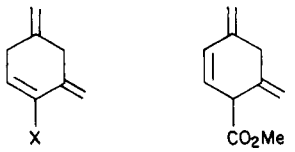
Spectral properties of the two reaction products[7] permit assignment to isomeric bis(methylene)cyclohexenes **6b** and **7**, products that result from extrusion of formaldehyde



6a, b **7**

from either bridgehead diene **2b** or propellanes **4b** and **5b**. Quite surprisingly, under the reaction conditions, bridgehead diene **2b** is found to be the principle precursor of **6b** and **7** and *not* propellanes **4b** and **5b**.

The isolation of highly strained bridgehead dienes from these reactions affirms the remarkable utility of the Diels–Alder cycloaddition for the synthesis of novel, highly strained bridgehead alkenes. Chemical and spectroscopic investigations of these compounds is continuing.

Acknowledgment. Financial support from the National Science Foundation (CHE 82-11401) is greatly appreciated.

Supplementary Material Available: Spectral data for **2a**, **2b**, **3a**, **3b**, **4a**, **4b**, **5b**, **6a**, **6b**, and **7** (5 pages). Ordering information is given on any current masthead page.

(11) Isomerization of bicyclo[3.1.0]hex-2-ene to 1,4-cyclohexadiene is exothermic by 11 kcal/mol (Ellis, R. J.; Frey, H. M. *J. Chem. Soc. A* **1966**, 553). The equilibrium **2a** ⇄ **4a** + **5a** lies exclusively to the right (350 °C), $\Delta H > 4$ kcal/mol. The bridgehead diene system **2a** represents a shift of at least 15 kcal/mol in the thermodynamics of the isomerization. Other examples of "wrong-way" homo 1,5-hydrogen shifts have also been noted: (a) Kirsch, R.; Priebe, H.; Hopf, H. *Tetrahedron Lett.* **1984**, *25*, 53, (b) Klarmer, F.; Rungeler, W.; Malfeld, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 595.

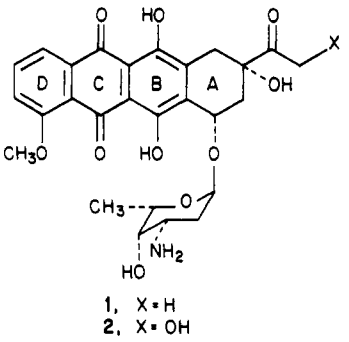
K. J. Shea,* L. D. Burke
Department of Chemistry
University of California
Irvine, California 92717
Received November 9, 1984

Anthracyclinones by Oxidative Dearomatization: Total Synthesis of SM-173B and Aranciamycinone

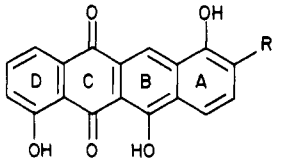
Summary: The aromatic naphthacenequinone **11** was converted by selective oxidative dearomatization of the A ring to enone **12** which was transformed into the aglycons SM-173B (**4**) and aranciamycinone (**5**).

Sir: The clinically important antineoplastic activities of certain anthracycline antibiotics, notably daunorubicin (**1**) and doxorubicin (adriamycin, **2**), have led to the development of a formidable array of strategies for the total synthesis of anthracyclinones.[1] None of these strategies, however, generate natural aglycons from fully aromatic tetracyclic precursors. We now demonstrate the first synthetic conversion of a naphthacenequinone (**3**) to a natural anthracyclinone.

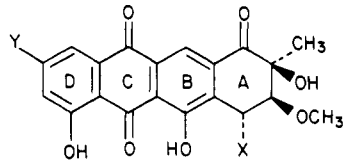
Our synthetic targets were the aglycons SM-173B (**4**)[2]



1, X = H
2, X = OH



3, R = H
11, R = CH_3



4, X = Y = H
5, X = OH; Y = H
6, X = OH; Y = OCH_3

and aranciamycinone (**5**),[3] which, like the related steffimycinone (**6**),[4] have not yet been synthesized.[5] The appropriate naphthacene precursor to these targets was the dark red trihydroxyquinone **3**, most conveniently prepared by regiospecific condensation[6] of ester **7** with the naphthalene **8** followed by methylation, phthalide reduction, cyclization in CF_3COOH–$(CF_3CO)_2O$, and Jones oxidation. The resulting trimethoxyquinone **9**[7] was demethylated ($NaSC_2H_5$, DMF, reflux, 18 h) to **3** in 35% overall yield from **8**. Introduction of the methyl group at C-9 (anthracyclinone numbering) was achieved by the selective Mannich reaction of quinone **3** using a slight excess of HCHO and pyrrolidine (THF, 40 °C, 80% yield) to yield amine **10** and then reductive elimination (1.1 equiv of $Na_2S_2O_4$, aqueous DMF, room temperature to 160 °C, 20 min, 90% yield) to the methyl quinone **11** [^{1}H NMR (Me_2SO-d_6) δ 2.43, CH_3]. This unusual sequence probably proceeds through the hydroquinone by the intramolecular redox chemistry suggested in Scheme I.

With quinone **11** in hand, we proceeded to test our hypothesis that in such systems only the A ring is a true phenol, whereas rings B and D are deactivated toward oxidation. Reaction of **11** with 1.05 equiv of $Pb(OAc)_4$[8] (THF–HOAc, 4 °C, 2 h) proceeded cleanly to give 50–55% of the acetoxy enone **12** [mp 226–230 °C; IR ($CHCl_3$) 1730, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.23 (H-7, d, J = 10.2 Hz), 6.29 (H-8, d, J = 10.2 Hz). Reactions at the A-ring double bond of **12** proved unexpectedly frustrating. Both catalytic (H_2, Pd–C) and hydride reduction ($NaBH_4$) of **12** regenerated quinone **11**. Treatment of **12** with Br_2/CCl_4, *m*-CPBA, CF_3CO_3H or *t*-BuOOH/$VO(AcAc)_2$[9] gave back

(1) A comprehensive review is provided by Arcamone (Arcamone, F. In "Doxorubicin"; Academic Press: New York, 1981), and by the earlier review of Kelly (Kelly, T. R. *Annu. Rep. Med. Chem.* **1979**, *14*, 288).

(2) Fujiwara, A.; Tozoe, M.; Hoshino, T.; Sekine, Y.; Fujiwara, M. *Tennen Yuko Kagobutsu Toronkai Koen'Yoshishu*, 22nd, **1979**, 448, cited in *Chem. Abstr.* **1980**, *93*, 130479*u*.

(3) Keller-Schierlein, W.; Sauerbier, J.; Vogler, U.; Zähner, H. *Helv. Chim. Acta* **1970**, *53*, 779.

(4) Kelly, R. C.; Schletter, I.; Koert, J. M.; MacKellar, F. A.; Wiley, P. F. *J. Org. Chem.* **1977**, *42*, 3591.

(5) Synthesis of 8-demethoxyaranciamycinone by way of intramolecular Wittig cyclization has been described by Krohn and Broser (Krohn, K. and Broser, E. *Liebigs Ann. Chem.* **1982**, 1907. See also: Krohn, K.; Broser, E. *J. Org. Chem.* **1984**, *49*, 3766. The absolute configuration depicted in **5** is based on the latter paper. For an approach to the steffimycinone series, see: Gesson, J. P.; Jacquesy, J. C.; Renoux, B. *Tetrahedron Lett.* **1983**, *24*, 2761.

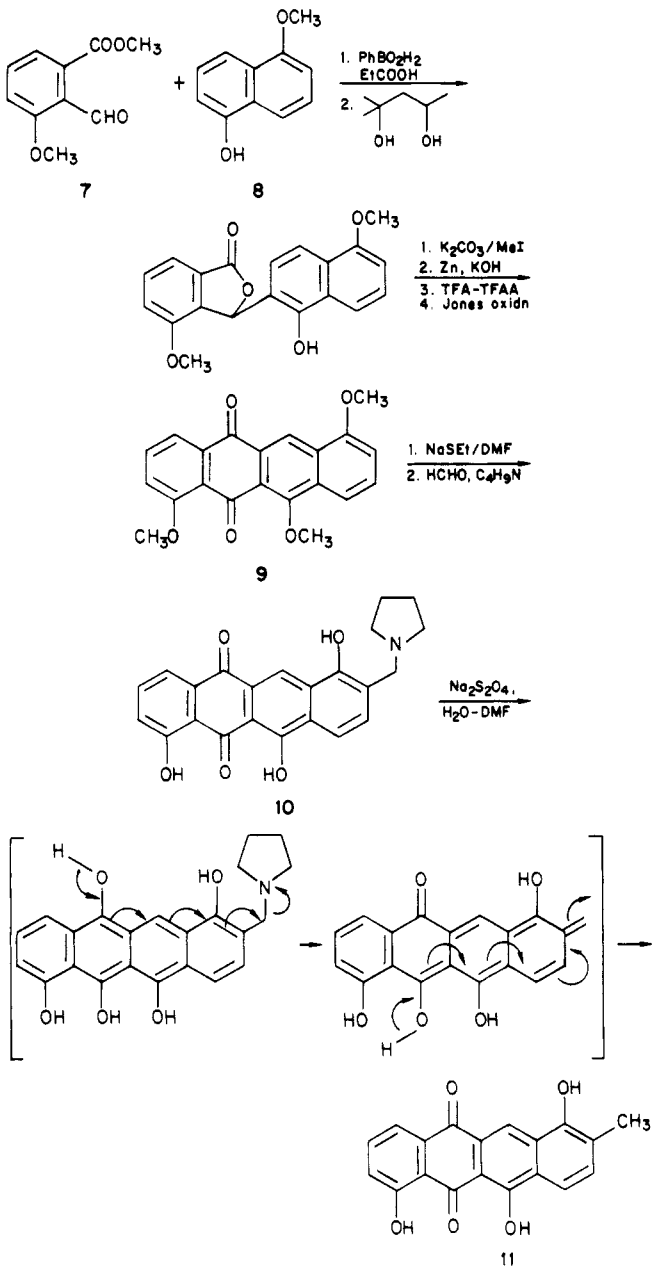
(6) Broadhurst, M. J.; Hassall, C. H. *J. Chem. soc., Perkin Trans. 1* **1982**, 2227.

(7) Trimethoxyquinone **9** had mp 235–236 °C. All intermediates gave correct C, H analyses or mass spectra, as well as 400-MHz ^{1}H NMR spectra consistent with the proposed structures.

(8) Metlesics, W.; Schinzel, E.; Vilesek, H.; Wessely, F. *Monatsh. Chem.* **1957**, *88*, 1069. Cavill, G. W. K.; Cole, E. R.; Gilham, P. T.; McHugh, D. J. *J. Chem. Soc.* **1954**, 2785.

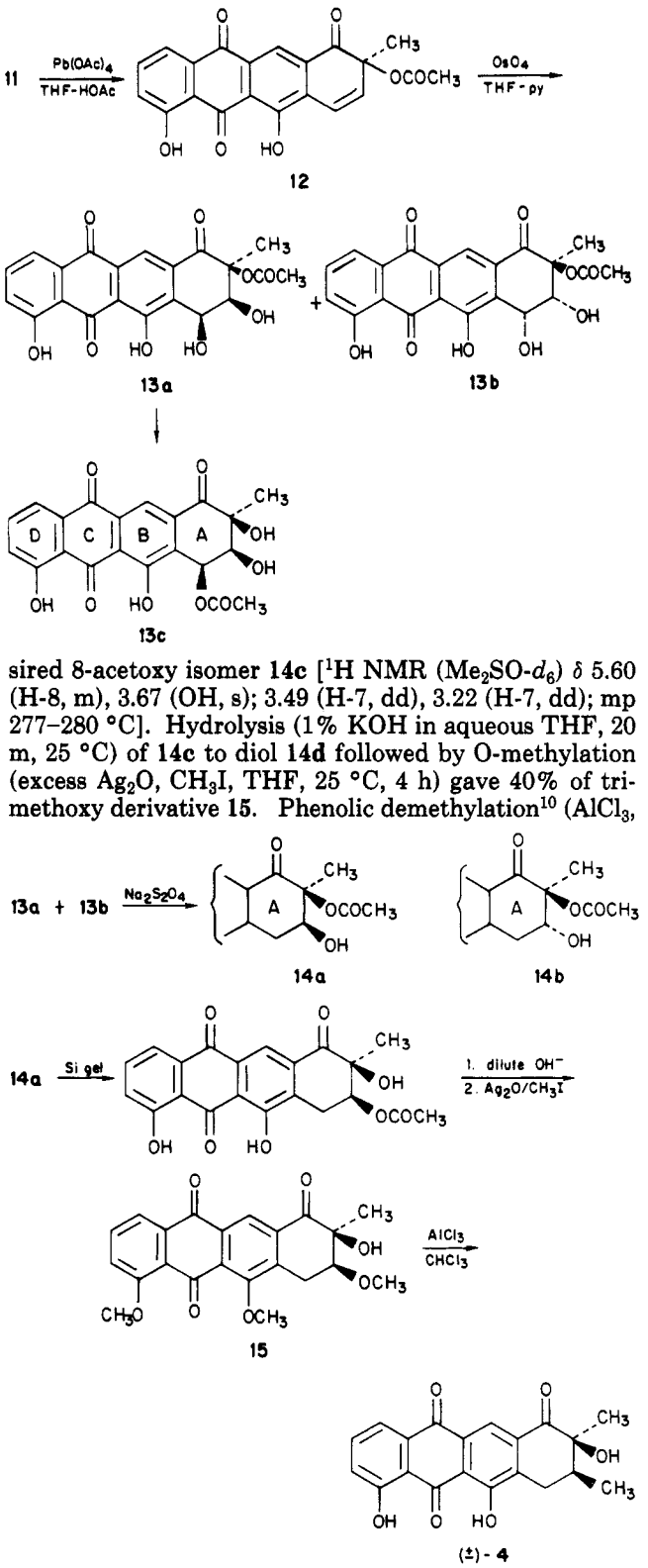
0022-3263/85/1950-0727$01.50/0

Scheme I



starting material. Bromination of **12** in HOAc gave a mixture of 8-bromo-7-acetoxy stereoisomers which could not be converted to epoxides or useful 7,8-diol derivatives. Uniquely productive in our hands was reaction of enone **12** with 1.05 equiv of OsO_4 (THF–pyridine, 2 days, 25 °C) to give a 1:1 mixture of the 7,8-*cis*-diols **13a** and **13b**. These could be differentiated by silica gel chromatography, which leaves isomer **13b** [^{1}H NMR (Me_2SO-d_6) δ 4.38 (H-8), 5.20 (H-7), $J_{7,8}$ = 4.1 Hz] unchanged but transforms the 7,8,9-all-cis isomer **13a** [^{1}H NMR (Me_2SO-d_6) δ 4.56 (H-8), 5.34 (H-7), $J_{7,8}$ = 4.1 Hz] by sequential 1,2-acyl shifts to the *all-cis*-7-acetoxy-8,9-diol isomer **13c** [^{1}H NMR (Me_2SO-d_6) δ 4.37 (H-8), 6.62 (H-7), $J_{7,8}$ = 4.0 Hz].

A-ring stereocontrol was achieved by reduction of the osmylation product mixture (1.5 equiv of $Na_2S_2O_4$, aqueous THF-HOAc, 20 m, 25 °C) to the 7-deoxy compounds **14a** and **14b** (1:1, 70% from **12**), which on silica gel chromatography (5:1 $CHCl_3$–Et_2O) transformed **14a** into the desired 8-acetoxy isomer **14c** [^{1}H NMR (Me_2SO-d_6) δ 5.60 (H-8, m), 3.67 (OH, s); 3.49 (H-7, dd), 3.22 (H-7, dd); mp 277–280 °C]. Hydrolysis (1% KOH in aqueous THF, 20 m, 25 °C) of **14c** to diol **14d** followed by O-methylation (excess Ag_2O, CH_3I, THF, 25 °C, 4 h) gave 40% of trimethoxy derivative **15**. Phenolic demethylation[10] ($AlCl_3$, $CHCl_3$, 1 h, 25 °C) gave 66% yield of the 8-OCH_3 compound [^{1}H NMR ($CDCl_3$) δ 3.95 (H-8, dd), 3.78 (9-OH, s), 3.66 (H-7, dd), 3.45 (8-OCH_3, s), 3.05 (H-7, dd), 1.43 9-CH_3, s)]. This monomethoxy compound was shown by NMR and TLC to be identical with (racemic) aglycon SM-173B by comparison with a sample of natural SM-173B (**4**)

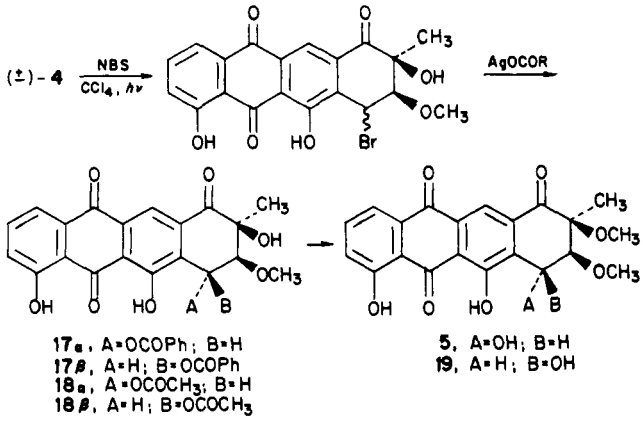


(9) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(10) For recent examples of selective deblocking of related phenolic ethers in the presence of aliphatic methoxyl, see: Penco, S.; Angelucci, F.; Ballabio, M.; Vigevani, R.; Arcamone, F. *Tetrahedron Lett.* **1980**, *21*, 2253. Giardino, P.; Vigevani, A.; Bernardi, L.; Arcamone, F. *Gazz. Chim. Ital.* **1980**, *110*, 101.

prepared in our laboratory by dithionite reduction of naturally derived aranciamycinone.[11]

Air oxidation of synthetic SM-173B (4) in the presence of base[5] gave intractable products. However, homolytic bromination proceeded smoothly (1.5 equiv of NBS, CCl_4, $h\nu$, 40–45 °C, 1 h) to give 16 which was converted by $AgOCOC_6H_5$ in C_6H_6 (25 °C, 20 m) to an overall 80% yield of 10:1 mixture of 7α/7β-benzoyloxy epimers (17α and 17β). Surprisingly, mild base hydrolysis of this 10:1



17α, A=OCOPh; B=H
17β, A=H; B=OCOPh
18α, A=OCOCH3; B=H
18β, A=H; B=OCOCH3

5, A=OH; B=H
19, A=H; B=OH

mixture gave in nearly quantitative yield a 2:1 mixture of racemic aranciamycinone 5 and its 7β epimer (19). In contrast, reaction of 16 with AgOAc in C_6H_6 (25 °C, 20 min) gave 60–70% of a 10:1 mixture of 7α/7β-acetates (18α and 18β) which with dilute base (1% KOH, aqueous THF, 25 °C, 30 min) gave a corresponding 10:1 ratio of racemic aranciamycinone (5) and its 7β epimer. Hydrolysis of the benzoates (17) but not the acetates (18) thus *takes place in part by alkyl–oxygen scission, probably via a quinone methide mechanism.*

The synthetic (±)-aranciamycinone (5) thus obtained in ca. 60% yield from SM-173B (4) showed TLC and a 400-MHz NMR spectrum [^{1}H NMR ($CDCl_3$) δ 12.73, 11.88 (1 H each, s), 8.41 (1 H, s), 7.91 (1 H, d), 7.76 (1 H, 5), 7.36 (1 H, d), 5.41 (H-7, dd), 3.81 (H-8, d), 3.56 (3 H, s), 3.22 (HO-7, d), 1.52 (3 H, s)] indistinguishable from naturally derived 5 obtained by mild acid hydrolysis[3] of aranciamycin kindly provided by Professor K. Krohn (Braunschweig) and Dr. A. Fujiwara (Nippon Roche).

Efforts to explore the generality of this novel strategy for the synthesis of other anthracyclinones are in progress.[12]

(11) Direct dithionite reduction of natural aranciamycin to SM-173B could not be achieved, although such reductive deglycosidation is common for other anthracyclines (cf. Smith, T. H.; Fujiwara, A. N.; Lee, W. W.; Wu, H. Y.; Henry, D. W. *J. Org. Chem.* **1977**, *42*, 3653).

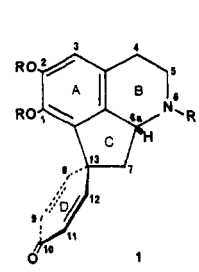
(12) Partial support of this research by Grant CA-11326, awarded by the National Cancer Institute, USPHS, is gratefully acknowledged.

Andrew S. Kende,* Stephen Johnson
Department of Chemistry
University of Rochester
Rochester, New York 14627
Received September 18, 1984

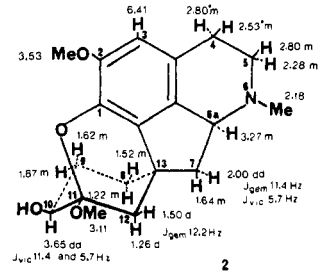
(-)-Misramine: An Unusual Proaporphine Alkaloid

Summary: (-)-Misramine (2), the first pentacyclic proaporphine alkaloid, has been found in Egyptian *Roemeria hybrida* and *R. dodecandra* (Papaveraceae).

Sir: Over 40 naturally occurring monomeric proaporphines are known. These possess skeleton 1. In certain instances, some or all of the double bonds of ring D may be reduced. Proaporphines are optically active and incorporate either the *R* absolute configuration as in 1 or the alternate *S* configuration.[1]



1



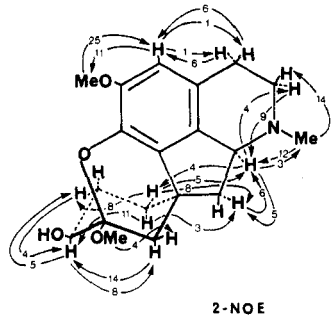
2

We describe the alkaloid (-)-misramine (2), $C_{19}H_{25}O_4N$, mp 103–105 °C (MeOH), found in Egyptian *Roemeria hybrida* (L.) DC. and *R. dodecandra* Stapf (Papaveraceae),[2] which is the first proaporphine to possess a pentacyclic rather than the usual tetracyclic nucleus.

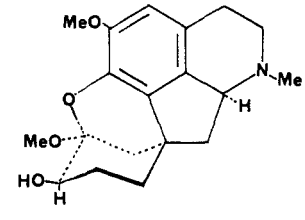
The IR spectrum of misramine is devoid of carbonyl absorption;[3] and the UV spectrum, λ_{max} (MeOH) 231, 285 nm (log ε 4.33, 3.94), is typical of a tetrahydroisoquinoline system possessing two oxygenated substituents on ring A.

The 360-MHz NMR spectrum in C_6D_6 is presented around expression 2. Salient features are an aromatic methoxyl singlet at δ 3.53 and only one aromatic proton in the form of a singlet at δ 6.41. An *N*-methyl absorption falls at δ 2.18, and an aliphatic methoxyl singlet is found relatively upfield at δ 3.11. There is also an aliphatic proton absorption split as a doublet of doublets at δ 3.65 which represents the hydrogen geminal to the alcoholic function.

Assignment of the complex pattern of aliphatic protons in (-)-misramine was made possible by extensive spin decoupling experiments, as well as by a detailed NMR



2-NOE



3

NOEDS study whose results are given in expression 2-NOE.[4] An interconnecting skein of enhancements running from the C-5 to the C-9 hydrogens was of critical importance in settling the relative stereochemistry of the alkaloid, and in eliminating from consideration alternate structure 3. Thus, irradiation of the H-5α absorption at δ 2.28 produced a 9% NOE of the H-6a multiplet at δ 3.27. In turn, irradiation at δ 3.27 led to a 5% enhancement of

(1) For reviews on the proaporphines, see: (a) Stuart, K. L.; Cava, M. P. *Chem. Rev.* **1968**, *68*, 321. (b) Bernauer, K.; Hofheinz, W. *Fortschr. Chem. Org. Naturst.* **1968**, *26*, 245. (c) Shamma, M. "The Isoquinoline Alkaloids"; Academic Press: New York, 1972; Chapter 9. (d) Shamma, M.; Moniot, J. L. "Isoquinoline Alkaloid Research: 1972–1977"; Plenum Press: New York, 1978; Chapter 9.

(2) The above-ground parts of *R. hybrida* were collected in the spring, 30 km west of Alexandria, and weighed 3.3 kg wet. The yield of misramine was 20 mg. The alkaloid was also found in *R. dodecandra*, but in lesser amounts.

(3) (-)-Misramine (2): ν_{max} ($CHCl_3$) 3530, 2470, 1435 cm^{-1}; MS, *m/z* (relative intensity) 332 $(M + 1)^+$ (15), 331 $(M)^+$ (71), 330 (86), 317 (21), 316 (100), 314 (19), 312 (21), 298 (32), 288 (48), 270 (32), 256 (32), 255 (22), 242 (12), 239 (11), 237 (11), 230 (23), 229 (16), 228 (12), 223 (11), 218 (19), 216 (11), 214 (10), 207 (14), 188 (21), 187 (13).

0022-3263/85/1950-0729$01.50/0