Indole Diterpene Synthetic Studies. 8. The Total Synthesis of (+)-Paspalicine and (+)-Paspalinine

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Abstract: The development of a unified synthetic strategy for the indole diterpene tremorgens has led to the first total synthesis of (+)-paspalicine (**2**) and (+)-paspalinine (**3**), in 22 and 23 steps, respectively. The cornerstone of the approach is the intermediacy of (−)-**20**; this proposed common precursor to the simple indole diterpenes was generated in nine steps from (+)-Wieland–Miescher ketone (**26**) in our earlier synthesis of (−)-paspaline (**1**). Key transformations include installation of the indole unit via the Gassman protocol, alkylation of the thermodynamic anion of dimethylhydrazone **74** with epoxide (−)-**24**, and $RhCl_3$-promoted isomerization of the β,γ-unsaturated ketone in (+)-**81** to afford (+)-paspalicine (**2**). (+)-Paspalinine (**3**) in turn was secured via SeO_2 oxidation of **2**, a particularly noteworthy result given the importance of the C(4b) hydroxyl group for tremorgenic activity. MM2 calculations revealed that **2** and **3** embody the less stable relative configuration of the F- and G-ring bicyclic ketal moiety.

The indole diterpenes comprise an important class of architecturally complex, biologically significant fungal metabolites (Figure 1). All but the simplest examples (i.e., **1** and **2**) induce tremors in animals,[1] and recent work has revealed potent insecticidal activity against common crop pests.[2] Paspaline (**1**),[3] paspalicine (**2**),[3] paspalinine (**3**),[1b,4] and the paspalitrems (**6–8**)[1b,5] derive from the fungus *Claviceps paspali*; **3** and **6–8** cause the Paspalum staggers, a livestock syndrome associated with feeding on ergotized *Paspalum* grass.[1b] Whereas dehydroxypaxilline[6] (**4**) has not yet been subjected to biological screening, the C(4b)-hydroxy congener paxilline (**5**) acts both as a tremorgen and an insecticide.[2a,c,7] Paxilline also appears to serve as a pivotal biosynthetic precursor of more complex tremorgens including the penitrems (**10–15**),[8] janthitrems (**17–19**),[9] and lolitrem B (**16**).[1a,10]

Pursuant to our long-standing interest in the development of unified synthetic strategies, we have undertaken a program aimed initially at construction of the simple indole diterpenes—paspaline (**1**), paspalicine (**2**), paspalinine (**3**), dehydroxypaxilline (**4**), and paxilline (**5**)—from a tricyclic common intermediate (**20**, Scheme I).[11] Importantly, bioassay of synthetic intermediates and analogues may also facilitate identification of the pharmacophore responsible for tremorgenic activity. In 1988, we recorded a second-generation scheme for elaboration of **20** to the inactive biosynthetic intermediate (−)-paspaline (**1**).[11c-e] We now describe in detail the first total syntheses of (+)-paspalicine (**2**) and (+)-paspalinine (**3**).[11g] This venture, which constitutes the first synthesis of a biologically active indole diterpene tremorgen (i.e., **3**), also demonstrates the flexibility of our unified strategy and sets the stage for ongoing efforts directed toward **4**, **5**, and more complex tremorgens including the penitrems.

Retrosynthetic Analysis. We envisioned construction of the four remaining simple indole diterpenes from advanced intermediate **21**, as outlined in Scheme I. Specifically, paspalicine (**2**) would arise via oxidation of the secondary hydroxyl in **21** and olefin isomerization. For paspalinine (**3**) two scenarios were contemplated: the first involved epoxidation of **21**, oxidation to the ketone, and epoxide ring opening, whereas the second entailed direct allylic oxidation of the enone moiety in paspalicine. Dehydroxypaxilline (**4**) would derive from reductive cleavage of the bicyclic ketal of **2**. Finally, paxilline (**5**) could be secured by elaboration of dehydroxypaxilline or paspalinine or alternatively via reduction of the ketal in **21** followed by the three-step sequence proposed for conversion of **21** to **3**.

The key advanced intermediate **21** would arise via intramolecular ketalization upon deprotection of the diol unit of **22**, with correct relative stereochemistry controlled by the configuration at C(14). Disconnection of the side chain from ring **E** then affords indole **23** and epoxide **24**; in the synthetic direction, coupling via the Stork metalloenamine procedure was envisioned.[12] Epoxide **24** would ultimately derive from Sharpless asymmetric epoxidation of 3-methyl-2-buten-1-ol (**25**), whereas elaboration of the indole

(1) (a) Gallagher, R. T.; White, E. P.; Mortimer, P. H. *N. Z. Vet. J.* **1981**, *29*, 189. (b) Cole, R. J.; Dorner, J. W.; Lansden, J. A.; Cox, R. H.; Pape, C.; Cunfer, B.; Nicholson, S. S.; Bedell, D. M. *J. Agric. Food. Chem.* **1977**, *25*, 1197.

(2) (a) Dowd, P. F.; Cole, R. J.; Vesonder, R. F. *J. Antibiot.* **1988**, *41*, 1868. (b) Prestridge, R. A.; Gallagher, R. T. *Proc. N. Z. Weed Pest Control Conf.* **1985**, *38*, 38. (c) Gallagher, R. T.; Prestridge, R. A. *Proceedings of the International Symposium on Acremonium Grass Interactions*; Quisenberry, S., Joost, R. E., Eds.; Baton Rouge, 1990; pp 80–82. (d) Prestridge, R. A.; Gallagher, R. T. *Ecol. Entomol.* **1988**, *13*, 429.

(3) (a) Fehr, T.; Acklin, W. *Helv. Chim. Acta* **1966**, *49*, 1907. (b) Springer, J. P.; Clardy, J. *Tetrahedron Lett.* **1980**, 231.

(4) Gallagher, R. T.; Finer, J.; Clardy, J.; Leutwiler, A.; Weibel, F.; Acklin, W.; Arigoni, D. *Tetrahedron Lett.* **1980**, 235, and references cited therein.

(5) Dorner, J. W.; Cole, R. J.; Cox, R. H.; Cunfer, B. M. *J. Agric. Food. Chem.* **1984**, *32*, 1069.

(6) Nozawa, K.; Nakajima, S.; Kawai, K.; Udagawa, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2607.

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(8) (a) Wilson, B. J.; Wilson, C. H.; Hayes, A. W. *Nature* **1968**, *220*, 77. (b) de Jesus, A. E.; Steyn, P. S.; van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Chem. Commun.* **1981**, 289. (c) de Jesus, A. E.; Steyn, P. S.; van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1847. (d) de Jesus, A. E.; Steyn, P. S.; van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Perkin Trans 1* **1983**, 1857.

(9) (a) Gallagher, R. T.; Latch, G. C. M.; Keogh, R. G. *Appl. Environ. Microbiol.* **1980**, *39*, 272. (b) de Jesus, A. E.; Steyn, P. S.; van Heerden, F. R.; Vleggaar, R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 697.

(10) Gallagher, R. T.; Hawkes, A. D.; Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1984**, 614.

(11) For contributions 1–7 in this series, see: (a) Smith, III, A. B.; Mewshaw, R. *J. Am. Chem. Soc.* **1985**, *107*, 1769. (b) Mewshaw, R. E.; Taylor, M. D.; Smith, III, A. B. *J. Org. Chem.* **1989**, *54*, 3449. (c) Smith, III, A. B.; Leenay, T. L. *Tetrahedron Lett.* **1988**, *29*, 2787. (d) Smith, III, A. B.; Leenay, T. L. *Tetrahedron Lett.* **1988**, *29*, 2791. (e) Smith, III, A. B.; Leenay, T. L. *J. Am. Chem. Soc.* **1989**, *111*, 5761. (f) Smith, III, A. B.; Haseltine, J. L.; Visnick, M. *Tetrahedron* "Symposium in Print" **1989**, *45*, 2431. (g) Preliminary communication: Smith, III, A. B.; Sunazuka, T.; Leenay, T. L.; Kingery-Wood, J. *J. Am. Chem. Soc.* **1990**, *112*, 8197. For related studies, see: (h) Smith, III, A. B.; Visnick, M. *Tetrahedron Lett.* **1985**, *26*, 3757. (i) Smith, III, A. B.; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* "Symposium in Print" **1986**, *42*, 2957. (j) Haseltine, J. N.; Visnick, M.; Smith, III, A. B. *J. Org. Chem.* **1988**, *53*, 6160.

(12) (a) Stork, G.; Benaim, J. *J. Am. Chem. Soc.* **1971**, *93*, 5938. (b) Stork, G.; Benaim, J. *Org. Synth.* **1977**, *57*, 69; *Organic Synthesis*; Wiley: New York, 1988; Collect. Vol. VI, p 242.

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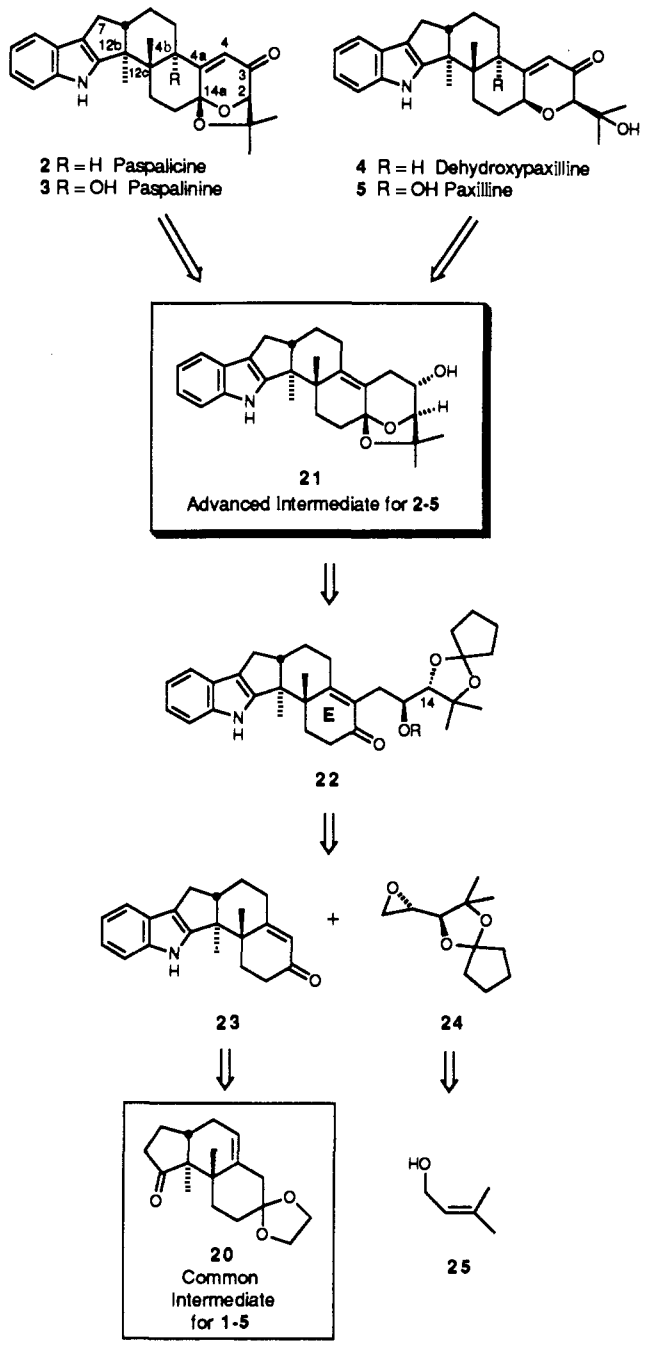
Scheme I



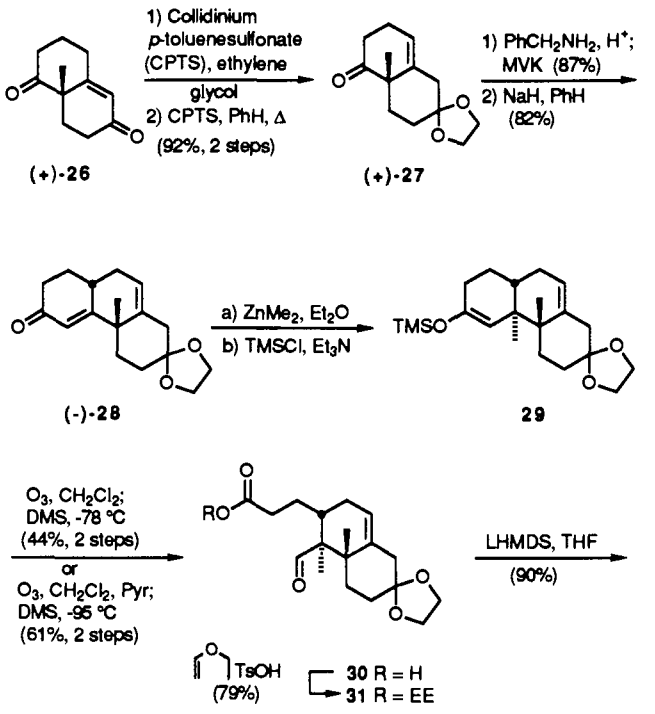
moiety would transform common intermediate (−)-**20** to **23**.

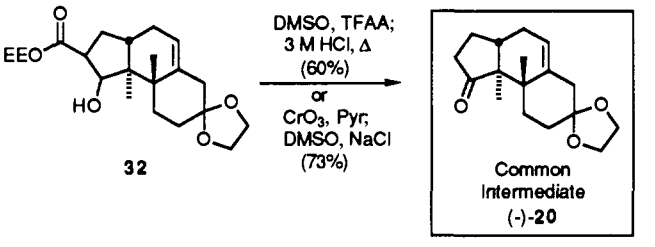
An Improved Synthesis of Common Intermediate 20. As implemented previously, the synthesis of (−)-**20** proceeded in nine steps (11% overall yield) from (+)-Wieland–Miescher ketone (**26**, Scheme II).[11e] Notwithstanding the efficiency of the basic approach, the production of large quantities of material was complicated by three problematic transformations: (1) selective ozonolysis of the enol ether moiety of **29** in the presence of the trisubstituted olefin, (2) oxidation of **32** to the corresponding β-keto ester, and (3) decarbalkoxylation of the latter intermediate.

The selectivity of the ozonolysis reaction improved markedly upon the inclusion of two equivalents of pyridine. Slomp and Johnson observed earlier that pyridine enhanced the discrimination among competing olefins in this process.[13] The reaction also was carried out at lower temperature (−90 vs −78 °C) with the aid of a mechanically refrigerated bath. In this fashion, the yield of carboxy aldehyde **30** was improved from 44% to 64%.

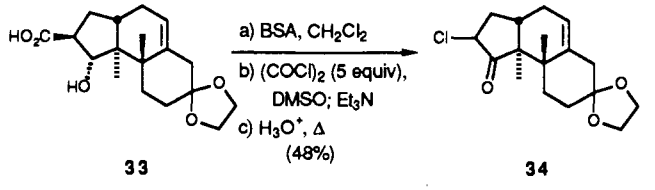
(13) Slomp, G., Jr.; Johnson, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 915.

Scheme II





Scheme III



We next focused our attention on the oxidation of alcohol **32**. The Swern procedure[14] proved incompatible with the resultant β-keto ester. In related experiments described earlier,[15] we observed that this reagent, derived from oxalyl chloride and dimethyl sulfoxide (DMSO), can effect electrophilic chlorination of enolizable carbonyl compounds. For example, addition of the trimethylsilyl ester derived from **33** to the preformed oxalyl chloride–DMSO complex, followed by acidification and mild warming to effect decarboxylation, afforded α-chloro ketone **34** exclusively in 48% yield (Scheme III).[15] The unexpected generation of **34** presumably involved reaction of the initially formed β-keto ester with base and excess oxidant. Indeed, treatment of the derived TMS ester of **33** with 1.05 equiv of oxalyl chloride and 2.5 equiv of DMSO afforded cyclopentanone **20** in 60% yield after decarboxylation, with no detectable chlorination.

The substitution of trifluoroacetic anhydride[16] for oxalyl chloride likewise produced an intriguing byproduct, α-methylenecyclopentanone **42**, admixed with the desired cyclopentanone **20** (ratio ca. 1:3). A possible pathway for the formation of **42** is shown

(14) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(15) Smith, III, A. B.; Leenay, T. L.; Liu, H.-J.; Nelson, L. A. K.; Ball, R. G. *Tetrahedron Lett.* **1988**, *29*, 49.
(16) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329.

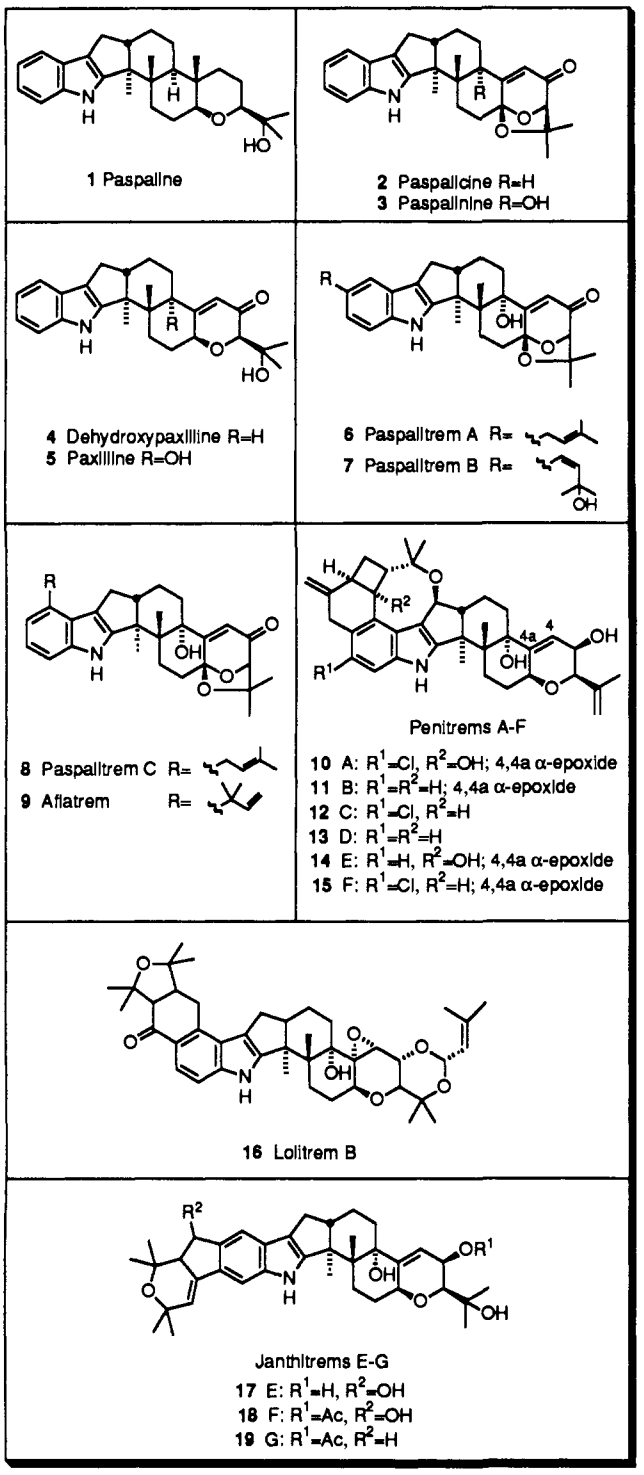
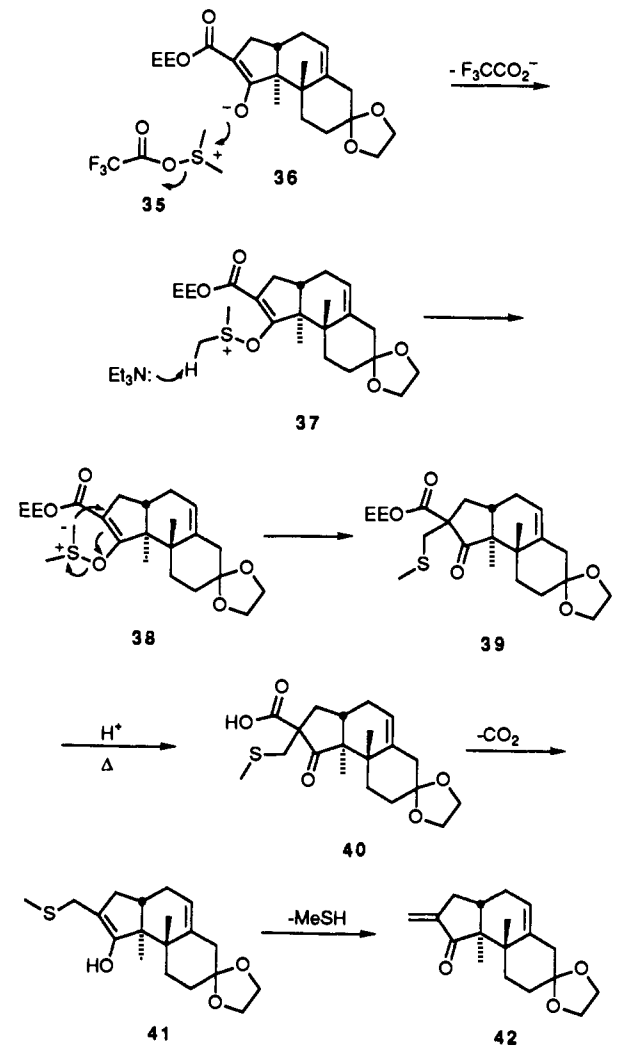


Figure 1. Structures of the indole diterpenes.

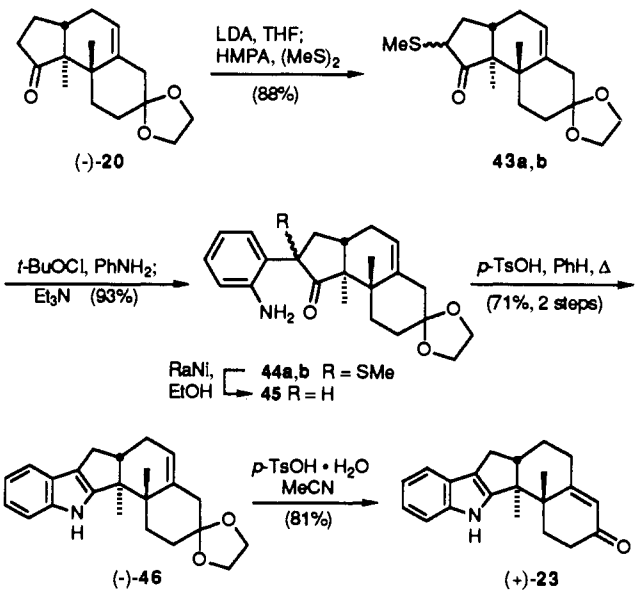
in Scheme IV. Reaction of the enolate of the derived β-keto ester (**36**) with excess oxidant **35** would generate sulfonium intermediate **37**. Deprotonation of the latter followed by 2,3-sigmatropic rearrangement would then give **39**. Upon heating to 70 °C in the presence of acid, ester hydrolysis and decarboxylation would furnish **41**. Finally, elimination of methanethiol would afford exomethylene **42**. The isolation of **39** would provide evidence to support the proposed sequence; however, in deference to our synthetic objectives, we did not pursue this possibility.

Further experiments established that Collins oxidation[17] of **32** consistently afforded superior results, furnishing (−)-**20** as the sole

Scheme IV



Scheme V



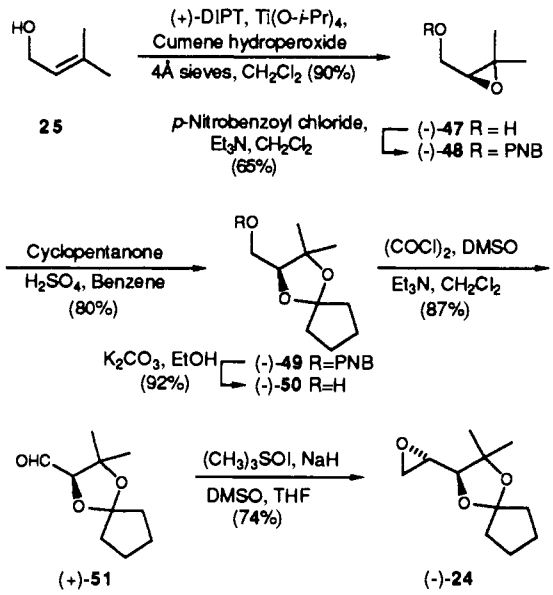
product in 73% overall yield after decarboxylation (Scheme II).

The final difficult step was decarbalkoxylation of the intermediate β-keto ester. Here the Krapcho procedure,[18] which entails exposure to sodium chloride in hot DMSO, proved highly satis-

(17) (a) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363. (b) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

(18) (a) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957. (b) For a review, see: Krapcho, A. P. *Synthesis* **1982**, 805, 893.

Scheme VI



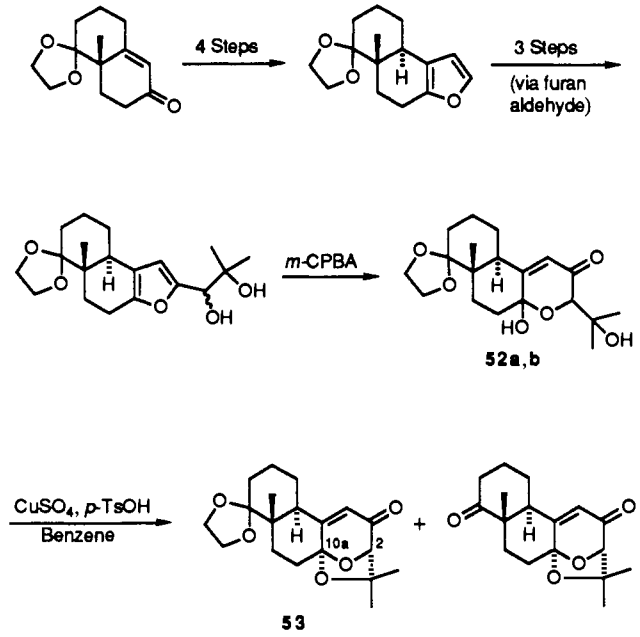
factory. These three enhancements of the original scheme increased the overall yield of (−)-**20** from 11% to 21%; moreover, the last three steps (i.e., **30** → **20**) could be carried out without purification of intermediates.

Execution of the Gassman Indole Protocol. Rings **A** and **B** were then installed via the Gassman indole protocol[19] (Scheme V), as in the earlier paspaline synthesis.[11b] To this end, deprotonation of common intermediate (−)-**20** with LDA at 0 °C, followed by addition of HMPA and dimethyl disulfide, furnished an inseparable mixture (ca. 1:1) of thiomethyl ketones **43a,b** in 88% yield. Treatment with *N*-chloroaniline and exposure of the resultant azasulfonium salt to triethylamine then gave the aniline derivatives **44a,b** (93%). Desulfurization with Raney nickel in ethanol at room temperature provided **45** in 82% yield, whereupon acid-catalyzed cyclization (*p*-TsOH) afforded indole ketal (−)-**46** (87%). Finally, hydrolysis of the dioxolane moiety with *p*-TsOH·H_2O in acetonitrile generated the requisite enone (+)-**23** (81%). The overall yield for this five-step sequence was 47%.

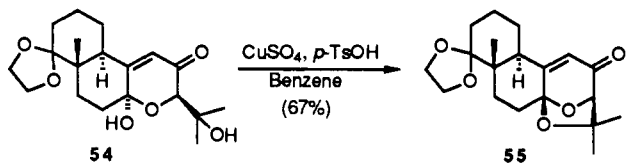
Stereoselective Synthesis of Epoxide (−)-24. With enone (+)-**23** in hand, we turned to the preparation of epoxide **24** (Scheme VI). Sharpless asymmetric epoxidation of 3-methyl-2-buten-1-ol (**25**) and protection of the resultant epoxy alcohol (−)-**47** as the *p*-nitrobenzoate ester furnished (−)-**48** in >95% ee after one recrystallization.[20] Acid-mediated ring opening of the epoxide with cyclopentanone generated the protected diol (−)-**49** in 80% yield. Debenzoylation with K_2CO_3 in ethanol followed by Swern oxidation then gave aldehyde (+)-**51** (80%, two steps). Corey methylenation[21] of the latter proceeded with excellent stereoselectivity to afford the desired epoxide (−)-**24** as a 98:2 mixture of diastereomers. As anticipated, the result was in accord with the Felkin–Anh transition-state model.[22] The antipode (+)-**24**, required for subsequent experiments (vide infra), was prepared in similar fashion by using D-tartrate in the Sharpless reaction.

MM2 Evaluation of the Bicyclic Ketal Stereochemistry: Enthalpic Preference for the Unnatural Configuration. In conjunction with the successful syntheses of enone (+)-**23** and epoxide (−)-**24**, we also explored the elaboration of the **D–G** rings of paspalicine and paspalinine in a model study (vide infra). In 1989, while these efforts were underway, Saxton et al. described an alternative approach to the paspalicine **D–G** rings (Scheme VII).[23] In the

Scheme VII



Scheme VIII



key step, treatment of the diastereomeric diols **52** with acid and copper(II) sulfate reportedly furnished a single bicyclic ketal **53**, accompanied by some deketalized material. Moreover, NOE studies suggested that **53** possessed the undesired 2*S*,10a*R* configuration.

In a followup study, Saxton has now demonstrated that cyclization of diol **54** actually furnishes the desired ketal **55** exclusively, in 67% yield (Scheme VIII).[24] The latter result, which supersedes their initial findings, is substantiated by single-crystal X-ray analyses of both **54** and **55**. Prior to this very recent disclosure, however, we were intrigued by the earlier report and the inauspicious suggestion that the unnatural ketal stereochemistry is thermodynamically preferred.

We elected to evaluate this possibility by calculating the enthalpy differences for pairs of diastereomeric ketals.[25] We first compared the paspalicine and paspalinine model compounds **56** and **57** (vide infra) with the corresponding α-linked ketals **58** and **59** (Figure 2). The computations were executed with the MM2 force field as supplied with version 2.5 of MACROMODEL.[26] For each structure, calculations were performed with two initial geometries, incorporating chair conformations for ring **D** and both chair and boat conformations for ring **E**. Each system was allowed to minimize until the gradient RMS was <0.01. Comparisons of the resultant energy minima revealed that the aberrant C(2,10a) diastereomers (**58** and **59**) are indeed favored thermodynamically vis-à-vis the paspalicine and paspalinine model systems (**56** and **57**); the corresponding enthalpies differed by 2.77 and 3.91 kcal/mol, respectively.

These remarkable results led us to evaluate paspalicine (**2**) and paspalinine (**3**) in similar fashion. Again the unnatural 2*S*,14a*R*

(19) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5495.
(20) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(21) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(22) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199, 2205. Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.
(23) Ali, A.; Saxton, J. E. *Tetrahedron Lett.* **1989**, *30*, 3197.
(24) Guile, S.; Saxton, J. E.; Thornton-Pett, M. *Tetrahedron Lett.* **1991**, *32*, 1381. Also see: Ali, A.; Guile, S. D.; Saxton, J. E.; Thornton-Pett, M. *Tetrahedron* **1991**, *47*, 6407.
(25) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
(26) Still, W. C.; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; DeGunst, F.; Hasel, W. Department of Chemistry, Columbia University, New York, NY 10027.

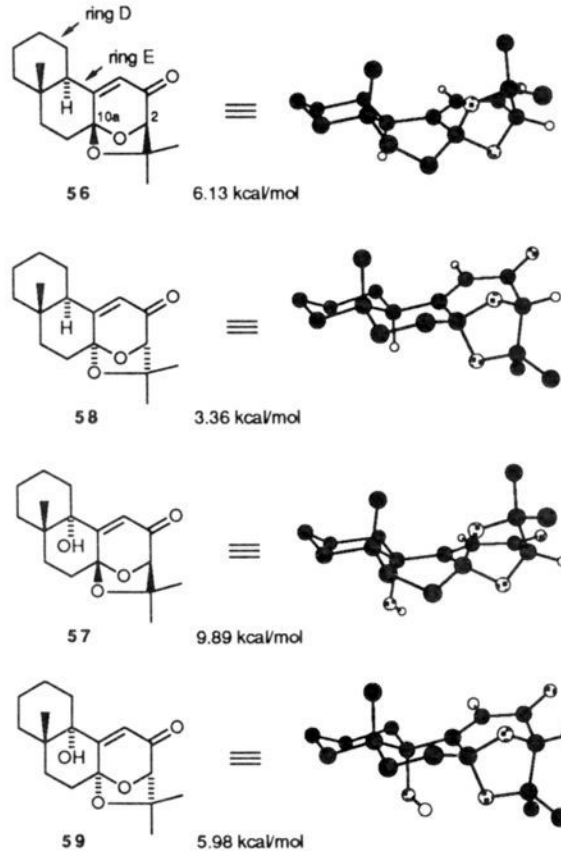


Figure 2. MM2 energy minima for model compounds **56** and **57** and ketal diastereomers **58** and **59**.

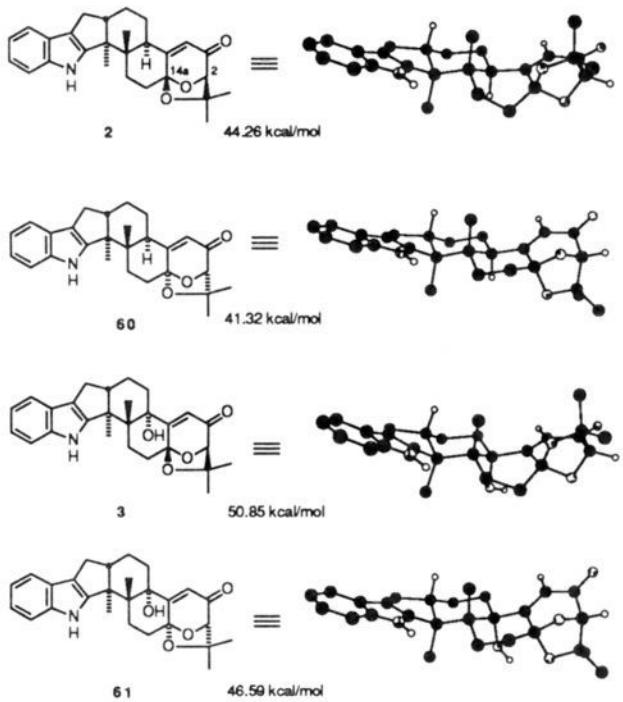
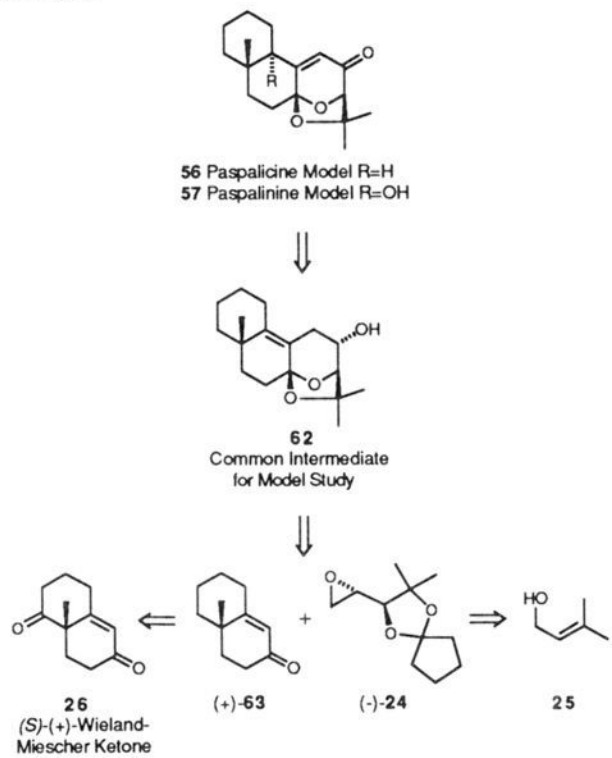


Figure 3. MM2 energy minima for paspalicine (**2**), paspalinine (**3**), and ketal diastereomers **60** and **61**.

stereochemistry of the bicyclic ketal moiety in **60** and **61** was strongly preferred; the energy differences for the paspalicine- and paspalinine-derived diastereomer pairs were 2.94 and 4.26 kcal/mol, respectively (Figure 3). Incorporation of the C(4b) α-hydroxyl increases the predicted energetic advantage of the unnatural stereochemistry for both the model and natural

Scheme IX



structures. The MM2 data strongly underscore the requirement for a stereocontrolled synthetic approach to the **F** and **G** rings of **2** and **3**. Ironically, the enthalpic preference for the undesired ketal configuration has been validated even though the experimental result that inspired our calculations proved to be spurious. Bioassay of unnatural diastereomers may elucidate the influence of bicyclic ketal stereochemistry upon the tremorgenic activity of paspalinine and its congeners.

Development of a Viable End-Game Protocol: Model Studies. In preparation for coupling of enone (+)-**23** with epoxide (−)-**24**, we investigated the construction of model compounds **56** and **57**, corresponding to the **D–G** rings in paspalicine (**2**) and paspalinine (**3**). This exercise was designed to facilitate refinement of our end-game strategy for the simple indoles and also to generate analogues for use in defining structure–activity relationships. To accommodate the latter studies, we employed optically active material in these investigations.

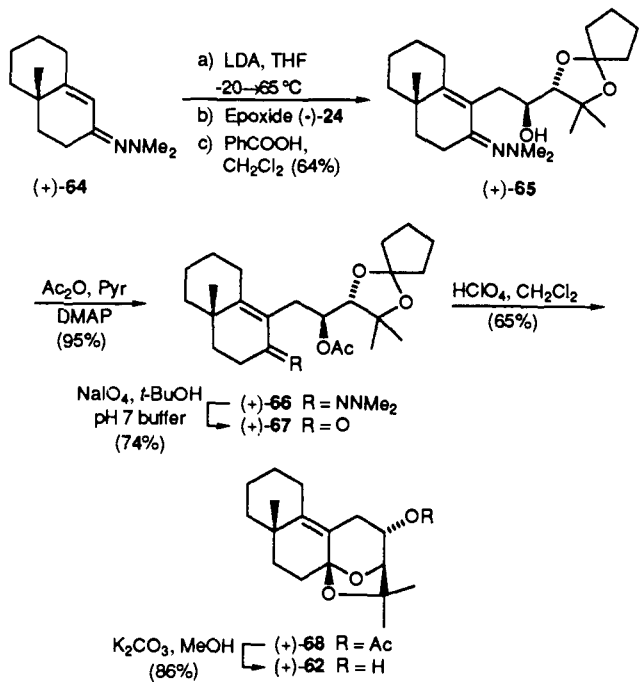
The synthetic plan for the model study is outlined in Scheme IX. Intermediate **62**, the tetracyclic analogue of **21**, would arise via union of enone (+)-**63** with epoxide (−)-**24**. The enone in turn would derive from (*S*)-(+)-Wieland–Miescher ketone (**26**).[27]

The Stork metalloenamine protocol,[12] designed to circumvent dialkylation at the α-position of an enone, appeared to be the method of choice for union of (−)-**24** and (+)-**63**. Indeed, the requisite dimethylhydrazone **64** had been successfully alkylated in this fashion.[12b] In the event, coupling of (+)-**64** with epoxide (−)-**24** (Scheme X) initially proved to be highly capricious. After considerable experimentation we found that rigorous exclusion of oxygen, as described in the Experimental Section, led to reproducible generation of the requisite alcohol in 60–65% yield as a mixture of double bond isomers. Brief exposure to benzoic acid then gave exclusively the α,β-isomer (+)-**65**, which was cleanly separated from the starting hydrazone (+)-**64** and epoxide (−)-**24** by flash column chromatography.

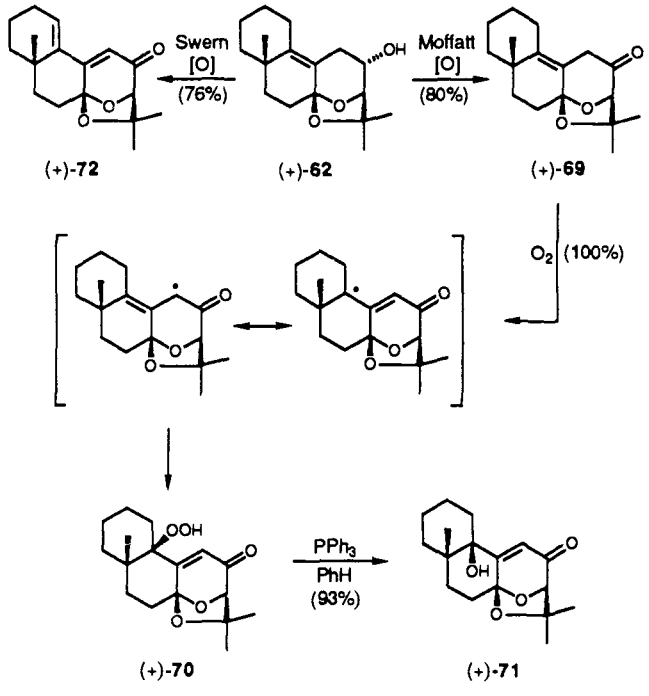
Acetylation of **65** furnished (+)-**66** in 95% yield (Scheme X). For removal of the hydrazone moiety we evaluated numerous

(27) For the synthesis of the enantiomer (−)-**63**, see: Pfau, M.; Revial, G.; Guingant, A.; d' Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273. For the resolution of (±)-**63**, see: Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021.

Scheme X

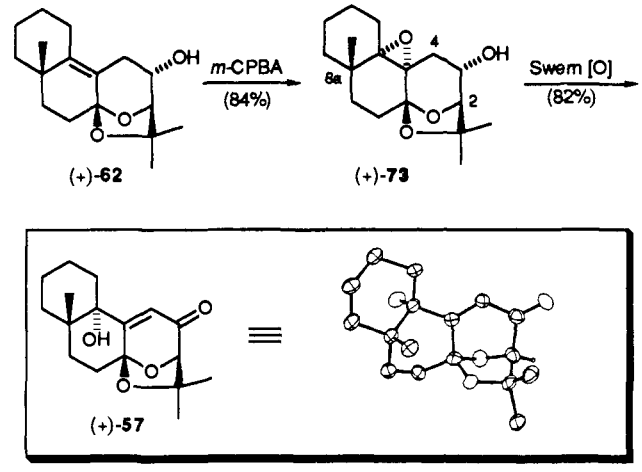


Scheme XI



reagents including $BF_3 \cdot Et_2O$,[28] methyl iodide,[29] and copper salts,[30] as well as acidic,[31] heterogeneous,[32] and oxidative[33] protocols. Best results were obtained by using Corey's sodium periodate method,[33] which produced (+)-**67** in 74% yield. Acid-catalyzed ketal hydrolysis and cyclization afforded the dioxabicyclooctane (+)-**68** (65%). Finally, deacetylation generated (+)-**62**, the proposed common intermediate for synthesis of the tetracyclic model compounds.

Scheme XII



Moffatt oxidation[34] of (+)-**62** afforded β,γ-unsaturated ketone (+)-**69** in 80% yield (Scheme XI). Remarkably, neither base (e.g., 1,8-diazabicyclo[4.3.0]undec-7-ene or Et_3N) nor rhodium chloride[35] isomerized the double bond of **69** into conjugation. Detailed investigation of these surprising results was deferred until the behavior of the real system could be explored; fortunately, the latter isomerization proceeded readily (vide infra). Model enone **69** did prove to be very susceptible to autoxidation, quantitatively affording hydroperoxide (+)-**70** within 48 h at 5 °C and much more rapidly at room temperature. Similar autoxidation of steroids has been attributed[36] to hydrogen atom abstraction followed by oxygenation of the resultant radical (cf., Scheme XI). Reduction of (+)-**70** with triphenylphosphine provided alcohol (+)-**71**, the C(4b) epimer of paspalinine analogue (+)-**57**. Swern oxidation of (+)-**62** unexpectedly produced dienone (+)-**72** (76%).

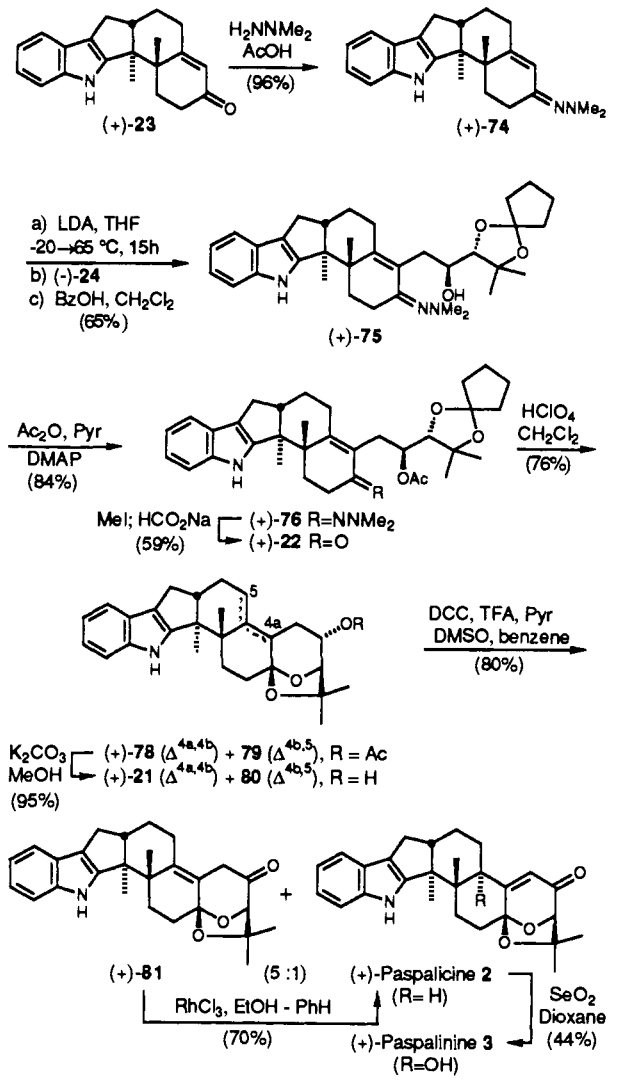
Elaboration of the second model system, paspalinine analogue **57**, proceeded uneventfully (Scheme XII). Stereocontrolled epoxidation of homoallylic alcohol (+)-**62** with *m*-chloroperbenzoic acid provided the desired α-epoxide (+)-**73** as the sole product; the selectivity presumably derived from the combined directing effects of the hydroxyl and C(8a) methyl groups. Swern or Moffatt oxidation with concomitant elimination and epoxide ring opening then furnished (+)-**57**. Single-crystal X-ray analysis confirmed that the paspalinine functionality had been installed with the requisite relative stereochemistry.

Total Synthesis of (+)-Paspalicine and (+)-Paspalinine. The model experiments greatly facilitated coupling of enone (+)-**23** with epoxide (−)-**24** (Scheme XIII). The enone was first converted to the corresponding dimethylhydrazone (+)-**74** in 96% yield. The optimized alkylation conditions developed earlier were then extended to the indole system; further refinement led to an extended metalation reaction time, and an additional equivalent of base was added to deprotonate the indole. This protocol afforded the requisite alcohol (+)-**75** in 65% yield (75% based on recovered starting material).

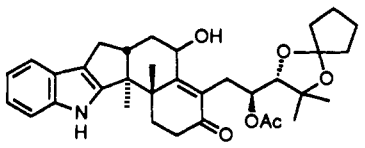
Acetylation of (+)-**75** furnished (+)-**76**. However, removal of the hydrazone moiety proved more difficult in this case; the sodium periodate method furnished (+)-**22** in only 45% yield. Superior results were obtained via quaternization with methyl iodide and hydrolysis of the derived salt with sodium formate in ethoxyethanol,[37] which afforded (+)-**22** as the major product (ca. 59% yield). A minor side product was tentatively identified as γ-hydroxy enone **77** via NMR analysis. Exposure of (+)-**22** to perchloric acid removed the cyclopentylidene moiety with con-

(28) (a) Gawley, R. E.; Termine, E. J. *Synth. Commun.* **1982**, *12*, 15. (b) Sacks, C. E.; Fuchs, P. L. *Synthesis* **1976**, 456.
(29) (a) Avaro, M.; Levisalles, J.; Rudler, H. *J. Chem. Soc., Chem. Commun.* **1969**, 445. (b) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, 7.
(30) Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 3667.
(31) Ballini, R.; Petrini, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2563.
(32) (a) Laszlo, P.; Polla, E. *Tetrahedron Lett.* **1984**, *25*, 3309. (b) For a general review, see: Cornelis, A.; Laszlo, P. *Synthesis* **1985**, 909.
(33) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3.
(34) (a) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661. (b) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670.
(35) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102.
(36) Nickon, A.; Mendelson, W. L. *J. Org. Chem.* **1965**, *30*, 2087.
(37) Stork, G.; Ponaras, A. A. *J. Org. Chem.* **1976**, *41*, 2937.

Scheme XIII



comitant cyclization to give a 2:1 mixture of bicyclic ketals (+)-**78** and **79**. Deacetylation followed by flash chromatography then led to alcohols (+)-**21** (67%) and **80** (28%).



77

Moffatt oxidation of advanced intermediate (+)-**21** furnished a 5:1 mixture of β,γ-enone (+)-**81** and paspalicine (**2**) in 80% yield. The former isomerized readily upon exposure to rhodium(III) chloride,[38] affording **2** as the sole product in 70% yield; alternatively, the crude mixture of **81** and **2** could be employed in the isomerization reaction. The total synthesis of (+)-paspalicine (**2**) thus entailed 22 steps and proceeded in 1.2% overall yield. The spectroscopic data and melting point for synthetic paspalicine were identical with those of the natural product.[39] The formulation of synthetic (+)-**2** was also verified by single-crystal X-ray analysis (Figure 4).

For the final elaboration of paspalinine, advanced intermediate (+)-**21** was initially subjected to epoxidation with *m*-CPBA as

(38) Clive, D. L. J.; Joussef, A. C. *J. Org. Chem.* **1990**, *55*, 1096.

(39) We thank Professor D. Arigoni of the Eidgenossichen Technischen Hochschule, Zurich, for generous samples of natural paspalicine and paspalinine.

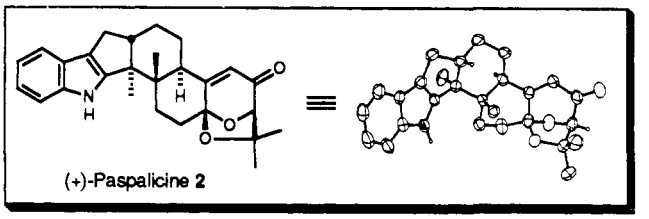
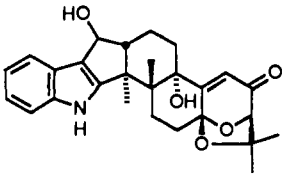


Figure 4. ORTEP drawing of synthetic (+)-**2**.

in the model study. Unfortunately, the 3 position of the indole underwent rapid oxidation (i.e., within 10 min), whereas the C(4a,4b) double bond was unaffected. Allylic oxidation of paspalicine (**2**) was next explored; exposure to selenium dioxide in dioxane generated two products in approximately equal amounts. Synthetic (+)-paspalinine (**3**), isolated in 44% yield, was indistinguishable from a sample of natural material. Structure **82** has been tentatively proposed for the second product on the basis of NMR and MS analysis. Introduction of the C(4b) hydroxyl in this fashion bodes well for the creation of bioactive analogues, as this moiety appears to play a major role in conferring tremorgenic activity.



82

Summary. The first total syntheses of (+)-paspalicine (**2**) and (+)-paspalinine (**3**) have been achieved via a unified strategy which previously furnished (−)-paspaline (**1**). Moreover, the overall yield for the nine-step conversion of (+)-Wieland–Miescher ketone to the common intermediate (−)-**20** was increased from 11% to 21%. The paspalinine venture comprises the initial construction of an active indole diterpene tremorgen. Bioassay of synthetic intermediates is expected to facilitate identification of the pharmacophore responsible for biological activity.

Experimental Section[40]

Carboxy Aldehyde 30. A solution of TMS enol ether **29** (18.5 g, 51 mmol) in methylene chloride (925 mL) and pyridine (5.8 mL, 75 mmol) was cooled to −90 °C. Ozone was bubbled through the solution for ca. 1 h until all starting material was consumed. Argon was then passed through the solution for 15 min, and dimethyl sulfide (10 mL, 140 mmol) was added. After 45 min the solution was warmed to room temperature and stirred for 15 h. Concentration in vacuo and flash chromatography

(40) Reactions were carried out under an argon atmosphere with freshly distilled solvents unless otherwise stated. Diethyl ether and THF were distilled under argon from sodium/benzophenone ketyl. Benzene and dichloromethane were distilled from calcium hydride. *n*-Butyllithium was purchased from Aldrich and standardized by titration with diphenylacetic acid or menthol/triphenylmethane. LDA was generated immediately prior to use by reaction of *n*-butyllithium with freshly distilled diisopropylamine (CaH_2). Unless stated otherwise, all reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using 0.25-mm precoated silica gel plates (E. Merck). Column chromatography was performed with silica gel 60 (particle size 0.040–0.063 mm) supplied by E. Merck. All melting points were obtained on a Bristoline heated-stage microscope and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer with polystyrene as external standard. Carbon and proton NMR spectra were measured on a Bruker AM-500 (500 MHz) or, where specified, a Bruker AM-250 (250 MHz) spectrometer. Chemical shifts are reported relative to internal tetramethylsilane or chloroform. Mass spectra were obtained with a VG micromass 70/70 H high-resolution electron impact/chemical ionization spectrometer or a VG ZAB-E spectrometer. Microanalyses were performed by Robertson Labs, Madison, NJ. Single-crystal X-ray data were collected with an Enraf Nonius CAD-4 automated diffractometer. Gas chromatography was carried out with a Hewlett Packard 5790A capillary instrument equipped with a 25-m × 0.2-mm Hewlett Packard cross-linked methyl silicone gum (HP-1) column. High performance liquid chromatography was performed with a Waters analytical/semiprep system employing a 25-cm × 10-mm Beckman 5μ Ultrasphere silica column. The OxiClear unit was purchased from LabClear, 508 29th Avenue, Oakland, CA 94601 [(800)-227-1084].

(2% → 5% methanol in methylene chloride) afforded **30** (10.0 g, 64% yield): colorless oil; $[\alpha]^{25}_D$ −124.5° (*c* 2.85, $CHCl_3$); IR ($CHCl_3$) 3500–2400 (m, br), 2980 (m), 2940 (m), 2890 (m), 1715 (s), 1450 (w), 1420 (w), 1370 (w), 1230 (w), 1115 (w), 1080 (w), 945 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (s, 3 H), 1.17–1.99 (complex m, 7 H), 1.27 (s, 3 H), 2.15–2.61 (complex m, 6 H), 3.95 (m, 4 H), 5.36 (m, 1 H), 9.79 (s, 1 H), CO_2H not resolved; high-resolution mass spectrum (CI, NH_3) *m/z* 340.2129 [$(M + NH_4)^+$; calcd for $C_{18}H_{30}O_5N$ 340.2124].

Chloro Ketone 34. A solution of DMSO (81 μL, 1.15 mmol) in 0.4 mL of dichloromethane was added dropwise to a solution of oxalyl chloride (50 μL, 0.575 mmol) in 0.4 mL of dichloromethane at −78 °C under argon. In a separate flask, bis(trimethylsilyl)acetamide (57 μL, 0.23 mmol) was added to a slurry of hydroxy acid **33** (37 mg, 0.115 mmol) in 1 mL of dichloromethane, and the mixture was swirled until the acid dissolved. Following addition of the latter to the oxalyl chloride–DMSO reagent, the resultant solution was stirred for 45 min at −65 °C. Triethylamine (200 μL, 1.38 mmol) was added, and the mixture was stirred for an additional 15 min before warming to room temperature. The reaction mixture was quenched with water and extracted with ether. The ether layer was discarded, and the aqueous layer was acidified with 3 N HCl to pH ~4 and extracted with ethyl acetate (4 × 30 mL). The organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in benzene and heated at 65 °C for 15 min to complete decarboxylation. After concentration in vacuo, flash chromatography (hexane–ethyl acetate, 8:1) gave 14 mg (48% yield) of α-chloro ketone **34** as an oil: IR ($CHCl_3$) 3000 (m), 2980 (s), 2890 (s), 1750 (s), 1455 (w), 1365 (m), 1230 (m), 1080 (m), 1015 (m), 910 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.05 (s, 3 H), 1.11 (s, 3 H), 1.64–2.36 (complex m, 9 H), 2.57 (m, 2 H), 3.95 (m, 4 H), 4.02 (dd, *J* = 8.6, 10.4 Hz, 1 H), 5.35 (m, 1 H); high-resolution mass spectrum (Cl, NH_3) *m/z* 311.1391 [$(M + H)^+$; calcd for $C_{17}H_{24}O_3Cl$ 311.1414].

Cyclopentanone 20. A. Via Swern Oxidation of 33. A solution of DMSO (190 μL, 2.7 mmol) in 2 mL of dichloromethane was added dropwise to a solution of oxalyl chloride (104 μL, 1.19 mmol) in dichloromethane (3 mL) at −78 °C. In a separate flask, bis(trimethylsilyl)acetamide (267 μL, 1.08 mmol) was added to a slurry of acid **33** (349 mg, 1.08 mmol) in dichloromethane (4 mL), and the flask was swirled until the acid dissolved. The resultant trimethylsilyl ester solution was added to the oxalyl chloride/DMSO complex, and the reaction mixture then was stirred for 45 min at −65 °C. Following addition of triethylamine (680 μL, 4.9 mmol), the mixture was stirred for an additional 15 min, warmed to room temperature, and partitioned between water and ether. The ether layer was discarded, and the aqueous layer was acidified with 3 N HCl (pH ~3–4) and extracted with ethyl acetate (4 × 30 mL). The organic layers were dried ($MgSO_4$) and concentrated in vacuo. A solution of the residue in benzene (15 mL) was heated at 65 °C for 30 min to complete decarboxylation. Concentration in vacuo and flash chromatography (hexane–ethyl acetate, 6:1) gave 178 mg (60% yield) of cyclopentanone **20** as a colorless solid: mp 114–115 °C; $[\alpha]^{22}_D$ −196° (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2980 (s), 2900 (s), 2840 (w), 1730 (s), 1365 (m), 1250 (m), 1120 (m), 1090 (m), 1040 (m), 1020 (m), 950 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 1.13 (s, 3 H), 1.58–2.60 (complex m, 13 H), 3.94 (m, 4 H), 5.33 (m, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 11.9, 19.8, 23.8, 27.5, 28.8, 30.2, 37.7, 37.8, 40.1, 41.3, 52.7, 64.0, 64.2, 108.8, 121.6, 139.8, 221.4; high-resolution mass spectrum (CI, NH_3) *m/z* 277.1817 [$(M + H)^+$; calcd for $C_{17}H_{25}O_3$ 277.1804]. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.65; H, 8.66.

α-Methylene Cyclopentanone 42. A solution of DMSO (3.2 mL, 44.7 mmol) in methylene chloride (11 mL) was added over a 10-min period to a solution of trifluoroacetic anhydride (2.9 mL, 20.6 mmol) in methylene chloride (11 mL) and cooled to −78 °C, and the resultant mixture was stirred for 1 h. Alcohol **32** (2.7 g, 6.9 mmol) in methylene chloride (21 mL) was then added over a 20-min period. The reaction was stirred for 1 h, and triethylamine (9.6 mL, 68.8 mmol) then was added dropwise. After 5 min, the ice bath was removed. The mixture was stirred for 1 h, poured into saturated sodium bicarbonate, and extracted with methylene chloride. The organic layer was dried with magnesium sulfate and concentrated in vacuo. The residue was dissolved in THF (30 mL), and the solution was treated at room temperature with 0.2 M HCl (3.45 mL); after 1 h an additional 1 mL of dilute acid was added. The mixture was stirred 2.25 h further, poured into brine, and extracted with ethyl acetate. Following concentration of the organic layer in vacuo, the resultant oil was taken up in benzene (17.5 mL) and heated at reflux for 1.5 h. The solution then was cooled, poured into 0.5 M NaOH, and extracted with ethyl acetate. The organic layer was dried with magnesium sulfate and concentrated in vacuo. Flash chromatography (10% EtOAc in hexanes) afforded **42** (Rf 0.76, 7.5% yield) and cyclopentanone **20** (R_f 0.7, 20% yield). **42**: colorless oil; IR ($CHCl_3$) 3020 (m), 3005 (m), 2960 (m), 1720 (s), 1635 (m), 1440 (w), 1360 (m), 1260 (m), 1210 (m), 1085 (s), 1010 (s), 1000 (s), 940 (m), 910 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (s, 3 H), 1.15 (s, 3 H), 1.70 (ddd, *J* = 3.3, 6.7, 13.1 Hz, 1 H), 1.82 (td, *J* = 3.8, 13.5 Hz, 1 H), 1.92 (td, *J* = 3.9, 13.5 Hz, 1 H), 1.98–2.35 (comp m, 6 H), 2.53 (ddd, *J* = 2.8, 6.0, 14.4 Hz, 1 H), 2.64 (m, 1 H), 3.94 (m, 4 H), 5.34 (m, 2 H), 6.01 (dd, *J* = 1.2, 2.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.4, 19.9, 27.4, 29.1, 30.1, 31.1, 34.5, 40.5, 41.5, 53.1, 64.2, 64.4, 109.0, 118.1, 121.4, 140.2, 144.6, 208.4; high-resolution mass spectrum (CI, CH_4) *m/z* 289.1783 [$(M + H)^+$; calcd for $C_{18}H_{25}O_3$ 289.1804].

Cyclopentanone 20. B. Via Collins Oxidation of 32. A solution of pyridine (39.7 mL, 490 mmol) in methylene chloride (510 mL) was treated with chromium trioxide (24.5 g, 245 mmol), and the mixture was stirred for 15 min at room temperature. A solution of alcohol **32** (16.1 g, 40.8 mmol) in methylene chloride (170 mL) was added in one portion, and the mixture was stirred for 30 min and poured into 5% NaOH. The organic layer was washed three times with 5% NaOH and then successively with 5% HCl, saturated sodium bicarbonate solution, and brine. Concentration gave a crude oil (14.0 g) which was taken up in DMSO (36 mL) and H_2O (2.0 mL). NaCl was added (2.5 g, 43 mmol), and the mixture was warmed to 70 °C for 3 h. After cooling to ambient temperature, the mixture was poured into water and extracted with ethyl acetate. Flash chromatography (8% EtOAc in hexanes) furnished **20** (8.3 g, 73% yield).

Methylthio Cyclopentanones 43a,b. A stirred solution of diisopropylamine (2.62 mL, 18.7 mmol) in 20 mL of THF was cooled to 0 °C and treated with *n*-butyllithium (2.5 M, 6.22 mL, 15.6 mmol). After 10 min, a solution of ketone **20** (2.15 g, 7.78 mmol) in 30 mL of THF was added dropwise, and the resultant solution was stirred for 10 min at 0 °C. HMPA (15 mL) and dimethyl disulfide (2.45 mL, 27.2 mmol) were then added, and the mixture was stirred for an additional 15 min. The reaction mixture was poured into water and extracted with ether, and the organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (hexane–ethyl acetate, 15:1) afforded 2.51 g (88% yield) of **43a,b** as an oil. NMR analysis revealed a 1:1 mixture of epimers: IR ($CHCl_3$) 3000 (s), 2980 (s), 2900 (s), 1725 (s), 1430 (w), 1370 (w), 1240 (m), 1090 (m), 1030 (m), 910 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97, 0.98 (s, s, diastereomers, 3 H), 1.12, 1.23 (s, s, diastereomers, 3 H), 1.60–2.42 (complex m, 9 H), 2.20, 2.21 (s, s, diastereomers, 3 H), 2.55 (m, 2 H), 3.09 (m, 1 H), 3.94 (m, 4 H), 5.34 (m, 1 H); high-resolution mass spectrum (CI, NH_3) *m/z* 323.1712 [$(M + H)^+$; calcd for $C_{18}H_{27}O_3S$ 323.1681].

Anilino Cyclopentanones 44a,b. A solution of aniline (0.65 mL, 7.19 mmol) in 30 mL of dichloromethane was cooled to −78 °C and treated with *tert*-butyl hypochlorite (0.86 mL, 7.19 mmol) dissolved in 30 mL of dichloromethane. After 15 min, a solution of **43a,b** (2.21 g, 6.84 mmol) in 30 mL of dichloromethane was introduced dropwise, and the mixture was stirred 1 h at −78 °C. Triethylamine (2.1 mL, 15.05 mmol) was added, and the reaction mixture was warmed to room temperature and poured into water. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Flash chromatography (hexane–ethyl acetate, 6:1) afforded 2.64 g (93% yield) of ketones **44a,b** as a mixture of diastereomers. For characterization, the diastereomers were separated via preparative thin-layer chromatography on a 0.5-mm E. Merck TLC plate (20 × 20 cm; hexane–ethyl acetate, 4:1, four developments).

44a: colorless solid; mp 185–187 °C (dec); $[\alpha]^{25}_D$ −90° (*c* 0.365, $CHCl_3$); IR ($CHCl_3$) 3440 (w), 3320 (w), 2990 (s), 2890 (s), 1730 (s), 1620 (m), 1500 (m), 1450 (m), 1370 (w), 1240 (m), 1080 (m), 1025 (m), 950 (w), 860 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.20 (s, 3 H), 1.25 (s, 3 H), 1.66–2.28 (complex m, 9 H), 1.94 (s, 3 H), 2.51 (m, 1 H), 3.01 (dd, *J* = 6.2, 13.1 Hz, 1 H), 3.95 (m, 4 H), 4.64 (br s, 2 H), 5.30 (s, 1 H), 6.65 (m, 2 H), 7.10 (m, 2 H); high-resolution mass spectrum (CI, NH_3) *m/z* 414.2096 [$(M + H)^+$; calcd for $C_{24}H_{32}O_3NS$: 414.2103]. Anal. Calcd for $C_{24}H_{31}O_3NS$: C, 69.70; H, 7.55. Found: C, 69.87; H, 7.70.

44b: colorless solid; $[\alpha]^{25}_D$ +15.4° (*c* 0.58, $CHCl_3$); IR ($CHCl_3$) 3430 (w), 3330 (w), 3000 (s), 2980 (s), 1720 (s), 1620 (m), 1500 (m), 1455 (m), 1370 (w), 1240 (m), 1085 (m), 1015 (m), 910 (m), 860 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.00 (s, 3 H), 1.34 (s, 3 H), 1.75–2.35 (complex m, 8 H), 1.88 (s, 3 H), 2.55 (m, 2 H), 2.72 (dd, *J* = 6.1, 13.7 Hz, 1 H), 3.96 (m, 4 H), 4.63 (br s, 2 H), 5.34 (m, 1 H), 6.67 (m, 2 H), 7.10 (m, 2 H); high-resolution mass spectrum (CI, NH_3) *m/z* 414.2141 [$(M + H)^+$; calcd for $C_{24}O_{32}O_3NS$ 414.2103].

Indole Precursor 45. A solution of **44a,b** (2.59 g, 6.26 mmol) in 200 mL of absolute ethanol was stirred with an excess of W-2 Raney Nickel

(41) von Dumont, R.; Pfander, H. *Helv. Chim. Acta* **1983**, *66*, 814.
(42) Weibel, F. R. Ph.D. Thesis, Eidgenossische Technische Hochschule, Zurich, 1979.

(Aldrich) for 2 h at room temperature. The supernatant was decanted and filtered through a pad of Florisil. The catalyst was washed thoroughly with ethyl acetate, and the washings were then filtered. Concentration in vacuo and flash chromatography (hexane–ethyl acetate, 5:1 → 2:1) furnished 1.89 g (82% yield) of **45** as a colorless solid: mp 150–152 °C; $[\alpha]^{25}_D$ +69° (*c* 1.19, $CHCl_3$); IR ($CHCl_3$) 3420 (w), 3350 (w), 3000 (s), 2980 (s), 2890 (s), 2840 (w), 1725 (s), 1630 (m), 1500 (m), 1460 (m), 1370 (m), 1240 (m), 1080 (m), 1020 (m), 860 (w), 810 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.00 (s, 3 H), 1.21 (s, 3 H), 1.66–2.34 (complex m, 9 H), 2.39–2.63 (m, 2 H), 3.59 (dd, *J* = 8.3, 11.4 Hz, 1 H), 3.95 (m, 4 H), 4.09 (br s, 2 H), 5.39 (m, 1 H), 6.78 (m, 2 H), 7.06 (m, 2 H); high-resolution mass spectrum (CI, NH_3) *m/z* 367.2151 (M^+; calcd for $C_{23}H_{29}O_3N$ 367.2147]. Anal. Calcd for $C_{23}H_{29}O_3N$: C, 75.17; H, 7.95. Found: C, 74.84; H, 7.72.

Indole Ketal 46. A solution of *p*-toluenesulfonic acid (44 mg, 0.23 mmol) in benzene (40 mL) was heated at reflux under a Dean-Stark trap for 15 min. A solution of ketone **45** (1.69 g, 4.59 mmol) in 30 mL of benzene was then added and heated at reflux for 15 min. After cooling to room temperature, the mixture was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Flash chromatography (hexane–ethyl acetate, 5:1) yielded 1.39 g (87% yield) of indole **46** as a colorless solid: mp 159–160 °C; $[\alpha]^{25}_D$ −112.8° (*c* 1.09, $CHCl_3$); UV (95% EtOH) λ_{max} 218 (ε 33 600), 269 (ε 5700) nm; IR ($CHCl_3$) 3470 (m), 3330 (br), 3000 (m), 2970 (s), 2930 (s), 2880 (s), 2840 (m), 1450 (m), 1360 (m), 1300 (m), 1230 (m), 1080 (m), 1010 (m), 900 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.99 (s, 3 H), 1.23 (s, 3 H), 1.50 (m, 1 H), 1.70–2.58 (complex m, 8 H), 2.77–2.89 (m, 2 H), 3.98 (m, 4 H), 5.47 (m, 1 H), 7.10 (m, 2 H), 7.32 (m, 1 H), 7.46 (m, 1 H), 7.77 (br s, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.1, 21.7, 26.8, 27.2, 30.9, 31.5, 41.1, 41.8, 46.2, 48.7, 64.3, 64.5, 109.1, 111.4, 118.2, 118.5, 119.6, 120.5, 123.5, 124.9, 139.0, 140.2, 149.4; high-resolution mass spectrum (CI, NH_3) *m/z* 350.2106 [$(M + H)^+$; calcd for $C_{23}H_{28}O_2N$ 350.2120]. Anal. Calcd for $C_{23}H_{27}O_2N$: C, 79.05; H, 7.79. Found: C, 78.81; H, 7.85.

Indole Enone 23. A vigorously stirred solution of indole **46** (934 mg, 2.68 mmol) in 54 mL of acetonitrile was cooled to 0 °C and treated with $TsOH·H_2O$ (1.52 g, 8.0 mmol). After 15 min, the reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (hexane–ethyl acetate, 3:1) afforded 661 mg (81% yield) of indole enone **23** as a colorless solid: mp 219–221 °C; $[\alpha]^{25}_D$ +150.5° (*c* 1.025, $CHCl_3$); UV (95% EtOH) λ_{max} 219 (ε 46 000), 267 (ε 7500) nm; IR ($CHCl_3$) 3470 (w), 3350 (br), 3000 (m), 2940 (m), 2870 (m), 2850 (m), 1665 (s), 1450 (m), 1300 (m), 1240 (m), 1180 (w), 910 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.95 (s, 3 H), 1.37 (s, 3 H), 1.90 (m, 3 H), 2.39–2.73 (complex m, 6 H), 2.83 (dd, *J* = 6.6, 13.6 Hz, 1 H), 3.12 (m, 1 H), 5.94 (m, 1 H), 7.12 (m, 2 H), 7.33 (m, 1 H), 7.47 (m, 1 H), 7.70 (br s, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 16.7, 19.8, 24.3, 27.3, 31.6, 33.3, 33.8, 42.8, 48.0, 50.3, 111.6, 118.6, 118.9, 119.8, 121.0, 124.8, 127.4, 140.3, 147.6, 169.3, 198.5; high-resolution mass spectrum (CI, NH_3) *m/z* 306.1811 [$(M + H)^+$; calcd for $C_{21}H_{24}ON$ 306.1858].

Epoxide 47. In a 500-mL, round-bottomed flask were flame-dried under vacuum 8.1 g of powdered 4 Å molecular sieves. Dichloromethane (200 mL), 3-methyl-2-butene-1-ol (**25**) (20 mL, 0.197 mol), and (+)-diisopropyl tartrate (3.1 mL, 14.7 mmol) were added, and the mixture was cooled to −20 °C. After the introduction of $Ti(O\text{-}i\text{-}Pr)_4$ (2.9 mL, 9.8 mmol), the mixture was stirred for 30 min. Cumene hydroperoxide (80%, 62 mL, 0.325 mmol) was then added over 2.5 h, and the mixture was stirred an additional 0.5 h. Following the addition of citric acid monohydrate (2.28 g, 10.8 mmol) and diethyl ether (120 mL), the reaction was warmed to room temperature and stirred overnight. Filtration through a pad of Celite and concentration in vacuo furnished an oil which was subjected to flash chromatography (hexane–ether, 1:1), affording 18.1 g (90% yield) of epoxide **47** as a colorless oil: $[\alpha]^{21}_D$ −18° (*c* 2, $CHCl_3$) {lit. value for enantiomer[41] $[\alpha]^{25}_D$ + 21.0° (*c* 1.71 $CHCl_3$)}; IR ($CHCl_3$) 3430 (br), 3000 (m), 2970 (s), 2930 (s), 1455 (w), 1385 (m), 1230 (m), 1120 (w), 1030 (m), 855 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.32 (s, 3 H), 1.35 (s, 3 H), 2.39 (br s, 1 H), 2.99 (dd, *J* = 4.3, 6.7 Hz, 1 H), 3.68 (m, 1 H), 3.85 (m, 1 H).

***p*-Nitrobenzoate 48.** Alcohol **47** (7.0 g, 68.5 mmol) was dissolved in methylene chloride (100 mL) at room temperature and triethylamine (11.4 mL, 82 mmol) was added. After 10 min the solution was cooled to 0 °C, and a solution of *p*-nitrobenzoyl chloride (12.7 g, 68.5 mmol) in methylene chloride (130 mL) was added over 20 min via a cannula. The mixture was stirred 10 min further and then filtered to remove triethylamine hydrochloride. The filtrate was poured into dilute sodium bicarbonate solution and extracted with methylene chloride. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in diethyl ether (350 mL) and allowed to crystallize at −25 °C for 15 h, affording **48** 11.2 g, 65% yield) as colorless prisms: $[\alpha]^{24}_D$ −36° (*c* 0.50, $CHCl_3$); {lit.[20] $[\alpha]^{25}_D$ −36.09° (*c* 4.94, $CHCl_3$)}; mp 109–110 °C (lit.[20] 109.5–110 °C).

Cyclopentylidene Ketal 49. A solution of epoxide **48** (12.70 g, 5.06 mmol) in benzene (170 mL) was cooled to 0 °C, and cyclopentanone (22.4 mL, 25.3 mmol) was added in one portion followed by concentrated H_2SO_4 (1.0 mL). After 45 min the reaction was allowed to warm to room temperature for 75 min. The mixture was then poured into saturated sodium bicarbonate solution and extracted with diethyl ether. Flash chromatography (15% EtOAc in hexanes) gave **49** (13.36 g, 80% yield) as a colorless solid: mp 110 °C; $[\alpha]^{24}_D$ −36° (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3020 (m), 2975 (s), 2875 (m), 1730 (s), 1610 (m), 1530 (s), 1410 (w), 1400 (m), 1370 (m), 1360 (s), 1320 (s), 1280 (s), 1105 (s), 1020 (m), 970 (m), 870 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 3 H), 1.38 (s, 3 H), 1.66–1.70 (comp m, 4 H), 1.83 (m, 2 H), 1.90 (m, 2 H), 4.00 (dd, *J* = 4.8, 6.9 Hz, 1 H), 4.44 (m, 2 H), 8.23 (d, *J* = 8.6 Hz, 2 H), 8.30 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 23.4, 23.8, 26.2, 38.3, 38.4, 64.4, 79.2, 80.7, 118.1, 123.6, 130.8, 135.1, 150.7, 164.5; high-resolution mass spectrum (CI, NH_3) *m/z* 336.1442 [$(M + H)^+$; calcd for $C_{17}H_{22}NO_6$ 336.1447]. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31. Found: C, 60.88; H, 6.34.

Alcohol 50. A solution of ester **49** (27.3 g, 81.4 mmol) in absolute ethanol (675 mL) was treated with K_2CO_3 (14.0 g, 101 mmol). The reaction mixture was stirred for 90 min at room temperature and then filtered. Concentration in vacuo and flash chromatography (20% → 30% Et_2O in pentane) provided alcohol **50** (14.00 g, 92% yield) as a colorless oil: $[\alpha]^{22}_D$ −4.6° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3600 (w), 3450 (br), 3000 (m), 2980 (s), 1370 (m), 1340 (m), 1190 (m), 1110 (s), 1035 (m), 970 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.12 (s, 3 H), 1.34 (s, 3 H), 1.60–1.90 (m, 8 H), 2.16 (br s, 1 H), 3.60–3.85 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 23.4, 23.8, 26.3, 38.2, 38.4, 61.6, 78.9, 83.9, 117.6; high-resolution mass spectrum (CI, NH_3) *m/z* 186.1234 (M^+; calcd for $C_{10}H_{18}O_3$ 186.1256). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.27; H, 10.04.

Aldehyde 51. A solution of DMSO (17.2 mL, 243 mmol) in dichloromethane (80 mL) was added dropwise over a 30-min period to a solution of oxalyl chloride (10.6 mL, 121 mmol) in dichloromethane (300 mL) at −78 °C under argon. The mixture was stirred for 30 min, and a solution of alcohol **50** (15.09 g, 81 mmol) in dichloromethane (160 mL) was then added. The resultant mixture was stirred for 60 min at −75 °C, treated with triethylamine (67.7 mL, 486 mmol), stirred 10 min further, and warmed to room temperature. After addition of water and extraction with diethyl ether, the organic layers were dried over $NaSO_4$ and concentrated in vacuo. Flash chromatography (10% diethyl ether in pentane) furnished **51** (12.93 g, 87% yield) as a colorless liquid: $[\alpha]^{25}_D$ +62.3° (*c* 2.3, $CHCl_3$); IR ($CHCl_3$) 2980 (s), 2875 (m), 1735 (s), 1370 (m), 1340 (m), 1215 (m), 1150 (s), 1115 (s), 970 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (s, 3 H), 1.42 (s, 3 H), 1.62–1.99 (m, 8 H), 3.95 (d, *J* = 2.4 Hz, 1 H), 9.70 (d, *J* = 2.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.3, 23.4, 23.7, 26.9, 38.2, 38.3, 81.1, 87.1, 119.8, 200.7; high-resolution mass spectrum (CI, NH_3) *m/z* 185.1173 [$(M + H)^+$; calcd for $C_{10}H_{17}O_3$ 185.1178].

Epoxy Ketal 24. Dimethylsulfoxonium methylide was prepared by adding 97% sodium hydride (184 mg, 7.47 mmol) to a solution of trimethylsulfoxonium iodide (1.795 g, 8.15 mmol) in DMSO (13 mL) and stirring for 30 min at room temperature. The ylide was cooled to 10 °C, and a solution of aldehyde **51** (1.25 g, 6.79 mmol) in 1:1 THF/DMSO (8 mL) was added. After 20 min, the reaction mixture was quenched with water and extracted with ether. The organic layers were washed with brine, dried ($MgSO_4$), and carefully concentrated in vacuo. Flash chromatography (hexane–ether, 10:1) afforded 1.0 g (74% yield) of **24** as a colorless liquid: $[\alpha]^{22}_D$ −0.27° (*c* 4.4, $CHCl_3$); IR ($CHCl_3$) 2980 (s), 1370 (w), 1340 (m), 1190 (m), 1150 (s), 1110 (w), 975 (w), 895 (w), 870 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 3 H), 1.35 (s, 3 H), 1.64–1.90 (m, 8 H), 2.72 (dd, *J* = 2.5, 5.1 Hz, 1 H), 2.86 (dd, *J* = 3.8, 5.2 Hz, 1 H), 3.00 (m, 1 H), 3.25 (d, *J* = 7.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.9, 23.4, 23.8, 26.6, 38.2, 38.5, 45.9, 49.7, 80.4, 83.7, 118.3; high-resolution mass spectrum (CI, NH_3) *m/z* 198.1262 (M^+; calcd for $C_{11}H_{18}O_3$ 198.1256). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.55; H, 8.87.

Model Coupled Alcohol 65. THF employed in this reaction was distilled twice, first from sodium benzophenone ketyl and again after heating at reflux over LAH for ≥5 days. The reaction was carried out in a one-piece apparatus consisting of a 50-mL, round-bottomed flask and a 3-cm water-jacketed condenser, the latter fitted with a 14/20 joint. The vessel was capped with a septum, twice flame-dried in vacuo, cooled, and flushed with oxygen-free argon. Argon was passed through an OxiClear purification unit[40] and a 3-ft $CaCl_2/CaSO_4$ drying tube prior to use. Gas-tight syringes were employed for all transfers. A solution of diiso-

propylamine (0.30 mL, 2.13 mmol) in THF (4 mL) was cooled to −20 °C, *n*-BuLi (0.62 mL, 2.80 M in hexanes) was added dropwise, and the mixture stirred for 15 min. A solution of dimethylhydrazone **64**[12b] (400 mg, 1.94 mmol) in THF (6 mL) was added over 5 min, and the cooling bath was then removed. After 15 min, the flask was placed in a 65 °C oil bath. At 2-h intervals, a stream of argon was passed over the reaction mixture for ca. 45 s. After 8 h, the reaction mixture was cooled in an ice bath, and epoxide **24** (0.4 mL) was added neat. The ice bath was then removed, and the reaction was allowed to stir at room temperature for 14 h. The mixture was quenched with pH 7 buffer and extracted with diethyl ether. The combined organic fractions were washed with brine and dried over sodium sulfate. Following concentration in vacuo, the residue was dissolved in dichloromethane (20 mL), benzoic acid (240 mg, 1.97 mmol) was added, and the mixture was stirred at room temperature for 30 min. The mixture was then poured into saturated sodium bicarbonate solution and extracted with dichloromethane. Flash chromatography (15% → 20% → 25% EtOAc in hexanes) afforded **65** (460 mg, 64% yield) as a yellow oil: $[\alpha]^{25}_D$ +373° (*c* 0.54, $CHCl_3$); IR ($CHCl_3$) 3140 (m, br), 2960 (s), 2940 (s), 2860 (s), 2840 (m), 1665 (w), 1600 (m), 1465 (m), 1450 (m), 1430 (m), 1370 (m), 1330 (m), 1190 (m), 1105 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17 (s, 3 H), 1.23 (s, 3 H), 1.24–1.36 (comp m, 2 H), 1.38 (s, 3 H), 1.55–1.83 (comp m, 13 H), 1.90 (br d, *J* = 12.8 Hz, 1 H), 1.98 (td, *J* = 4.2, 14.2 Hz, 1 H), 2.19 (ddd, *J* = 5.2, 13.4, 15.1 Hz, 1 H), 2.45–2.48 (comp m, 2 H), 2.50 (s, 6 H), 2.85 (br d, *J* = 14.5 Hz, 1 H), 2.90 (d, *J* = 14.4 Hz, 1 H), 3.08 (dt, *J* = 4.0, 15.0 Hz, 1 H), 3.32 (d, *J* = 9.2 Hz, 1 H), 3.47 (td, *J* = 1.6, 8.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 22.4, 23.3, 23.4, 23.6, 27.0, 27.3, 27.9, 33.9, 36.1, 37.9, 38.1, 38.4, 42.2, 47.5, 72.3, 80.5, 85.4, 116.4, 127.4, 153.4, 168.4; high-resolution mass spectrum (CI, NH_3) *m/z* 405.3107 [(M + H)$^+$; calcd for $C_{24}H_{41}N_2O_3$ 405.3118].

Dimethylhydrazone Acetate 66. Acetic anhydride (0.85 mL, 9.15 mmol) and DMAP (56 mg, 0.46 mmol) were added to a solution of **65** (370 mg, 0.91 mmol) in pyridine (4.5 mL), and the resultant mixture was warmed to 40 °C for 15 h. After cooling, the reaction was quenched with saturated sodium bicarbonate solution and extracted with diethyl ether. Concentration in vacuo and flash chromatography (15% EtOAc in hexanes) provided **66** (386 mg, 95% yield) as a yellow solid: mp 102.5–104 °C; $[\alpha]^{24}_D$ +393° (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 2940 (s), 2860 (s), 2820 (m), 2670 (w), 1730 (s), 1610 (w), 1470 (m), 1450 (m), 1435 (m), 1385 (m), 1370 (m), 1335 (m), 1240 (s), 1190 (m), 1110 (m), 1022 (m), 970 (m), 905 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 3 H), 1.16 (s, 3 H), 1.28 (s, 3 H), 1.92 (s, 3 H), 1.51–2.05 (comp m, 18 H), 2.51 (s, 6 H), 2.54 (m, 1 H), 2.82 (br d, *J* = 14.6 Hz, 1 H), 3.04 (dt, *J* = 3.5, 15.4 Hz, 1 H), 3.23 (br d, *J* = 13.6 Hz, 1 H), 3.62 (d, *J* = 8.0 Hz, 1 H), 5.27 (ddd, *J* = 2.8, 7.9, 10.6 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 21.6, 22.0, 22.4, 22.7, 23.5, 23.7, 27.0, 27.6, 27.7, 29.6, 35.9, 38.2, 38.4, 38.7, 42.5, 47.4, 71.8, 80.0, 84.4, 117.2, 125.7, 150.6, 162.9, 169.3; high-resolution mass spectrum (CI, NH_3) *m/z* 447.3282 [(M + H)$^+$; calcd for $C_{26}H_{43}N_2O_4$ 447.3221]. Anal. Calcd for $C_{26}H_{42}N_2O_4$: C, 69.92; H, 9.48. Found: C, 70.32; H, 9.51.

Enone Acetate 67. A solution of sodium periodate (540 mg, 2.52 mmol) in H_2O (5.5 mL) was added in one portion to a mixture of dimethylhydrazone acetate **66** (510 mg, 1.14 mmol), *t*-BuOH (16.4 mL), and pH 7 buffer (3.3 mL). The resulting suspension was stirred rapidly at room temperature. After 18 and 24 h supplemental portions of sodium periodate (150 mg each) were added. After 40 h the mixture was filtered, and filtrate was diluted with diethyl ether and washed with water. Concentration and flash chromatography (hexanes–CH_2Cl_2–Et_2O, 3:1:1) gave **67** (345 mg, 74% yield) as a colorless oil: $[\alpha]^{25}_D$ +62° (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 3050 (w), 3020 (m), 3000 (s), 2960 (s), 2880 (m), 1745 (s), 1675 (s), 1615 (w), 1460 (m), 1440 (w), 1395 (m), 1380 (m), 1345 (m), 1250 (s), 1220 (s), 1120 (m), 1035 (m), 980 (w), 910 (w), 865 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 3 H), 1.22 (s, 3 H), 1.27 (s, 3 H), 1.35–1.44 (comp m, 2 H), 1.57–1.86 (comp m, 13 H), 1.93 (m, 1 H), 1.96 (s, 3 H), 2.07 (td, *J* = 4.8, 14.4 Hz, 1 H), 2.33 (dt, *J* = 3.7, 16.3 Hz, 1 H), 2.47–2.60 (comp m, 2 H), 2.86 (br d, *J* = 14.5 Hz, 1 H), 2.98 (dd, *J* = 4.5, 13.8 Hz, 1 H), 3.61 (d, *J* = 8.9 Hz, 1 H), 4.53 (td, *J* = 4.6, 8.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 21.6, 22.1, 22.3, 23.5, 23.8, 26.8, 27.1, 28.0, 28.6, 33.8, 36.6, 37.9, 38.0, 38.3, 42.1, 71.9, 80.0, 83.6, 117.2, 128.7, 164.1, 169.6, 198.7; high-resolution mass spectrum (CI, isobutane) *m/z* 404.2581 (M$^+$; calcd for $C_{24}H_{36}O_5$ 404.2563.)

Dioxabicyclooctane Acetate 68. A solution of enone **67** (147 mg, 0.36 mmol) in methylene chloride (3.6 mL) was cooled to 0 °C, and perchloric acid (70%, 54 μL) was added dropwise. The mixture was stirred at 0 °C for 2 h and then quenched with saturated sodium bicarbonate solution. The aqueous layer was extracted with methylene chloride. Concentration and flash chromatography (hexanes–CH_2Cl_2–Et_2O, 3:1:1) provided ketal **68** (75 mg, 65% yield) as a colorless solid: mp 76–78 °C; $[\alpha]^{25}_D$ +66° (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) 3040 (w), 3020 (m), 2980 (s), 2945 (s), 2875 (m), 1740 (s), 1470 (m), 1455 (m), 1380 (m), 1310 (w), 1255 (s), 1215 (m), 1170 (m), 1120 (m), 1100 (m), 1065 (m), 1050 (m), 1040 (m), 970 (m), 915 (w), 895 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 3 H), 1.12–1.69 (comp m, 7 H), 1.32 (s, 3 H), 1.43 (s, 3 H), 1.73–1.80 (comp m, 2 H), 1.88 (dt, *J* = 4.0, 14.2 Hz, 1 H), 2.11 (s, 3 H), 2.13 (m, 1 H), 2.34 (br d, *J* = 14.5 Hz, 1 H), 2.53 (d, *J* = 16.3 Hz, 1 H), 2.73 (ddd, *J* = 1.9, 5.5, 16.3 Hz, 1 H), 4.03 (s, 1 H), 5.03 (dt, *J* = 1.5, 5.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 21.4, 22.0, 22.5, 25.1, 27.5, 28.1, 29.2, 30.3, 35.1, 36.9, 42.1, 69.3, 78.5, 83.2, 106.3, 122.9, 140.0, 171.0; high-resolution mass spectrum (CI, NH_3) *m/z* 321.2037 [(M + H)$^+$; calcd for $C_{19}H_{29}O_4$ 321.2066].

Alcohol 62. Potassium carbonate (69 mg, 0.50 mmol) was added to a solution of ketal **68** (107 mg, 0.33 mmol) in methanol (4.4 mL), and the mixture was stirred at room temperature for 50 min. After filtration and concentration in vacuo, flash chromatography (20% EtOAc in hexanes) afforded **62** (80 mg, 86% yield) as a colorless oil: $[\alpha]^{25}_D$ +53° (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 3560 (w), 3020 (m), 2980 (s), 2950 (s), 2870 (m), 1460 (m), 1390 (m), 1375 (m), 1250 (m, br), 1165 (m), 1120 (m), 1060 (s), 1050 (s), 1000 (m), 960 (m), 940 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 3 H), 1.28 (m, 2 H), 1.31 (s, 3 H), 1.38 (s, 3 H), 1.44–1.64 (comp m, 5 H), 1.71–1.85 (comp m, 3 H), 2,13 (td, *J* = 3.8, 14.6 Hz, 1 H), 2.41 (br d, *J* = 16.0 Hz, 1 H), 2.50 (br d, *J* = 11.6 Hz, 1 H), 2.55 (d, *J* = 15.2 Hz, 1 H), 2.70 (ddd, *J* = 2.1, 4.4, 15.2 Hz, 1 H), 3.85 (br d, *J* = 7.1 Hz, 1 H), 3.94 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ.20.4, 22.0, 22.2, 25.1, 27.6, 30.4, 31.3, 35.2, 37.2, 42.8, 67.0, 78.4, 85.9, 106.7, 123.5, 141.6; high-resolution mass spectrum (CI, NH_3) *m/z* 279.1992 [(M + H)$^+$; calcd for $C_{17}H_{27}O_3$ 279.1960].

Dienone 72. A solution of oxalyl chloride (62 μL, 0.71 mmol) in CH_2Cl_2 (1 mL) was cooled to −65 °C, and a solution of DMSO (100 μL, 1.42 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise. After 5 min, the reaction mixture was warmed to −20 °C, and a solution of alcohol **62** (33 mg, 0.12 mmol) in CH_2Cl_2 (0.9 mL) was added dropwise. The reaction was stirred for 30 min and then treated with triethylamine (0.4 mL, 1.42 mmol). The cooling bath was removed 5 min later. The reaction was stirred 15 min further and poured into saturated sodium bicarbonate solution. Flash chromatography (7.5% EtOAc in hexanes) furnished dienone **72** (25 mg, 76% yield) as a colorless solid: mp 59.5–60 °C; $[\alpha]^{25}_D$ +22° (*c* 0.7, $CHCl_3$); UV (MeOH) λ_{max} 306.4 nm (ε 8800); IR ($CHCl_3$) 2980 (m), 2940 (s), 2860 (m), 1725 (w), 1675 (s), 1620 (w), 1590 (w), 1370 (w), 1270 (m), 1065 (m), 1030 (m), 960 (w), 905 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ.1.14 (s, 3 H), 1.23 (s, 3 H), 1.42 (s, 3 H), 1.48 (td, *J* = 3.7, 12.8 Hz, 1 H), 1.60–1.74 (comp m, 4 H), 1.81–1.98 (comp m, 3 H), 2.20 (m, 2 H), 4.27 (s, 1 H), 6.00 (s, 1 H), 6.25 (t, *J* = 4.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 23.0, 26.3, 29.1, 29.7, 31.7, 34.5, 38.8, 78.2, 88.4, 104.7, 116.9, 131.4, 139.5, 164.3, 196.0; high-resolution mass spectrum (CI, NH_3) *m/z* 275.1656 [(M + H)$^+$; calcd for $C_{17}H_{23}O_3$ 275.1647].

β,γ-Enone 69. Alcohol **62** (115 mg, 0.41 mmol) was dissolved in benzene (2.1 mL) and DMSO (0.55 mL), and DCC (258 mg, 1.25 mmol), pyridine (33 μL, 0.41 mmol), and trifluoroacetic acid (16 μL, 0.21 mmol) were added sequentially. The reaction was stirred at room temperature for 7 h and then filtered. The filtrate was diluted with diethyl ether and washed with water. After drying over sodium sulfate, the ether was removed in vacuo. The residue was then taken up in CH_2Cl_2 (0.5 mL) and adsorbed onto silica. After concentration in vacuo, the silica was loaded onto a flash column and eluted (8.5% EtOAc in hexanes), providing **69** (90 mg, 80% yield) as a colorless oil: $[\alpha]^{25}_D$ +37° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 2990 (m), 2920 (s), 2850 (m), 1725 (s), 1440 (m), 1390 (w), 1360 (m), 1250 (w), 1150 (m), 1050 (m), 960 (m), 910 (m), 880 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 3 H), 1.12–1.38 (comp m, 2 H), 1.24 (s, 3 H), 1.35 (s, 3 H), 1.50 (td, *J* = 4.3, 13.1 Hz, 1 H), 1.53–1.82 (comp m, 4 H), 1.91–2.09 (comp m, 4 H), 2.16 (br d, *J* = 13.6 Hz, 1 H), 3.04 (d, *J* = 22.0 Hz, 1 H), 3.21 (d, *J* = 21.4 Hz, 1 H). 4.08 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.0, 22.7, 24.9, 25.3, 27.4, 28.3, 34.9, 35.5, 35.9, 38.5, 39.3, 79.2, 87.7, 106.5, 121.1, 141.5, 206.4; high-resolution mass spectrum (CI, NH_3) *m/z* 277.1822 [(M + H)$^+$; calcd for $C_{17}H_{25}O_3$ 277.1803].

Hydroperoxide 70. In a typical experiment, enone **69** (ca. 10 mg), either neat or dissolved in benzene (1 mL) or Et_2O (1 mL), was allowed to stand at 5 °C for 15 h in the presence of trace amounts of oxygen to afford hydroperoxide **70** almost quantitatively as a colorless solid: mp 44 °C; $[\alpha]^{25}_D$ +340° (*c* 0.24, $CHCl_3$); IR ($CHCl_3$) 3540–3300 (w), 2980 (s), 2940 (s), 2860 (m), 1685 (s), 1450 (m), 1385 (m), 1370 (m), 1275 (m), 1050 (m), 1000 (m), 960 (w), 905 (m), 880 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 3 H), 1.24 (s, 3 H), 1.45 (s, 3 H), 1.47–1.58 (comp m, 3 H), 1.25–1.32 (comp m, 2 H), 1.78 (m, 3 H), 1.95 (ddd, *J* = 4.6, 12.5, 14.2 Hz, 1 H), 2.11 (ddd, *J* = 5.0, 12.6, 14.6 Hz, 1 H), 2.25 (ddd, *J* = 4.6, 7.1, 14.6 Hz, 1 H), 2.34 (m, 1 H), 4.30 (d, *J* = 0.7 Hz, 1 H), 6.16 (d, *J* = 0.7 Hz, 1 H), 7.88 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 21.3, 22.9, 23.3, 26.3, 28.9, 29.2, 29.7, 32.9, 37.0,

38.2, 77.2, 79.7, 87.2, 105.1, 126.4, 195.0; high-resolution mass spectrum (CI, NH_3) m/z 309.1674 [$(M + H)^+$; calcd for $C_{17}H_{24}O_5$ 309.1702].

Hydroxy Enone 71. A solution of hydroperoxide **70** (1.7 mg, 0.005 mmol) in benzene (0.1 mL) was treated with triphenylphosphine (2.4 mg, 0.009 mmol), and the mixture was stirred 20 min at room temperature. The reaction mixture was then loaded onto a preparative TLC plate (0.5 mm, 8 cm × 8 cm) and developed once with hexanes–diethyl ether–methylene chloride (4:3:3) to afford **71** (1.5 mg, 93% yield) as a colorless oil: $[\alpha]^{24}_D$ +313° (c 0.35, $CHCl_3$); IR ($CHCl_3$) 3520 (w, br), 2980 (m), 2940 (s), 2850 (m), 1690 (s), 1450 (m), 1370 (m), 1270 (m), 1100 (m), 1060 (m), 1040 (m), 1000 (m), 880 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 3 H), 1.20 (s, 3 H), 1.23–1.36 (comp m, 3 H), 1.42 (s, 3 H), 1.46–1.53 (comp m, 2 H), 1.58 (m, 1 H), 1.69 (br d, J = 13.4 Hz, 1 H), 1.79 (td, J = 4.2, 14.0 Hz, 1 H), 1.91 (m, 2 H), 2.05 (td, J = 4.5, 14.4 Hz, 1 H), 2.21 (td, J = 5.2, 14.6 Hz, 1 H), 2.61 (s, 1 H), 4.25 (d, J = 0.6 Hz, 1 H), 6.16 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 21.7, 22.8, 23.7, 28.5, 29.0, 29.3, 31.0, 33.5, 37.7, 75.3, 80.3, 87.1, 104.3, 122.8, 162.4, 195.1; high-resolution mass spectrum (CI, NH_3) m/z 293.1791 [$(M + H)^+$; calcd for $C_{17}H_{25}O_4$ 293.1753].

Epoxy Alcohol 73. A solution of alcohol **62** (140 mg, 0.50 mmol) in methylene chloride (8.4 mL) was cooled to 0 °C, treated with m-CPBA (130 mg, 0.75 mmol), and stirred for 75 min. Sodium bisulfite solution (10%, 5 mL) was added, the ice bath was removed, and the mixture was allowed to stir for 15 min. Concentration in vacuo and flash chromatography (20% EtOAc in hexanes) furnished **73** (124 mg, 84% yield) as an oil: $[\alpha]^{25}_D$ +4.1° (c 0.44, $CHCl_3$); IR ($CHCl_3$) 3580 (m), 3020 (m), 2990 (s), 2960 (s), 2880 (m), 1480 (m), 1460 (m), 1400 (m), 1380 (m), 1330 (w), 1250 (m, br), 1170 (s), 1065 (s), 1045 (s), 1005 (s), 955 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (ddd, J = 1.9, 6.7, 13.1 Hz, 1 H), 1.07 (s, 3 H), 1.32 (s, 3 H), 1.34 (s, 3 H), 1.40–1.49 (comp m, 3 H), 1.55–1.60 (comp m, 3 H), 1.69–1.80 (comp m, 3 H), 1.90 (ddd, J = 2.0, 6.1, 15.8 Hz, 1 H), 2.07 (ddd, J = 6.7, 14.3, 15.7 Hz, 1 H), 2.60 (dd, J = 4.5, 14.8 Hz, 1 H), 2.88 (d, J = 11.5 Hz, 1 H), 3.92 (m, 1 H), 4.05 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 20.5, 21.2, 23.6, 24.2, 29.2, 30.0, 31.4, 32.0, 33.5, 38.0, 64.5, 66.7, 67.9, 79.1, 86.4, 105.6; high-resolution mass spectrum (CI, NH_3) m/z 312.2198 [$(M + NH_3)^+$; calcd for $C_{17}H_{30}NO_4$ 312.2175].

Paspalinine Model 57. A solution of oxalyl chloride (55 μL, 0.63 mmol) in methylene chloride (3.3 mL) was cooled to −78 °C, and a solution of DMSO (89 μL, 1.26 mmol) in CH_2Cl_2 (1.7 mL) was added dropwise. The mixture was stirred for 15 min, a solution of epoxy alcohol **73** (124 mg, 0.42 mmol) in CH_2Cl_2 (3.3 mL) was introduced, and the reaction was stirred 60 min further. Triethylamine (0.35 mL, 2.52 mmol) was then added at −78 °C, and after 10 min the cooling bath was removed, and the mixture was allowed to warm to room temperature. After 45 min, water was added, and the mixture was extracted with dichloromethane. Flash chromatography (15% EtOAc in hexanes) gave **57** (101 mg, 82% yield) as a colorless solid: mp 109.5–110.5 °C (heptane); $[\alpha]^{24}_D$ +330° (c 0.24, $CHCl_3$); IR ($CHCl_3$) 3600 (w), 3000 (m), 2960 (s), 2890 (w), 1705 (s), 1470 (w), 1400 (w), 1380 (m), 1285 (m), 1165 (m), 1050 (m), 1010 (s), 925 (m), 905 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 3 H), 1.18 (s, 3 H), 1.25–1.38 (comp m, 2 H), 1.42 (s, 3 H), 1.50 (m, 2 H), 1.64–1.79 (comp m, 7 H), 1.86 (dd, J = 8.1, 13.6 Hz, 1 H), 2.61 (dt, J = 10.4, 13.5 Hz, 1 H), 4.29 (d, J = 0.9 Hz, 1 H), 5.87 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 20.8, 23.0, 23.7, 27.7, 28.9, 30.0, 32.7, 31.2, 36.4, 74.7, 78.5, 88.0, 104.3, 119.0, 169.4, 196.9; high-resolution mass spectrum (CI, isobutane) m/z 293.1739 [$(M + H)^+$; calcd for $C_{17}H_{25}O_4$ 293.1753].

Dimethylhydrazones 74a,b. To a stirred solution of enone **23** (0.894 g, 2.92 mmol) in 40 mL of absolute ethanol were added N,N-dimethylhydrazine (1.11 mL, 14.64 mmol) and a catalytic amount of acetic acid (ca. 40 μL). The mixture was stirred at room temperature for 24 h and then concentrated. Flash chromatography (hexane–ethyl acetate, 1:1) gave 1.105 g (96% yield) of a 2:1 mixture of (Z)- and (E)-dimethylhydrazones **74a,b**, as determined by ^1H NMR: yellow oil; IR ($CHCl_3$) 3470 (m), 3350 (br), 3010 (m), 2960 (s), 2860 (m), 1620 (w), 1450 (m), 1305 (m), 1225 (m), 980 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.91 (s, 3 H), 1.27, 1.29 (s, s, diastereomers, 3 H), 1.73–1.85 (m, 3 H), 2.28–2.65 (complex m, 5 H), 2.53, 2.54 (s, s, diastereomers, 6 H), 2.78 (m, 1 H), 3.12 (m, 2 H), 6.05, 6.61, (s, s, diastereomers, 1 H), 7.09 (m, 2 H), 7.33 (m, 1 H), 7.45 (m, 1 H), 7.89 (br s, 1 H); high-resolution mass spectrum (CI, NH_3) m/z 348.2417 [$(M + H)^+$; calcd for $C_{23}H_{30}N_3$ 348.2440].

Indole Alcohol 75. For a description of the apparatus and general procedures employed in this experiment, see the preparation of alcohol **65**. A solution of diisopropylamine (0.77 mL, 5.50 mmol) in THF (6 mL) was cooled to −20 °C, n-butyllithium (2.8 M, 1.70 mL, 4.75 mmol) was added, and the mixture was stirred for 15 min. Following dropwise addition over 6 min of a solution of hydrazones **74a,b** (869 mg, 2.50 mmol) in THF (6.5 mL), the mixture was stirred at 0 °C for 15 min, warmed to room temperature, and then heated at 65 °C for 15 h. After 2 h of heating, the reaction vessel was flushed with argon for 60 s. The solution was cooled to room temperature, and epoxide **24** (595 mg, 3.0 mmol) was added neat. The reaction was stirred for 3 h, quenched with pH 7 buffer, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was then treated with benzoic acid (305 mg, 2.50 mmol) in dichloromethane (25 mL) at room temperature for 1 h to isomerize the double bond into conjugation. The reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with dichloromethane, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (hexane–ethyl acetate, 4:1) afforded 793 mg (65% yield) of **75** as a yellow foam and 142 mg (14% yield) of recovered **74a,b**.

75: $[\alpha]^{24}_D$ +370° (c 0.15, $CHCl_3$); IR ($CHCl_3$) 3470 (m), 3250 (br), 2970 (s), 2870 (s), 1450 (m), 1365 (w), 1330 (w), 1300 (m), 1225 (m), 1200 (m), 1100 (m), 970 (w), cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.91 (s, 3 H), 1.25 (s, 3 H), 1.30 (s, 3 H), 1.41 (s, 3 H), 1.51–1.93 (complex m, 13 H), 2.16–2.64 (complex m, 4 H), 2.54 (s, 6 H), 2.79 (m, 1 H), 3.07 (m, 2 H), 3.37 (m, 2 H), 3.50 (m, 1 H), 7.09 (m, 2 H), 7.32 (m, 1 H), 7.45 (m, 1 H), 7.81 (br s, 1 H), O*H* not resolved; high-resolution mass spectrum (FAB, p-nitrobenzyl alcohol matrix) m/z 546.3720 [$(M + H)^+$; calcd for $C_{34}H_{48}O_3N_3$, 546.3695].

Acetate 76. A stirred solution of alcohol **75** (793 mg, 1.4 mmol) in pyridine (14 mL) was treated with 4-(dimethylamino)pyridine (89 mg, 0.7 mmol) and acetic anhydride (1.37 mL, 14 mmol). The mixture was stirred for 17 h at 45 °C under argon, cooled to 0 °C, and quenched with saturated sodium bicarbonate solution. After extraction with ethyl acetate, the organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (15% EtOAc in hexanes) gave acetate **76** (717 mg, 84% yield) as a yellow solid: mp 188 °C; $[\alpha]^{24}_D$ +195° (c 0.28, $CHCl_3$); UV (absolute EtOH) λ_{max} 245 (ϵ 10 100), 282 (ϵ 8100) nm; IR ($CHCl_3$) 3485 (m), 2965 (s), 2860 (s), 1730 (s), 1665 (w, br), 1450 (s, br), 1370 (s), 1330 (m), 1300 (m), 1230 (s, br), 1110 (s), 1020 (m), 970 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (s, 3 H), 1.16 (s, 3 H), 1.24 (s, 3 H), 1.29 (s, 3 H), 1.65–1.91 (comp m, 12 H), 1.95 (s, 3 H), 2.09–2.16 (m, 1 H), 2.28 (m, 1 H), 2.38 (dd, J = 10.3, 13.4 Hz, 1 H), 2.56 (s, 6 H), 2.65 (app t, J = 10.9 Hz, 1 H), 2.76 (dd, J = 6.5, 13.4 Hz, 1 H), 3.04 (br d, J = 17.7 Hz, 1 H), 3.09 (m, 1 H), 3.25 (br d, J = 15.0 Hz, 1 H), 3.36 (br d, J = 13.2 Hz, 1 H), 3.66 (d, J = 8.2 Hz, 1 H), 5.30 (m, 1 H), 7.06–7.12 (comp m, 2 **H**), 7.32 (d, J = 6.9 Hz, 1 H), 7.44 (d, J = 8.0, 1 H), 7.77 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.3, 20.4, 21.1, 21.6, 22.8, 23.5, 23.8, 25.0, 27.0, 27.4, 28.0, 29.7, 30.6, 31.4, 38.4, 38.7, 42.8, 47.5, 48.1, 50.8, 71.8, 80.1, 84.4, 111.5, 117.2, 118.5, 118.8, 119.7, 120.7, 125.0, 129.6, 140.1, 147.8, 149.0, 161.9, 169.4; high-resolution mass spectrum (CI, NH_3) m/z 588.3784 [$(M + H)^+$; calcd for $C_{36}H_{50}N_3O_4$ m/z 588.3801].

Enone 22 and Alcohol 77. Iodomethane (77 μL, 1.2 mmol) was added to a solution of dimethylhydrazone acetate **76** (72 mg, 0.12 mmol) in acetonitrile (2.5 mL), and the mixture was stirred for 18 h at room temperature. Following concentration in vacuo, the residue was dissolved in 90% methoxyethanol (6.2 mL) containing sodium formate (167 mg, 24 mmol). The mixture was heated to 110 °C for 20 h under argon, then cooled to room temperature, poured into water, and extracted with ethyl acetate. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (12% EtOAc in hexanes) gave enone **22** (39 mg, 59% yield) and alcohol **77** (15 mg, 22% yield).

22: colorless solid; mp 110 °C: $[\alpha]^{24}_D$ +26° (c 0.31, $CHCl_3$); UV (absolute EtOH) λ_{max} 240 (ϵ 8800), 280 (ϵ 7400) nm; IR ($CHCl_3$) 3480 (m), 2980 (s), 2940 (s), 2880 (s), 1730 (s), 1670 (s), 1450 (s, br), 1370 (s), 1330 (m), 1300 (m), 1230 (s, br), 1110 (s), 1030 (m, br), 920 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (s, 3 H), 1.06 (s, 3 H), 1.27 (s, 3 H), 1.34 (s, 3 H), 1.50–1.95 (comp m, 13 H), 1.98 (s, 3 H), 2.25–2.35 (m, 1 H), 2.40 (dd, J = 10.3, 13.4 Hz, 1 H), 2.47 (d, J = 11.6 Hz, 1 H), 2.58–2.66 (comp m, 2 H), 2.79 (dd, J = 6.5, 13.5 Hz, 1 H), 3.06–3.13 (comp m, 2 H), 3.62 (d, J = 8.9 Hz, 1 H), 4.87–4.90 (m, 1 H), 7.08 (m, 2 H), 7.29 (d, J = 6.8 Hz, 1 H), 7.43 (d, J = 7.7 Hz, 1 H), 7.75 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6, 20.0, 21.0, 22.3, 23.6, 23.9, 24.5, 26.9, 27.3, 28.5, 29.6, 31.6, 33.7, 38.1, 38.4, 43.5, 47.6, 50.9, 71.8, 80.1, 83.6, 111.6, 117.3, 118.6, 119.1, 119.8, 121.0, 124.9, 132.5, 140.2, 148.1, 161.8, 169.7, 197.5; high-resolution mass spectrum (CI, NH_3) m/z 545.3141 (M^+; calcd for $C_{34}H_{43}NO_5$ 545.3111).

77: colorless oil; IR ($CHCl_3$) 3480 (m), 3010 (m), 2970 (s), 2850 (w), 1735 (s), 1665 (s), 1595 (w), 1370 (m), 1330 (m), 1300 (m), 1220 (s, br), 1100 (s), 1020 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (s, 3 H), 1.08 (s, 3 H), 1.32 (s, 3 H), 1.53 (s, 3 H), 1.40 (m, 1 H), 1.58–1.71 (comp m, 6 H), 1.76–1.88 (comp m, 3 H), 2.06 (s, 3 H), 2.07–2.13 (comp m, 2 H), 2.44 (dd, J = 10.4, 13.5 Hz, 1 H), 2.60 (m, 2 H), 2.75 (m, 2 H), 2.86 (dd, J = 6.7, 13.5 Hz, 1 H), 3.15 (dd, J = 7.0, 13.7 Hz, 1 H),

3.56 (m, 1 H), 3.68 (d, J = 8.9 Hz, 1 H), 5.04 (m, 2 H), 7.11 (m, 2 H), 7.31 (dd, J = 1.7, 6.5 Hz, 1 H), 7.47 (dd, J = 1.8, 6.5 Hz, 1 H), 7.73 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.9, 20.9, 21.6, 22.1, 23.6, 23.9, 26.6, 27.0, 28.8, 31.3, 32.5, 33.8, 38.2, 38.4, 41.8, 42.9, 50.5, 67.5, 71.9, 80.3, 83.4, 111.5, 117.6, 118.7, 119.3, 119.8, 121.0, 124.9, 134.4, 140.3, 147.9, 160.6, 169.7, 198.6; high-resolution mass spectrum (CI, NH_3) m/z 561.3152 (M^+; calcd for $C_{34}H_{43}NO_6$ (561.3090).

Bicyclic Ketals 21 and 80. A solution of enone **22** (45 mg, 0.083 mmol) in dichloromethane (8 mL) was cooled to 0 °C, treated with 70% $HClO_4$ (12 μL, 0.083 mmol), and stirred for 1 h. THe mixture was quenched with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic phases were washed with brine, dried over $MgSO_4$, and concentrated. The residue was filtered through silica to furnish a 2:1 mixture of bicyclic ketals (29 mg). The latter was dissolved in methanol (2.1 mL), potassium carbonate (17.5 mg, 0.12 mmol) was added, and the mixture was stirred at room temperature for 3 h. After filtration and concentration, preparative TLC (20 × 20 cm, 0.5 mm, 50% EtOAc in hexanes, one development) afforded alcohol **21** (17.4 mg, 67% yield) and the isomer **80** (7.2 mg, 28% yield).

21: colorless solid; mp 245 °C; $[\alpha]^{24}_D$ +20° (c 0.22, $CHCl_3$); IR ($CHCl_3$) 3560 (w, br), 3480 (m), 2940 (s), 2880 (s), 1725 (w, br), 1445 (s, br), 1370 (m), 1305 (m), 1230 (m, br), 1130 (s), 1110 (s), 995 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 1.18 (s, 3 H), 1.34 (s, 3 H), 1.41 (s, 3 H), 1.60 (br d, J = 12.4 Hz, 1 H), 1.75 (comp m, 2 H), 1.92–1.97 (comp m, 2 H), 2.17–2.30 (m, 2 H), 2.39 (m, 3 H), 2.65 (m, 1 H), 2.72–2.80 (m, 2 H), 3.03 (comp m, 1 H), 3.89 (br d, J = 11.6 Hz, 1 H), 3.97 (br s, 1 H), 7.06 (m, 2 H), 7.29 (d, J = 8.5 Hz, 1 H), 7.42 (d, J = 8.5 Hz, 1 H), 7.71 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.5, 20.0, 20.3, 24.7, 25.6, 29.4, 29.7, 30.2, 30.3, 32.4, 42.1, 48.0, 50.6, 67.3, 78.7, 86.1, 106.0, 111.5, 118.5, 118.9, 119.7, 120.7, 125.0, 128.4, 133.4, 139.2, 148.9; high-resolution mass spectrum (CI, NH_3) m/z 420.2519 [(M + H)$^+$; calcd for $C_{27}H_{34}NO_3$ 420.2538].

80: colorless solid; mp 122 °C; $[\alpha]^{24}_D$ −69° (c 0.30, $CHCl_3$); IR ($CHCl_3$) 3550 (w, br), 3480 (m), 2930 (s), 2850 (s), 1730 (w, br), 1450 (m, br), 1370 (m), 1300 (m), 1130 (s, br), 1070 (s), 990 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (s, 3 H), 1.21 (s, 3 H), 1.32 (s, 3 H), 1.38 (s, 3 H), 1.60 (br d, J = 12.5 Hz, 1 H), 1.83 (br d, J = 13.1 Hz, 1 H), 2.17–2.48 (comp m, 9 H), 2.78–2.87 (comp m, 2 H), 3.74 (br d, J = 11.7 Hz, 1 H), 3.92 (br s, 1 H), 6.01 (br s, 1 H), 7.06 (m, 2 H), 7.29 (d, J = 7.1 Hz, 1 H), 7.43 (d, J = 6.8 Hz, 1 H), 7.73 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3, 20.5, 22.1, 25.1, 27.0, 27.2, 29.2, 29.7, 31.0, 32.3, 41.5, 45.4, 49.2, 65.3, 79.4, 86.3, 109.0, 111.4, 118.5, 118.6, 119.6, 120.7, 122.4, 124.9, 140.3, 142.6, 149.1; high-resolution mass spectrum (CI, NH_3) m/z 420.2501 [(M + H)$^+$; calcd for $C_{27}H_{34}NO_3$ 420.2538].

β,γ-Enone 81. A solution of alcohol ketal **21** (6.0 mg, 0.014 mmol) in benzene (0.7 mL) and DMSO (0.7 mL) was treated with pyridine (7 μL, 0.084 mmol), trifluoroacetic acid (2.2 μL, 0.028 mmol), and DCC (36 mg, 0.17 mmol) and then stirred at room temperature for 19 h. The mixture was filtered and partitioned between diethyl ether and water. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Preparative TLC (10 × 10 cm, 0.5 mm, hexanes–diethyl ether–methylene chloride, 2:1:1, one development) furnished β,γ-enone **81** (3.8 mg, 63% yield) and paspalicine (**2**) (0.9 mg, 15% yield). **81**: colorless solid; mp 230 °C; $[\alpha]^{24}_D$ +61° (c 0.2, $CHCl_3$); IR ($CHCl_3$) 3480 (m), 2940 (s), 2860 (m), 1725 (s), 1450 (m, br), 1370 (m), 1300 (m), 1230 (w, br), 1150 (s), 1100 (s), 1060 (m), 1040 (m), 920 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (s, 3 H), 1.23 (s, 3 H), 1.26 (s, 3 H), 1.37 (s, 3 H), 1.68 (ddd, J = 4.5, 12.9, 25.7 Hz, 1 H), 1.77 (m, 2 H), 2.04 (m, 1 H), 2.17 (m, 1 H), 2.29–2.38 (comp m, 3 H), 2.44 (ddd, J = 1.9, 4.5, 15.5 Hz, 1 H), 2.73 (dd, J = 6.5, 12.6 Hz, 1 H), 3.00 (m, 1 H), 3.12 (dd, J = 2.3, 20.5 Hz, 1 H), 3.35 (d, J = 20.5 Hz, 1 H), 4.10 (s, 1 H), 7.05–7.10 (comp m, 2 H), 7.31 (dd, J = 2.8, 6.7 Hz, 1 H), 7.42 (dd, J = 1.8, 7.5 Hz, 1 H), 7.76 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6, 21.8, 22.2, 24.4, 25.7, 27.3, 28.1, 30.7, 31.1, 40.5, 41.6, 48.3, 51.1, 79.1, 88.4, 105.7, 111.5, 118.5, 118.8, 119.7, 120.8, 124.9, 126.2, 138.7, 140.1, 148.9, 205.3; high-resolution mass spectrum (CI, NH_3) m/z 418.2339 [(M + H)$^+$; calcd for $C_{27}H_{32}NO_3$ 418.2382].

Paspalicine (2). A solution of β,γ-enone **81** (3.0 mg) and rhodium trichloride (1 mg) in absolute ethanol (0.2 mL) and benzene (0.8 mL) was heated to reflux for 17 h (oil bath temperature 100 °C). The mixture was cooled to room temperature, filtered, and concentrated in vacuo. Preparative TLC (10 × 10 cm, 0.5 mm, hexanes–diethyl ether–dichloromethane, 2:1:1, one development) gave paspalicine (**2**) (2.0 mg, 70% yield) as a colorless solid: mp 229–234 °C (dec [ether–methanol, 3:1 (v/v)] [natural product:[3a] mp ca. 230 °C dec; mmp 227–232 °C dec]; $[\alpha]^{24}_D$ +128° (c 0.23, $CHCl_3$) {natural product:[3a] $[\alpha]_D$ +173° (c 0.5, $CHCl_3$)}; IR ($CHCl_3$) 3480 (m), 2960 (s), 2860 (m), 1680 (s), 1620 (w), 1450 (m), 1370 (m), 1295 (m), 1255 (m), 1130 (s), 1000 (w), 965 (m), 910 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 3 H), 1.13 (s, 3 H), 1.20 (s, 3 H), 1.41 (s, 3 H), 1.50 (m, 1 H), 1.72 (ddd, J = 4.2, 12.9, 25.9 Hz, 1 H), 1.81–1.99 (comp m, 4 H), 2.12 (td, J = 7.6, 15.3 Hz, 1 H), 2.38 (dd, J = 10.4, 13.3 Hz, 1 H), 2.46 (dd, J = 7.6, 12.3 Hz, 1 H), 2.71 (dd, J = 6.4, 13.2 Hz, 1 H), 2.80 (m, 1 H), 2.98 (dt, J = 3.3, 10.5 Hz, 1 H), 4.30 (d, J = 1.3 Hz, 1 H), 5.75 (br s, 1 H), 7.05–7.11 (comp m, 2 H), 7.31 (d, J = 7.5 Hz, 1 H), 7.42 (d, J = 7.5 Hz, 1 H), 7.70 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 21.5, 23.2, 23.7, 23.8, 27.6, 28.4, 28.9, 29.2, 37.3, 39.8, 48.2, 51.3, 77.8, 88.3, 103.9, 111.5, 118.3, 118.5, 119.8, 120.0, 120.7, 125.1, 140.0, 149.4, 172.0, 195.9; high-resolution mass spectrum (CI, NH_3) m/z 418.2399 [(M + H)$^+$; calcd for $C_{27}H_{32}NO_3$ 418.2382].

Paspalinine (3) and Diol 82. A solution of paspalicine (**2**) (2.0 mg, 4.8 mmol) in dioxane (0.2 mL) was treated with selenium dioxide (2 mg, 0.019 mmol) and stirred at 85 °C for 80 min under argon. The mixture was cooled to room temperature, poured into water, and extracted with ethyl acetate. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Preparative TLC (10 × 10 cm, 0.5 mm, 35% EtOAc in hexanes, one development) afforded paspalinine (**3**) (0.9 mg, 44% yield) and **82** (0.8 mg, 40% yield).

3: colorless solid; mp 213–216 °C dec [natural product: mp 213–215 °C dec; mmp 211–215 °C dec]; $[\alpha]^{24}_D$ +138° (c 0.12, $CHCl_3$); {lit.[42] $[\alpha]^{25}_D$ +186.4 (c 1.115, $CHCl_3$)}; IR ($CHCl_3$) 3580 (w), 3480 (m), 2930 (s), 2860 (s), 1680 (s), 1450 (s, br), 1360 (m), 1300 (m), 1260 (m), 1130 (s), 1000 (m), 970 (m), 910 (m), 890 (m), 610 (m) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 0.85–1.10 (comp m, 2 H), 1.10 (s, 3 H), 1.12 (s, 3 H), 1.24 (s, 3 H), 1.30 (s, 3 H), 1.28–1.37 (comp m, 2 H), 1.68 (m, 1 H), 2.03 (dd, J = 8.7, 13.4 Hz, 1 H), 2.14 (br s, 1 H), 2.24 (app t, J = 11.8 Hz, 1 H), 2.37 (dd, J = 9.9, 12.2 Hz, 1 H), 2.54–2.64 (comp m, 2 H), 2.85 (dt, J = 10.2, 13.5 Hz, 1 H), 4.28 (s, 1 H), 5.54 (s, 1 H), 6.97 (br s, 1 H), 7.17–7.24 (comp m, 3 H), 7.61 (dd, J = 3.9, 6.2 Hz, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 16.4, 21.2, 23.1, 23.5, 27.0, 27.8, 28.7, 28.8, 33.3, 39.8, 46.7, 51.7, 77.3, 78.7, 88.3, 104.8, 111.9, 117.4, 118.0, 119.1, 120.2, 121.0, 127.5, 140.6, 151.8, 170.3, 196.4; high-resolution mass spectrum (CI, NH_3) m/z 434.2364 [(M + H)$^+$; calcd for $C_{27}H_{32}NO_4$ 434.2331].

82: colorless oil; IR ($CHCl_3$) 3480 (w), 3000 (w), 2940 (m), 2860 (m), 1700 (m), 1450 (m), 1370 (w), 1140 (s), 1110 (s), 1005 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (s, 3 H), 1.23 (s, 3 H), 1.30 (s, 3 H), 1.46 (s, 3 H), 1.67–1.85 (comp m, 3 H), 1.92–2.04 (comp m, 2 H), 2.13–2.29 (comp m, 3 H), 2.34 (dd, J = 10.5, 13.5 Hz, 1 H), 2.70 (m, 1 H), 2.76 (dd, J = 6.5, 13.4 Hz, 1 H), 2.92 (m, 1 H), 4.32 (s, 1 H), 6.08 (s, 1 H), 7.09 (m, 2 H), 7.31 (d, J = 7.7 Hz, 1 H), 7.43 (d, J = 6.9 Hz, 1 H), 7.69 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.1, 21.8, 22.7, 23.2, 27.1, 28.8, 29.5, 29.7, 30.2, 35.5, 44.5, 49.2, 51.5, 74.8, 77.2, 79.1, 87.9, 105.6, 111.5, 117.7, 118.6, 119.8, 120.0, 120.9, 125.0, 140.1, 150.2, 169.4, 195.8; high-resolution mass spectrum (CI, NH_3) m/z 434.1943 [(M − CH_3)$^+$; calcd for $C_{26}H_{28}NO_5$ 434.1967].

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Supplementary Material Available: Tables of experimental details, positional parameters, and thermal parameters for X-ray analyses of paspalicine and compound **57** (17 pages). Ordering information is given on any current masthead page.