cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.20–3.00 (m, 3 H), 3.10–3.35 (m, 1 H), 3.46 and 3.52 (s, total 3 H), 3.66 and 3.67 (s, total 3 H), 3.70 and 3.71 (s, total 3 H), 4.80–5.00 (m, 1 H), 5.10–5.30 (m, 2 H), 5.50–5.95 (m, 1 H), 7.48 (m, 1 H) ppm; MS m/z (relative intensity) 270 (M^+, 20), 238 (21), 178 (77), 165 (20), 84 (100). Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 58.02; H, 6.65.

Acknowledgment. We thank the National Science Council of the Republic of China for generous support of this research.

Total Synthesis of (±)-Dihydropinidine, (±)-Monomorine I, and (±)-Indolizidine 223AB (Gephyrotoxin 223AB) by Intramolecular Nitroso Diels–Alder Reaction

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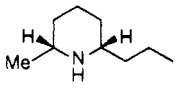
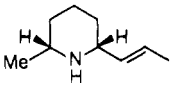
The total synthesis of alkaloids possessing saturated nitrogen heterocyclic ring systems such as (±)-dihydropinidine (**1**), (±)-monomorine I (**3**), and (±)-indolizidine 223AB (gephyrotoxin 223AB) (**4**) is described. The synthetic strategy for a general approach to these alkaloids is based on highly regio- and stereoselective intramolecular acyl nitroso Diels–Alder cycloaddition leading to bicyclic oxazinolactams **13** and **36**. Subsequent introduction of the C-8 alkyl side chain was elaborated by means of a completely stereocontrolled process involving Grignard reaction followed by reduction. The bicyclic oxazines **22**, **39**, and **49** thus obtained were then subjected to reductive N–O bond cleavage, affording the *cis*-2,6-dialkylpiperidines **17**, **40**, and **50**, which were led to the alkaloids **1**, **3**, and **4**, respectively, through intramolecular ring closure in the latter two cases.

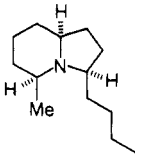
Hetero Diels–Alder reactions in which the *C*-nitroso moiety (RN=O) functions as a heterodienophile provide cyclic derivatives of hydroxylamine, namely, 3,6-dihydro-1,2-oxazines.[1-3] A synthetically important feature of this cycloaddition is the simultaneous introduction of nitrogen and oxygen functionalities into a 1,3-diene at the positions 1 and 4 with both regiochemical and stereochemical control. Compared to the intramolecular imino Diels–Alder reaction,[2] the intramolecular variant of the nitroso Diels–Alder reaction has received far less attention,[3b,h,4] despite the enormous potential it holds for alkaloid synthesis. With this in mind, we proceeded to investigate application of the intramolecular nitroso Diels–Alder cycloaddition in the synthesis of alkaloids possessing saturated nitrogen heterocyclic ring systems such as the piperidine and octahydroindolizidine skeletons. In this paper, we describe the development of a successful new approach to (±)-dihydropinidine (**1**), (±)-monomorine I (**3**), and (±)-indolizidine 223AB (gephyrotoxin 223AB)[5] (**4**) based on an intramolecular nitroso Diels–Alder strategy involving a high degree of stereocontrol.[7]



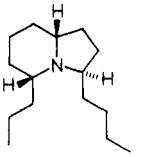
1



2



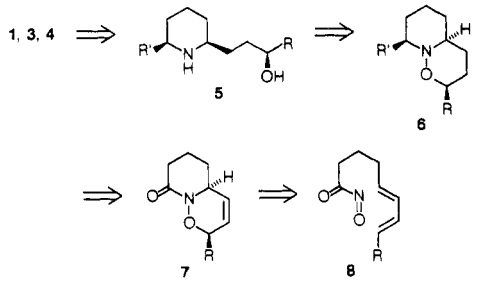
3



4

Our synthetic strategy for a general approach to these nitrogen-containing natural products **1**, **3**, and **4** is illustrated in Scheme I. Key features involved in this approach are an intramolecular Diels–Alder cycloaddition of

Scheme I



5 **6** **7** **8**

† Deceased Nov 12, 1988.

(1) For a review of the hetero Diels–Alder reaction of nitroso compounds, see: Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1.

(2) For reviews of heterodienophile Diels–Alder reactions, see: (a) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949. (b) Weinreb, S. M.; Staib, R. S. *Tetrahedron* **1982**, *38*, 3127. (c) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16. (d) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (e) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Sysnthesis*; Academic Press: New York, 1987.

(3) For recent entries into natural products utilizing nitroso Diels–Alder reactions, see: (a) Leonard, N. J.; Playtis, A. J. *J. Chem. Soc., Chem. Commun.* **1972**, 133. (b) Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. (c) Keck, G. E.; Webb, R. R., II *J. Org. Chem.* **1982**, *47*, 1302. (d) Jung, M.; Offenbächer, G.; Retey, J. *Helv. Chim. Acta* **1983**, *66*, 1915. (e) Boldwin, J. E.; Bailey, P. D.; Gallacher, G.; Singleton, K. A.; Wallace, P. M. *J. Chem. Soc., Chem. Commun.* **1983**, 1049. Baldwin, J. E.; Otsuka, M.; Wallace, P. M. *Ibid.* **1985**, 1549. Baldwin, J. E.; Bailey, P. D.; Gallacher, G.; Otsuka, M.; Singleton, K. A.; Wallace, P. M. *Tetrahedron* **1984**, *40*, 3696. Baldwin, J. E.; Otsuka, M.; Wallace, P. M. *Ibid.* **1986**, *42*, 3097. (f) Iida, H.; Watanabe, Y.; Kibayashi, C. *Tetrahedron Lett.* **1984**, *25*, 5091. Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Org. Chem.* **1985**, *50*, 1818. (g) Defoin, A.; Fritz, H.; Geffroy, G.; Streith, J. *Tetrahedron Lett.* **1986**, *27*, 4727. (h) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2341.

(4) Keck, G. E. *Tetrahedron Lett.* **1978**, 4767.

(5) We comply with the proposal by Daly[6] that it is preferable to discontinue use of the term gephyrotoxin for the simple indolizidine class of dendrobatid alkaloids and to refer to it simply as indolizidines. Thus the former conventional name gephyrotoxin 223AB is termed indolizidine 223AB in this paper.

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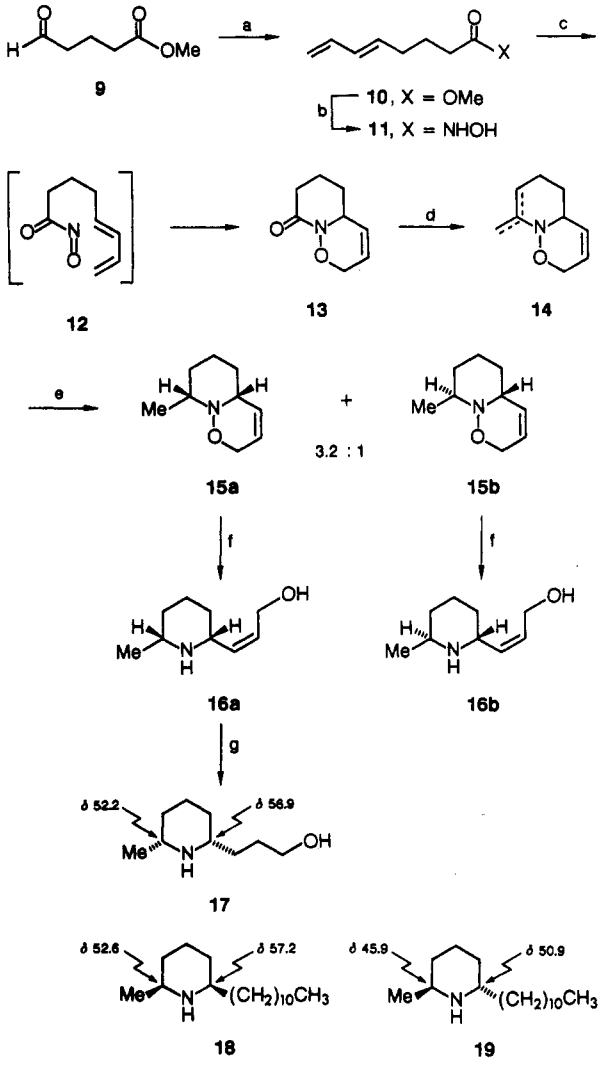
Scheme II[a]



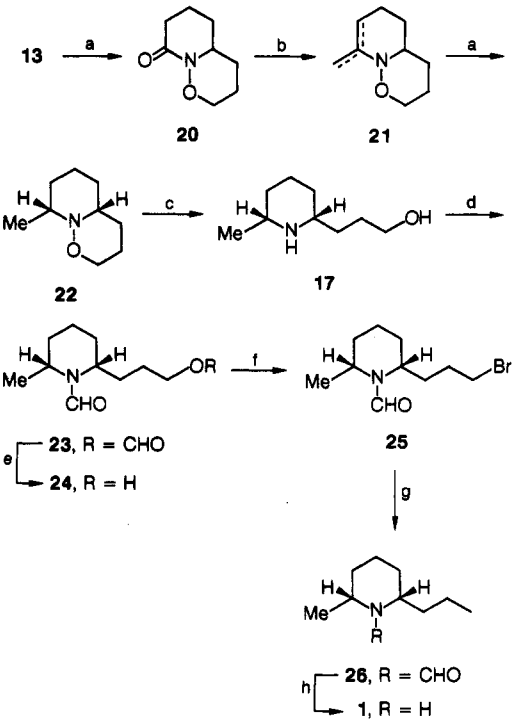
[a] (a) $Ph_3P{=}CHCH{=}CH_2$, Et_2O; (b) $NH_2OH{\cdot}HCl$, KOH, MeOH; (c) n-$Pr_4N(IO_4)$, $CHCl_3$; (d) MeMgBr, Et_2O; (e) $NaBH_3CN$, MeOH, pH 3.8–5.4 (HCl–MeOH, bromocresol green); (f) Zn, AcOH–H_2O; (g) H_2, 5% Pd/C, MeOH.

the acyl nitroso compound 8 and a stereoselective introduction of an alkyl side chain (R′) into the C-8 position of the oxazinolactam ring followed by reductive cleavage of the N–O bond.

Results and Discussion

1. Synthesis of (±)-Dihydropinidine. In order to realize the retrosynthetic approach outlined in Scheme I, we initially undertook the synthesis of (±)-dihydropinidine (**1**),[8,9] the dihydro derivative of pinidine (**2**), isolated from various species of *Pinus*.[10] Thus, as shown in Scheme II,

Scheme III[a]



[a] (a) H_2, 5% Pd/C, MeOH, 3 h; (b) MeMgBr, Et_2O; (c) H_2, 5% Pd/C, MeOH, 2 days; (d) HCO_2H, toluene; (e) NH_3, MeOH; (f) PBr_3, CH_2Cl_2; (g) H_2, 5% Pd/C, NEt_3, MeOH; (h) 10% HCl.

methyl (5*E*)-5,7-octadienoate (**10**), prepared by the Wittig reaction of methyl 5-oxopentanoate (**9**), was converted to the hydroxamic acid **11** in 73% yield by treatment with hydroxylamine in methanolic KOH. Oxidation of **11** with tetrapropylammonium periodate in chloroform at 0 °C generated the acyl nitroso compound **12** in situ. Under the reaction conditions, **12** smoothly underwent [4 + 2] cycloaddition to give the bicyclic oxazinolactam **13** in 86% yield. The Grignard reaction of **13** with methylmagnesium bromide in ether provided unstable **14** as a 1:1 equilibrium mixture of endocyclic and exocyclic enamines, which, without isolation, was immediately subjected to reduction with sodium cyanoborohydride in acidic medium, leading to an inseparable mixture of the cis and trans oxazines **15a** and **15b** in a ratio of 3.2:1.[11] The cis and trans relative stereochemistry adjacent to the ring nitrogen for **15a** and **15b**, respectively, was proven by the conversion of **15a** to the corresponding 2,6-dialkylpiperidine **17**. Thus, the mixture of **15a** and **15b** was subjected to reductive N–O bond cleavage by treatment with zinc and aqueous acetic acid to give a mixture of **16a** and **16b** in 73% yield. Repeated chromatography of the mixture on aluminum oxide provided **16a** as a pure major diastereomer, which was hydrogenated to produce **17**. The cis relationship of the C-2 and C-6 alkyl substituents in **17** was confirmed by its ^{13}C NMR spectrum, which showed the C-2 and C-6 signals

(6) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1986; Vol. 4, Chapter 1.

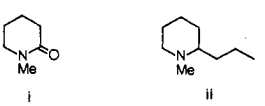
(7) Preliminary accounts of this work have appeared in the following: (a) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534. (b) Iida, H.; Watanabe, Y.; Kibayashi, C. *Tetrahedron Lett.* **1986**, *27*, 5513.

(8) Hill, R. K.; Yuri, T. *Tetrahedron* **1977**, *33*, 1569.

(9) For recent syntheses of dihydropinidine, see: (a) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 3369. (b) Comins, D. L.; Foley, M. A. *Ibid.* **1988**, *29*, 6711.

(10) (a) Tallent, W. H.; Stromberg, V. L.; Horning, E. C. *J. Am. Chem. Soc.* **1955**, *77*, 6361. (b) Tallent, W. H.; Horning, E. C. *Ibid.* **1956**, *78*, 4467. (c) Hill, R. K.; Chan, T. H.; Joule, J. A. *Tetrahedron* **1965**, *21*, 147.

(11) This sequence for C-alkylation consisting of the Grignard reaction and the subsequent stereocontrolled reduction could be successfully applied in this and following cases of the bicyclic oxazinolactams; however, when it was applied (PrMgBr, Et_2O, then $NaBH_3CN$, HCl/MeOH) to *N*-methyl-δ-valerolactam (i), only a trace amount of *N*-methylconiine (ii) was formed: ^{13}C NMR ($CDCl_3$) δ 14.5 (q), 18.6 (t), 24.4 (t), 25.8 (t), 30.7 (t), 35.2 (t), 42.9 (q), 57.2 (t), 63.9 (d); mass spectrum, *m/z* (relative intensity) 141 (M^+, 8), 140 (74), 98 (8), 87 (12), 85 (68), 83 (100).



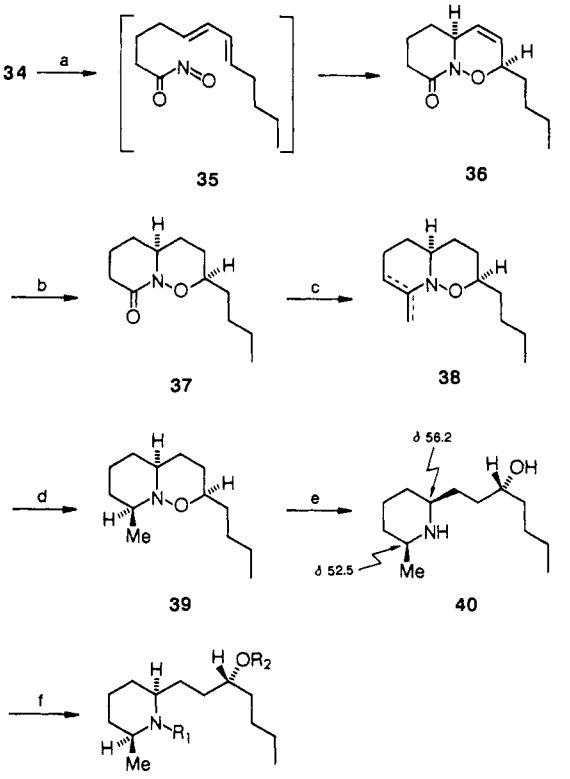
at δ 56.9 and 52.2, respectively, in much better agreement with those reported (δ 57.2 and 52.6) for the fire ant venom isosolenopsin A (**18**) than those (δ 50.9 and 45.9) for solenopsin A (**19**) (Scheme II).[12]

A highly stereoselective preparation of the desired isomer **17** was achieved by employing the alternative sequence outlined in Scheme III. Thus, after catalytic hydrogenation of **13** to **20**, the reaction with methylmagnesium bromide in ether generated the unstable enamine **21**, which subsequently underwent hydrogenation over palladium on carbon in methanol for 3 h to afford **22**. In this procedure, prolonged hydrogenation (2 days) resulted in further hydrogenolysis of the N–O bond, yielding the *cis*-dialkylpiperidine **17** as a single diastereomer in 66% overall yield from **20**. Heating **17** with formic acid in toluene produced the formamide **24** along with a considerable amount of the amide formate **23**. This mixture of **23** and **24** was exposed to ammonia in methanol at room temperature to give **24** in 81% yield. Bromination of **24** (PBr_3, CH_2Cl_2) followed by hydrogenation of the resulting bromide **25** over palladium on carbon in the presence of triethylamine gave **26** (44% yield from **24**), which was deprotected by treatment with acid to provide (±)-dihydropinidine (**1**) in 86% yield.

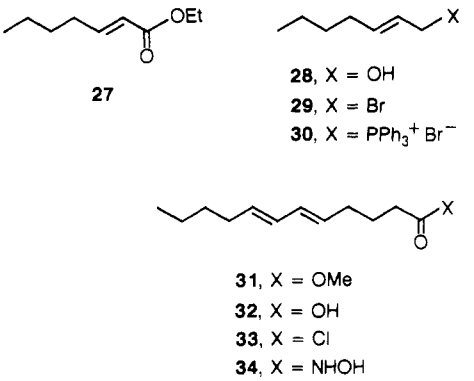
2. Synthesis of (±)-Monomorine I. Having developed the method for the construction of *cis*-2-alkyl-6-methylpiperidines based on an intramolecular nitroso Diels–Alder reaction followed by a highly stereoselective introduction of the methyl group, we then explored an extension of this methodology to the synthesis of (±)-monomorine I (**3**). This substance has been isolated from Pharaoh ants (*Monomorium pharaonis* L.) and has attractant and trail-initiating activity.[13] Due to its interesting biological properties, monomorine I (**3**) has been the subject of extensive synthetic efforts, which have culminated in several total syntheses of racemic material[14,15] and a chiral synthesis of the unnatural (–) enantiomer.[16] An enantioselective total synthesis of the natural (+) enantiomer of **3** has been achieved recently in our laboratory.[17]

Reduction of ethyl (*E*)-2-heptenoate (**27**), accessible by the Wittig reaction of 4-pentanal with [(ethoxycarbonyl)methylene]triphenylphosphorane, with AlH_3 afforded 2-heptenol (**28**) in 80% yield. Bromination of **28** with PBr_3 gave **29**, which was then converted to the triphenylphosphonium bromide **30**. The ylide produced from **30** (*n*-BuLi, THF, –5 °C) was allowed to react with methyl 5-oxopentanoate (**9**) in THF–HMPA (9:1) at –5 °C to furnish methyl (5*E*,7*E*)-dodecadienoate (**31**). Since the resulting material included ca. 25% (by ^1H NMR) of the 5*Z* isomer of **31**, this mixture was irradiated (hexane, I_2) to generate the isomerically pure 5*E*,7*E* ester **31** in 89% yield. Compound **31** was converted to the acid chloride **33** by saponification and chlorination [$(COCl)_2$], which was then reacted with hydroxylamine under aqueous alkaline conditions to form hydroxamic acid **34** in 58% overall yield from **31**. The overall yield of this product could be improved if **31** was exposed to hydroxylamine under alkaline conditions as described above for the preparation of **11** from **10**. In this manner pure **34** was directly obtained from **31** in 81% yield after recrystallization.

Scheme IV[a]



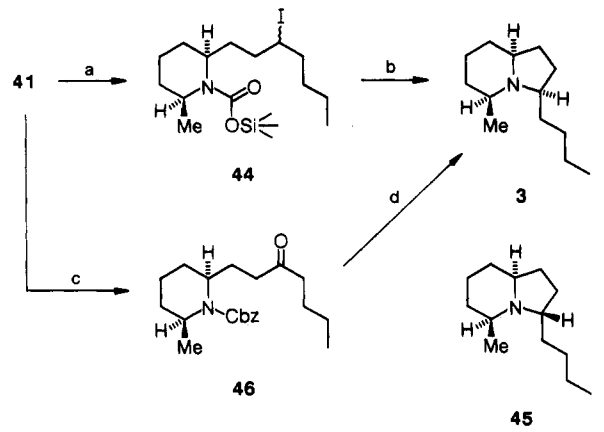
[a] (a) *n*-$Pr_4N(IO_4)$, $CHCl_3$; (b) H_2, 5% Pd/C, MeOH; (c) MeMgBr, Et_2O; (d) H_2, 5% Pd/C, MeOH; (e) Zn, AcOH–H_2O; (f) $PhCH_2OCOCl$ (1.5 equiv), aqueous Na_2CO_3, CH_2Cl_2.



Periodate oxidation [*n*-$Pr_4N(IO_4)$, $CHCl_3$, 0–4 °C] of this hydroxamic acid **34** generated the acyl nitroso compound **35** in situ, which spontaneously underwent intramolecular [4 + 2] cycloaddition to give the bicyclic 1,2-oxazine **36** in 82% yield (Scheme IV). Hydrogenation of **36** to **37** (90% yield) followed by a Grignard reaction (MeMgBr, Et_2O) afforded the somewhat unstable enamine **38**, which was hydrogenated, leading to **39** as a single isomer (71% yield from **37**). Reductive N–O bond cleavage of **39** with zinc in aqueous aceitc acid furnished the *cis*-2,6-dialkylpiperidine **40** in 68% yield. That **40** bears the 2- and 6-alkyl substituents in a cis relationship was confirmed by ^{13}C NMR in the same manner as described above for **17** (Scheme II). The signals for the C-2 and C-6 ring carbons appear at δ 56.2 and 52.5, closer to those reported for

(12) Moriyama, Y.; Huynh, D.-D.; Monneret, C.; Huu, Q.-K. *Tetrahedron Lett.* **1977**, 825.
(13) Ritter, F. J.; Rotgans, I. E. M.; Talman, E.; Verwiel, P. E. J.; Stein, F. *Experientia* **1973**, *29*, 530.
(14) (a) Oliver, J. E.; Sonnet, P. E. *J. Org. Chem.* **1974**, *39*, 2662. (b) Sonnet, P. E.; Oliver, J. E. *J. Heterocycl. Chem.* **1975**, *12*, 289. (c) Sonnet, P. E.; Netzel, D. A.; Mendoza, R. *Ibid.* **1979**, *16*, 1041.
(15) (a) Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193. (b) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 102. (c) Yamaguchi, R.; Hata, E.; Matsuki, T.; Kawanisi, M. *J. Org. Chem.* **1987**, *52*, 2094.
(16) Royer, J.; Husson, H.-P. *J. Org. Chem.* **1985**, *50*, 670.
(17) Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1988**, *29*, 5767.

Scheme V[a]



[a] (a) Me_3SiI, CH_2Cl_2; (b) MeOH; (c) $CrO_3 \cdot 2Py$, CH_2Cl_2; (d) H_2, 5% Pd/C, MeOH.

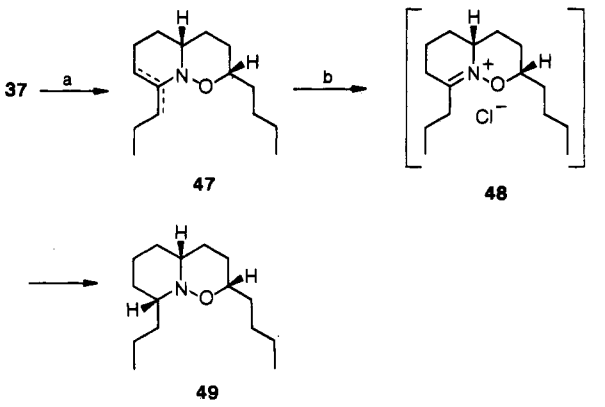
isosolenopsin A (**18**) than for solenopsin A (**19**). Treatment of **40** with benzyl chloroformate (1.5 equiv) afforded the benzyl carbamate **41** (53%), accompanied by a mixture of the *O*-monoacyl and *N,O*-diacyl products **42** (6%) and **43** (32%), which could readily be reconverted to the starting amino alcohol **40** by hydrogenolysis (H_2, Pd/C). Thus, the actual yield of **41** based on recovered **40** was 85%.

When treated with iodotrimethylsilane at room temperature, **41** underwent benzyl cleavage along with spontaneous iodination of the secondary alcohol to produce the silyl ester **44** (Scheme V). In situ cyclization was carried out by exposing **44** to methanol at room temperature to provide (±)-monomorine I (**3**) and its C-3 epimer **45** in 42% and 40% yields from **41**, respectively. An appreciable improvement of the diastereoselectivity in the cyclization to monomorine I was obtained by the following sequence: Compound **41** was converted to the ketone **46** by Collins oxidation in 94% yield. On reductive cyclization (H_2, Pd/C, MeOH) of **46**, (±)-monomorine I (**3**) was formed in 71% yield, along with (±)-3-epimonomorine I (**45**) as a minor isomer (15%). The resulting alkaloid **3** was spectrally and chromatographically identical with authentic samples of (−)- and (+)-monomorine I.[17]

3. Synthesis of (±)-Indolizidine 223AB. Indolizidine 223AB (**4**), one of the neurotoxin alkaloids isolated in minute quantity from skin extract of neotropical poison-dart frogs (family Dendrobatidae),[18,19] has attracted a vast amount of interest because of its unusual biological characteristics. Numerous groups have thus been involved in the development of methodology for the total synthesis of this molecule. These efforts have recently resulted in the syntheses of stereoisomers of **4**,[15a,20] racemic **4**,[21] and the unnatural enantiomer (−)-**4**.[22]

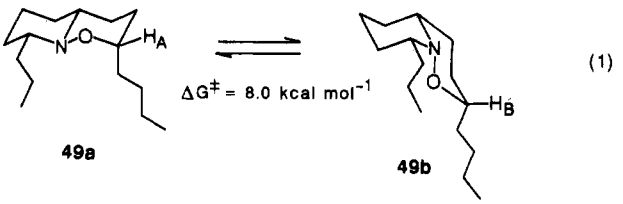
From the above survey of results indicating the synthetic potential of the oxazinolactam intermediate **37** in hand, we envisaged the preparation of indolizidine 223AB (**4**) which consists of extension of the methodology based on intramolecular nitroso Diels–Alder cycloaddition and the introduction of the alkyl side chain, both with complete stereocontrol.

Scheme VI[a]



[a] (a) PrMgBr, Et_2O; (b) $NaBH_3CN$, MeOH, pH 3.8–5.4 (HCl–MeOH, bromocresol green).

Our synthesis was initiated with the Grignard reaction of **37** using propylmagnesium bromide to give the enamine **47**, which was subsequently subjected to reduction with sodium cyanoborohydride under acidic conditions, resulting in the exclusive formation of **49** (70% yield from **37**) (Scheme VI). TLC and GLC indicated that the product obtained is a single isomer. However, the ^{13}C NMR spectrum of **49** at 24 °C showed pairs of resonances for each of the carbons in the molecule. From this the possibility arose that **49** is actually a diastereomeric mixture. In order to shed light on this, a series of ^{13}C NMR spectra (50.1 MHz) of **49** in pyridine-d_5 were taken under gated proton-decoupled conditions as a function of temperature in the range of 24–100 °C. Each pair of signals collapsed into a single line at high temperatures. These observations strongly indicate that **49** exists in a conformational equilibrium with nearly equal populations of **49a** and **49b** (eq 1) due to nitrogen inversion. The exchange rates (R) between **49a** and **49b** were calculated by using the extended Bloch equation[23] from the temperature dependence of the peak separations for several sets of doublets in the spectrum. Plots of $\ln R$ vs $1/T$ exhibited a straight line, from which the inversion barrier ($\Delta G^{\ddagger}$) was found to be about 8.0 kcal mol^{-1}.



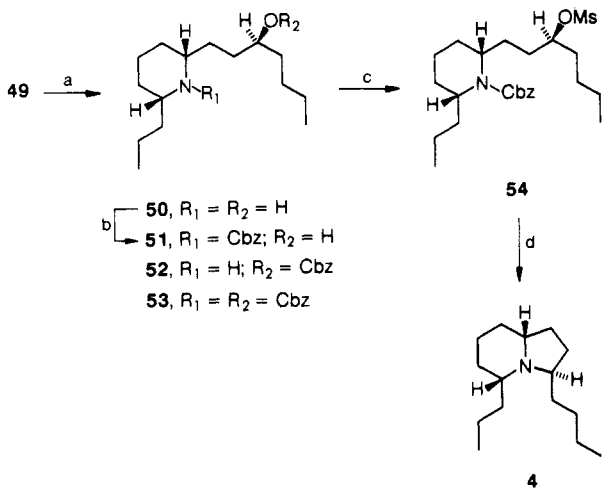
(1)

The ^1H NMR spectra (270 MHz) in pyridine-d_5 of **49** at 27.5 °C also showed two sets of multiplets at δ 3.87 ($W_{1/4}$ = 23.9 Hz) and 3.72 ($W_{1/4}$ = 31.6 Hz) with an integration ratio of 10:9 for the C-2 proton, indicative of the equatorial hydrogen in **49a** and the axial hydrogen in **49b**, respectively. The C-2 proton signals converged to a single resonance at δ 3.88 at 100 °C.

The exclusive formation of **49** can be rationalized as the result of a stereoelectronically controlled hydride addition to the transient iminium salt **48** generated from **47** under acidic conditions. Due to inversion at nitrogen, there are four possible transient structures A–D for the product as shown in Figure 1 which maintain maximum π-overlap with respect to the approaching hydride ion (paths a–d)

(18) Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M.; Myers, C. W. *Toxicon* **1978**, *16*, 163.
(19) Spande, Th. F.; Daly, J. W.; Hart, D. J.; Tsai, Y.-M.; Macdonald, T. L. *Experientia* **1981**, *37*, 1242.
(20) (a) Hart, D. J.; Tsai, Y.-M. *J. Org. Chem.* **1982**, *47*, 4403. (b) Stevens, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 103. (c) Nakagawa, Y.; Stevens, R. V. *J. Org. Chem.* **1988**, *53*, 1871.
(21) Broka, C. A.; Eng, K. K. *J. Org. Chem.* **1986**, *51*, 5043.
(22) Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, *26*, 1515.
(23) Becker, E. D. In *High Resolution NMR*, 2nd ed.; Academic Press: New York, 1980; p 243.

Scheme VII[a]



[a] (a) Zn, AcOH–H_2O; (b) $PhCH_2OCOCl$ (1.3 equiv), aqueous Na_2CO_3, CH_2Cl_2; (c) MsCl, NEt_3, CH_2Cl_2; (d) H_2, 5% Pd/C, MeOH.

and the developing nitrogen lone pair.[24] Two of these structures (B and C) are boat shaped, and the other two (A and D) are of more stable chair shapes. One of the latter (D), leading to the trans isomer, in which 4a-H and 8-H are trans to each other, is disfavored due to a strong steric interaction between the butyl group and the incoming hydride ion (via path d). On the other hand, transient structure A can accommodate the entering hydride ion (via path a) without steric interference of the 2-butyl side chain, thereby leading to the cis isomer **49**.

With the required stereochemistry thus established, the only requirement in order to complete the synthesis was constructing the pyrrolidine moiety of the target molecule. Reductive cleavage (Zn, aqueous AcOH) of the N–O bond in **49** gave the *cis*-dialkylpiperidine **50** (85%) (Scheme VII). Exposure of this material to benzyl chloroformate (1.3 equiv) in an alkaline solution furnished the hydroxy carbamate **51** (36%), along with **52** (24%) and **53** (25%). The latter two products could easily be hydrogenated back to the starting amino alcohol **50**. Thus the actual yield of **51** based on recovered **50** was 71%. Finally, the hydroxy carbamate **51** was converted to the mesylate **54**, which upon hydrogenation (Pd/C, MeOH) provided (±)-indolizidine 223AB (**4**) with complete stereoinversion at C-3 (in **54**) in 83% yield. Synthetic material thus prepared was found to have identical spectra (^1H and ^{13}C NMR and mass) with those of natural (+)-indolizidine 223AB.

The synthesis of (±)-indolizidine 223AB achieved here in a completely stereocontrolled manner is distinguished from the previous efforts[21,22] by the fact that the entire sequence provided single diastereomers in the desired sense and thus involved no separation of stereoisomers.

In conclusion, these results established a general strategy for a successful approach to nitrogen-containing natural products by means of a both completely regio- and stereocontrolled process involving intramolecular acyl nitroso Diels–Alder cycloaddition and the subsequent introduction of the alkyl side chain into the oxazinolactam.

Experimental Section

General Methods. Melting points (uncorrected) were determined by using a Yanagimoto micro melting point apparatus. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNMFX 270 spectrometer or a Bruker AM-400 instrument (at 270 and 67.8 MHz, respectively, unless otherwise noted). Mass spectra were obtained with a Shimadzu LKB 9000 or a Hitachi M-80 mass spectrometer. GLC was performed on a Shimadzu GC-7AG instrument with a flame-ionization detector and a 2-m column of 10% QF-1 on Chromosorb WAW DMCS (60–80 mesh). TLC was run on Merck precoated silica gel 60-F 254 and aluminum oxide 60-F 254 plates. Preparative TLC was run on Merck aluminum oxide 150-F 254. Merck silica gel 60 (230–400 mesh) and Woelm activated aluminum oxide (neutral, activity I) were used for column chromatography.

Methyl (5*E*)-5,7-Octadienoate (10). To a stirred, cooled (0–5 °C) suspension of allyltriphenylphosphonium bromide (25.0 g, 65 mmol) in ether (350 mL) was slowly added 41 mL of a 1.6 M solution of *n*-BuLi (65 mmol) in hexane. The mixture was stirred at 0–5 °C for 1 h, and a solution of **9** (7.7 g, 59 mmol) in ether (70 mL) was added. The resulting mixture was stirred at room temperature for 1 h. The ether solution was washed with water, dried ($MgSO_4$), and concentrated by rotary evaporation. To the residue was added 400 mL of *n*-pentane–ether (2:1), and the resulting solid triphenylphosphine oxide was filtered. The filtrate was concentrated by rotary evaporation, the residue was dissolved in hexane (400 mL), and iodine (100 mg) was added to the solution. The resulting solution was irradiated through a Pyrex filter with a 100-W high-pressure mercury lamp. After removal of the solvent, the residual oil was purified by distillation to give **10** (3.9 g, 43%): bp 72–75 °C (5 mmHg) [lit.[25] bp 31–32 °C (0.1 mmHg)]; IR ($CHCl_3$) 1735, 1600, 960, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (2 H, m), 2.12 (2 H, m), 2.32 (2 H, t, J = 7.4 Hz), 3.66 (3 H, s), 4.97 (1 H, d, J = 9.9 Hz), 5.09 (1 H, d, J = 16.8 Hz), 5.66 (1 H, m), 6.06 (1 H, m), 6.30 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 24.4 (t), 31.9 (t), 33.4 (t), 51.5 (q), 115.2 (t), 131.9 (d), 133.8 (d), 137.1 (d), 174.0 (s); mass spectrum, m/z (relative intensity) 154 (M^+, 5), 139 (100), 128 (35), 121 (48), 111 (58), 93 (41), 79 (78).

(*E*)-*N*-Hydroxy-5,7-octadienamide (11). To a stirred solution of hydroxylamine hydrochloride (1.6 g, 23 mmol) in methanol (15 mL) was added a solution of KOH (2.0 g, 36 mmol) in methanol (10 mL) at room temperature. After removal of the precipitated salt by filtration, **10** (2.6 g, 17 mmol) was added to the filtrate and the mixture was stirred overnight at room temperature. The reaction mixture was poured into 5% HCl (70 mL) and extracted with $CHCl_3$, and the organic phase was washed with water and dried ($MgSO_4$). Evaporation of the solvent afforded **11** (1.9 g, 73%) as a colorless wax: IR ($CHCl_3$) 3260, 1675, 960, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (2 H, m), 2.13 (4 H, m), 4.98 (1 H, d, J = 10.2 Hz), 5.11 (1 H, d, J = 16.8 Hz), 5.64 (1 H, m), 6.04 (1 H, m), 6.29 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 24.7 (t), 31.7 (t), 32.2 (t), 115.4 (t), 132.1 (d), 133.5 (d), 137.0 (d), 171.5 (s); mass spectrum, m/z (relative intensity) 155 (M^+, 9), 139 (21), 123 (17), 114 (27), 95 (58), 79 (75), 75 (81), 67 (100).

4a,5,6,7-Tetrahydropyrido[1,2-*b*][1,2]oxazin-8(2*H*)-one (13). To an ice-cold, stirred solution of tetrapropylammonium periodate (7.4 g, 20 mmol) in $CHCl_3$ (350 mL) was slowly added a solution of **11** (2.7 g, 17 mmol) in $CHCl_3$ (200 mL). The mixture was stirred for 1 h, washed with 5% $Na_2S_2O_3$ and then water, and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by column chromatography on silica gel with $CHCl_3$–hexane (2:3) to give **13** (2.3 g, 86%) as a colorless oil: IR ($CHCl_3$) 1660, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56–2.60 (6 H, series of m), 4.27–4.46 (2 H, unresolved), 4.66 (1 H, m), 5.72 (1 H, d, J = 10.2 Hz), 5.92 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 19.3 (t), 30.0 (t), 33.3 (t), 56.8 (d), 69.3 (t), 124.5 (d), 126.6 (d), 166.0 (s); mass spectrum, m/z (relative intensity) 153 (M^+, 14), 106 (8), 95 (26), 85 (63), 83 (100); exact mass calcd for $C_8H_{11}NO_2$ 153.0789, found 153.0754. Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.42; H, 7.27; N, 8.86.

***cis*- and *trans*-8-Methyl-2,4a,5,6,7-pentahydropyrido[1,2-*b*][1,2]oxazine (15a and 15b).** To an ice-cold stirred ethereal solution (100 mL) of methylmagnesium bromide, prepared from 1.0 g (41 mmol) of Mg and 4.2 g (44 mmol) of bromomethane, was added dropwise a solution of **13** (2.6 g, 17 mmol) in ether (20 mL). After addition was completed, the mixture was stirred at room temperature for 1 h, quenched with 10% NaOH (30 mL),

(24) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032.

(25) Hudlicky, T.; Sheth, J. P. *Tetrahedron Lett.* **1979**, 2667.

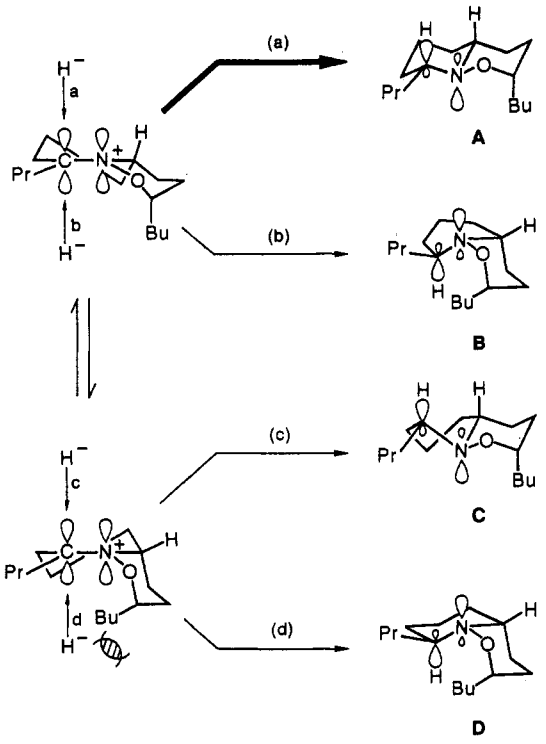


Figure 1. Stereoelectronic and steric factors for hydride additions to iminium intermediate **48**.

and filtered through Celite. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed by rotary evaporation. The residue was dissolved in methanol (8 mL), cooled to 0 °C, and made acidic to bromocresol green (pH 3.8–5.4) with 10% ethanolic HCl. To this stirred mixture was added $NaBH_3CN$ (1.3 g, 21 mmol), and then 10% ethanolic HCl was added dropwise to maintain acidity to the indicator (yellow coloring) during reduction. After 30 min at 0 °C, the reaction mixture was concentrated by rotary evaporation and the residue was made alkaline with 10% NaOH and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and concentrated to leave an oil, which was purified by chromatography on silica gel with $CHCl_3$–hexane (1:1) to give a diastereomeric mixture (2.2 g, 85%) of **15a** and **15b** in a ratio of 3.2:1 (determined by ^1H NMR) as a colorless oil. For **15a** (major isomer): ^1H NMR ($CDCl_3$) δ 1.19 (3 H, d, J = 6.9 Hz), 1.38 (3 H, m), 1.70 (3 H, m), 2.60 (1 H, m), 3.12 (1 H, m), 4.15 and 4.52 (1 H each, AB q with fine splitting, J = 15.4 Hz), 5.60 and 5.80 (1 H each, AB q with fine splitting, J = 11.6 Hz); ^{13}C NMR ($CDCl_3$) δ 19.4 (q), 23.8 (t), 31.4 (t), 34.2 (t), 59.9 (d), 63.1 (d), 68.5 (t), 125.6 (d), 128.7 (d). For **15b** (minor isomer): ^1H NMR ($CDCl_3$) δ 2.03 (1 H, m), 3.55 (1 H, br d, J = 12.0 Hz), other peaks overlapping with peaks for **15a**; ^{13}C NMR ($CDCl_3$) δ 21.1 (t), 25.0 (q), 30.6 (t), 37.5 (t), 59.4 (d), 59.9 (d), 69.1 (t), 125.3 (d), 127.6 (d).

***cis*- and *trans*-(*E*)-2-(3-Hydroxy-1-propenyl)-6-methylpiperidine (16a and 16b).** To a stirred solution of 1.4 g (9 mmol) of the 3.2:1 mixture of **15a** and **15b** in 60% aqueous AcOH (25 mL) was added Zn dust (1.5 g, 23 mmol) in small portions at room temperature. Then the mixture was heated to 60 °C, and stirring was continued for 7 h. The mixture was cooled in an ice bath, made alkaline with 20% NaOH, and filtered through Celite. The filtrate was extracted with $CHCl_3$, washed with brine, dried ($MgSO_4$), and rotary evaporated. The residue was chromatographed on aluminum oxide with $CHCl_3$–hexane (3:2) to give a 3.2:1 diastereomeric mixture (1.04 g, 73%) of **16a** and **16b** as a colorless oil, which solidified on standing in a refrigerator. Repeated chromatography of this mixture on aluminum oxide with $CHCl_3$–hexane (3:2) followed by recrystallization from hexane provided a pure sample of the major product **16a** as colorless needles: mp 47–50 °C; ^1H NMR ($CDCl_3$) δ 1.08 (3 H, d, J = 6.9 Hz), 1.0–1.9 (6 H, series of m), 2.71 (1 H, m), 3.44 (1 H, m), 3.90 (2 H, br), 4.09 (1 H, dd, J = 15.3, 6.9 Hz), 4.26 (1 H, d, J = 15.3, 6.9 Hz), 5.50 (1 H, m), 5.69 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 22.7 (q), 24.4 (t), 32.1 (t), 33.5 (t), 52.0 (d), 54.4 (d), 59.0 (t), 131.6 (d), 133.6 (d); mass spectrum, m/z (relative intensity) 155 (M^+, 10), 140 (25), 138 (25), 135 (39), 122 (34), 120 (40), 80 (53), 41 (100). For **16b** (minor isomer): ^1H NMR ($CDCl_3$) δ 2.11 (1 H, m), other peaks overlapping with peaks for **16a**; ^{13}C NMR ($CDCl_3$) δ 18.2, 27.4, 27.5, 29.8, 54.4 (overlapping), 58.4, 131.0, 135.2. Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.89; H, 11.36; N, 8.95.

2,3,4,4a,5,6-Hexahydropyrido[1,2-*b*][1,2]oxazin-8(7*H*)-one (20). A solution of **13** (1.3 g, 8.5 mmol) in methanol (90 mL) was hydrogenated over 5% palladium on carbon (150 mg) at atmospheric pressure for 3 h. After removal of the catalyst and evaporation of the solvent, the residue was chromatographed on silica gel with $CHCl_3$–hexane (4:1) to give **20** (1.0 g, 76%) as a colorless oil: IR ($CHCl_3$) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50–2.10 (8 H, m), 2.44 (2 H, m), 3.75 (1 H, m), 3.84 (1 H, t, J = 11.5 Hz), 4.20 (1 H, dd, J = 11.5, 4.6 Hz); ^{13}C NMR ($CDCl_3$) δ 19.0 (t), 24.8 (t), 30.6 (t), 30.8 (t), 33.5 (t), 59.0 (d), 72.1 (t), 166.1 (s); mass spectrum, m/z (relative intensity) 155 (M^+, 49), 126 (5), 99 (14), 86 (97), 69 (100). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.20; H, 8.47; N, 8.85.

***cis*-2-(3-Hydroxypropyl)-6-methylpiperidine (17). A. Preparation from 16a.** A solution of **16a** (100 mg, 0.65 mmol) in methanol (10 mL) was hydrogenated over 5% palladium on carbon (15 mg) for 3 h. The reaction mixture was filtered and concentrated to a solid, which was purified by chromatography on aluminum oxide with $CHCl_3$ to give **17** (82 mg, 80%) as colorless crystals: mp 58–60 °C; IR ($CHCl_3$) 3350, 3150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (3 H, d, J = 6.3 Hz), 0.90–1.85 (10 H, series of m), 2.56 (1 H, m), 2.66 (1 H, m), 3.58 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 22.7 (q), 24.7 (t), 30.5 (t), 32.2 (t), 34.3 (t), 36.4 (t), 52.2 (d), 56.9 (d), 62.9 (t); mass spectrum, m/z (relative intensity) 158 (M^+ + 1, 1), 157 (M^+, 1), 156 (M^+ – 1, 1), 142 (6), 98 (100). Anal. Calcd for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.84; H, 12.18; N, 8.84.

B. Preparation from 20. In the manner described above for the preparation of **15a/15b**, **20** (1.8 g, 12 mmol) was subjected to the Grignard reaction with methylmagnesium bromide and worked up. The crude oily product **21** was dissolved in methanol (100 mL) and hydrogenated over 5% palladium on carbon (150 mg). After 3 h, the main product generated was found to be the bicyclic oxazine **22**. Hydrogenation was discontinued after 2 days, at which time no oxazine **22** remained (TLC). The reaction mixture was worked up as in preparation A to give **17** (1.2 g, 66% from **20**).

***cis*-*N*-Formyl-2-(3-hydroxypropyl)-6-methylpiperidine (24).** A mixture of 99% formic acid (400 mg, 8.7 mmol) and **17** (1.00 g, 6.4 mmol) in toluene (60 mL) was refluxed for 7 h. The reaction mixture was concentrated by rotary evaporation to give an oily product, which was found to contain a minor amount of the *N*,*O*-diformyl derivative **23** (1720, 1660 cm^{-1}). The product was dissolved in methanol (20 mL) containing a saturated ammonia solution in methanol (5 mL), and the resulting solution was stirred overnight at room temperature. Evaporation of the solvent in vacuo left an oil, which was purified by chromatography on aluminum oxide with $CHCl_3$–hexane (1:1) to give **24** (950 mg, 81%) as a colorless oil. This compound was found to be a 1:1 mixture of isomers based on restricted rotation about the C–N bond of the *N*-formyl moiety:[26] IR ($CHCl_3$) 3450, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 and 1.31 (1:1 ratio, total 3 H, each d, J = 7.2 Hz), 1.45–1.85 (10 H, unresolved), 2.36 and 2.89 (each $^1/_2$ H, br), 3.56 ($^1/_2$ H, m), 3.65 (2 H, m), 3.85, 4.45, and 4.62 (each $^1/_2$ H, m), 7.29 and 8.08 (each $^1/_2$ H, s); mass spectrum, m/z (relative intensity) 185 (M^+, 6), 154 (4), 142 (4), 126 (100), 98 (21); exact mass calcd for $C_{10}H_{19}NO_2$ 185.1415, found 185.1387.

***cis*-*N*-Formyl-2-(3-bromopropyl)-6-methylpiperidine (25).** To a stirred solution of **24** (500 mg, 2.7 mmol) in CH_2Cl_2 (50 mL) was added dropwise PBr_3 (1.00 g, 3.7 mmol) at room temperature. Stirring was continued for 5 h at room temperature, and the reaction was quenched with 5% $NaHCO_3$ (30 mL). The organic

(26) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 261.

layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was washed with brine and dried ($MgSO_4$). After the solvent was rotary evaporated, the residue was chromatographed on aluminum oxide with $CHCl_3$–hexane (2:3) to give **25** (370 mg, 55%) as a colorless oil. This compound was found to be a 1:1 mixture of the rotamers due to the *N*-formyl group as in **24**: IR ($CHCl_3$) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 and 1.32 (1:1 ratio, total 3 H, each d, J = 7.2 Hz), 1.55–1.95 (10 H, unresolved), 3.45 (2 H, m), 3.56, 3.84, 4.46, and 4.63 (each $^1/_2$ H, m), 7.99 and 8.11 (each $^1/_2$ H, s); mass spectrum, m/z (relative intensity) 249 (M^+ + 1, 0.5), 247 (M^+ – 1, 0.5), 232 (2), 204 (1), 168 (0.6), 126 (100).

(±)-*N*-Formyldihydropinidine (26). A solution of **25** (195 mg, 0.8 mmol) in methanol (30 mL) containing triethylamine (150 mg, 1.5 mmol) was hydrogenated over 5% palladium on carbon (20 mg) for 15 h. The mixture was filtered, and the solvent was rotary evaporated. The residue was dissolved in CH_2Cl_2 (30 mL), washed with 5% HCl and then brine, and dried ($MgSO_4$). Evaporation of the solvent left an oil, which was purified by chromatography on aluminum oxide with $CHCl_3$–hexane (3:7) to give **26** (106 mg, 80%) as a colorless oil. This compound was found to be a 1:1 mixture of rotamers due to the *N*-formyl group as in **24**: IR ($CHCl_3$) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3 H, t, J = 7.2 Hz), 1.23 and 1.30 (1:1 ratio, total 3 H, d, J = 7.2 Hz), 1.47–1.85 (10 H, unresolved), 3.52, 3.81, 4.42, and 4.62 (each $^1/_2$ H, m), 7.99 and 8.09 (each $^1/_2$, s); mass spectrum, m/z (relative intensity) 170 (M^+ + 1, 2), 169 (M^+, 4), 154 (8), 127 (12), 126 (100), 98 (29); exact mass for $C_{10}H_{19}NO$ (M^+) 169.1466, found 169.1460.

(±)-Dihydropinidine (1). A mixture of **26** (100 mg, 0.6 mmol) and 10% HCl (5 mL) was refluxed for 7 h. The mixture was rotary evaporated to give a solid, which was recrystallized from ethanol–ethyl acetate to afford the hydrochloride of 1 (90 mg, 86%) as colorless needles: mp 215–217 °C (lit.[8] mp 210–213 °C); ^1H NMR ($CDCl_3$) δ 1.03 (3 H, t, J = 7.2 Hz), 1.37 (3 H, d, J = 6.5 Hz), 1.26–1.74 (7 H, series of m), 1.95 (2 H, m), 2.07 (1 H, br d), 3.11 (1 H, m), 3.22 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 19.5 (t), 19.6 (q), 23.5 (t), 29.2 (t), 31.7 (t), 37.1 (t), 55.0 (d), 58.7 (d). Anal. Calcd for $C_9H_{19}N$·HCl: C, 60.83; H, 11.34; N, 7.88. Found: C, 61.01; H, 11.42; N, 7.93.

An aqueous solution of pinidine hydrochloride (1·HCl) described above was made alkaline with 20% KOH and extracted with ether. The ether solution was dried ($MgSO_4$), and the solvent was evaporated to leave **1** as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.91 (3 H, m), 0.96–1.50 (1 H, m), 1.06 (3 H, d, J = 6.3 Hz), 1.34 (5 H, m), 1.60 (3 H, br t), 1.76 (1 H, m), 2.50 (1 H, m), 2.62 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 14.3 (q), 19.2 (t), 23.1 (q), 25.0 (t), 32.3 (t), 34.5 (t), 39.7 (t), 52.6 (d), 57.0 (d).

Ethyl (*E*)-2-Heptenoate (27). To an ice-cold, stirred solution of [(ethoxycarbonyl)methylene]triphenylphosphorane (178 g, 0.51 mol) in CH_2Cl_2 (700 mL) was added dropwise a solution of pentanal (44 g, 0.51 mol) in CH_2Cl_2 (300 mL). The mixture was stirred overnight at room temperature, and the solvent was removed by rotary evaporation. To the residue was added petroleum ether (2 L), and resulting solid material was collected by filtration and washed with the same solvent. After the combined extract solution was concentrated, the residual oil was distilled to give **27** (68.7 g, 86%) as a colorless liquid: bp 87–88 °C (15 mmHg); IR (neat) 1710, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, m), 1.15–1.50 (4 H, m, containing 3 H, t, J = 7.3 Hz at δ 1.27), 2.18 (2 H, m), 4.19 (2 H, q, J = 7.0 Hz), 5.80 (1 H, d, J = 15.6 Hz), 6.96 (1 H, dt, J = 15.6, 7.3 Hz); mass spectrum, m/z (relative intensity) 156 (M^+, 14), 127 (24), 111 (93), 99 (64), 83 (100). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.16; H, 10.44.

(*E*)-2-Heptenol (28). To an ice-cold, stirred suspension of $LiAlH_4$ (17.2 g, 0.45 mol) in ether (500 mL) was added dropwise a solution of $AlCl_3$ (20.0 g, 0.15 mol) in ether (250 mL). The mixture was stirred at room temperature for 30 min and ice-cooled again. To this cold mixture was added dropwise a solution of **27** (46.9 g, 0.30 mol) in ether (500 mL), and the resulting mixture was stirred at 0 °C for 2 h. The reaction was quenched by addition of ether saturated with water followed by 10% NaOH. The mixture was filtered thorugh Celite, and the ethereal solution was dried ($MgSO_4$). After evaporation of the solvent, the residue was distilled to give **28** (27.4 g, 80%) as an oil: bp 78–80 °C (16 mmHg); IR (neat) 3300, 965 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3 H, br t), 1.15–1.75 (6 H, series of m), 2.02 (1 H, br m), 3.60 (2 H, t, J = 6.0 Hz), 4.06 (1 H, d, J = 5.5 Hz), 5.64 (1 H, m); mass spectrum, m/z (relative intensity) 114 (M^+, 3), 96 (12), 81 (24), 68 (16), 57 (100). Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.53; H, 12.42.

(*E*)-1-Bromo-2-heptene (29). To a stirred solution of **28** (11.4 g, 0.10 mol) in petroleum ether (120 mL) was added dropwise a solution of PBr_3 (45 g, 0.17 mol) in the same solvent (50 mL) at –10 °C. After 2 h, the mixture was poured into ice–water (150 mL) and the organic phase was separated. The aqueous phase was extracted with ether, and the combined organic phase was washed with 5% $NaHCO_3$ and dried ($MgSO_4$). After evaporation of the solvent, the residue was distilled to give **29** (11.5 g, 65%) as a colorless liquid: bp 64–65 °C (16 mmHg); IR (neat) 1650, 960, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, m), 1.36 (4 H, m), 2.08 (2 H, m), 3.95 (2 H, d, J = 6.0 Hz), 5.74 (2 H, m); mass spectrum, m/z (relative intensity) 178 (M^+ + 1, 1.5), 176 (M^+ – 1, 1.5), 136 (1), 133 (1), 119 (1), 97 (68), 83 (64), 55 (100). Anal. Calcd for $C_7H_{13}Br$: C, 47.48; H, 7.40. Found: C, 47.67; H, 7.42.

(*E*)-2-Heptenyltriphenylphosphonium Bromide (30). To a solution of **29** (42.5 g, 0.24 mol) in benzene (500 mL) was added a solution of triphenylphosphine (63.0 g, 0.24 mol) in the same solvent (500 mL). The mixture was refluxed for 2 h and allowed to stand overnight at room temperature. Crystals separated and were collected by filtration and recrystallized from acetone–hexane to give **30** (90.6 g, 86%) as colorless granules: mp 159–161 °C; IR (KBr) 1120, 995, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (3 H, t, J = 6.9 Hz), 1.16 (4 H, m), 1.95 (2 H, m), 4.61 (2 H, dd, J = 14.8, 7.2 Hz), 5.28 (1 H, m), 5.90 (1 H, m), 7.55–7.90 (15 H, m); ^{13}C NMR ($CDCl_3$) δ 13.8 (q), 22.0 (t), 28.1 (t), 30.7 (t), 32.4 (t), 113.8 (d), 118.2 (s), 130.4 (d), 133.9 (d), 135.1 (d), 143.0 (d). Anal. Calcd for $C_{25}H_{28}BrP$: C, 68.34; H, 6.42. Found: C, 68.24; H, 6.40.

Methyl (5*E*,7*E*)-5,7-Dodecadienoate (31). To a cold (–5 °C), stirred suspension of **30** (15.8 g, 36 mmol) in THF (470 mL) was added dropwise 23 mL of a 1.6 M solution of *n*-BuLi (37 mmol) in hexane under N_2, and the resulting deep red solution was stirred at –5 °C for 20 min. To this mixture was added a solution of **9** (4.7 g, 36 mmol) in 70 mL of THF–HMPA (9:1) with stirring at –5 °C, and stirring was continued for 1 h. The mixture was quenched by addition of water (5 mL) and concentrated. Hexane (500 mL) was added, and the mixture was filtered through Celite. The solution was washed with water, dried over $MgSO_4$, and filtered. A part of the resulting solution was concentrated to give an oily product, which was found to be a mixture of **31** and its 5*Z* isomer in a ratio of 4:1 by ^1H NMR. Thus, after addition of I_2 (200 mg), the hexane solution of the products was irradiated through Pyrex with a 100-W high-pressure mercury lamp for 1 h. The reaction mixture was concentrated by rotary evaporation and purified by chromatography on silica gel with benzene–hexane (1:1) to give **31** (6.7 g, 89%) as a colorless oil: IR ($CHCl_3$) 1735, 985 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 6.9 Hz), 1.33 (4 H, m), 1.71 (2 H, m), 2.10 (4 H, m), 2.31 (2 H, t, J = 8.0 Hz), 3.65 (3 H, s), 5.55 (2 H, m), 5.99 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 22.3 (t), 24.6 (t), 31.6 (t), 31.9 (t), 32.3 (t), 33.4 (t), 51.5 (q), 130.1 (d), 130.5 (d), 131.5 (d), 133.1 (d), 174.1 (s); mass spectrum, m/z (relative intensity) 210 (M^+, 35), 136 (80), 107 (15), 93 (62), 79 (100); exact mass for $C_{13}H_{22}O_2$ (M^+) 210.1619, found 210.1606.

(5*E*,7*E*)-5,7-Dodecadienoic Acid (32). To a solution of KOH (600 mg) in 95% ethanol (20 mL) was added **31** (1.26 g, 6.0 mmol), and the mixture was refluxed for 1 h. The reaction mixture was concentrated by rotary evaporation, and the residue was acidified with 10% HCl and extracted with ether. The ether solution was washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel with $CHCl_3$–benzene (1:1) to give **32** (0.96 g, 82%) as a colorless oil: IR ($CHCl_3$) 1715, 995 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 6.9 Hz), 1.35 (4 H, m), 1.72 (2 H, m), 2.09 (4 H, m), 2.36 (2 H, t, J = 8.0 Hz), 5.52 (2 H, m), 5.99 (2 H, m), 11.70 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 22.3 (t), 24.3 (t), 31.6 (t), 31.8 (t), 32.3 (t), 33.4 (t), 130.1 (d), 130.3 (d), 131.7 (d), 133.2 (d), 180.3 (s); mass spectrum, m/z (relative intensity) 196 (M^+, 43), 136 (33), 93 (81), 80 (94), 67 (100). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.56; H, 10.18.

(5*E*,7*E*)-*N*-Hydroxydodecadienamide (34). A. Preparation from Acid 32. To an ice-cold, stirred solution of **32** (2.0 g, 10 mmol) in benzene (50 mL) was added oxalyl chloride (5.0 g, 39 mmol), and the mixture was stirred at room temperature. The mixture was concentrated by rotary evaporation to give crude

33, which without purification was dissolved in $CHCl_3$ (30 mL). The resulting solution was added dropwise to an ice-cold, stirred mixture of hydroxylamine hydrochloride (1.0 g, 14 mmol), Na_2CO_3 (2.0 g, 19 mmol), water (20 mL), and $CHCl_3$ (20 mL). The mixture was stirred at room temperature for 3 h and made acidic with 10% HCl. The organic phase was separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with brine and dried ($MgSO_4$). Evaporation of the solvent followed by recrystallization from hexane afforded **34** (1.5 g, 71%) as colorless crystals: mp 78–80 °C; IR (KBr) 3260, 1660, 1620, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 6.9 Hz), 1.32 (4 H, m), 1.69 (2 H, m), 2.10–2.17 (6 H, m), 5.56 (2 H, m), 5.96 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 22.3 (t), 25.1 (t), 31.6 (t), 31.8 (t), 32.3 (t), 130.1 (d), 130.3 (d), 131.6 (d), 133.2 (d), 171.9 (d); mass spectrum, m/z (relative intensity) 211 (M^+, 2), 193 (10), 136 (38), 93 (56), 79 (100). Anal. Calcd for $C_{12}H_{21}NO_2 \cdot {}^1/_5H_2O$: C, 67.07; H, 10.04; N, 6.52. Found: C, 67.43; H, 10.15; N, 6.49.

B. Preparation from Ester 31. A solution of KOH (1.5 g, 27 mmol) in methanol (5 mL) was added to a solution of hydroxylamine hydrochloride (1.0 g, 14 mmol) in methanol (9 mL) with stirring. The solid salt which separated was filtered, and to the filtrate was added a solution of **31** (2.1 g, 10 mmol) in methanol (5 mL). After the mixture was allowed to stand overnight at room temperature, the mixture was poured into 5% HCl (50 mL) and extracted with $CHCl_3$. The $CHCl_3$ solution was worked up as above to give **34** (1.7 g, 81%).

***rel*-(2*R*,4a*S*)-2-Butyl-4a,5,6,7-tetrahydropyrido[1,2-*b*][1,2]oxazin-8(2*H*)-one (36).** In the manner described for the preparation of **13**, **34** (3.2 g, 15 mmol) was subjected to the cycloaddition. The crude product was purified by chromatography on silica gel with $CHCl_3$–benzene (1:1) to give **36** (2.6 g, 82%) as a colorless oil: IR ($CHCl_3$) 1675, 1410 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 6.9 Hz), 1.25–2.60 (12 H, series of m), 4.24–4.40 (2 H, m), 5.66 (1 H, d, J = 9.0 Hz), 5.90 (1 H, d, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 20.0 (t), 22.6 (t), 28.1 (t), 30.3 (t), 33.0 (t), 33.6 (t), 56.9 (d), 79.3 (d), 125.7 (d), 128.2 (d), 166.0 (s); mass spectrum, m/z (relative intensity) 209 (M^+, 33), 148 (20), 126 (55), 114 (29), 96 (33), 95 (100). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.48; H, 9.31; N, 6.47.

***rel*-(2*R*,4a*S*)-2-Butyl-3,4,4a,5,6,7-hexahydropyrido[1,2-*b*][1,2]oxazin-8(2*H*)-one (37).** A solution of **36** (2.1 g, 10 mmol) in methanol (150 mL) was hydrogenated over 5% palladium on carbon (200 mg) for 3 h. Filtration and evaporation gave an oil, which was purified by chromatography on silica gel with $CHCl_3$–benzene (2:3) to give **37** (1.9 g, 90%) as a colorless oil: IR ($CHCl_3$) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 6.9 Hz), 1.20–2.56 (16 H, series of m), 3.67 (1 H, m), 4.15 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 19.6 (t), 22.6 (t), 26.5 (t), 26.7 (t), 28.4 (t), 29.3 (t), 31.3 (t), 33.6 (t), 58.8 (d), 79.1 (d), 166.5 (s); mass spectrum, m/z (relative intensity) 211 (M^+, 12), 194 (6), 164 (12), 154 (8), 140 (12), 127 (13), 114 (100), 98 (71), 86 (19). Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 67.81; H, 10.21; N, 6.43.

***rel*-(2*R*,4a*S*,8*S*)-2-Butyl-8-methyl-2,3,4,4a,5,6,7,8-octahydropyrido[1,2-*b*][1,2]oxazine (39).** In the manner described for the preparation of **15a**/**15b**, **37** (1.21 g, 5.7 mmol) was subjected to the Grignard reaction with methylmagnesium bromide. Workup provided crude **21**, a methanol solution of which was immediately subjected to catalytic hydrogenation over 5% palladium on carbon (100 mg) for 4 h. The usual workup and chromatography of the crude product on silica gel with benzene–hexane (1:2) afforded **39** (855 mg, 71%) as a colorless oil: IR ($CHCl_3$) 2940, 2875, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7.0 Hz), 1.09 (3 H, d, J = 6.6 Hz), 1.20–2.45 (18 H, series of m), 3.86 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 20.3 (q), 22.7 (t), 23.8 (t), 27.2 (t), 28.4 (t), 28.7 (t), 30.7 (t), 33.1 (t), 34.3 (t), 60.3 (d), 64.8 (d), 76.3 (d); mass spectrum, m/z (relative intensity) 211 (M^+, 9), 196 (39), 114 (58), 98 (18), 85 (69), 83 (100); exact mass for $C_{13}H_{25}NO$ (M^+) 211.1936, found 211.1971.

***rel*-[2*S*,6*S*,2(3*R*)]-2-(3-Hydroxyheptyl)-6-methylpiperidine (40).** In a similar manner to that described for the preparation of **16a**/**16b**, **39** (800 mg, 3.8 mmol) was treated with 60% aqueous AcOH (50 mL) and Zn dust (900 mg, 14 mmol) at 60 °C for 9 h. The usual workup and chromatography of the crude product on silica gel with $CHCl_3$–methanol (50:1) gave a solid, which was recrystallized from acetonitrile to afford **40** (550 mg, 68%) as colorless fine needles: mp 69–71 °C; IR ($CHCl_3$) 3600–3250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7.0 Hz), 1.10 (3 H, d, J = 6.6 Hz), 1.20–1.85 (16 H, series of m), 2.65 (2 H, m), 3.3–3.8 (2 H, br, containing 1 H, m at δ 3.51); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 22.7 (q), 22.9 (t), 24.7 (t), 28.3 (t), 30.8 (t), 33.3 (t), 33.9 (t), 34.1 (t), 37.5 (t), 52.5 (d), 56.2 (d), 71.5 (d); mass spectrum, m/z (relative intensity) 214 (M^+ + 1, 9), 213 (M^+, 3), 212 (4), 198 (9), 156 (25), 99 (21), 98 (100); exact mass for $C_{13}H_{27}NO$ 213.2092, found 213.2079. Anal. Calcd for $C_{13}H_{27}NO$: C, 73.18; H, 12.75; N, 6.56. Found: C, 72.91; H, 12.82; N, 6.82.

***rel*-[2*S*,6*S*,2(3*R*)]-*N*-[(Benzyloxy)carbonyl]-2-(3-hydroxyheptyl)-6-methylpiperidine (41).** To a solution of **40** (430 mg, 2.0 mmol) in CH_2Cl_2 (50 mL) was added a solution of Na_2CO_3 (450 mg) in water (10 mL), and the mixture was cooled in an ice bath. To this mixture was added dropwise a solution of benzyl chloroformate (520 mg, 3.1 mmol) in CH_2Cl_2 (10 mL) with stirring, and the mixture was stirred at room temperature for 4 h. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with water, dried ($MgSO_4$), and concentrated to give an oily product, which was chromatographed on silica gel. The first fraction eluted with benzene gave *rel*-[2*S*,6*S*,2(3*R*)]-*N*-[(benzyloxy)carbonyl]-2-[3-[[(benzyloxy)carbonyl]oxy]heptyl]-6-methylpiperidine (**43**) (310 mg, 32%) as a colorless oil: IR ($CHCl_3$) 1740, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 7.0 Hz), 1.14 (3 H, d, J = 6.6 Hz), 1.20–1.75 (16 H, series of m), 4.13 (1 H, br m), 4.39 (1 H, br m), 4.67 (1 H, br m), 5.14 (4 H, m), 7.15–7.5 (10 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 14.1 (q), 20.5 (q), 22.5 (t), 27.3 (t), 27.8 (t), 30.2 (t), 30.7 (t), 31.9 (t), 33.8 (t), 46.1 (d), 50.5 (d), 66.9 (t), 69.3 (t), 79.2 (d), 127.9 (d), 128.2 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.8 (d), 135.6 (s), 137.1 (s), 155.1 (s), 155.9 (s); mass spectrum, m/z (relative intensity) 346 (M^+ – Cbz, 1), 232 (9), 188 (23), 180 (12), 151 (25), 107 (67), 92 (40), 91 (100), 89 (49).

The second fraction eluted with $CHCl_3$–benzene (1:1) gave **41** (370 mg, 53%) as a colorless oil: IR ($CHCl_3$) 3550–3300, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7.0 Hz), 1.18 (3 H, d, J = 6.6 Hz), 1.25–1.75 (16 H, unresolved), 3.60 (1 H, br m), 4.19 (1 H, br m), 4.38 (1 H, br m), 5.13 (2 H, s), 7.25–7.44 (5 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 14.1 (q), 20.6 (q), 22.8 (t), 27.3 (t), 28.0 (t), 30.2 (t), 30.9 (t), 34.4 (t), 37.5 (t), 46.1 (d), 49.9 (d), 67.0 (t), 70.6 (d), 127.9 (d), 128.5 (d), 137.0 (s), 156.2 (s); mass spectrum, m/z (relative intensity) 348 (M^+ + 1, 0.2), 347 (M^+, 0.2), 302 (0.3), 288 (2), 232 (41), 188 (89), 91 (100).

The third fraction eluted with $CHCl_3$–methanol (97:3) gave *rel*-[2*S*,6*S*,2(3*R*)]-2-[3-[[(benzyloxy)carbonyl]oxy]heptyl]-6-methylpiperidine (**42**) (42 mg, 6%) as a colorless oil: IR ($CHCl_3$) 3500–3150, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 7.0 Hz), 1.20–1.90 (19 H, unresolved), 2.11 (1 H, br), 2.85 (1 H, br), 2.99 (1 H, br), 4.67 (1 H, m), 5.16 (2 H, s), 7.32–7.44 (5 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 19.8 (q), 22.5 (t), 23.1 (t), 27.3 (t), 28.1 (t), 29.2 (t), 30.1 (t), 30.9 (t), 33.6 (t), 54.5 (d), 58.1 (d), 69.5 (t), 78.2 (d), 128.3 (d), 128.5 (d), 135.5 (s), 155.0 (s); mass spectrum, m/z (relative intensity) 347 (M^+, 0.5), 281 (1), 232 (1), 212 (6), 196 (5), 194 (10), 180 (8), 152 (8), 138 (49), 136 (11), 112 (20), 98 (100).

Compounds **42** and **43** could be quantitatively converted to **41** by hydrogenolysis over 5% palladium on carbon in methanol.

***rel*-(2*S*,6*S*)-*N*-[(Benzyloxy)carbonyl]-2-(3-oxoheptyl)-6-methylpiperidine (46).** To a cold (5–10 °C), stirred solution of Collins' reagent, prepared from 100 mg (1.0 mmol) of CrO_3 and pyridine (5 mL), in CH_2Cl_2 (15 mL) was added a solution of **41** (45 mg, 0.13 mmol) in CH_2Cl_2 (3 mL). The resulting mixture was stirred at 5–10 °C for 1 h and poured into ice–water (10 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with water, dried ($MgSO_4$), and concentrated. The residual oil was purified by chromatography on silica gel with $CHCl_3$–benzene (1:4) to give **46** (42 mg, 94%) as a colorless oil: IR ($CHCl_3$) 1715, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 7.0 Hz), 1.20 (3 H, d, J = 7.2 Hz), 1.25–1.90 (12 H, series of m), 2.30 (4 H, m), 4.19 (1 H, m), 4.42 (1 H, m), 5.13 (2 H, s), 7.25–7.40 (5 H); ^{13}C NMR ($CDCl_3$) δ 13.8 (q), 14.1 (q), 20.6 (q), 22.3 (t), 26.0 (t), 28.3 (t), 28.8 (t), 30.2 (t), 40.3 (t), 42.5 (t), 46.1 (d), 50.0 (d), 66.9 (t), 127.9 (d), 128.5 (d), 137.1 (s), 155.9 (s), 210.6 (s); mass spectrum, m/z (relative intensity) 346 (M^+ + 1, 0.3), 286 (3), 245 (5), 232 (9), 210 (20), 188 (57), 154 (64), 91 (100).

(±)-Monomorine I (3). A. Preparation from 41. To a stirred solution of **41** (100 mg, 0.29 mmol) in CH_2Cl_2 (1.5 mL) was added iodotrimethylsilane (120 mg, 0.60 mmol) at room temperature. After the mixture was stirred overnight at room temperature, the solvent was evaporated to give crude **44** as an oil, which was dissolved in methanol (5 mL), and the solution was stirred overnight. After evaporation of the solvent, 5% aqueous ammonia (1 mL) was added and the mixture was extracted with CH_2Cl_2, dried over K_2CO_3, and concentrated. The red-brown residual oil was purified by preparative TLC on basic aluminum oxide with $CHCl_3$–hexane (9:1). The faster moving band gave **3** (12 mg, 42%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3 H, t, J = 7.0 Hz), 1.12 (3 H, d, J = 6.4 Hz), 1.15–1.90 (16 H, m), 2.06 (1 H, br s), 2.20 (1 H, br s), 2.46 (1 H, br t, J = 8.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.23 (q), 22.94 (q), 23.00 (t), 25.02 (t), 29.45 (t), 29.86 (t), 30.44 (t), 31.05 (t), 35.99 (t), 39.82 (t), 60.35 (d), 62.99 (d), 67.27 (d); mass spectrum, m/z (relative intensity) 195 (M^+, 1), 194 (1), 180 (5), 139 (11), 138 (100). ^1H and ^{13}C NMR and mass spectra of synthetic **3** were identical with those of authentic spectra of (–)-monomorine I, and TLC behavior of this product was identical with that of authentic (+)-monomorine I previously synthesized[17] in our laboratory.

The slower moving band gave (±)-3-epimonomorine I (**45**) (11 mg, 40%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7.0 Hz), 1.11 (3 H, d, J = 6.2 Hz), 1.16–1.95 (16 H, unresolved), 2.40 (1 H, m), 2.53 (1 H, m), 3.29 (1 H, br t); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 20.4 (q), 23.0 (t), 24.7 (t), 24.9 (t), 26.4 (t), 29.2 (t), 30.0 (t), 32.4 (t), 34.6 (t), 52.0 (d), 58.8 (d), 59.0 (d); mass spectrum, m/z (relative intensity) 195 (M^+, 1), 194 (2), 180 (7), 139 (11), 138 (100).

B. Preparation from 46. A solution of **46** (40 mg, 0.12 mmol) in methanol (8 mL) was hydrogenated over 5% palladium on carbon (10 mg) for 8 h. Filtration and evaporation provided an oil, which was worked up in a manner identical with that employed in preparation A to provide **3** (16 mg, 71%) and **45** (3.4 mg, 15%).

***rel*-(2*S*,4a*R*,8*R*)-2-Butyl-8-propyl-2,3,4,4a,5,6,7,8-octahydropyrido[1,2-*b*][1,2]oxazine (49).** In the manner described for the preparation of **15a/15b**, **37** (1.5 g, 7.1 mmol) was subjected to the Grignard reaction with propylmagnesium bromide [prepared from 1-bromopropane (2.1 g, 17 mmol) and Mg (410 mg, 17 mmol)], affording **47**, which was subsequently reduced with $NaBH_3CN$ in acidic media. Workup and chromatography on silica gel with benzene–hexane (1:1) gave **49** (1.2 g, 70% from **37**) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.90 (6 H, m), 1.20–2.15 (20 H, series of m), 2.31 (1 H, br m), 2.56 and 2.81 (total 1 H in 9:10 ratio, each br m), 3.61 and 3.86 (total 1 H in 9:10 ratio, each br m); ^1H NMR (C_5D_5N, 27.5 °C) δ 0.90 (6 H, m), 1.20–2.45 (21 H, series of m), 2.54 and 2.74 (total 1 H in 9:10 ratio, each br m), 3.72 and 3.87 (total 1 H in 9:10 ratio, each br m); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 14.2 (q), 14.3 (q), 14.5 (q), 18.7 (t), 19.7 (t), 22.5 (t), 22.7 (t), 23.8 (t), 24.5 (t), 24.7 (t), 27.0 (t), 27.3 (t), 27.8 (t), 28.4 (t), 28.9 (t), 29.3 (t), 30.8 (t), 31.1 (t), 33.1 (t), 34.9 (t), 35.5 (t), 36.2 (t), 58.4 (d), 63.6 (d), 64.9 (d), 65.1 (d), 76.4 (d), 79.3 (d); mass spectrum, m/z (relative intensity) 239 (M^+, 6), 197 (16), 196 (100), 142 (10), 85 (34), 83 (52); exact mass for $C_{15}H_{29}NO$ (M^+) 239.2249, found 239.2226.

***rel*-(2*R*,6*R*)-2-(3-Hydroxyheptyl)-6-propylpiperidine (50).** In a similar manner to that described for the preparation of **16a/16b**, **49** (840 mg, 3.5 mmol) was treated with 60% acetic acid (50 mL) and Zn dust (1.0 g, 15.3 mmol) at 60 °C for 9 h. The usual workup and chromatography on silica gel with $CHCl_3$–10% methanolic ammonia (98:2) gave **50** (720 mg, 85%) as a colorless solid: mp 53–55 °C; IR (KBr) 3500–3200; ^1H NMR ($CDCl_3$) δ 0.90 (6 H, m), 1.20–1.85 (20 H, series of m), 2.52 (1 H, m), 2.66 (1 H, m), 3.50 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 14.2 (q), 19.1 (t), 22.9 (t), 24.6 (t), 28.2 (t), 31.4 (t), 32.0 (t), 33.3 (t), 34.0 (t), 37.4 (t), 39.3 (t), 56.3 (d), 56.8 (d), 71.3 (d); mass spectrum, m/z (relative intensity) 241 (M^+, 0.9), 240 (2), 198 (39), 180 (23), 166 (7), 126 (100), 96 (10). Anal. Calcd for $C_{15}H_{31}NO \cdot {}^1/_{10}H_2O$: C, 74.07; H, 12.93; N, 5.76. Found: C, 74.15; H, 13.07; N, 5.74.

***rel*-[2*S*,6*S*,2(3*R*)]-*N*-[(Benzyloxy)carbonyl]-2-(3-hydroxyheptyl)-6-propylpiperidine (51).** To a ice-cold, stirred solution of **50** (600 mg, 2.5 mmol) in CH_2Cl_2 (60 mL) was added a solution of Na_2CO_3 (550 mg, 5.2 mmol) in water (10 mL). To this mixture was added dropwise a solution of benzyl chloroformate (520 mg, 3.1 mmol) in CH_2Cl_2 (10 mL) with stirring, and the mixture was further stirred at room temperature for 4 h. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with water, dried ($MgSO_4$), and concentrated to give an oily product, which was chromatographed on silica gel. The first fraction eluted with benzene gave *rel*-[2*S*,6*S*,2(3*R*)]-*N*-[(benzyloxy)carbonyl]-2-[3-[[(benzyloxy)carbonyl]oxy]heptyl]-6-propylpiperidine (**53**) (310 mg, 25%) as a colorless oil: IR ($CHCl_3$) 1740, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (6 H, t, J = 6.6 Hz), 1.15–1.70 (20 H, series of m), 4.18 (2 H, br), 4.65 (1 H, br), 5.10 (2 H, s), 5.14 (2 H, s), 7.2–7.4 (10 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 14.0 (q), 14.4 (q), 20.6 (t), 22.5 (t), 27.3 (t), 27.6 (t), 28.2 (t), 30.7 (t), 32.0 (t), 33.8 (t), 37.0 (t), 50.6 (d), 66.9 (t), 69.3 (t), 79.3 (d), 127.9 (d), 128.2 (d), 128.4 (d), 128.6 (d), 135.5 (s), 137.1 (s), 155.1 (s), 156.1 (s); mass spectrum, m/z (relative intensity) 509 (M^+, 0.1), 466 (17), 374 (4), 314 (3), 270 (3), 260 (23), 216 (36), 180 (33), 91 (100).

The second fraction eluted with $CHCl_3$–benzene (3:7) afforded **51** (335 mg, 36%) as a colorless oil: IR ($CHCl_3$) 3430, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (6 H, m), 1.17–1.77 (20 H, series of m), 3.60 (1 H, br s), 4.19 (2 H, br s), 5.11 (2 H, s), 7.36 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 14.1 (q), 20.6 (t), 22.8 (t), 27.5 (t), 28.0 (t), 30.6 (t), 34.3 (t), 37.0 (t), 37.5 (t), 49.8 (d), 50.6 (d), 67.1 (t), 70.7 (d), 127.9 (d), 128.0 (d), 128.4 (d), 137.0 (s), 156.4 (s); mass spectrum, m/z (relative intensity) 375 (M^+, 0.2), 332 (9), 288 (34), 260 (25), 240 (13), 216 (58), 180 (14), 91 (100).

The third fraction eluted with $CHCl_3$–benzene (7:3) gave *rel*-[2*S*,6*S*,2(3*R*)]-2-[3-[[(benzyloxy)carbonyl]oxy]heptyl]-6-propylpiperidine (**52**) (220 mg, 24%) as a colorless oil: IR ($CHCl_3$) 3300–3200, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (6 H, m), 1.20–1.80 (20 H, unresolved), 2.47 (2 H, br m), 4.70 (1 H, m), 5.14 (2 H, s), 7.25–7.4 (5 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 14.2 (q), 19.1 (t), 22.5 (t), 24.7 (t), 27.3 (t), 30.4 (t), 32.5 (t), 32.8 (t), 33.6 (t), 39.6 (t), 56.9 (d), 69.3 (t), 79.2 (d), 128.2 (d), 128.6 (d), 135.5 (s), 155.1 (s); mass spectrum, m/z (relative intensity) 375 (M^+, 0.6), 332 (21), 180 (99), 166 (81), 126 (100), 108 (25), 91 (37).

Compounds **52** and **53** could be quantitatively converted to **50** by hydrogenation over 5% palladium on carbon in methanol.

***rel*-[2*S*,6*S*,2(3*R*)]-*N*-[(Benzyloxy)carbonyl]-2-[3-[(methylsulfonyl)oxy]heptyl]-6-propylpiperidine (54).** To a cold (–10 °C), stirred solution of **41** (140 mg, 0.37 mmol) and triethylamine (80 mg, 0.8 mmol) in CH_2Cl_2 (12 mL) was added a solution of methanesulfonyl chloride (50 mg, 0.44 mmol) in CH_2Cl_2 (1 mL) via a syringe. After the mixture was stirred for 5 min at –10 °C, it was poured into ice–water (10 mL) and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was washed with brine and dried ($MgSO_4$). Evaporation of the solvent and chromatography on silica gel with $CHCl_3$ afforded **54** (130 mg, 83%) as a colorless oil: IR ($CHCl_3$) 1680, 1360 (sh), 1340 (sh), 1335, 1175, 915; ^1H NMR ($CDCl_3$) δ 0.90 (6 H, m), 1.20–1.75 (20 H, series of m), 2.96 (3 H, s), 4.20 (2 H, br s), 4.65 (1 H, br s), 5.13 (2 H, br s), 7.36 (5 H, br s); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 14.0 (q), 20.6 (t), 22.4 (t), 27.1 (t), 27.6 (t), 28.0 (t), 30.4 (t), 32.3 (t), 34.3 (t), 37.0 (t), 38.7 (q), 50.5 (d), 50.6 (d), 67.0 (t), 84.1 (d), 127.9 (d), 128.4 (d), 137.0 (s), 156.1 (s); mass spectrum, m/z (relative intensity) 422 (M^+ + 1, 0.08), 410 (2), 366 (3), 314 (2), 270 (10), 260 (33), 180 (16), 170 (4), 91 (100).

(±)-Indolizidine 223AB (4). A solution of **54** (100 mg, 0.24 mmol) in methanol (20 mL) was hydrogenated over 5% palladium on carbon (15 mg) for 5 h. Filtration and evaporation left an oil, which was basified with 5% aqueous ammonia, extracted with $CHCl_3$, and dried ($MgSO_4$). Evaporation of the solvent followed by chromatography of the residue on silica gel with $CHCl_3$–10% methanolic ammonia (99:1) provided **4** (43 mg, 81%) as a pale yellow oil: IR ($CHCl_3$) 2970 (sh), 2950, 2880, 2820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (6 H, m), 1.0–1.95 (20 H, series of m), 2.36 (2 H, m), 3.30 (1 H, br t); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 14.5 (q), 19.0 (t), 23.0 (t), 24.6 (t), 25.1 (t), 26.4 (t), 29.1 (t), 30.0 (t), 30.8 (t), 32.2 (t), 35.8 (t), 56.8 (d), 58.6 (d), 59.3 (d); mass spectrum, m/z (relative intensity) 223 (M^+, 2), 222 (3), 181 (14), 180 (99), 167 (14), 166 (100), 124 (6), 122 (3), 81 (6), 55 (13); exact mass for $C_{15}H_{29}N$ (M^+) 223.2300, found 223.2297. The spectral (^1H and ^{13}C NMR and mass) characteristics of this material were identical with those of natural (+)-indolizidine 223AB.

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Two New Rearranged Abietane Diterpene Quinones from *Salvia aegyptiaca* L.

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Two novel diterpene quinones with rearranged abietane skeletons, aegyptinones A (1) and B (2), have been isolated from the antimicrobial petrol extract of *Salvia aegyptiaca* L. roots. Their structures have been established primarily by interpretation of detailed NMR data obtained from the experiments COSY, NOESY, INAPT, and QUAT, as well as other spectroscopic evidence. The structure of 1 was further confirmed by single-crystal X-ray analysis.

Salvia plants have been extensively studied in the last few years. The reported tanshinone and royleanone diterpene quinones are the subject of great interest, due to their antimicrobial and/or anticancer properties.[1-3] In a screening of Egyptian *Salvia* species for antimicrobial activity, we found that most were inhibitors of a variety of microorganisms. This activity prompted us to explore their chemistry.[4-8] In a continuation of these studies, we now report[9] the isolation and characterization of two novel structurally related, rearranged abietane diterpene quinones from the roots of *Salvia aegyptiaca* L., one of the common plants hitherto unexamined.

The petrol extract of *S. aegyptiaca* roots showed potent inhibitory activity against *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Candida albicans*. When this extract was chromatographed on silica gel column, followed by preparative TLC, it afforded two major colored crystalline components, 1 and 2. Physiochemical properties of these compounds indicated that both were homologous components, related to the tanshinones.[1,3,10]

Table I. ^1H (δ, Multiplicity, Coupling Constants in Hertz) and ^{13}C NMR (δ, Multiplicity) Assignments at 300 and 75 MHz in $CDCl_3$, Respectively, of Aegyptinones A (1) and B (2)

	1		2	
atom no.	^1H	^{13}C	^1H	^{13}C
1	2.72 b t (6.3)	19.1 t	2.75 b t (6.3)	19.6 t
2	1.87 m	28.5 t	1.87 m	29.0 t
3	1.68 m	37.7 t	1.68 m	38.2 t
4	-	34.9 s	-	n.o.[a]
5	-	141.2 s	-	n.o.
6	-	152.6 s	-	n.o.
7	7.58 s	121.6 d	8.12 s	125.7 d
8	-	125.5 s	-	n.o.
9	-	126.2 s	-	n.o.
10	-	144.0 s	-	n.o.
11	-	184.5 s	-	n.o.
12	-	176.2 s	-	n.o.
13	-	118.2 s	-	n.o.
14	-	171.0 s	-	n.o.
15	3.61 m	34.6 d	3.50 m	33.5 d
16α	4.39 dd (8.7, 5.5)	81.3 t	3.89 m	66.0 t
16β	4.90 t (8.7)		3.95 m	
17	1.38 d (6.8)	18.8 q	1.33 d (6.7)	15.0 q
18	1.35 s	31.9 q	1.35 s	31.4 q
19	1.35 s	31.9 q	1.35 s	31.4 q
20	2.60 s	16.6 q	2.60 s	17.2 q

[a] N.o. = not observed.

Aegyptinone A (1), $C_{20}H_{22}O_3$ (HRMS), was obtained as dark-orange prisms, mp 136 °C. The evidence for structure 1 is as follows: The UV and IR absorption spectra were consistent of an *o*-naphthoquinone chromophore[10] and somewhat similar to those of cryptotanshinone (3).[3] The MS showed mass peaks at m/z 178, 165, and 152, typical of tanshinone fragmentations.[3] The ^1H NMR assignments were made based on COSY and NOE experiments. The

(1) Fang, C.; Chang, P.; Hsu, T. *Hua Husueb Hsueb* Pao **1978**, *34*, 197; *Chem. Absr.* **1978**, *88*, 177078z.
(2) Kupchan, S. M.; Karim, A.; Marcks, C. *J. Am. Chem. Soc.* **1968**, *90*, 5923-5924.
(3) Ontisuka, M.; F-Ujiu, M.; Shinma, N.; Maruyama, H. B. *Chem. Pharm. Bull.* **1983**, *31*, 1670-1675.
(4) Haddad, D. Y.; Saleh, M. R. I.; Sabri, N. N. *J. Pharm. Sci., U.A.R.* **1962**, *7*, 215-222.
(5) Saleh, M. R. I.; Sabri, N. N.; Haddad, D. Y. *J. Pharm. Sci. U.A.R.* **1964**, *5*, 65-72.
(6) Saleh, M. R. I.; Sabri, N. N.; El-Masry, S. *J. Pharm. Sci. U.A.R.* **1978**, *19*, 313-318.
(7) Saleh, M. R. I.; Sabri, N. N. *Egypt. J. Pharm. Sci.* **1979**, *20*, 411-415.
(8) Sabri, N. N.; Abou-Donia, A. A.; Assad, A. M.; Ghazy, N. M.; El-Lakany, A. M.; Tempesta, M. S.; Sanson, D. R. *Planta Medica*, in press.
(9) (a) Tempesta, M. S.; Sanson, D. R.; Schlemper, E. O.; Sabri, N. N.; Abou-Donia, A. A.; El-Lakany, A. E., presented in part in the 16th International Symposium on the Chemistry of Natural Products (IUPAC), May 29-June 3, 1988, Kyoto, Japan; Abstr. PA132. (b) Sanson, D. R.; Tempesta, M. S.; El-Lakany, A. E.; Abou-Donia, A. A., presented in part at the 22nd Midwest Regional Meeting of the American Chemical Society, Nov 5-6, 1987, Wichita, KS; Abstr. 616.
(10) Kakisawa, H.; Hayashi, T.; Okazaki, I.; Ohashi, M. *Tetrahedron Lett.* **1968**, *28*, 3231-3234.

0022-3263/89/1954-4097$01.50/0