario, before such an optimization was attempted During the course of these studies, we determined that indole **27** could be conveniently prepared via the modified Madelung condensation of Fuhrer and Gschwend [34] In this procedure, the monoanion derived from **26** (LDA, THF, 0°C) was first acylated with dimethylbutyrolactone, subsequent treatment with excess *n*-butyllithium in THF at ambient temperature then provided indole **27**, the overall yield for this two-step sequence was 70% Clearly, the modified Madelung condensation could also serve as recourse in the synthesis of the penitrems, in the event that further improvement in the one-step indole process was not forthcoming

(v) Construction of the F and A Rings An Initial Assault Before the tandem Mannich cyclization-gramine fragmentation sequence could be explored, two preliminary operations were required These were conversion of the primary alcohol to the corresponding aldehyde to establish the proper oxidation state for the Mannich reaction, and removal of the MOM ether in order that the resultant tertiary alcohol be free to capture the cation formed during the gramine fragmentation

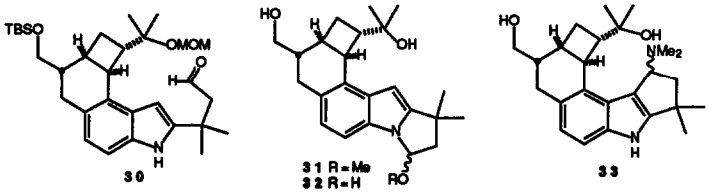
Oxidation of the primary hydroxyl group proved to be non-trivial, in that the choice of reagents was considerably constrained by the relative reactivity of the indole nucleus We found, however, that a variety of DMSO-based oxidations were effective For example, when indole **24** was exposed to the sulfur trioxide-pyridine complex in DMSO,[35] hemiaminal **28** was isolated in 78% yield Alternatively, and somewhat surprisingly, Moffatt oxidation[36] of **24** (DCC, TFA, and pyridine in DMSO/benzene) led to the isolation of aldehyde **29** (96% yield), which converted slowly to **28** upon prolonged standing The latter conversion could be easily promoted by treatment with either base or acid Similar oxidation of our more advanced indole (**27**) proceeded without event to afford aldehyde **30** in 80% yield

Deprotection of the tertiary hydroxyl in **30** was then accomplished most cleanly with camphorsulfonic acid in methanol, the resulting mixture of anomeric methyl oxaminals (**31**) was hydrolyzed using camphorsulfonic acid in THF/water to provide hemiaminal **32** These conditions also led to hydrolysis of the TBS ether Notwithstanding this fact, we were now in a position to investigate construction of the **A** and **F** rings

We had speculated that exposure of **32**, or more precisely the corresponding aldehyde, to Mannich reaction conditions (i e , Me_2NH, AcOH/THF) would lead to cyclization at C(3), providing gramine analog **33** [8] In the event however



28 **29**

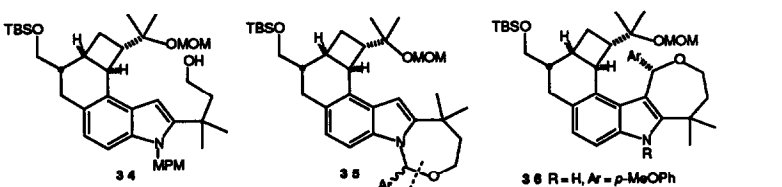


30 **31** R = Me **32** R = H **33**

a surprisingly large number of polar compounds were obtained, as well as some decomposition Despite this disappointment, the desired conversion was also attempted by treating **32** with mild acid in benzene In this case a facile reaction occurred, resulting in the formation of a substantially less polar material, the mass balance was 89% While the structure was not immediately discernable (*vide infra*), a combination of chemical and spectroscopic evidence suggested that the problem with the projected cyclization might be solved if we were to protect first the indole nitrogen, thereby preventing aminal formation

(vi) **Development of a Novel Indole Protection Protocol** Several factors determined the choice of a viable protecting group for the indole nitrogen Aside from the usual concerns of facile installation and removal, in conjunction with quired stability during the intervening reactions, the electronic aspects of the projected Mannich cycl ramine fragmentation mandated maintenance of significant electron density in the indole nucleus Typical indc . .cting groups, such as sulfonamides and carbamates, were expected to reduce that character to an extent where the Mannich reaction would necessitate detrimentally vigorous conditions This consideration was particularly wornsome vis a vis the more functionalized penitrems

Ultimately the *p*-methoxybenzyl group (MPM) was selected We anticipated that a three-step sequence for MPM installation, involving protection of the primary hydroxyl group in **27**, benzylation of the indole nitrogen, and then deprotection of the alcohol would be least troublesome It quickly became apparent however that this tactic leads to *C*-alkylation of the indole nucleus instead of nitrogen protection Presumably an unfavorable combination of the hard-soft acid-base nature of the ambident substrate and chosen electrophile was in play [37] Forced to seek an alternative mode of nitrogen protection, we turned to a maneuver employed frequently in the carbohydrate field [38] We reasoned that, if a cyclic oxaminal such as **35** involving indole **27** and *p*-methoxybenzaldehyde could be formed, it might then be possible to reduce selectively the benzylic C-O bond, thereby introducing the MPM group on nitrogen [39] In practice, however, acid-catalyzed trans-acetalization between **27** and the methyl acetal of *p*-methoxybenzaldehyde[40] led to a 35% yield of the *vinylogous* oxaminal **36** The hard-soft ambident character of the indole ring system was again apparent When an even softer electrophile, in the way of the methyl acetal of 2,4-dimethoxybenzaldehyde was employed,[41] the yield of the oxaminal (37) increased to 90%



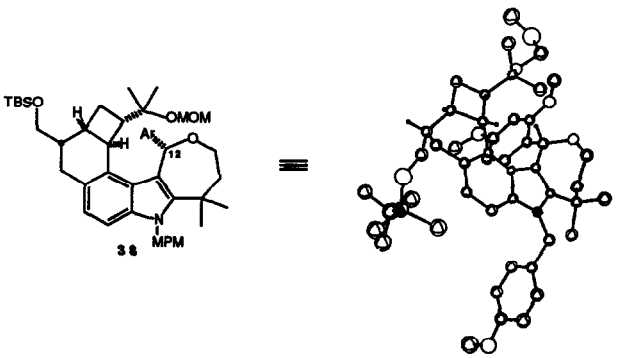
34 **35**

36 R = H, Ar = *p*-MeOPh
37 R = H, Ar = 2,4-dimethoxyphenyl
38 R = MPM Ar = 2,4-dimethoxyphenyl

Despite these unexpected observations, a solution to the protection problem presented itself In particular, it occurred to us that the 3-position of the indole nucleus in **37** might now be sufficiently hindered, relative to the nitrogen, that alkylation with *p*-methoxybenzyl chloride would occur selectively on nitrogen This proved to be the case, alkylation with sodium hydride and *p*-methoxybenzyl chloride produced **38** as a colorless crystalline solid (mp 150 5-152 5°C, 80% yield from **27**) A minor amount of *C*-alkylation was also observed (7%) The structure of **38**, initially assigned on the basis

of high-field NMR, was confirmed by single-crystal X-ray analysis [22] Importantly, the derived ORTEP plot not only established the presence of the *N*-*p*-methoxybenzyl group, but also confirmed the relative stereochemistry at C(12) in **37** and **38**

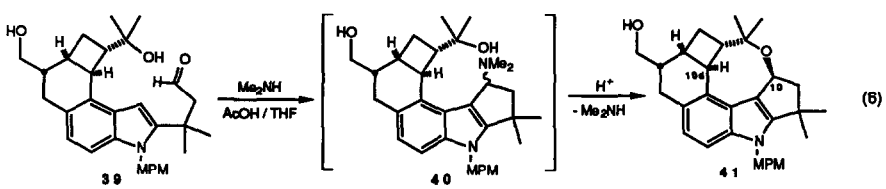
Having succeeded in introducing a nitrogen protecting group, it was now necessary to regenerate the primary hydroxyl group A variety of acidic conditions were examined Although silyl ether cleavage was competitive in most cases, this process could be suppressed when isopropyl alcohol was employed as the nucleophilic component, in conjunction with acetic acid/THF Under these conditions, alcohol **34** was obtained in near quantitative yield



38

To prepare for the intramolecular Mannich condensation, **34** was converted to aldehyde **39** in three steps These were tosylation of the primary alcohol, cleavage of the MOM and TBS ethers, and Kornblum oxidation [42] Use of the two-step Kornblum procedure instead of the previously exploited DMSO-based oxidations permitted convenient removal of the protecting groups without concern for competitive acetal formation or premature cyclization

The Mannich reaction of **39** was then executed employing dimethylamine in acetic acid/THF at room temperature Monitoring of the reaction progress by TLC revealed that the starting aldehyde was slowly replaced by a more polar material, which we presumed to be tertiary amine **40** However, before complete consumption of the starting material occurred, the amine itself was supplanted by a compound less polar than the initial aldehyde After several hours at ambient temperature, work-up led to a single product, tentatively assigned structure **41** by ^{1}H and ^{13}C NMR analysis To our delight both cyclizations had taken place! The yield was 87%



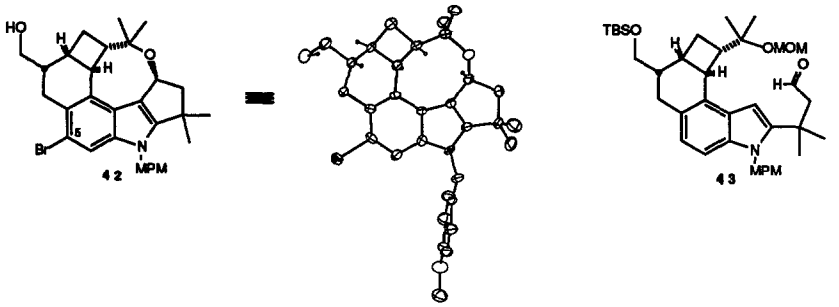
39 **40** **41** (5)

Assignment of the relative stereochemistry at C(10) in **41** was based on a series of NMR ^{1}H-^{1}H NOE experiments [43] In particular, irradiation of the C(10)-methine hydrogen induced a 3% enhancement of the C(10d)-cyclobutyl methine resonance and a 9% enhancement of one of the methyl singlets On the basis of the chemical shift (δ1 41) and the observed NOE enhancement, this methyl group was assumed to be syn to the C(10)-methine hydrogen on the ether bridge Subsequent irradiation of this methyl signal produced a simultaneous enhancement of both the C(10)-methine and C(10d)-methine proton resonances (3% and 4% respectively) Such NOE enhancements are only consistent with a syn disposition of the C(10)- and C(10d)-methine protons Thus the required β-ether linkage in **41** was clearly in evidence

While oxocane **41** was not a crystalline solid, we found that bromide **42**, obtained in 83% yield by treatment of **41** with NBS in acetonitrile, could be isolated as colorless prisms (m p 178 5-182 5°C) suitable for X-ray analysis [22] The derived ORTEP confirmed both the presence of the 8-membered ring and the β-configuration at C(10) We note in passing that a chlorine atom resides at the corresponding C(5)-position in penitrems A, C, and F Thus an analogous chlorination in the latter stages of our penitrem venture would permit access to these tremorgens

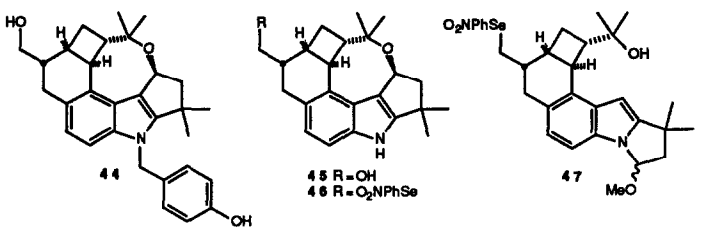
Finally, a marked improvement in the oxocane construction was discovered when we determined that an equivalent bis-cyclization proceeds directly with **43**, obtained from **34** in 88% yield via Moffatt oxidation More precisely, exposure of

43 to camphorsulfonic acid in methanol/toluene led to deprotection of both hydroxyl groups with concomitant bis-cyclization, oxocane 41 was available in 50-60% yield



(vii) Completion of Indole-Oxocane 23. The Frustration of Protecting Groups. Having established a synthetic pathway to the indole-oxocane skeleton, only deprotection of the indole nitrogen and introduction of the exo-methylene functionality remained to complete the target structure

Attention was first given to removal of the *p*-methoxybenzyl group Standard oxidative and reductive means of excision were uniformly futile [44] Ultimately, an unconventional tactic based on the nucleophilic cleavage of alkyl aryl ethers proved successful Treatment of 41 with sodium thioethoxide in DMF[45] at 150°C delivered demethylated material (44) in 65% yield in conjunction with 9% of the fully deprotected indole 45 Fragmentation of 44 to 45 could then be effected by exposure to potassium bicarbonate in DMF at reflux An attempt at combining both steps through the use of potassium thioethoxide went unrewarded Notwithstanding this shortcoming, the overall yield of 45 from 41 was 50%



At this point, conversion of the hydroxymethyl group to the exo-methylene unit proved relatively straightforward Exploiting the selenation procedure developed by Grieco, *o*-nitrophenyl selenide 46 was prepared in high yield,[46] oxidative elimination[47] then produced the target indole-oxocane 23 in 66% yield for the two steps

Oxocane-fused indole 23 was fully characterized, and the derived data compared with that obtained by Steyn et al for penitrem D [2c] We found that an excellent correlation exists between the spectral properties of 23 and penitrem D This correlation lends further support to the penitrem structures proposed by Steyn [2]

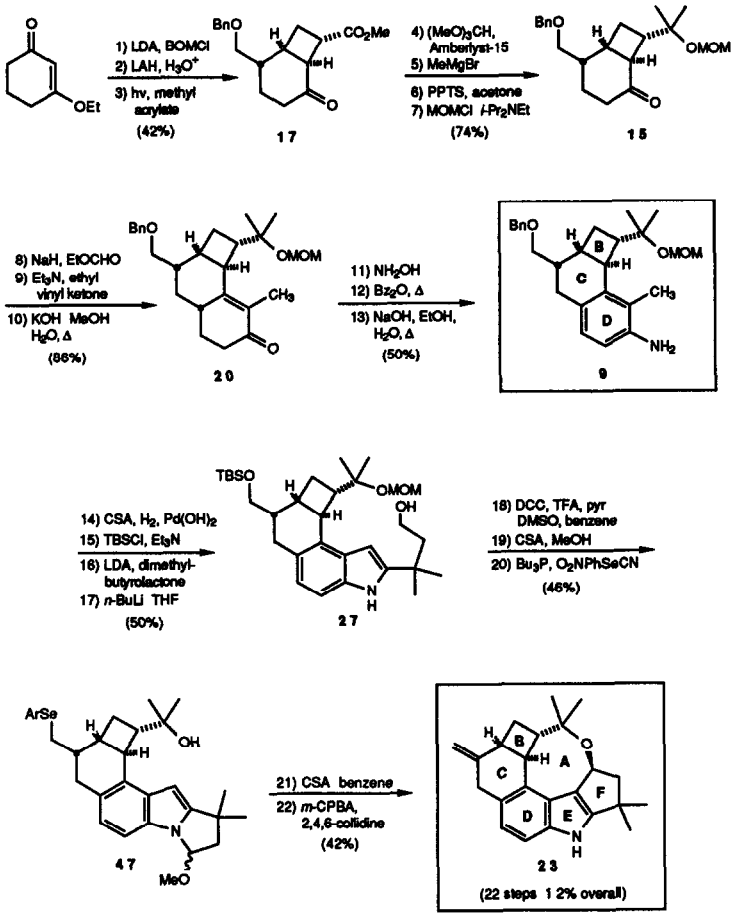
(viii) A More Concise Route to Indole-Oxocane 23 Resolution of the Protecting Group Problem. Although we had succeeded in preparing 23 and thereby had vouchsafed the general premises inherent in our penitrem synthetic strategy, we considered the precise course of events to be somewhat unsatisfactory The obligatory use of nitrogen protection to enable assembly of the A and F rings was certainly the least attractive aspect of the synthetic sequence (9 → 23) Moreover, this requirement was exacerbated by the unexpectedly problematic installation and removal of the MPM group We therefore decided to reexamine our earlier observations involving unprotected intermediates

Ultimately it was determined that the compound obtained in the attempted cyclization of 32 was a macrocyclic dimer involving the primary hydroxyl group and the anomeric center [48] Having identified the intervening reaction path, we were able to obviate its interference simply by inverting the sequence of synthetic operations (i e , selenation of the primary hydroxyl group prior to cyclization) As in the previous case, selenation ($O_2NPhSeCN$, Bu_3P, THF, RT)[46] of 31 provided 47 in good yield Execution of the bis-cyclization then led to 46, again obtained as a single diastereomer by ^1H and ^{13}C NMR, in 58-64% yield That 46 was identical in all respects with the material previously obtained by selenation of alcohol 45 was established by careful spectroscopic comparison

It should be emphasized that this new *four*-step sequence, bridging intermediates **27** and **46**, gave an overall yield of 28% versus 13% for the *eight*-step sequence involving nitrogen protection Thus a major improvement was in hand

(Ix) Summary In conclusion, we have completed an economic (i e , short) synthesis of an advanced tricyclic aniline (**9**) which embodies the B-C-D rings of penitrem D as outlined in Scheme III In addition, we demonstrated the viability of two strategic transformations by successfully completing construction of an A-B-C-D-E-F hexacyclic analog (**23**) of the natural product These achievements affirm the potential of the proposed penitrem synthetic strategy Further progress in this area will be reported in due course

Scheme III



Experimental Section

Materials and Methods *n*-Butyllithium was purchased from Aldrich Chemical Company and standardized by titration with diphenylacetic acid [49] Reactions were monitored by thin-layer chromatography (TLC) using 0 25 mm E Merck pre-coated silica gel plates Flash column chromatography[50] was performed with the solvents indicated using silica gel-60 (particle size 0 040-0 063 mm) supplied by E Merck High performance liquid chromatography was performed with a Waters analytical chromatograph employing a model 6000A solvent delivery system, a U6K injector, and either an R-400 refractive index or model 440 UV absorbance detector The column was of dimensions 4 6 mm x 25 cm and was packed with 5μ Ultrasphere-Si [TM]

All melting points were determined on a Bristoline heated-stage microscope and are corrected The IR and ^{1}H NMR spectra were obtained for $CHCl_3$ and $CDCl_3$ solutions respectively unless otherwise noted Infrared spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer Proton NMR spectra were recorded on a Bruker AM-250 spectrometer or a Bruker WH-500 spectrometer and are reported as δ values relative to tetramethylsilane Carbon-13 NMR spectra were obtained on a Bruker AM-250 spectrometer (62 9 MHz) or a Bruker WH-500 spectrometer (125 8 MHz) High-resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Service Center on a VG micromass 70/70H high-resolution double-focusing electron impact/chemical ionization spectrometer or a VG ZAB-E mass

spectrometer The single-crystal X-ray diffraction structure determinations were carried out using an Enraf Nonius CAD-4 automated diffractometer

Enone 16 Lithium diisopropylamide was generated at 0°C by the addition of *n*-butyllithium (38 80 mL, 2 40 M in hexanes, 93 1 mmol) to a solution of diisopropylamine (13 05 mL, 93 1 mmol) in THF (150 mL) After 20 min stirring, the solution was cooled to -78°C and 3-ethoxy-2-cyclohexenone[51] (10 88g, 77 6 mmol) in THF (20 mL) was added dropwise The solution was stirred for 1 h, after which time benzyl chloromethyl ether (12 96 mL, 93 2 mmol) was added by syringe over 3 min The reaction was allowed to warm to -35°C over 1 h, and was then submerged in an acetonitrile/dry ice bath, and stirred an additional 4 h The alkylation was quenched by the rapid addition of saturated sodium bicarbonate solution (150 mL) while stirring vigorously The mixture was poured into a separatory funnel and extracted with ether Combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure Flash column chromatography (hexanes/ethyl acetate, 3 1) gave the alkylated vinylogous ester (17 73 g, 87 7%) as a slightly yellow oil IR ($CHCl_3$) 3015 (s), 1645 (s), 1605 (s), 1385 (s), 1365 (s), 1225 (s), 1195 (s), 1103 (s), 698 (s) cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 7 37-7 23 (m, 5H), 5 34 (s, 1H), 4 53 (app s, 2H), 3 93-3 84 (m, 3H), 3 62 (1/2 ABX, J_{BA} = 9 3, J_{BX} = 8 0 Hz, 1H), 2 60-2 42 (m, 3H), 2 24 (app dq, J = 4 7, 13 3 Hz, 1H), 1 90 (dddd, J = 6 7, 8 9, 11 0, 13 2 Hz, 1H), 1 36 (app t, J = 7 0 Hz, 3H), chemical ionization mass spectrum, *m/e* 261 1466 (M+H calcd for $C_{16}H_{21}O_3$, 261 1491)

A solution of the alkylated vinylogous ester (17 84 g, 68 5 mmol) in diethyl ether (50 mL) was cannulated over 10 min into a suspension of lithium aluminum hydride (1 95 g, 51 4 mmol) in ether (200 mL) stirring at -78°C The cold bath was removed upon complete addition, and after a further 30 min, the reaction was slowly quenched by the successive dropwise addition of water (2 mL), 15% aqueous sodium hydroxide solution (2 mL), and water (6 mL) Upon continued stirring, a fine white suspension was achieved, this solid was removed by vacuum filtration, washing well with ether The filtrate was stirred vigorously with a solution of dilute hydrochloric acid (8 mL) in water (200 mL) When TLC analysis (hexanes/ether, 1 1) indicated complete transformation, the layers were separated, and the aqueous layer was extracted with ether Combined organic layers were washed with saturated sodium bicarbonate solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure Flash column chromatography (hexanes/ether, 3 2) gave the enone (16, 13 67 g, 92 2%) as a colorless oil IR ($CHCl_3$) 3020 (s), 2870 (s), 1680 (s), 1460 (m), 1367 (m), 1230 (m), 1115 (s), 700 (s) cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 7 44-7 27 (m, 5H), 6 97 (ddd, J = 1 3, 2 6, 10 2 Hz, 1H), 6 06 (ddd, J = 0 5, 2 5, 10 2 Hz, 1H), 4 55 (app s, 2H), 3 51 (1/2 ABX, J_{AB} = 9 0, J_{AX} = 6 6 Hz, 1H), 3 46 (1/2 ABX, J_{BA} = 9 0, J_{BX} = 6 7 Hz, 1H), 2 74 (app dddd, J = 2 6, 5 0, 9 3, 16 5 Hz, 1H), 2 53 (app dt, J = 4 7, 16 8 Hz, 1H), 2 38 (ddd, J = 4 9, 12 3, 17 2 Hz, 1H), 2 13 (app ddq, J = 1 3, 4 8, 13 3 Hz, 1H), 1 81 (dddd, J = 4 9, 9 8, 12 4, 13 3 Hz, 1H), λ_{max} (EtOH) 223 8s (ε 1,300), 211 2 (ε 16,000)nm, chemical ionization mass spectrum, *m/e* 217 1220 (M+H calcd for $C_{14}H_{17}O_2$, 217 1229)

Ketoester 17 A pyrex irradiation vessel was charged with a solution of cyclohexenone **16** (24 02 g, 111 1 mmol) and methyl acrylate (75 mL, 830 mmol) in methylene chloride (1 35 L) The solution was degassed by bubbling argon through it for 1 5 h Maintaining an inert atmosphere, the solution was irradiated for 6 h at 4°C with a G E 1000 watt lamp Progress of the reaction was easily monitored by TLC (hexanes/ether, 1 1, double development) Upon completion of the reaction, the volatiles were completely evaporated from the mixture under reduced pressure, and ether (250 mL) was then added as well as sufficient methylene chloride to solubilize all polymer Silica gel (300 mL) and hexanes (250 mL) were added successively Solvent was again evaporated under reduced pressure until a total volume of approximately 700 mL was achieved Ether was added with swirling until a homogeneous mixture was obtained Vacuum filtration, washing with ether, and concentration of the filtrate under reduced pressure gave a colorless oil almost free of polymer The purification process was repeated using 100 mL of ether, 50 mL of silica gel, and 100 mL of hexanes Final evaporation of solvents under reduced pressure afforded the mixture of photoproducts (31 60 g, 91 8%) as a colorless oil The mixture was not separated, but used directly in the next reaction The major isomer (17) was isolated for characterization by HPLC (hexanes/ethyl acetate, 9 1) IR ($CHCl_3$) 3015 (s), 2950 (m), 2865 (m), 1730 (s), 1710 (s), 1440 (m), 1225 (s), 1205 (s), 1090 (s), 695 (m) cm^{-1}, ^1H NMR (250 MHz, C_6D_6) δ 7 32-7 08 (m, 5H), 4 21 (ABq, J = 13 3, Δν = 4 7 Hz, 2H), 3 34 (dd, J = 6 6, 15 3 Hz, 1H), 3 34 (s, 3H), 3 25-3 16 (m, 1H), 2 94 (1/2 ABX, J_{AB} = 9 1, J_{AX} = 5 7 Hz, 1H), 2 88 (1/2 ABX, J_{BA} = 9 1, J_{BX} = 6 8 Hz, 1H), 2 35-2 17 (m, 2H), 2 15-1 94 (m, 2H), 1 79-1 65 (m, 1H), 1 60-1 49 (m, 1H), 1 46-1 33 (m, 1H), 1 13 (app ddt, J = 7 1, 9 6, 13 3 Hz, 1H), ^{13}C NMR (62 9 MHz, C_6D_6) δ 209 7, 174 3, 139 1, 128 6, 127 7, 73 1, 72 7, 51 5, 46 6, 39 6, 37 8, 36 4, 29 3, 25 6, chemical ionization mass spectrum, *m/e* 303 1576 (M+H calcd for $C_{18}H_{23}O_4$, 303 1596)

Ketal 18 A portion of the above mixture of photoproducts (1 83 g, 6 03 mmol) in trimethyl orthoformate (12 mL, 0 11 mol) was treated at 0°C with Amberlyst 15 ion-exchange resin (529 mg) After stirring for 2 h at 0°C, the mixture was filtered through a plug of cotton into a separatory funnel containing ether and saturated sodium bicarbonate solution After thorough shaking, the organic layer was isolated, and the aqueous layer was extracted with ether Combined organic layers were concentrated under reduced pressure to provide the mixture of ketals as a colorless oil The isomers were not separated, but used directly in the next reaction The major isomer was isolated for characterization by HPLC (hexanes/ethyl acetate, 9 1) IR (CCl_4) 2950 (s), 2855 (m), 1740 (s), 1435 (m), 1205 (s), 1175 (s), 1105 (s), 1055 (s), 725 (m), 695 (m), 675 (m) cm^{-1}, ^1H NMR (250 MHz, C_6D_6) δ 7 28-7 07 (m, 5H), 4 26 (app s, 2H), 3 37 (s, 3H), 3 35-3 14 (m, 2H), 3 10 (s, 3H), 3 08-2 98 (m, 2H), 2 96 (s, 3H), 2 31-2 20 (m, 1H), 1 98-1 87 (m, 2H), 1 71-1 49 (m, 3H), 1 39 (app dt, J = 2 7, 13 2 Hz, 1H), 1 14 (app dq, J = 2 3, 12 9 Hz, 1H), ^{13}C NMR (62 9 MHz, C_6D_6) δ 174 6, 139 4, 128 5, 127 5, 127 3, 99 9, 74 4, 73 1, 51 1, 48 1, 47 3, 42 0, 41 1, 39 0, 33 8, 30 2, 29 5, 24 3, chemical ionization mass spectrum, *m/e* 317 1757 (M+H calcd for $C_{20}H_{29}O_5$, 317 1753)

The preceding mixture of ketals was dissolved in benzene (7 mL) was cannulated over 10 min into a stirred solution of methyl magnesium bromide (5 04 mL, 3 0 M in diethyl ether, 15 1 mmol) in benzene (390 mL) while cooling the reaction with a water bath The reaction was stirred an additional 25 min and poured into a separatory funnel containing ether and saturated sodium bicarbonate solution After thorough shaking, the organic layer was isolated, and the aqueous layer was extracted with ether Combined organic layers were dried over $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure to provide the mixture of alcohols The isomers were not separated, but used directly in the next reaction The major isomer was isolated by HPLC (hexanes/ethyl acetate, 4 1) IR (CCl_4) 3550-3370 (m), 2970 (s), 2860 (m), 1455 (m), 1360 (m), 1205 (m), 1175 (s), 1095 (s), 1050 (s), 725 (m), 695 (m) cm^{-1}, ^1H NMR (250 MHz, C_6D_6) δ 7 33-7 06 (m, 5H), 4 33 (app s, 2H), 4 09 (s, 1H), 3 20 (1/2 ABX, J_{AB} = 8 7, J_{AX} = 4 6 Hz, 1H), 3 11 (1/2 ABX, J_{BA} = 8 8, J_{BX} = 6 2 Hz, 1H), 2 94 (s, 3H), 2 83 (s, 3H), 2 67-2 49 (m, 2H), 1 87-1 63 (m, 4H), 1 55-1 30 (m, 4H), 1 28 (s, 3H), 1 23 (s, 3H), ^{13}C NMR (62 9 MHz, C_6D_6) δ 139 4, 128 5, 127 6, 100 3, 74 7, 73 2, 69 7, 48 2, 47 4, 47 2, 40 5, 38 0, 32 3, 31 0, 28 6, 27 8, 25 5, 25 3, chemical ionization mass spectrum, *m/e* 317 2088 (M+H calcd for $C_{21}H_{33}O_4$, 317 2117)

The above mixture of alcohols was dissolved in acetone (20 mL) and treated with pyridinium *p*-toluenesulfonate (20 mg), stirring for 20 min at ambient temperature The solvent was then evaporated under reduced pressure, and flash column chromatography (hexanes/ethyl acetate, 3 1) gave the major ketone (18, 944 mg, 52% from 16) as a colorless oil IR ($CHCl_3$) 3600 (w), 3620-3200 (w), 3000 (s), 2970 (s), 2930 (s), 2860 (m), 1695 (s), 1455 (m), 1370 (m), 1225 (s), 1105 (s), 695 (s) cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 7 39-7 28 (m, 5H), 4.52 (app s, 2H), 3 49 (1/2 ABX, J_{AB} = 9 2, J_{AX} = 4 8 Hz, 1H), 3 32 (1/2 ABX, J_{BA} = 9 0, J_{BX} = 7 2 Hz, 1H), 3 01 (app t, J = 8 7 Hz, 1H), 2 60 (app dt, J = 9 1, 9 6 Hz, 1H), 2 46-2 40 (m, 2H), 2 25-1 68 (m, 6H), 1 61-1 44 (m, 1H), 1 15 (s, 3H), 1 14 (s, 3H), ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 214 8, 138 2, 128 3, 127 5, 127 4, 73 1, 72 8, 70 6, 48 7, 44 9, 40 1, 38 4, 33 5, 27 0, 26 2, 26 0, chemical ionization mass spectrum, *m/e* 303 1940 (M+H calcd for $C_{19}H_{27}O_3$, 303 1960) Anal. Calcd for $C_{19}H_{26}O_3$ C, 75 46, H, 8 67 Found C, 75 26, H, 8 82

MOM Ether 15 Chloromethyl methyl ether (0 89 mL, 11 7 mmol) was added to a solution of alcohol 18 (2 36 g, 7 80 mmol) and *N*-ethyldiisopropylamine (5 00 mL, 28 6 mmol) in methylene chloride (45 mL) while stirring at 0°C The reaction was stirred at ambient temperature for 46 h, an additional portion of chloromethyl methyl ether (0 30 mL, 3 9 mmol) being added at 4 h Subsequent extractive aqueous work-up and flash column chromatography (hexanes/ether, 4 1) gave the MOM ether (2 26 g, 84%) as a colorless oil IR ($CHCl_3$) 3010 (s), 2980 (s), 2935 (s), 1695 (s), 1455 (m), 1370 (m), 1225 (s), 1145 (s), 1095 (s), 1040 (s), 910 (m), 695 (m) cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 7 39-7 24 (m, 5H), 4 73 (ABq, J = 7 2, Δν = 14 8 Hz, 2H), 4 51 (ABq, J = 12 2, Δν = 5 0 Hz, 2H), 3 47 (1/2 ABX, J_{AB} = 9 1, J_{AX} = 4 9 Hz, 1H), 3.37 (s, 3H), 3 30 (1/2 ABX, J_{BA} = 9 1, J_{BX} = 7 3 Hz, 1H), 3 12-3 05 (m, 1H), 2 63-2 53 (m, 1H), 2 45-2 39 (m, 2H), 2 30-2 10 (m, 3H), 2 03-1 95 (m, 1H), 1 74-1 64 (m, 1H), 1 52 (app ddt, J = 8 5, 11 2, 13 4 Hz, 1H), 1 17 (s, 3H), 1 11 (s, 3H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 214 0, 138 4, 128 3, 127 5, 127 4, 91 0, 75 7, 73 2, 72 9, 55 1, 48 7, 45 0, 40 4, 38 6, 33 9, 26 3, 26 1, 23 5, 23 3, chemical ionization mass spectrum, *m/e* 347 2207 (M+H calcd for $C_{21}H_{31}O_4$, 347 2222) Anal. Calcd for $C_{21}H_{30}O_4$ C, 72 80, H, 8 73 Found C, 72 94, H, 8 71

Diol 19 Platinum on carbon (122 mg, 10% catalyst content) was added to ketone 18 (217 mg, 0 718 mmol) in methanol (25 mL) and stirred vigorously under a hydrogen atmosphere (balloon) for 5.5 h The hydrogen was then evacuated and the catalyst filtered off Evaporation of the solvent under reduced pressure and flash column chromatography (hexanes/ethyl acetate, 4 1 → straight ethyl acetate) gave the diol (91 mg, 42%) as a glass which crystallized on standing Recrystallization from hexanes/ethyl acetate/diethyl ether gave colorless prisms suitable for X-ray diffraction analysis m p 112 5-115°C, IR ($CHCl_3$) 3595 (w), 3520-3110 (m), 3010 (s), 2970 (s), 2930 (s), 2860 (m), 1455 (m), 1225 (s), 1050 (m), 785 (m), 695 (m) cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 7 42-7 23 (m, 5H), 4 49 (app s, 2H), 3 62-3 56 (m, 3H), 3 36 (1/2 ABX, J_{AB} = 9 1, J_{AX} = 4.8 Hz, 1H), 3 24 (1/2 ABX, J_{BA} = 9 0, J_{BX} = 6 7 Hz, 1H), 2 66-2 52 (m, 2H), 1 88-1 35 (m, 7H), 1 19 (s, 3H), 1 10 (s, 3H), 1 01-0 81 (m, 1H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 138 5, 128 2, 127 3, 74 3, 72 9, 70 0, 67 6, 44 9, 40 4, 39 7, 32 7, 31 0, 28 2, 27 6, 26 3, 24 0, chemical ionization mass spectrum, *m/e* 304 2024 (M^+ calcd for $C_{19}H_{28}O_3$, 304 2038) Anal. Calcd for $C_{19}H_{28}O_3$ C, 74 96, H, 9 27 Found C, 74 86, H, 9 21

Enone 20 Ketone 15 (4 54 g, 13 1 mmol) in THF (26 mL) was cannulated into a suspension of sodium hydride (1 88 g, 80% dispersion in mineral oil, 62 7 mmol) in ethyl formate (12 80 mL, 158 mmol) and THF (100 mL) stirring at 0°C The reaction was stirred at ambient temperature under an inert atmosphere for 6 5 h, after which the mixture was poured into saturated ammonium chloride solution Dilute hydrochloric acid was added until the aqueous phase showed a pH of 5 (pH paper) The layers were separated, and the aqueous layer was extracted with ether Combined organic layers were washed with saturated sodium bicarbonate solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure The crude vinylogous acid (5 22 g, 13 9 mmol) was treated at 0°C with ethyl vinyl ketone (5 00 mL, 50.2 mmol) and triethylamine (2 00 mL) The reaction was stirred at 0°C for 1 h and at ambient temperature for 36 h Excess reagents were evaporated under reduced pressure to afford the alkylated product (6 97 g) The slightly yellow oil was dissolved in 50% aqueous methanol (240 mL), potassium hydroxide (2 55 g, 45 4 mmol) was added, and the mixture was heated at reflux under argon for 2 5 h Methanol was evaporated from the cooled reaction mixture under reduced pressure, and the aqueous mixture was then saturated with sodium chloride and extracted with ether Washing of the combined extracts with brine, drying over $MgSO_4$, filtration, and evaporation of solvents under reduced pressure gave a yellow residue Flash column chromatography (hexanes/ethyl acetate, 3 1) supplied the enone (20, 4 66 g, 86% from 15) as a colorless oil IR ($CHCl_3$) 3010 (s), 2985 (s), 2935 (s), 1660 (s), 1655 (s), 1455 (m), 1365 (m), 1145 (s), 1090 (s), 1040 (s), 910 (m), 695 (m) cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 7 39-7 28 (m, 5H), 4 69 (ABq, J = 7 2, Δν = 12 9 Hz, 2H), 4 52 (app s, 2H), 3 61 (dd, J = 7 9, 9 5 Hz, 1H), 3 44 (1/2 ABX, J_{AB} = 9 0, J_{AX} = 4 6 Hz, 1H), 3 35 (s, 3H), 3.25 (1/2 ABX, J_{BA} = 8 9, J_{BX} = 7 4 Hz, 1H), 2 60-2 22 (m, 4H), 2 13-1 89 (m, 5H), 1 86 (d, J = 2 0 Hz, 3H), 1 63-1 46 (m, 2H), 1 11 (s, 3H), 1 04 (s, 3H), 0 90 (app q, J = 12 4 Hz, 1H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 199 6, 159 5, 138 3, 129 6, 128 2, 127 4, 127 3, 91 0, 75 5, 73 8, 73 1, 55 1, 51 3, 39 9, 37 9, 36 9, 36 5, 36 4, 33 5, 29 0, 26 0, 23 6, 23 4, 11 7, λ_{max} (EtOH) 256 4 (ε 17,000), 205 2 (ε 13,000) nm, chemical ionization mass spectrum, *m/e* 413 2646 (M+H calcd for $C_{26}H_{37}O_4$, 413 2692) Anal. Calcd for $C_{26}H_{36}O_4$ C, 75 69, H, 8 79 Found C, 75 72, H, 8 78

Oxime 21 Hydroxylamine hydrochloride (1 19 g, 17 1 mmol) was added to enone 20 (4 66 g, 11 3 mmol) and sodium acetate (2 78 g, 33 9 mmol) in methanol (20 mL) The reaction was heated at reflux for 40 min, poured into water, and extracted with chloroform Combined extracts were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* Flash column chromatography (hexanes/ethyl acetate, 4 1) gave the oxime (4 21 g, 87%) as an oil which crystallized on standing Recrystallization from hexanes/methylene chloride gave colorless plates m p 118 5-119 5°C, IR ($CHCl_3$) 3585 (w), 3600-3120 (m), 3010 (s), 2970 (s), 2935 (s), 2860 (s), 1455 (m), 1365 (m), 1225 (m), 1145 (m), 1095 (s), 1045 (s), 945 (s), 695 (m) cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 9.38 (br s, 1H), 7 39-7 27 (m, 5H), 4 69 (ABq, J = 7 1 Hz, Δν = 16 6 Hz, 2H), 4 51 (app s, 2H), 3 63 (app t, J = 8 3 Hz, 1H), 3 43 (1/2 ABX, J_{AB} = 9 0, J_{AX} = 4 5 Hz, 1H), 3 36 (s, 3H), 3 26-3 15 (m, 2H), 2 53-2 29 (m, 2H), 2 03-1 75 (m, 6H), 1 91 (d, J = 1 7 Hz, 3H), 1 51 (dd, J = 7 9, 10 0 Hz, 1H), 1 35-1 18 (m, 1H), 1 08 (s, 3H), 1 05 (s, 3H), 0 80 (app q, J = 12 4 Hz, 1H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 158 3, 146 4, 138 5, 128 3, 127 4, 123 5, 91 1, 75 6, 74 2, 73 1, 55 1, 51 1, 39 8, 37 0, 36 6, 35 5, 33 7, 28 4, 26 0, 23 9, 23 6, 21 3, 13 4, chemical ionization mass spectrum, *m/e* 428 2837 (M+H calcd for $C_{26}H_{38}O_4N$, 428 2801) Anal. Calcd for $C_{26}H_{37}O_4N$ C, 73 04, H, 8 72, N, 3 28 Found C, 72 77, H, 8 77, N, 3 37

Benzamide 22 Oxime 21 (3 38 g, 7 91 mmol) and benzoic anhydride (16 93 g, 74.8 mmol) in dry xylenes (34 mL) were heated to 150° ± 2°C (bath temperature) under argon for 50 min The amber liquid was allowed to cool, hexanes were added (34 mL) as well as enough chloroform to achive total solution Flash column chromatography (hexanes/ethyl acetate, 4 1) gave the benzamide (4 44 g) as a colorless glass This material was not purified further, but used directly in the next reaction Analytically pure material was obtained by washing an ether solution of the product with aqueous bicarbonate and crystallizing the residue of evaporation from methylene chloride/hexanes This procedure gave colorless prisms m p 151-153°C, IR ($CHCl_3$) 3430 (w), 3010 (s), 2970 (m), 2930 (m), 1675 (s), 1510 (s), 1485 (s), 1225 (s), 1205

(s), 1095 (s), 1040 (s), 705 (s) cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 7.88 (d, J = 6.8 Hz, 2H), 7 63-7 45 (m, 5H), 7 36-7 21 (m, 5H), 7 06 (d, J = 8 0 Hz, 1H), 4 67 (app s, 2H), 4 33 (ABq, J = 12.4, Δν = 4.5 Hz, 2H), 3 91-3.84 (m, 1H), 3 35 (s, 3H), 3 13 (dd, J = 4 7, 15 2 Hz, 1H), 2 96-2 87 (m, 3H), 2 55-2 48 (m, 1H), 2 30 (s, 3H), 2.26-2 17 (m, 3H), 1 83-1 71 (m, 1H), 1 23 (s, 3H), 1 12 (s, 3H), chemical ionization mass spectrum, *m/e* 513 2864 (M^+ calcd for $C_{33}H_{39}O_4N$, 513 2879) Anal. Calcd for $C_{33}H_{39}O_4N$ C, 77 16, H, 7 65, N, 2 73 Found C, 76 99, H, 7 69, N, 2 67

Aniline 9 A stirred solution of benzamide **22** (5 75 g) and sodium hydroxide (22 g, 550 mmol) in aqueous ethanol (44 mL EtOH, 14 mL H_2O) was heated at reflux under argon for 7 25 h The reaction mixture was cooled and diluted with brine (100mL) Extraction with ether, concentration, and flash column chromatography (hexanes/ethyl acetate, 3 2) gave the aniline (2 38 g, 57% from **21**) as a slightly yellow oil, as well as a small amount of recovered benzamide (270 mg, 5 1% from **21**)

9 IR ($CHCl_3$) 3510-3410 (w), 3410-3300 (w), 3005 (s), 2925 (s), 2855 (s), 1617 (m), 1485 (s), 1455 (m), 1365 (m), 1205 (m), 1145 (s), 1095 (s), 1040 (s), 905 (m), 695 (m) cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) δ 7 30-7 21 (m, 5H), 6.81 (d, J = 7 8 Hz, 1H), 6 49 (d, J = 7 8 Hz, 1H), 4 66 (ABq, J = 7 3, Δν = 9 3 Hz, 2H), 4 31 (ABq, J = 12 0, Δν = 12 0 Hz, 2H), 3 85-3 82 (m, 1H), 3 44 (br s, 2H), 3 35 (s, 3H), 3 05 (dd, J = 4 6, 15 0 Hz, 1H), 2 96-2 90 (m, 2H), 2 78 (dd, J = 2 0, 13 1 Hz, 1H), 2 47-2 43 (m, 1H), 2 27-2 19 (m, 2H), 2 17-2 14 (m, 1H), 2 13 (s, 3H), 1 76-1 70 (m, 1H), 1 20 (s, 3H), 1 12 (s, 3H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 142 7, 139 2, 138 6, 128 1, 127 4, 127 3, 127 2, 126 6, 119 2, 112 6, 91 0, 76 5, 72 8, 72 6, 55 0, 52 0, 37 4, 32 6, 30 1, 29 7, 25 0, 23 8, 23 0, 13 0, λ_{max} (EtOH) 292 0 (ε 1,900), 238 4 (ε 7,200), 214 4 (ε 26,000) nm, chemical ionization mass spectrum, *m/e* 409 2596 (M^+ calcd for $C_{26}H_{35}O_3N$, 409 2617) Anal. Calcd for $C_{26}H_{35}O_3N$ C, 76.25, H, 8 61, N, 3 42 Found C, 76 34, H, 8 72, N, 3 47

Alcohol 25 Palladium hydroxide on carbon (436 mg, 20% catalyst content, 0 62 mmol) was added to aniline **9** (2 00 g, 4 88 mmol) and (1*S*)-(+)-10-camphorsulfonic acid (910 mg, 3 92 mmol) in EtOAc (50 mL) The mixture was stirred under a hydrogen atmosphere (balloon) for 22 5 h The hydrogen was then evacuated, *N*-ethyldiisopropylamine (1 00 mL, 5 74 mmol) and hexanes (30 mL) were added, and the mixture was filtered through a plug of silica, washing well with ethyl acetate/hexanes (7 3) Evaporation of solvents *in vacuo* and flash column chromatography (ethyl acetate/hexanes, 3 2) gave the alcohol (1 31 g, 84%) as a colorless glass IR ($CHCl_3$) 3620 (w), 3450 (w), 3390 (w), 3700-3190 (w), 3010 (m), 2985 (m), 2940 (m), 1620 (m), 1485 (m), 1145 (m), 1045 (s) cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 6 83 (d, J = 7 9 Hz, 1H), 6 51 (d, J = 7 9 Hz, 1H), 4 68 (ABq, J = 7 3, Δν = 3 9 Hz, 2H), 3 91-3 85 (m, 1H), 3 45 (br s, 2H), 3 37 (s, 3H), 3 16-3 04 (m, 3H), 3 76 (app dt, J = 2 2, 15 2 Hz, 1H), 2 47-2 39 (m, 1H), 2 32-2 19 (m, 2H), 2 14 (s, 3H), 2 08-1 98 (m, 1H), 1 81-1 66 (m, 1H), 1 65 (br s, 1H), 1 20 (s, 3H), 1 12 (s, 3H), chemical ionization mass spectrum, *m/e* 319 2139 (M^+ calcd for $C_{19}H_{29}NO_3$, 319 2147)

TBS Ether 26 *t*-Butyldimethylsilyl chloride (2 10 g, 13 9 mmol) was added to a solution of alcohol **25** (2 05 g, 6 42 mmol), *N*-ethyldiisopropylamine (10 4 mL, 59 7 mmol), and 4-dimethylaminopyridine (90 mg, 0 74 mmol) in methylene chloride (37 mL) stirring at 0°C After 40 min at 0°C, the cold bath was removed and the reaction was stirred at ambient temperature for 1 33 h Extractive aqueous work-up and flash column chromatography (hexanes/ethyl acetate, 4 1) gave the silyl ether (2 36 g, 85%) as a colorless oil IR ($CHCl_3$) 3450 (w), 3380 (w), 2960 (s), 2930 (s), 2860 (s), 1622 (m), 1485 (m), 1475 (m), 1255 (m), 1145 (m), 1095 (s), 1040 (s), 838 (s) cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) δ 6 80 (d, J = 7 9 Hz, 1H), 6 50 (d, J = 7 9 Hz, 1H), 4 68 (ABq, J = 7 3, Δν = 9.8 Hz, 2H), 3.81 (app t, J = 8 5 Hz, 1H), 3 45 (br s, 2H), 3 37 (s, 3H), 3 04 (dd, J = 6 9, 9 8 Hz, 1H), 2 99 (dd, J = 4 5, 14 7 Hz, 1H), 2 99 (dd, J = 8 7, 9 9 Hz, 1H), 2 75 (app dt, J = 1 6, 14 5 Hz, 1H), 2 42-2 31 (m, 1H), 2 27-2 18 (m, 2H), 2 13 (s, 3H), 2 03-1 94 (m, 1H), 1 78-1 67 (m, 1H), 1 20 (s, 3H), 1 12 (s, 3H), 0 84 (s, 9H), -0 10 (s, 3H), -0 11 (s, 3H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 142 7, 139 3, 127 7, 126 8, 119 3, 112 8, 91 1, 76 6, 64 8, 55 1, 52 1, 39 9, 32 8, 29 8, 29 3, 25 9, 25 2, 23 9, 23 1, 18 2, 13 1, -5 5, λ_{max} (EtOH) 291 6 (ε 1,700), 237 6 (ε 6,600), 214 4 (ε 20,000) nm, chemical ionization mass spectrum, *m/e* 433 3018 (M^+ calcd for $C_{25}H_{43}NO_3Si$, 433 3012) Anal. Calcd for $C_{25}H_{43}NO_3Si$ C, 69 23, H, 9 99, N, 3 23 Found C, 69 30, H, 10 12, N, 3 49

Indole 24 *s*-BuLi (17 15 mL, 1 3 M in cyclohexane, 22 3 mmol) was added dropwise to a solution of *N*-trimethylsilyl-*o*-toluidine[6c] (1 82 g, 10 1 mmol) in diethyl ether (40 mL) at 0°C The pale yellow suspension was stirred at ambient temperature for 1 5 h, cooled to -78°C, and quenched with dimethylbutyrolactone[30] (2 02 g, 17 7 mmol) in one portion The reaction was allowed to warm to ambient temperature and was then poured into aqueous ammonium chloride solution (50% sat'd) Extraction with ether, washing of the combined extracts with brine, and drying over $MgSO_4$ gave a slightly yellow solution Concentration *in vacuo* and flash column chromatography (hexanes/ethyl acetate, 3 2) afforded the indole (1 29 g, 63%) as a colorless oil which crystallized on standing Recrystallization from ether/hexanes gave colorless prisms m p 96-97°C, IR ($CHCl_3$) 3600 (w), 3470 (s), 3410 (m), 3650-3150 (m), 3005 (s), 2970 (s), 1460 (s), 1405 (m), 1295 (s), 1225 (s), 1015 (s), 785 (s), 690 (s) cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 8 37 (br s, 1H), 7 53 (dd, J = 1 0, 7 2 Hz, 1H), 7 28 (d, J = 7 9 Hz, 1H), 7 12 (app dt, J = 1 4, 7 5 Hz, 1H), 7 06 (app dt, J = 1 2, 7 1 Hz, 1H), 6 25-6 24 (m, 1H), 3 56 (app t, J = 6 9 Hz, 2H), 1 88 (app t, J = 7 0 Hz, 2H), 1 58 (br s, 1H), 1 37 (s, 6H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 146 6, 135 9, 128 2, 121 2, 119 9, 119 6, 110 5, 98 0, 59 9, 45 3, 33 9, 28 5, λ_{max} (EtOH) 289 2 (ε 6,000), 278 8 (ε 7,800), 272 6 (ε 7,800), 221 8 (ε 26,000) nm, chemical ionization mass spectrum, *m/e* 203 1300 (M^+ calcd for $C_{13}H_{17}NO$, 203 1310) Anal. Calcd for $C_{13}H_{17}NO$ C, 76 81, H, 8 43, N, 6 89 Found C, 77 08, H, 8 65, N, 6 67

Indole 27 A solution of aniline **26** (2 36 g, 5 44 mmol) in ether (30 mL) was cooled to -78°C *n*-BuLi (2 27 mL, 2 40 M in hexanes, 5 45 mmol) was added dropwise to this solution The metallation was stirred at ambient temperature for 10 min, then recooled to -78°C Trimethylsilyl chloride (0 69 mL, 5 4 mmol) was then added dropwise, and the reaction was stirred at -78°C for 5 min and at ambient temperature for 20 min The mixture was cooled to 0°C and *s*-BuLi (8 37 mL, 1 3 M in cyclohexane, 11 mmol) was added dropwise Stirring was continued at 0°C for 1 h, after which time the dianion was cooled to -78°C and dimethylbutyrolactone (0 80 mL, 7 4 mmol) was added in one portion Stirring at -78°C was continued for 15 min Quenching of the reaction was done at -78°C by rapid addition of saturated ammonium chloride solution while stirring vigorously Extraction, concentration, and flash column chromatography (hexanes/ethyl acetate, 7 3) gave, in order of elution, unconverted aniline **26** (1 32 g, 56%) and indole **27** (778 mg, 27%) as a slightly yellow glass

27 IR ($CHCl_3$) 3610 (w), 3475 (m), 3670-3090 (w), 2960 (s), 2930 (s), 2855 (s), 1472 (m), 1465 (m), 1255 (s), 1145 (m), 1095 (s), 1042 (s), 835 (s) cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) δ 8 18 (br s, 1H), 7 07 (d, J = 8 1 Hz, 1H), 6 90 (d, J = 8 1 Hz, 1H), 6 36 (d, J = 1 7 Hz, 1H), 4 74 (ABq, J = 7 1, Δν = 5 2 Hz, 2H), 3 82 (app t, J = 7 8 Hz, 1H), 3 59 (app q, J = 5 2 Hz, 2H), 3 44 (s, 3H), 3 20 (dd, J = 6 5, 9 9 Hz, 1H), 3 13 (dd, J = 8 3, 9 7 Hz, 1H), 3 10 (dd, J = 4 8, 15 2 Hz, 1H), 2 85 (dd, J = 3 2, 15 3 Hz, 1H), 2 59-2 46 (m, 1H), 2 28 (app dt, J = 6 9, 9 1 Hz, 1H), 2 19 (app dt, J = 7 4, 9 7 Hz, 1H), 2 12-2 00 (m, 1H), 1 92 (app t, J = 6 9 Hz, 2H), 1 86 (app dt, J = 5 3, 11 2 Hz, 1H), 1 60 (app t, J = 5 1 Hz, 1H), 1 39 (s, 6H), 1 26 (s, 3H),

1 22 (s, 3H), 0 85 (s, 9H), -0 09 (s, 6H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 145 4, 134 8, 131 3, 126 6, 126 0, 123.5, 108 0, 96 9, 91 0, 77 0, 65 0, 59 8, 55 1, 52 4, 45 5, 39 7, 33 9, 33 7, 30 1, 28 9, 28 6, 28 5, 25 9, 24 9, 23 9, 23 3, 18.3, -5 4, λ_{max} (EtOH) 276 0 (ε 7,300), 225 6 (ε 21,000) nm, chemical ionization mass spectrum, *m/e* 530 3705 (M+H calcd for $C_{31}H_{52}NO_4$, 530.3665) Anal. Calcd for $C_{31}H_{51}NO_4$ C, 70 27, H, 9 70, N, 2 64 Found C, 70 51, H, 9 83, N, 2 55

Aniline 26-α-*d*$_1$ Aniline **26** (200 mg, 0 461 mmol) in ether (2 mL) was silylated *in situ* and converted to its lithium dianion as above The reaction mixture was then cooled to -78°C and deuterium oxide (0 20 mL) in THF (0 50 mL) was added in one portion The reaction was stirred at ambient temperature for 10 min, poured into saturated ammonium chloride solution, and extracted with ether Combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* Flash column chromatography (hexanes/ethyl acetate, 7:3 → 3:2) returned the aniline (150 mg, 75%) as a colorless glass ^{1}H NMR (500 MHz, $CDCl_3$) δ 6 79 (d, J = 7 9 Hz, 1H), 6 49 (d, J = 7 9 Hz, 1H), 4 68 (ABq, J = 7 2, Δν = 9 8 Hz, 2H), 3 81 (app t, J = 8 5 Hz, 1H), 3 44 (br s, 2H), 3 36 (s, 3H), 3 06-2 97 (m, 3H), 2 76 (dd, J = 1 9, 13 0 Hz, 1H), 2 40-2 36 (m, 1H), 2 28-2 18 (m, 2H), 2 13 (s, 1.29H), 2 11 (t, J = 2 1 Hz, 1 14H), 1 98-1 95 (m, 1H), 1 74-1 69 (m, 1H), 1 20 (s, 3H), 1 12 (s, 3H), 0 84 (s, 9H), -0 097 (s, 3H), -0 104 (s, 3H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 142 6, 139 2, 127 6, 126 6, 119 2, 112 7, 91 0, 76 5, 64 7, 55 0, 52 0, 39 8, 32 7, 29 8, 29 2, 25 9, 25 2, 23 8, 23 0, 18 2, 13 0, 12 8 (t, J = 19 9 Hz), -5 49, -5 54

Preparation of 27 by Modified Madelung Condensation [34] *n*-Butyllithium (1 27 mL, 1 87 M in hexanes, 2 37 mmol) was added to diisopropylamine (0 36 mL, 2 6 mmol) in THF (5 mL) stirring at 0°C The solution was stirred at 0°C for 15 min, and a solution of aniline **26** (411 mg, 0 948 mmol) in THF (2 mL + 1 mL wash) was then added via cannula The reaction was stirred at 0°C for 15 min and cooled to -78°C Dimethylbutyrolactone (0 21 mL, 1 9 mmol) was added in one portion, and the reaction was stirred at 0°C for 50 min and at ambient temperature for 50 min The reaction was quenched at 0°C with saturated ammonium chloride solution Extraction and flash column chromatography (hexanes/ethyl acetate, 7 13) gave the amide (458 mg, 88%) as a slightly yellow glass IR ($CHCl_3$) 3440 (m), 3560-3100 (w), 2950 (s), 2930 (s), 2850 (s), 1660 (s), 1505 (s), 1472 (s), 1253 (m), 1144 (m), 1090 (s), 1035 (s), 833 (s) cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7 36 (d, J = 8 1 Hz, 1H), 7 32 (br s, 1H), 6 98 (d, J = 8 0 Hz, 1H), 4 66 (ABq, J = 7 2, Δν = 5 2, 2H), 3 81 (app t, J = 7 6 Hz, 1H), 3 77 (app q, J = 5 7 Hz, 1H), 3 36 (s, 3H), 3 04 (dd, J = 6 8, 9 8 Hz, 1H), 2 99 (app dt, J = 8 5, 9 9 Hz, 1H), 2 85 (br d, J = 14 8 Hz, 1H), 2 70 (app t, J = 5 4 Hz, 1H), 2 46-2 38 (m, 1H), 2 30-2 14 (m, 2H), 2 21 (s, 3H), 2 05-2 00 (m, 1H), 1 91 (app t, J = 6 1 Hz, 2H), 1 80-1 69 (m, 1H), 1.38 (s, 6H), 1 22 (s, 3H), 1 11 (s, 3H), 0 84 (s, 9H), -0 09 (s, 3H), -0 10 (s, 3H), chemical ionization mass spectrum, *m/e* 548 3695 (M+H calcd for $C_{31}H_{54}NO_5Si$, 548 3771)

n-BuLi (3 61 mL, 2 50 M solution in hexanes, 9 03 mmol) was added to a solution of the amide (1 237 g, 2 26 mmol) in THF (8 5 mL) stirring at 0°C The reaction was stirred at ambient temperature for 1 1 h, then quenched at 0°C with saturated NH_4Cl solution Extraction and flash column chromatography (hexanes/ethyl acetate, 3:2 → 7 13) gave, in order of elution, indole **27** (991 mg, 83%) as a slightly yellow glass in addition to some unconverted amide (71 mg, 5 7%) The indole was identical with material previously obtained from the dianion of *N*-TMS-**26** (*vide supra*)

Hemiaminal 28 Sulfur trioxide-pyridine complex (234 mg, 1 47 mmol) was added to a solution of alcohol **24** (50 mg, 0 25 mmol) and triethylamine (0 68 mL, 4 9 mmol) in DMSO (3 mL), and the reaction was stirred for 2h Extractive aqueous work-up and flash column chromatography (hexanes/ethyl acetate, 4 1) gave the hemiaminal (39 mg, 79%) as a colorless oil IR ($CHCl_3$) 3590 (w), 3640-3120 (w), 3010 (m), 2970 (s), 2930 (m), 1457 (s), 1363 (s), 1342 (m), 1305 (s), 1155 (m), 1075 (m), 1010 (m), 850 (w) cm^{-1}, ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.55-7 52 (m, 1H), 7 40-7 36 (m, 1H), 7 13 (app dt, J = 1 5, 7 0 Hz, 1H), 7 08 (app dt, J = 1 4, 7 2 Hz, 1H), 6 07 (d, J = 0 5 Hz, 1H), 5 97 (ddd, J = 2 4, 6 2, 7 3 Hz, 1H), 2 66 (1/2 ABX, J_{AB} = 13 7, J_{AX} = 6 2 Hz, 1H), 2 61 (d, J = 7 4 Hz, 1H), 2 25 (1/2 ABX, J_{BA} = 13 6, J_{BX} = 2 4 Hz, 1H), 1 50 (s, 3H), 1 37 (s, 3H), chemical ionization mass spectrum, *m/e* 202 1218 (M+H calcd for $C_{13}H_{15}NO$, 202 1232)

Aldehyde 29 Alcohol **24** was oxidized according to the procedure of Moffatt et al [36] Thus, dicyclohexylcarbodiimide (719 mg, 3 49 mmol) was added to a solution of alcohol **24** (59 mg, 0 29 mmol), pyridine (0 094 mL, 1 16 mmol), and trifluoroacetic acid (0 045 mL, 0.58 mmol) in benzene/DMSO (3 mL, 1 1, v/v), and the reaction was stirred at ambient temperature for 7 5 h Extractive aqueous work-up and flash column chromatography (hexanes/ethyl acetate, 4 1) gave the aldehyde (55 mg, 96%) as a colorless oil IR ($CHCl_3$) 3475 (m), 3410 (m), 3010 (m), 2970 (s), 1720 (s), 1460 (s), 1299 (s) cm^{-1}, ^{1}H NMR (250 MHz, $CDCl_3$) δ 9 60 (t, J = 2 4 Hz, 1H), 8 46 (br s, 1H), 7 54 (d, J = 7 2 Hz, 1H), 7 31 (d, J = 7 2 Hz, 1H), 7 14 (app dt, J = 1 4, 7 0 Hz, 1H), 7 07 (app dt, J = 1 2, 7 2 Hz, 1H), 6 28 (dd, J = 0 8, 2 2 Hz, 1H), 2 69 (d, J = 2 4 Hz, 2H), 1 49 (s, 6H), chemical ionization mass spectrum, *m/e* 202 1219 (M+H calcd for $C_{13}H_{16}NO$, 202 1232)

Aldehyde 30 Dicyclohexylcarbodiimide (674 mg, 3 27 mmol) was added to a solution of alcohol **27** (144 mg, 0 272 mmol), pyridine (0 088 mL, 1 1 mmol), and trifluoroacetic acid (0 042 mL, 0 55 mmol) in benzene/DMSO (3 mL, 1 1, v/v), and the reaction was stirred for 4 5 h Extractive aqueous work-up and flash column chromatography (hexanes/ethyl acetate, 4 1) gave the aldehyde (102 mg, 71%) as a colorless glass IR ($CHCl_3$) 3475 (w), 3510-3240 (w), 2955 (s), 2930 (s), 2860 (s), 1725 (s), 1265 (m), 1145 (m), 1090 (s), 1040 (s), 835 (s) cm^{-1}, ^{1}H NMR (250 MHz, $CDCl_3$) δ 9 62 (app t, J = 2 3 Hz, 1H), 8 31 (br s, 1H), 7 10 (d, J = 8 1 Hz, 1H), 6 93 (d, J = 8 2 Hz, 1H), 6 40-6 39 (m, 1H), 4 75 (app s, 2H), 3 81 (app t, J = 7 1 Hz, 1H), 3 42 (s, 3H), 3 22-3 07 (m, 3H), 2 86 (dd, J = 3 1, 15 4 Hz, 1H), 2 72 (app d, J = 2 4 Hz, 2H), 2 58-2 52 (m, 1H), 2.31-2 14 (m, 2H), 2 08-2 03 (m, 1H), 1 93-1 81 (m, 1H), 1 51 (app s, 6H), 1 26 (s, 3H), 1 21 (s, 3H), 0 85 (s, 9H), -0 092 (s, 3H), -0 095 (s, 3H), chemical ionization mass spectrum, *m/e* 527 3387 (M$^+$ calcd for $C_{31}H_{49}NO_4Si$, 527 3431)

Methyl Oxaminal 31 Camphorsulfonic acid (75 mg, 0 32 mmol) was added to a solution of aldehyde **30** (142 mg, 0 269 mmol) in methanol (4.5 mL), and the reaction was stirred at ambient temperature for 2 5 h Pyridine (0 10 mL) was added, and the solution was concentrated under reduced pressure Flash column chromatography (hexanes/ethyl acetate, 1 1 → 2.3) gave the methyl oxaminal (**31**, 71 mg, 69%) as a colorless glass IR ($CHCl_3$) 3605 (w), 3670-3200 (w), 3005 (s), 2965 (s), 2930 (s), 1430 (m), 1370 (m), 1210 (s), 1080 (s), 835 (m) cm^{-1}, ^{1}H NMR (250 MHz, $CDCl_3$) δ 7 18 (d, J = 8 1 Hz, 2H), 6 94 (d, J = 8 1 Hz, 2H), 6 17 (s, 1H), 6 15 (s, 1H), 5.59 (d, J = 6 2 Hz, 1H), 5 57 (d, J = 6 3 Hz, 1H), 3 79 (app t, J = 7 6 Hz, 2H), 3 50 (s, 3H), 3 48 (s, 3H), 3 23-3 14 (m, 6H), 2 87 (d, J = 15 4 Hz, 1H), 2 86 (d, J = 15.5 Hz, 1H), 2 56-2 46 (m, 4H), 2 36 (d, J = 13 3 Hz, 2H), 2 30-2 07 (m, 6H), 1 95-1 84 (m, 2H), 1 59 (s, 1H), 1.55 (s, 1H), 1 50 (s, 6H), 1 46 (s, 2H), 1 380 (s, 3 H), 1 375 (s, 3H), 1.29 (s, 3H), 1 28 (s, 3H), 1 17 (s, 3H), 1 16 (s, 3H), λ_{max} (EtOH) 275 2 (ε 5,400), 227 6 (ε 16,000), 210s (ε 12,000) nm, chemical ionization mass spectrum, *m/e* 384 2495 (M+H calcd for $C_{24}H_{34}NO_3$, 384 2538)

Hemiaminal 32 Camphorsulfonic acid (20 mg, 0 086 mmol) was added to a solution of methoxy anomers **31** (65 mg, 0 17 mmol) in THF/H_2O (3 mL, 2 1, v/v) The reaction was stirred for 40 min, then quenched with pyridine Extractive aqueous work-up followed by concentration from toluene (2 x 3 mL) *in vacuo* and flash column chromatography

(hexanes/ethyl acetate, 7 13) gave the hemiaminal (32, 48 mg, 77%, 1 1 ratio by ^{1}H NMR integration) as a colorless glass IR ($CHCl_3$) 3600 (w), 3680-3090 (m), 3005 (s), 2970 (s), 2930 (s), 1430 (s), 1370 (s), 1210 (s), 1145 (m), 1032 (m) cm^{-1}, ^{1}H NMR (250 MHz, $CDCl_3$) δ 7 17 (d, J = 7 6 Hz, 1H), 7 14 (d, J = 7 3 Hz, 1H), 6 89 (d, J = 8 1 Hz, 2H), 6 10 (s, 2H), 5 91 (br s, 2H), 3 74 (app t, J = 7 9 Hz, 2H), 3 53 (br s, 2H), 3 28-2 99 (m, 8H), 2 86-2 77 (m, 2H), 2 63 (dd, J = 6 1, 13 6 Hz, 2H), 2 55-2 40 (m, 2H), 2 25 (d, J = 13 5 Hz, 1H), 2 24 (d, J = 13 6 Hz, 1H), 2 19-1 96 (m, 6H), 1 89-1 79 (m, 2H), 1 66 (br s, 2H), 1 48 (s, 6H), 1 34 (s, 6H), 1 24 (s, 6H), 1 14 (s, 3H), 1 13 (s, 3H), chemical ionization mass spectrum, *m/e* 370 2364 (M+H calcd for $C_{23}H_{32}NO_3$, 370 2382)

Oxepane 36 Pyridinium *p*-toluenesulfonate (2 mg, 0 008 mmol) was added to a solution of alcohol **27** (44 mg,0 083 mmol) and *p*-anisaldehyde dimethyl acetal (0 044 mL, 0 25 mmol) in DMF (0 50 mL) The reaction was stirred at ambient temperature for 1 5 h Extractive aqueous work-up and flash column chromatography (hexanes/ether, 7.3 → 1 1) afforded the oxepane (19 mg, 35%) as a colorless glass IR ($CHCl_3$) 3490 (m), 3500-3300 (w), 3000 (m), 2960 (s), 2930 (s), 2855 (m), 1610 (w), 1510 (s), 1465 (m), 1245 (s), 1090 (s), 1038 (s), 835 (s) cm^{-1}, ^{1}H NMR (250 MHz, $CDCl_3$) δ 7 88 (br s, 1H), 7 10 (d, J = 8 0 Hz, 1H), 7 07 (d, J = 8 6 Hz, 2H), 6 92 (s, 1H), 6 91 (d, J = 7 9 Hz, 1H), 6 76 (d, J = 8 7 Hz, 2H), 4 68 (ABq, J = 7 3, Δν = 9 6 Hz, 2H), 3 91-3 76 (m, 2H), 3 76 (s, 3H), 3 57 (app t, J = 8 6 Hz, 1H), 3 35 (s, 3H), 3 06 (dd, J = 4 4, 15 0 Hz, 1H), 2 94 (d, J = 14 9 Hz, 1H), 2 79 (1/2 ABX, J_{AB} = 9 8, J_{AX} = 6 5 Hz, 1H), 2 67 (1/2 ABX, J_{BA} = 9 5, J_{BX} = 9 5 Hz, 1H), 2 26 (app q, J = 8 7 Hz, 1H), 2 06 (app q, J = 11 2 Hz, 1H), 1 96-1 50 (m, 5H), 1 50 (s, 3H), 1 31 (s, 3H), 1 12 (s, 3H), 1 05 (s, 3H), 0 80 (s, 9H), -0 19 (s, 3H), -0 21 (s, 3H), chemical ionization mass spectrum, *m/e* 648 4025 (M+H calcd for $C_{39}H_{58}NO_5Si$, 648 4084)

2,4-Dimethoxybenzaldehyde Dimethyl Acetal According to the method of Patwardhan and Dev,[19] 2,4-dimethoxybenzaldehyde (7 11g, 42 8 mmol) was stirred with Amberlyst-15 (800 mg) in trimethylorthoformate (30 mL, 270 mmol) at ambient temperature for 4 5 h The catalyst was filtered off and the colorless solution was concentrated *in vacuo* High-vacuum distillation (2 5 torr, 115°C) gave the acetal (6 48 g, 71%) as a colorless oil IR ($CHCl_3$) 3015 (s), 2945 (s), 2840 (s), 1620 (s), 1595 (s), 1510 (s), 1470 (s), 1415 (s), 1387 (s), 1365 (s), 1205 (s), 1160 (s), 1125 (s), 1100 (s), 1070 (s), 1045 (s) cm^{-1}, ^{1}H NMR (250 MHz, $CDCl_3$) δ 7 43 (d, J = 8 4 Hz, 1H), 6 49 (dd, J = 2 4, 8 3 Hz, 1H), 6 45 (d, J = 2 3 Hz, 1H), 5 60 (s, 1H), 3 82 (s, 3H), 3 81 (s, 3H), 3 34 (s, 6H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 160 9, 158 1, 128 0, 118 6, 103 7, 98 9, 98 2, 55 4, 55 2, 53 2, chemical ionization mass spectrum, *m/e* 212 1071 (M$^+$ calcd for $C_{11}H_{16}O_4$, 212 1048)

Oxepane 37 Pyridinium *p*-toluenesulfonate (30 mg, 0 12 mmol) was added to a solution of alcohol **27** (493 mg, 0 930 mmol) and 2,4-dimethoxybenzaldehyde dimethyl acetal (0 50 mL, 2 59 mmol) in DMF (10 mL) The reaction was stirred at ambient temperature for 50 min The product was typically not isolated at this point, but treated *in situ* with the subsequent alkylation conditions A sample of **37** for charactenzation could be isolated in the following manner Extractive aqueous work-up and flash column chromatography (hexanes/ether, 3 2 → 1 1) provided the oxepane as a colorless glass IR ($CHCl_3$) 3495 (m), 3540-3280 (w), 3010 (s), 2970 (s), 2940 (s), 2867 (s), 1617 (s), 1595 (s), 1510 (s), 1473 (s), 1446 (s), 1265 (s), 1165 (s), 1100 (s), 1045 (s), 840 (s) cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7 88 (br s, 1H), 7 07 (d, J = 8 0 Hz, 1H), 6 93 (s, 1H), 6 89 (d, J = 8 1 Hz, 1H), 6 52 (d, J = 2 2 Hz, 1H), 6 37 (d, J = 8 4 Hz, 1H), 6 09 (dd, J = 2 2, 8 5 Hz, 1H), 4 53 (ABq, J = 7 4, Δν = 19 7 Hz, 2H), 3 95 (s, 3H), 3 90 (ddd, J = 5 7, 10 3, 12 2 Hz, 1H), 3 76 (ddd, J = 3 0, 6 2, 12 3 Hz, 1H), 3 72 (s, 3H), 3 35 (app t, J = 8.3 Hz, 1H), 3 27 (s, 3H), 3 06 (dd, J = 4 2, 15 3 Hz, 1H), 2 94 (d, J = 15 2 Hz, 1H), 2 69 (1/2 ABX, J_{AB} = 9.8, J_{AX} = 5 9 Hz, 1H), 2 47 (1/2 ABX, J_{BA} = 9 8, J_{BX} = 9 8 Hz, 1H), 2 27 (app q, J = 9 5 Hz, 1H), 2 06 (app q, J = 11 5 Hz, 1H), 1 96 (ddd, J = 6 4, 10 1, 14 1 Hz, 1H), 1 88-1 82 (m, 1H), 1 72 (app dt, J = 4 0, 13 8 Hz, 1H), 1 61-1 53 (m, 2H), 1.53 (s, 3H), 1 45 (s, 3H), 1 15 (s, 6H), 0 79 (s, 9H), -0 24 (s, 3H), -0 26 (s, 3H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 160 4, 158 6, 142 6, 134 0, 133 2, 131 2, 127 0, 124 5, 124 1, 121 4, 111 5, 107 4, 102 6, 98 1, 90 8, 76 8, 73 8, 63 8, 62 7, 55 2, 54 9, 54 7, 52 2, 43 0, 39 3, 34 9, 33 1, 31 5, 29 9, 29 1, 28 8, 25 8, 24 8, 23 3, 23 2, 18 1, -5 7, -5 8, chemical ionization mass spectrum, *m/e* 678 4189 (M+H calcd for $C_{40}H_{60}NO_6Si$, 678 4189)

Indole 38 The preceding reaction mixture was cooled to 0°C and treated with sodium hydride (320 mg, 80% dispersion in mineral oil, 10 7 mmol) After stirring at 0°C for 10 min, *p*-methoxybenzyl chloride (0 80 mL, 5 9 mmol) was added and the reaction was stirred at ambient temperature for 1 25 h Extractive aqueous work-up and flash column chromatography (hexanes/ether, 1 1) afforded, in order of elution, a small quantity of *C*-alkylated product (53 mg, 7 1%) as a colorless glass and indole **38** (596 mg, 80% for two steps) as a slightly yellow glass which crystallized on standing Recrystallization of the latter compound from methylene chloride/methanol provided colorless prisms m p 150 5-152 5°C, IR ($CHCl_3$) 3010 (s), 2970 (s), 2940 (s), 2865 (s), 1615 (s), 1590 (s), 1515 (s), 1470 (s), 1392 (m), 1252 (s), 1160 (s), 1095 (s), 1040 (s), 837 (s) cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$) δ 6 96 (s, 1H), 6.86 (d, J = 8 8 Hz, 2H), 6 80 (app d, J = 2 0 Hz, 2H), 6 78 (d, J = 8 9 Hz, 2H), 6 63 (d, J = 8 4 Hz, 1H), 6 55 (d, J = 2 3 Hz, 1H), 6 20 (dd, J = 2 4, 8 5 Hz, 1H), 5 50 (ABq, J = 17 6, Δν = 15 3 Hz, 2H), 4 50 (ABq, J = 7 4, Δν = 15 2 Hz, 2H), 3 95 (s, 3H), 4 00-3 89 (m, 1H), 3 76 (app s, 6H), 3 64 (ddd, J = 3 0, 5 9, 11 5 Hz, 1H), 3 38 (app t, J = 8 5 Hz, 1H), 3 25 (s, 3H), 3 06 (dd, J = 4 2, 15 2 Hz, 1H), 2 92 (d, J = 15 2 Hz, 1H), 2 77 (dd, J = 5 9, 9 8 Hz, 1H), 2 54 (app t, J = 9 9 Hz, 1H), 2 31 (app q, J = 8 4 Hz, 1H), 2 11 (ddd, J = 6 1, 10 4, 14 8 Hz, 1H), 2 02 (app q, J = 11 4 Hz, 1H), 1 92-1 83 (m, 1H), 1 67-1 58 (m, 2H), 1 50 (s, 3H), 1 52-1 48 (m, 1H), 1 40 (s, 3H), 1 17 (s, 3H), 1 13 (s, 3H), 0 78 (s, 9H), -0 24 (s, 3H), -0 26 (s, 3H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 160 5, 158 8, 158 3, 145 4, 137 8, 133 1, 131 5, 130 7, 127 5, 126 8, 124 5, 124 2, 121 3, 115 8, 113 8, 107 3, 103 1, 98 0, 90 9, 77 0, 72 6, 63 9, 62 3, 55 3, 55 1, 54 9, 52 0, 48 9, 45 8, 39 2, 36 3, 33 2, 31 0, 30 1, 29 2, 26 9, 25 9, 25 0, 23 5, 23 1, 18 3, -5 6, -5 8, λ_{max} (EtOH) 284 8 (ε 14,000), 229 6 (ε 40,000), 211 6 (ε 37,000) nm, chemical ionization mass spectrum, *m/e* 798 484 (M+H calcd for $C_{48}H_{68}NO_7Si$, 798 4764) Anal. Calcd for $C_{48}H_{67}NO_7Si$ C, 72 23, H, 8 46, N, 1 75 Found C, 72 17, H, 8 59, N, 1 67

Alcohol 34 Indole **38** (566 mg, 0 709 mmol) was added to a solution of AcOH/THF/*i*-PrOH (10 mL, 3 1 1, v/v) The reaction was stirred at ambient temperature for 8 5 h, then poured into water and extracted with chloroform Combined extracts were washed successively with water and saturated sodium bicarbonate solution The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* Flash column chromatography (hexanes/ether/methanol, 50 50 0 → 49 49 2) afforded the alcohol (456 mg, 99%) as a colorless glass IR ($CHCl_3$) 2970 (s), 2940 (s), 2865 (m), 1615 (w), 1520 (s), 1470 (m), 1255 (s), 1095 (s), 1045 (s), 835 (s) cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$) δ 6 86 (d, J = 8 4 Hz, 1H), 6 82 (d, J = 9 1 Hz, 2H), 6 81 (d, J = 8 4 Hz, 1H), 6 77 (d, J = 9 1 Hz, 2H), 6 49 (s, 1H), 5 50 (s, 2H), 4 77 (ABq, J = 7 2, Δν = 6 8 Hz, 2H), 3 88 (app t, J = 7 5 Hz, 1H), 3 74 (s, 3H), 3 49-3 41 (m, 2H), 3 45 (s, 3H), 3 22 (dd, J = 6 4, 9 8 Hz, 1H), 3 12 (dd, J = 8 6, 9 7 Hz, 1H), 3 08 (dd, J = 4 8, 15 2 Hz, 1H), 2 85 (dd, J = 3 5, 15 2 Hz, 1H), 2 58-2 46 (m, 1H), 2 31 (app q, J = 7 0 Hz, 1H), 2 22 (app dt, J = 7 6, 9 6 Hz, 1H), 2 13-2 03 (m, 1H), 2 01-1 91 (m, 2H), 1 86 (app dt, J = 5 2, 11 6 Hz, 1H), 1 43 (s, 3H), 1 39 (s, 3H), 1 27 (s, 3H), 1 25 (s, 3H), 0 88 (app t, J = 6 0 Hz, 1H), 0 84 (s, 9H), -0 11 (app s, 6H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 158 4, 145 2, 137 5, 131 4, 130 2, 126 7, 126 3, 125 3, 123 7, 113 9, 107 3, 99 2, 91 0, 76 9, 64 8, 59 9,

55 1, 55 0, 52 4, 48 0, 44 1, 39 6, 34 6, 33 6, 30 0, 29 7, 29 3, 28 7, 25 9, 24.8, 23 9, 23 3, 18 2, -5 5, chemical ionization mass spectrum, *m/e* 650 4284 (M+H calcd for $C_{39}H_{60}NO_5SI$, 650 4240)

Aldehyde 39 *p*-Toluenesulfonyl chloride (50 mg, 0 26 mmol) was added to a solution of alcohol **34** (101 mg, 0 155 mmol) and 4-dimethylaminopyridine (10 mg, 0 082 mmol) in pyridine (2 mL) at 0°C, and the reaction was stirred at ambient temperature for 5 5 h Extractive aqueous work-up and azeotropic removal of pyridine with toluene under reduced pressure gave a yellow residue Flash column chromatography (hexanes/ether, 1 1) afforded the tosylate (112 mg, 94%) as a colorless glass IR ($CHCl_3$) 2960 (s), 2930 (s), 2860 (m), 1615 (w), 1515 (s), 1465 (m), 1365 (s), 1250 (s), 1175 (s), 1095 (s), 1035 (s), 960 (s), 835 (s), 655 (m) cm^{-1}, ^1H NMR (250 MHz, C_6D_6) δ 7 62 (d, J = 8 3 Hz, 2H), 7 08 (d, J = 8 3 Hz, 1H), 6 83 (d, J = 8 3 Hz, 1H), 6 69 (s, 1H), 6 64 (d, J = 8 1 Hz, 2H), 6 59 (app s, 4H), 5 10 (app s, 2H), 4 77 (ABq, J = 7 4, Δν = 7 3 Hz, 2H), 4 21 (app t, J = 6 1 Hz, 1H), 3 95-3 79 (m, 2H), 3 38 (s, 3H), 3 24 (s, 3H), 3 34-3 21 (m, 3H), 3 11 (dd, J = 3 5, 16 0 Hz, 1H), 2 65 (app t, J = 8 3 Hz, 1H), 2 39-2 18 (m, 3H), 2 07-1.85 (m, 3H), 1 85 (s, 3H), 1 21 (app s, 6H), 1 18 (s, 3H), 1 17 (s, 3H), 0 95 (s, 9H), -0 08 (s, 3H), -0 10 (s, 3H), chemical ionization mass spectrum, *m/e* 804 4394 (M+H calcd for $C_{46}H_{68}NO_7SSI$, 804 4329)

Camphorsulfonic acid (50 mg, 0 22 mmol) was added to a solution of the tosylate (150 mg, 0 187 mmol) in methanol (5 mL) The reaction was stirred at ambient temperature for 20 min and at 30-32°C for 5 5 h Pyridine (0 10 ml) was added and the methanol was evaporated *in vacuo* Flash column chromatography (hexanes/ether/methanol, 5.5 1) gave the diol (95 mg, 79%) as a slightly yellow glass IR ($CHCl_3$) 3600 (w), 3690-3260 (w), 3000 (m), 2970 (m), 2930 (m), 1615 (w), 1515 (s), 1357 (s), 1248 (s), 1175 (s), 960 (m), 655 (m) cm^{-1}, ^1H NMR (250 MHz, C_6D_6) δ 7 61 (d, J = 8.3 Hz, 2H), 7 02 (d, J = 8 3 Hz, 1H), 6 84 (d, J = 8 3 Hz, 1H), 6 76 (s, 1H), 6 64 (d, J = 8 2 Hz, 2H), 6 61 (d, J = 8 9 Hz, 2H), 6.55 (d, J = 8 9 Hz, 2H), 5 11 (app s, 2H), 4 03-3 84 (m, 3H), 3 21 (s, 3H), 3 17-3 14 (m, 3H), 2 92 (dd, J = 3 8, 15 4 Hz, 1H), 2 59-2 48 (m, 1H), 2 16 (app q, J = 9.4 Hz, 1H), 2 05-1.88 (m, 4H), 1 84 (s, 3H), 1 75 (app dt, J = 5 3, 10 3 Hz, 1H), 1 42 (br s, 1H), 1 21 (s, 3H), 1 18 (s, 3H), 1 17 (s, 3H), 1 15 (s, 3H), 0 78 (br s, 1H), chemical ionization mass spectrum, *m/e* 646 3177 (M+H calcd for $C_{39}H_{48}NO_6S$, 646 3202)

A 25 mL RB flask containing a mixture of the diol (44 mg, 0 068 mmol) and sodium bicarbonate (20 mg, 0 24 mmol) in DMSO (1 5 mL) was submerged in a 155°C oil bath for 10 min while stirring The reaction was allowed to cool, and extractive aqueous work-up and flash column chromatography (hexanes/ether/methanol, 1 1 0 → 5 5 1) gave the aldehyde (39, 23 mg, 70%) as a colorless glass IR ($CHCl_3$) 3605 (w), 3670-3220 (w), 3005 (s), 2970 (s), 2930 (s), 1722 (s), 1615 (w), 1515 (s), 1250 (s), 1175 (m), 1035 (m) cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 9 48 (app t, J = 2 8 Hz, 1H), 6 90 (d, J = 8 3 Hz, 1H), 6.83 (d, J = 8 3 Hz, 1H), 6 78 (app s, 4H), 6 51 (s, 1H), 5 50 (app s, 2H), 3 83 (app t, J = 8 6 Hz, 1H), 3 74 (s, 3H), 3 29 (d, J = 6 8 Hz, 1H), 3 26 (d, J = 8 3 Hz, 1H), 3 15 (1/2 ABX, J_{AB} = 15 5, J_{AX} = 4 7 Hz, 1H), 2 81 (1/2 ABX, J_{BA} = 15 5, J_{BX} = 4 0 Hz, 1H), 2 67 (d, J = 2 5 Hz, 1H), 2 66 (d, J = 2 4, 1H), 2 65-2 53 (m, 1H), 2 32-2 04 (m, 3H), 1 92 (app dt, J = 4 9, 9 9 Hz, 1H), 1 52 (app s, 6H), 1 31 (s, 3H), 1 21 (s, 3H), chemical ionization mass spectrum, *m/e* 490 2943 (M+H calcd for $C_{31}H_{40}NO_4$, 490.2957)

Oxocane 41 A solution of aldehyde **39** (44 mg, 0 090 mmol) in THF/acetic acid (2 mL, 1 1, v/v) was treated with dimethylamine (0 10 mL, 40 wt % aqueous solution, 0 89 mmol) and stirred at ambient temperature for 5 5 h The reaction mixture was concentrated *in vacuo* from toluene (2 x 10 mL) Flash column chromatography (hexanes/ethyl acetate, 3:2) gave the oxocane (37 mg, 87%) as a colorless glass Concentration of an ether/hexanes solution of **41** provided the compound as an amorphous solid m p 101 0-105 0°C, IR ($CHCl_3$) 3620 (w), 3700-3280 (w), 3010 (m), 2965 (s), 2940 (s), 1620 (m), 1520 (s), 1455 (m), 1255 (s), 1180 (m), 1043 (s) cm^{-1}, ^1H NMR (500 MHz, C_6D_6) δ 7 01 (d, J = 8 3 Hz, 1H), 6 88 (d, J = 8 3 Hz, 1H), 6 75 (d, J = 8 5 Hz, 2H), 6 58 (d, J = 8 7 Hz, 2H), 5 34 (dd, J = 4 6, 7 4 Hz, 1H), 4 92 (ABq, J = 17 1 Hz, Δν = 9 4 Hz, 2H), 3 71 (app t, J = 9 1 Hz, 1H), 3 48 (1/2 ABX, J_{AB} = 10 6, J_{AX} = 4.3 Hz, 1H), 3 30 (1/2 ABX, J_{BA} = 10 2, J_{BX} = 6 7 Hz, 1H), 3 22 (s, 3H), 2 89 (dd, J = 2 7, 14 7 Hz, 1H), 2.80 (dd, J = 7.5, 13 4 Hz, 1H), 2 68 (app q, J = 9 3 Hz, 1H), 2 58 (dd, J = 4 5, 13 4 Hz, 1H), 2 45 (dd, J = 11 8, 14 4 Hz, 1H), 1 99 (app q, J = 9 2 Hz, 1H), 1 80-1 69 (m, 2H), 1 61 (app t, J = 10 8 Hz, 1H), 1 41 (s, 3H), 1 28 (s, 3H), 1 22 (s, 3H), 1 17 (s, 3H), 0 96 (br s, 1H), ^{13}C NMR (62 9 MHz, C_6D_6) δ 159 1, 151 4, 140 8, 130 5, 128 7, 127 3, 122 3, 122 2, 119 0, 114 2, 108 0, 74 9, 68 4, 66 0, 57 7, 54 6, 52 0, 47 1, 44 3, 39 0, 36 3, 32 3, 31 5, 29 5, 29 1, 28 7, 27 8, 18 2, λ_{max} (EtOH) 286 0 (ε 12,000), 280 8 (ε 12,000), 229 2 (ε 36,000) nm, chemical ionization mass spectrum, *m/e* 472 2821 (M+H calcd for $C_{31}H_{38}NO_3$, 472 2851) Anal. Calcd for $C_{31}H_{37}NO_3$ C, 78 95, H, 7 91, N, 2 97 Found C, 78 72, H, 7 86, N, 2 85

Aldehyde 43 Dicyclohexylcarbodiimide (246 mg, 1 19 mmol) was added to a solution of alcohol **34** (129 mg, 0 198 mmol), pyridine (0 088 mL, 1 1 mmol), and trifluoroacetic acid (0 042 mL, 0 55 mmol) in benzene/DMSO (3 mL, 1 1, v/v) After stirring at ambient temperature for 4 5 h, extractive aqueous work-up and flash column chromatography (hexanes/ether, 1 1) provided the aldehyde (113 mg, 88%) as a colorless glass IR ($CHCl_3$) 2965 (s), 2940 (s), 2860 (s), 1725 (s), 1615 (w), 1520 (s), 1470 (m), 1255 (s), 1095 (s), 1043 (s), 838 (s) cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) δ 9 45 (app t, J = 2 7 Hz, 1H), 6 89 (d, J = 8 3 Hz, 1H), 6.82 (d, J = 8 3 Hz, 1H), 6 75 (app s, 4H), 6 53 (s, 1H), 5 51 (app s, 2H), 4 75 (ABq, J = 7 2, Δν = 7 2 Hz, 2H), 3 86 (app t, J = 7 9 Hz, 1H), 3 74 (s, 3H), 3 42 (s, 3H), 3 22 (dd, J = 6 3, 9 8 Hz, 1H), 3 14-3 05 (m, 2H), 2 84 (dd, J = 3 4, 15 4 Hz, 1H), 2 65 (app d, J = 2 8 Hz, 2H), 2 60-2 48 (m, 1H), 2 31 (app q, J = 9 3 Hz, 1H), 2 22 (app dt, J = 7 5, 9 6 Hz, 1H), 2 14-2 02 (m, 1H), 1,87 (app dt, J = 5 4, 11 4 Hz, 1H), 1 52 (s, 3H), 1 50 (s, 3H), 1 27 (s, 3H), 1 24 (s, 3H), 0 84 (s, 9H), -0 11 (s, 3H), -0 12 (s, 3H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 202 2, 158 5, 143 7, 137 5, 131 7, 129 6, 126 6, 126 5, 125 2, 124 1, 114 0, 107 3, 99 6, 91 0, 76 8, 64 7, 55 0, 54 9, 53 9, 52 4, 47 9, 39 5, 34 1, 33 5, 30 0, 29 3, 29 1, 28 7, 25 9, 24 8, 23 9, 23 2, 18 2, -5 5, chemical ionization mass spectrum, *m/e* 647 4048 (M^+ calcd for $C_{39}H_{57}NO_5Si$, 647 4006)

Preparation of 41 by Cyclization of 43 A solution of aldehyde **43** (127 mg, 0 196 mmol) in methanol (13 mL) was degassed with argon for 2 h at ambient temperature A solution of (1*S*)-(+)-10-camphorsulfonic acid (2 24 mL, 0 52 M in methanol, 1 2 mmol) was added, and the reaction was stirred at ambient temperature for 3 h Addition of toluene (15 mL) followed by concentration under reduced pressure (water bath at ambient temperature, 20 min) gave a bright blue mixture Pyridine (0 5 mL) was added, and all volatiles were evaporated *in vacuo* Flash column chromatography (petroleum ether/ethyl acetate, 3 7) gave the oxocane (56 mg, 61%) as a colorless glass Concentration of an ether/hexanes solution of **41** gave an amorphous solid identical with material obtained from exposure of **39** to Mannich conditions (*vide supra*)

Bromide 42 *N*-Bromosuccinamide (125 mg, 0 070 mmol) was added to a mixture of indole **41** (33 mg, 0 070 mmol) and sodium acetate (11 mg, 0 13 mmol) in acetonitrile (2 mL) at 0°C The reaction was stirred at 0°C for 30 min Pyridine (10 mL) was added and the mixture was concentrated *in vacuo* Flash column chromatography (hexanes/ethyl acetate, 4 1) afforded the bromide as a glass Crystallization from methylene chloride/hexanes gave colorless prisms (32 mg, 83%)

m p 178 5-182 5°C, IR ($CHCl_3$) 3620 (w), 3600-3300 (w), 2960 (s), 2930 (s), 1615 (m), 1515 (s), 1465 (s), 1250 (s), 1040 (s), 830 (m) cm^{-1}, ^1H NMR (500 MHz, C_6D_6) δ 7 45 (s, 1H), 6 73 (d, J = 8 7 Hz, 2H), 6 60 (d, J = 8 7 Hz, 2H), 5 28 (dd, J = 4 7, 7 5 Hz, 1H), 4 80 (ABq, J = 16 8, Δν = 20 2 Hz, 2H), 3 63 (app t, J = 9 1 Hz, 1H), 3 50 (1/2 ABX, J_{AB} = 15 5, J_{AX} = 3 1 Hz, 1H), 3 46 (1/2 ABX, J_{AB} = 10 6, J_{AX} = 4 3 Hz, 1H), 3 34 (1/2 ABX, J_{BA} = 10 3, J_{BX} = 6 4 Hz, 1H), 3 25 (s, 3H), 2 76 (1/2 ABX, J_{AB} = 13 3, J_{AX} = 7 5 Hz, 1H), 2 68 (app q, J = 9 5 Hz, 1H), 2 54 (1/2 ABX, J_{BA} = 13 3, J_{BX} = 4 7 Hz, 1H), 2 34 (1/2 ABX, J_{BA} = 15 1, J_{BX} = 11 8 Hz, 1H), 2 01 (app q, J = 9 3 Hz, 1H), 1 73-1 63 (m, 2H), 1 60 (app t, J = 10 2 Hz, 1H), 1 41 (s, 3H), 1 25 (s, 3H), 1 22 (s, 3H), 1 14 (s, 3H), 0 76 (br s, 1H), ^{13}C NMR (62 9 MHz, C_6D_6) δ 159 3, 152 1, 140 8, 132 5, 129 9, 127 2, 121 6, 119 1, 118 0, 114 3, 111 8, 74 9, 68 2, 65 5, 57 5, 54 6, 51 8, 47 0, 43 8, 39 0, 36 8, 32 0, 31 2, 29 3, 28 8, 28 7, 27 4, 18 2, λ_{max} (EtOH) 292 4 (ε 9,400), 285 6 (ε 9,200), 230 8 (ε 34,000), 205s (ε 23,000) nm, chemical ionization mass spectrum, *m/e* 551 1840 (M^+ calcd for $C_{31}H_{36}NO_3Br$, 551 1859) Anal. Calcd for $C_{31}H_{36}NO_3Br$ C, 67 63, H, 6 59, N, 2 54 Found C, 67 46, H, 6 66, N, 2 48

Phenol 44 and Indole 45 Indole 41 was demethylated according to the conditions of Feutrill and Mirrington [45a] Thus, ethanethiol in DMF (0 34 mL, 1 1, v/v, 2 3 mmol) was added dropwise to a suspension of sodium hydride (70 mg, 80% dispersion in mineral oil, 2 3 mmol) in DMF (3 mL) This mixture was stirred for 15 min, and a solution of indole 41 (24 mg, 0 051 mmol) in DMF (2 mL) was then added in one portion The reaction was heated (150°C bath) for 1 h After cooling, extractive aqueous work-up and flash column chromatography (hexanes/ethyl acetate, 3 1 → 1 1) gave, in order of elution, free indole 45 (1 6 mg, 8 9%) as a colorless solid and *p*-hydroxybenzylated indole 44 (15 mg, 65%) as a colorless glass A different sample of 45 was crystallized from ethanol/toluene to afford prisms [(m p 243°C (dec)]

45 IR (KBr pellet) 3600-3100 (s), 2960 (s), 2930 (s), 2865 (s), 1475 (s), 1445 (s), 1385 (s), 1368 (s), 1315 (s), 1025 (s), 795 (m) cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) δ 7 64 (br s, 1H), 7 04 (d, J = 8 1 Hz, 1H), 6 87 (d, J = 8 2 Hz, 1H), 5 23 (dd, J = 5 2, 7 3, 1H), 3 78 (app dt, J = 4 8, 10 3 Hz, 1H), 3 76 (app t, J = 9 3 Hz, 1H), 3 60 (app dt, J = 6 5, 10 8 Hz, 1H), 2 83 (1/2 ABX, J_{AB} = 14 7, J_{AX} = 3 0 Hz, 1H), 2 73 (dd, J = 7 3, 13 2 Hz, 1H), 2.56 (app q, J = 9 6 Hz, 1H), 2 43 (1/2 ABX, J_{BA} = 14 6, J_{BX} = 11 9 Hz, 1H), 2 25-2 18 (m, 2H), 2 06-1 88 (m, 3H), 1 50 (s, 3H), 1 42 (s, 3H), 1 33 (app t, J = 5 6 Hz, 1H), 1 30 (s, 3H), 1 10 (s, 3H), ^{13}C NMR (62 9 MHz, DMSO-d_6) δ 151 7, 138 8, 129 1, 126 8, 121 4, 120 9, 116 8, 108 7, 74 4, 68 1, 64 1, 55 6, 51 7, 43 9, 37 6, 35 4, 31 7, 30 8, 29 5, 28 7, 28 2, 27 3, 18 0, λ_{max} (EtOH) 282 8 (ε 7,100), 227 6 (ε 24,000), 208 8 (ε 17,000) nm, chemical ionization mass spectrum, *m/e* 351 2186 (M^+ calcd for $C_{23}H_{29}NO_2$, 351 2198)

44 IR ($CHCl_3$) 3590 (w), 3600-3100 (m), 2970 (s), 2930 (s), 1620 (m), 1523 (s), 1460 (s), 1388 (s), 1371 (s), 1353 (s), 1342 (s), 1212 (s), 1175 (s), 1045 (s), 825 (m) cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) δ 6 76 (d, J = 8 5 Hz, 2H), 6 74 (app s, 2H), 6 54 (d, J = 8 5 Hz, 2H), 6 49 (br s, 1H), 5 23 (dd, J = 5 1, 7 3 Hz, 1H), 5 06 (app s, 2H), 3 72 (app t, J = 9 2 Hz, 1H), 3 69 (dd, J = 4 3, 10 9 Hz, 1H), 3 49 (dd, J = 7 1, 10 7 Hz, 1H), 2 74-2 68 (m, 2H), 2 55 (app q, J = 9 4 Hz, 1H), 2 34 (dd, J = 11 9, 14 2 Hz, 1H), 2 25 (dd, J = 5 0, 13 4 Hz, 1H), 2 13 (app q, J = 9 5 Hz, 1H), 1 93 (app q, J = 9 5 Hz, 2H), 1 82 (app t, J = 10 4 Hz, 2H), 1 48 (s, 3H), 1 29 (s, 3H), 1 17 (s, 3H), 1 10 (s, 3H), ^{13}C NMR (125 8 MHz, $CDCl_3$) δ 155 1, 151 7, 140 0, 129 6, 129 4, 127 6, 127 2, 121 8, 121 1, 117 6, 115 5, 107 6, 75 5, 68 2, 66 1, 56 8, 51 5, 47 0, 43 6, 38 8, 35 7, 31 6, 31 2, 29 6, 28 3, 28 1, 27 6, 18 2, chemical ionization mass spectrum, *m/e* 457 2629 (M^+ calcd for $C_{30}H_{35}NO_3$, 457 2617)

Preparation of 45 by Fragmentation of 44 A mixture of indole 44 (60 mg, 0 13 mmol) and potassium bicarbonate (100 mg, 1 00 mmol) in DMF (5 mL) was heated at reflux for 2 h Extractive aqueous work-up and flash column chromatography (hexanes/ethyl acetate, 13 7) afforded free indole 45 (29 mg, 63%) as a colorless glass Crystallization from ethanol/toluene gave material identical with that obtained from the preceding reaction

Selenide 46 Alcohol 45 was converted to the corresponding *o*-nitrophenyl selenide according to the conditions of Grieco et al [46] Thus, tri-*n*-butylphosphine (0 030 mL, 0 12 mmol) was added to a solution of alcohol 45 (29 mg, 0 083 mmol) and *o*-nitrophenyl selenocyanate[47] (28 mg, 0 12 mmol) in THF (3 mL) at 0°C The reaction was stirred at 0°C for 10 min and at ambient temperature for 20 min Additional portions of *o*-nitrophenyl selenocyanate (14 mg, 0 060 mmol) and tri-*n*-butylphosphine (0 015 mL, 0 060 mmol) were then added, and the reaction mixture was stirred an additional 15 min One drop of methanol was added, and the solution was concentrated *in vacuo* Flash column chromatography (hexanes/ether, 3 2) afforded the selenide (42 5 mg, 96%) as a yellow glass Crystallization from methylene chloride/hexanes gave bright yellow prisms m p 173 5-179 5°C, IR ($CHCl_3$) 3480 (m), 3500-3240 (w), 3010 (m), 2960 (s), 2925 (s), 1520 (s), 1335 (s), 1305 (s), 1222 (s), 1035 (s) cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) δ 8 27 (dd, J = 1 4, 8 3 Hz, 1H), 7 73 (br s, 1H), 7 58 (dd, J = 1 3, 8 1 Hz, 1H), 7 50 (app dt, J = 1 4, 7 0 Hz, 1H), 7 29 (ddd, J = 1 4, 7 0, 8 4 Hz, 1H), 7 01 (d, J = 8 3 Hz, 1H), 6 84 (d, J = 8 2 Hz, 1H), 5 23 (dd, J = 5 2, 7 3 Hz, 1H), 3 79 (app t, J = 9 1 Hz, 1H), 3 19 (1/2 ABX, J_{AB} = 11 5, J_{AX} = 4 3 Hz, 1H), 2 97 (dd, J = 2 8, 14 7 Hz, 1H), 2 88 (1/2 ABX, J_{BA} = 11 5, J_{BX} = 8 5 Hz, 1H), 2 73 (1/2 ABX, J_{AB} = 13 3, J_{AX} = 7 4 Hz, 1H), 2 53 (app q, J = 9 2 Hz, 1H), 2 51 (d, J = 14 6 Hz, 1H), 2 31 (app q, J = 8 6 Hz, 1H), 2 21 (1/2 ABX, J_{BA} = 13 4, J_{BX} = 5 2 Hz, 1H), 2 16-2 08 (m, 1H), 2 07 (app dq, J = 2 7, 9 8 Hz, 1H), 1 97 (app dt, J = 1 5, 9 7 Hz, 1H), 1 50 (s, 3H), 1 38 (s, 3H), 1 28 (s, 3H), 1 11 (s, 3H), ^{13}C NMR (62 9 MHz, $CDCl_3$) δ 151 7, 147 0, 139 0, 133 9, 133 5, 129 1, 129 0, 127 4, 126 5, 125 3, 121 8, 118 2, 108 8, 75 0, 68 5, 55 8, 51 4, 40 2, 38 1, 36 4, 35 7, 35 1, 31 5, 29 8, 28 2, 27 8, 18 1, λ_{max} (EtOH) 395 6 (ε 4,500), 276 0 (ε 19,000), 258 4 (ε 20,000), 228 4 (ε 41,000), 212s (ε 36,000) nm, chemical ionization mass spectrum, *m/e* 536 1612 (M^+ calcd for $C_{29}H_{32}N_2O_3Se$, 536 1578) Anal. Calcd for $C_{29}H_{32}N_2O_3Se$ C, 65 04, H, 6 02, N, 5 23 Found C, 64 98, H, 6 06, N, 5 03

Olefin 23 *m*-Chloroperoxybenzoic acid (13 mg, 0 075 mmol) was added in one portion to a solution of selenide 46 (39 mg, 0 073 mmol) and 2,4,6-collidine (0 15 mL, 1 1 mmol) in CH_2Cl_2 (5 mL) at 0°C The oxidation was stirred at ambient temperature for 10 min, then diluted to 25 mL and stirred a further 22 h Concentration *in vacuo* and flash column chromatography (hexanes/ethyl acetate, 9 1 → 4 1) gave the olefin (16 8 mg, 69%) as a colorless solid Crystallization from ether/methylene chloride/hexanes gave analytically pure prisms mp 187°C (dec), IR ($CHCl_3$) cm^{-1}, ^1H NMR (500 MHz, acetone-d_6) δ 9 79 (br s, 1H), 7 02 (d, J = 8 2 Hz, 1H), 6 73 (d, J = 8 3 Hz, 1H), 5 21 (dd, J = 4 5, 7 5 Hz, 1H), 4 99 (d, 1 8 Hz, 1H), 4 79 (app t, 1 0 Hz, 1H), 3 91 (app t, J = 9 3 Hz, 1H), 3 41 (dd, J = 0 9, 14 7 Hz, 1H), 3 25 (d, J = 14 8 Hz, 1H), 3 12 (app tt, J = 1 2, 10 3 Hz, 1H), 2 71 (1/2 ABX, J_{AB} = 13 3, J_{AX} = 7 5 Hz, 1H), 2 27 (app q, J = 9 3 Hz, 1H), 2 21 (app dt, J = 2 7, 11 8 Hz, 1H), 2 12 (1/2 ABX, J_{BA} = 13 3, J_{BX} = 4 5 Hz, 1H), 2 11 (app dt, J = 9 2, 11 2 Hz, 1H), 1 51 (s, 3H), 1 36 (s, 3H), 1 30 (s, 3H), 1 02 (s, 3H), ^{13}C NMR (125 8 MHz, acetone-d_6) δ 152 7, 150 2, 140 4, 129 6, 127 9, 122 7, 121 3, 118 7, 110 1, 106 0, 75 0, 69 13, 69 08, 56 8, 53 1, 39 1, 38 7, 38 6, 34 8, 29 0, 28 7, 27 0, 18 2, λ_{max} (EtOH) 284 0 (ε 12,000), 222 4 (ε 34,000) nm, chemical ionization mass spectrum, *m/e* 333 2079 (M^+ calcd for $C_{23}H_{27}NO$, 333 2092) Anal. Calcd for $C_{23}H_{27}NO$ C, 82 84, H, 8 16, N, 4 20 Found C, 82 60, H, 8 14, N, 3 94

Selenide 47 Tri-*n*-butylphosphine (0 087 mL, 0 35 mmol) was added to a solution of alcohol **31** (64 mg, 0 17 mmol) and *o*-nitrophenyl selenocyanate[47] (83 mg, 0 37 mmol) in THF (5 mL) at 0°C The reaction was stirred at ambient temperature for 1 h, after which time methanol (13 drops) and chloroform (5 ml) were added, and the solution was concentrated *in vacuo* Flash column chromatography (hexanes/ethyl acetate, 13 7) gave a fraction (85 mg) containing the product Resubjection to flash column chromatography (hexanes/ether, 2:3) afforded the selenide (79 mg, 83%) as a bright yellow glass IR ($CHCl_3$) 3590 (w), 3590-3300 (w), 3010 (m), 2970 (s), 2930 (s), 1515 (s), 1337 (s), 1307 (s), 1210 (s), 1080 (s) cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 8 254 (d, J = 8 3 Hz, 1H), 8 249 (d, J = 8.3 Hz, 1H), 7 40 (app tt, J = 1 4, 8 2 Hz, 2H), 7 32 (d, J = 7 3 Hz, 2H), 7 28-7 20 (m, 4H), 6 98 (d, J = 8 2 Hz, 2H), 6 22 (s, 1H), 6 19 (s, 1H), 5 63-5 59 (m, 2H), 3 92-3 84 (m, 2H), 3 52 (s, 3H), 3 51 (s, 3H), 3 33 (dd, J = 4 3, 15 3 Hz, 2H), 2 97 (d, J = 15 5 Hz, 2H), 2 76 (app q, J = 5 4 Hz, 2H), 2 58 (app d, J = 7 2 Hz, 4H), 2 54 (dd, J = 5 9, 13 4 Hz, 1H), 2 53 (dd, J = 5 9, 13 4 Hz, 1H), 2 38 (d, J = 13 3 Hz, 2H), 2 30-2 10 (m, 6H), 1 99-1 87 (m, 2H), 1 52 (s, 3H), 1 51 (s, 3H), 1 45 (s, 2H), 1 40 (s, 6H), 1 30 (s, 3H), 1 28 (s, 3H), 1 20 (s, 3H), 1 18 (s, 3H), chemical ionization mass spectrum, *m/e* 568 1846 (M^+ calcd for $C_{30}H_{36}N_2O_4Se$, 568 1840)

Preparation of 46 by Cyclization of 47 Camphorsulfonic acid (5 mg, 0 02 mmol) was added to a solution of selenide anomers **47** (37 mg, 0 065 mmol) in benzene (2 mL) The reaction was stirred at ambient temperature for 50 min, after which time it was diluted with benzene (8 mL) and a second portion of camphorsulfonic acid (100 mg, 0 43 mmol) was added The mixture was stirred at ambient temperature for a further 40 min and at 70°C (bath temperature) for 30 min *N*-Ethyldiisopropylamine (0 20 mL) was then added, and the mixture was subjected to flash column chromatography (hexanes/ether, 3 2) to afford selenide **46** (22 6 mg, 65%) The product was crystallized from ether to provide material identical with that obtained from the selenylation of alcohol **45** (*vide supra*)

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