radical acceptor. It gave 1-phenyl-3-nonanone (**3h**). On the other hand, electron-rich olefins like vinyl butyl ether failed to react, a result that is consistent with the nucleophilic nature of the addition of acyl radicals to olefins.[3] Heptanal, which arose from carbonylation of the hexyl free radical, was the major product in such cases. Secondary alkyl iodides also were reactive (runs 2, 5, 7, 9). However, even under conditions of high dilution ($[1c]_0$ = 0.012 M), the greater tendency—compared to primary and secondary alkyl free radicals—of the adamantyl free radical to add to olefins[11] rather than undergo carbonylation led to a low yield of ketone **3c** (run 3). 2-Methylenecyclododecanone (**2e**) could also serve as the acyl radical acceptor. The reaction of CO, methyl iodide, and **2e** gave 2-acetonylcyclododecanone (**3j**) (run 10).[12]

Thus, a double alkylation of carbon monoxide via free radicals, which leads to unsymmetrical ketones, has been achieved. The use of free radical reactions in organic synthesis is now receiving considerable attention because such use is compatible with the presence of a variety of organic functional groups. In this respect, the benefits that can be realized by the use of *free radical carbonylation* are undoubtedly large. Additional applications of the reaction are now being investigated in our laboratory.

Supplementary Material Available: Detailed experimental procedures and the physical characteristics of the products (6 pages). Ordering information is given on any current masthead page.

(11) The nucleophilicity of the 1-adamantyl free radical has been described. See: Ohno, M.; Ishizaki, K.; Eguchi, S. *J. Org. Chem.* **1988**, *53*, 1285.

(12) This compound is a key intermediate in the synthesis of muscone and exaltone, see: Tsuji, J.; Yamada, T.; Shimizu, I. *J. Org. Chem.* **1980**, *45*, 5209.

First Total Synthesis of Amaryllidaceae Alkaloids of the 5,11-Methanomorphanthridine Type. An Efficient Total Synthesis of (±)-Pancracine[1]

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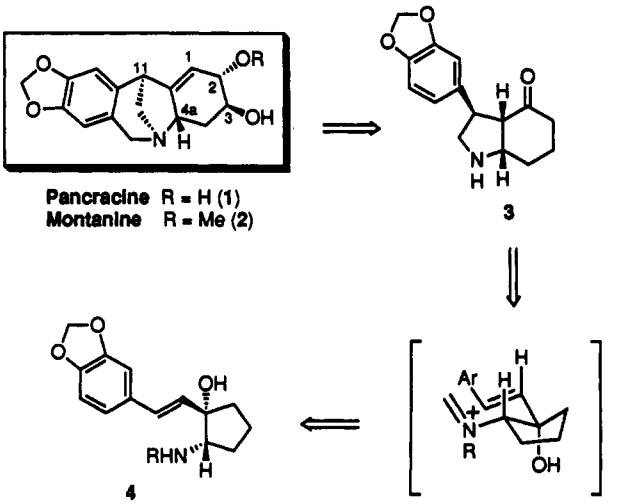
Summary: A tandem aza-Cope rearrangement–Mannich cyclization (**9** → **3**) is the central step in a concise total synthesis of (±)-pancracine.

Over a dozen alkaloids isolated from Amarylidaceae plant species have the unique 5,11-methanomorphanthridine skeleton; pancracine (**1**) and montanine (**2**) are representative examples.[2] Although a massive synthetic effort has been directed toward almost all other types of Amaryllidaceae alkaloids, the methanomorphanthridine group has received scant attention and no total syntheses have been realized.[3] In this paper we reveal a concise route to the methanomorphanthridine subset of Amaryllidaceae alkaloids and specifically describe an efficient and highly stereocontrolled total synthesis of (±)-pancracine (**1**).[4]

The heart of our synthetic plan is outlined in Scheme I and entails establishment of the key C(4a) and C(11) stereorelationship in the aryl *cis*-hydroindolone precursor **3**.[5,6] The well-established chair topography of the aza-Cope–Mannich transformation identifies **4** as the precursor of hydroindolone **3**.[5] The synthesis begins with easily

Scheme I



available aminocyclopentanone **5** (Scheme II).[7] Reaction of **5** with the alkynylcerium reagent[8] **6** prepared from 5-ethynyl-1,3-benzodioxole[9] took place with 13:1 facial selectivity, without competing ketone enolization, to afford **7** in 92% yield after purification.[10] Following removal of the cyanomethyl protecting group, propargyl alcohol **8** was reduced with $LiAlH_4$ to provide the crystalline (mp 68–69 °C) *E* allylic alcohol **9**. Reaction of this intermediate at

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(2) For comprehensive reviews, see: Martin, S. F. *Alkaloids (Academic Press)* **1987**, *30*, 251 and earlier reviews referenced therein.

(3) For synthetic approaches, see: (a) Sánchez, I. H.; Larraza, M. I.; Rojas, I.; Breña, F. K.; Flores, H. J.; Jankowski, K. *Heterocycles* **1985**, *23*, 3033. (b) Hoshino, O.; Ishizaki, M.; Saito, K.; Yumoto, K. *J. Chem. Soc., Chem. Commun.* **1990**, 420.

(4) (a) Wildman, W. C.; Brown, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 6439. (b) Sandberg, F.; Michel, K.-H. *Lloydia* **1963**, *26*, 78. (c) Ali, A. A.; Mesbah, M. K.; Frahm, A. W. *Planta Med.* **1984**, 188.

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(6) We employ the Wildman[4a] numbering system illustrated in Scheme I.

(7) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629.

(8) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

(9) Readily available from piperonal: Feuerstein, W.; Heimann, N. *Chem. Ber.* **1901**, *34*, 1468. Overman, L. E.; Wild, H. *Tetrahedron Lett.* **1989**, *30*, 647.

(10) Yields are for pure compounds purified by chromatography on silica gel and/or recrystallization. Melting points refer to analytical samples typically purified by additional recrystallization.

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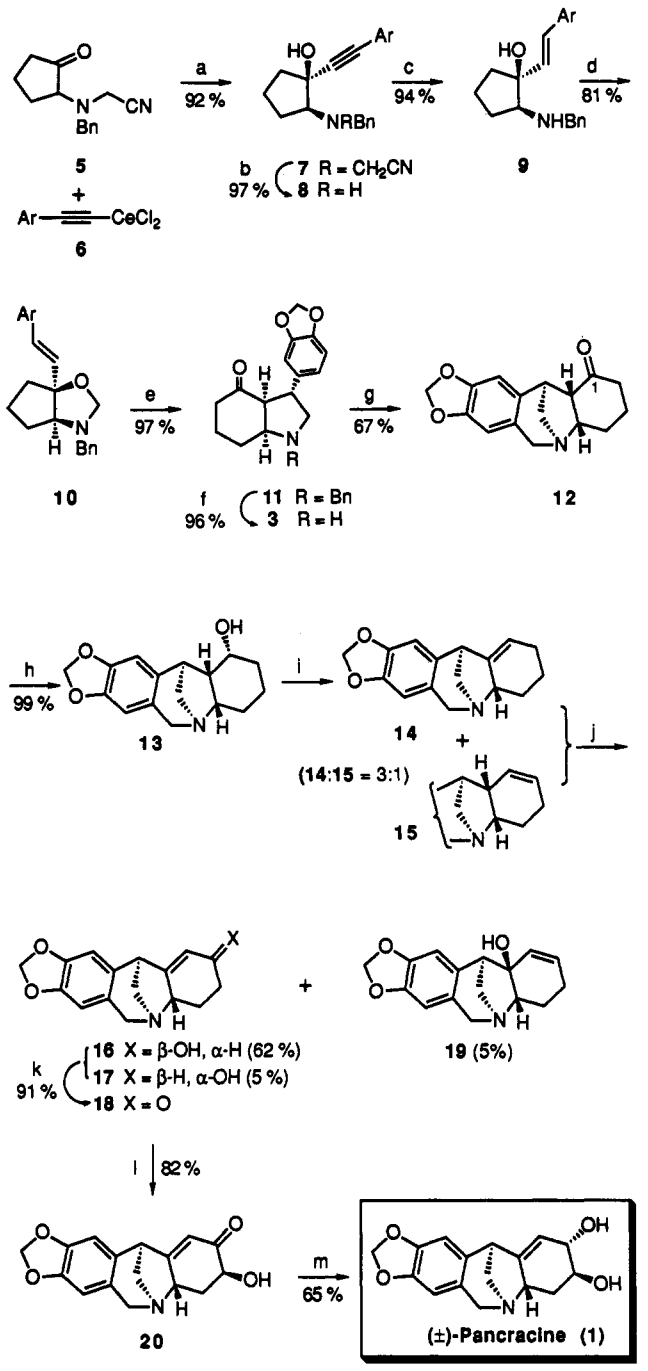
Scheme II[a]



[a] Ar = 3,4-(methylenedioxy)phenyl, Bn = CH_2Ph. Reaction details: (a) **6** (1.6 equiv), THF, −78 °C; (b) $AgNO_3$ (1.1 equiv), EtOH, 30 °C, sonication bath (8, mp 68–70 °C); (c) $LiAlH_4$ (3.5 equiv), Et_2O, −20 °C → reflux; (d) formalin (2 equiv), Na_2SO_4 (4 equiv), camphorsulfonic acid (0.2 equiv), CH_2Cl_2, 23 °C (**10**, mp 62–64 °C); (e) BF_3·OEt_2 (2.4 equiv), CH_2Cl_2, −20 → 23 °C; (f) H_2, Pd–C, HCl–MeOH (**3**, mp 208–210 °C); (g) formalin (50 equiv), Et_3N (2 equiv), MeOH, 23 °C; HCl–MeOH, 23 °C; (h) LiB(*sec*-Bu)$_3$H (2 equiv), THF, −78 °C (**13**, mp 214–216 °C); (i) $SOCl_2$ (13 equiv), $CHCl_3$, −30 → 23 °C; (j) SeO_2 (4.3 equiv), dioxane, 85 °C, 6 h; (k) Swern oxidation; (l) $Me_3SiOSO_2CF_3$ (10 equiv), Et_3N (30 equiv), Et_2O, −60 → 0 °C; OsO_4 (ca. 0.1 equiv), *N*-methylmorpholine *N*-oxide (3 equiv), *t*-BuOH–H_2O–pyridine, −5 → 23 °C, 6 h; (m) $NaBH_4$ (40 equiv), 1:1 HOAc–CH_3CN, −35 °C, 19 h.

room temperature with formalin and camphorsulfonic acid afforded the key rearrangement substrate **10** in 74% overall yield from the propargyl alcohol **7**.

Although the rearrangement of **10** could not be realized in satisfactory yield with protic acids,[4] a variety of Lewis acids occasioned the desired transformation to **11**. Of these, BF_3·OEt_2 was the most convenient, and exposure of **10** to 2.4 equiv of this Lewis acid provided a single hydroindolone **11**, which was isolated in crystalline form (mp 91–92 °C) in 97% yield. The small ^1H NMR coupling (J = 4.5 Hz) observed between the angular hydrogens confirmed the expected cis ring fusion of **11**. Hydrogenolysis of **11** followed by conventional Pictet–Spengler cyclization[11] of **3** afforded the crystalline (mp 101–103 °C) methanomorphanthridine ketone **12** in 42% overall yield from aminocyclopentanone **5**.

The C(1) carbonyl group of **12** provides an appropriate handle for developing the cyclohexenediol functionality of pancracine. Reduction of **12** with lithium tri-*sec*-butylborohydride[12] occurred with complete selectivity from the β-face to afford alcohol **13** in essentially quantitative yield. Dehydration of this intermediate with $SOCl_2$ at −30 °C proceeded in good yield to give a 3:1 mixture of the tri- and disubstituted alkenes **14** and **15**, respectively.[13] This mixture was not separated but directly oxidized with SeO_2[14] to afford a readily separable mixture of the equatorial secondary allylic alcohol **16** (62% from **13**), the axial secondary allylic alcohol **17** (5% from **13**), and the tertiary allylic alcohol **19** (5% from **13**). Swern oxidation[15] of alcohols **16** and **17** provided the desired enone **18** in 91% yield.[16]

The trans diol functionality of pancracine was then developed in the following manner. Enol silylation of **18**[17] followed by catalytic OsO_4 oxidation of the resulting dienoxysilane[18] afforded selectively the axial β-hydroxy enone **20** in 82% overall yield. Stereoselective acyloxyborohydride reduction[19] of **20** then provided (±)-pancracine in 65% yield. Synthetic (±)-pancracine showed spectroscopic and chromatographic properties indistinguishable from those of an authentic specimen.

In summary, the total synthesis of (±)-pancracine has been achieved in 13 chemical operations and 14% overall yield from aminocyclopentanone **5**. The efficiency of the conversion of the methanomorphanthridine ketone **12** to pancracine can likely be improved, and studies toward this end are underway. It is also expected that the tetracyclic intermediate **12** will serve as a general precursor to other Amaryllidaceae alkaloids of the methanomorphanthridine group. Since the α-methylbenzyl analogue of **5** is conveniently available in high optical purity, asymmetric synthesis of the methanomorphanthridine alkaloid class should be readily possible.[20] The overall efficiency of this first successful entry to this group of Amaryllidaceae alkaloids provides a further illustration of the power of the

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(12) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.
(13) A C(1) chloride was also isolated in 2% yield. Alkenes **14** and **15** could be separated, although inefficiently, by a combination of crystallization and chromatography.
(14) Cain, M.; Campos, O.; Guzman, F.; Cook, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 907.
(15) Swern, D.; Mancuso, A. J.; Huang, S.-L. *J. Org. Chem.* **1978**, *43*, 2480.
(16) Allylic alcohol **19** can be converted also to **18** by pyridinium chlorochromate oxidation, although the yield is <40%.
(17) Emde, H.; Götz, A.; Hofmann, K.; Simchen, G. *Liebigs Ann. Chem.* **1981**, 1643.
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(20) (a) Overman, L. E.; Sugai, S. *J. Org. Chem.* **1985**, *50*, 4154. (b) Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745.

aza-Cope–Mannich reaction for stereocontrolled alkaloid construction.

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Marked Leaving Group Strain in (*Z*)-2-Ethylidenebicyclo[2.2.2]oct-1-yl Triflate and Its Significant Relief in (*Z*)-2-Ethylidenebicyclo[3.2.2]non-1-yl Mesylate

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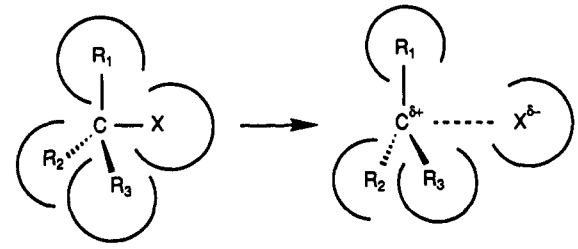
Summary: The rate of ethanolysis at 25 °C of (*Z*)-2-ethylidenebicyclo[2.2.2]oct-1-yl triflate [(*Z*)-**3**] is 217 times faster than that of its *E* isomer, whereas more flexible (*Z*)-2-ethylidenebicyclo[3.2.2]non-1-yl mesylate solvolyzes 3.4 times slower than its *E* isomer, indicating marked leaving-group strain in the ground state of (*Z*)-**3**, which is supported by MM2 calculations.

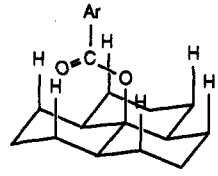
In the ionization of a crowded molecule $(R)_3CX$, both the back strain (B-strain) among the three alkyl groups and the front strain (F-strain) between the leaving group X and the alkyl groups are relieved, resulting in enhancement of solvolysis rates (Scheme I).[1,2] These phenomena have constituted one of the major subjects in computational chemistry.[2,3]

In principle, when the R groups are made bulkier, not only B-strain but also F-strain increases.[2f] Moreover, ionization may well cause an increase in strain between alkyl groups resulting from shortening of the C^+–C bond in the carbocation.[2j,4] Therefore, the rate enhancement solely due to F-strain is generally difficult to realize. Changing the size of the leaving group X in $(R)_3CX$ with varying sizes of the R group achieved considerable success.[2b,h,i] However, concomitant differential change in solvation should always be taken into account.[2g,5] Previously, the tosylate leaving group was suggested to cause greater F-strain than the bromide in bridgehead derivatives,[6] but this was questioned by recent calculations.[3a] The most straightforward approach would be to design a system that shows a dramatic reactivity change upon

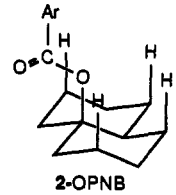
Scheme I



minimum structural modification with the B-strain and the leaving group being unchanged. In this context, the most unambiguous case reported so far would be the finding that *trans,trans,trans*-perhydro-9b-phenalyl *p*-nitrobenzoate (1-OPNB) solvolyzes 2860 times faster than *trans*-9-decalyl *p*-nitrobenzoate (2-OPNB) in 80% acetone at 25 °C.[2c] Since the rate enhancement essentially vanishes in the chloride 1-Cl, the major F-strain in 1-OPNB has been postulated to exist between the carbonyl group (and/or the aryl group) and the ring system.[2c,3c]



1-OPNB



2-OPNB

We now report another clear-cut example. The structural modification employed in the present study is much simpler than annulation of 2-OPNB leading to 1-OPNB. We compared the rates of ethanolysis between (*Z*)-2-ethylidenebicyclo[2.2.2]oct-1-yl triflate [(*Z*)-**3**], the *E* isomer [(*E*)-**3**], and the 2-methylene homologue **4**.[7] For a comparison, (*Z*)- and (*E*)-2-ethylidenebicyclo[3.2.2]non-1-yl

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(6) Bingham, R. C.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *93*, 3189.

(7) The new substrates (*Z*)-**3**, (*E*)-**3**, (*Z*)-**5**, and (*E*)-**5** were prepared as follows. A Wittig ethylidenation[8] of the *tert*-butyldimethylsilyl (BDMS) ether of 1-hydroxybicyclo[2.2.2]octan-2-one[9] afforded solely (*Z*)-**3**-OBDMS as an oil in 85% yield, which on olefin inversion by the phosphorus betaine method[10] gave (*E*)-**3**-OBDMS as an oil in 69% yield. In a similar Wittig ethylidenation of the BDMS ether of 1-hydroxybicyclo-[3.2.2]nonan-2-one[9,11] were isolated (*Z*)-**4**-OBDMS and (*E*)-**4**-OBDMS in 16% and 22% yields, respectively. The *Z* and *E* configurations were based on ^1H NMR NOE difference experiments: on irradiation of the olefinic proton, *Z* isomers showed NOEs on both the methyl and C(3) protons, whereas *E* isomers showed NOEs on only the methyl protons. The BDMS ethers were desilylated by treatment with tetrabutylammonium fluoride in THF and then converted to triflates or mesylates. The only impurity was the corresponding alcohol. The 2-methylene homolgoues **4** and **6** were described previously.[9]

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