New Methods for Alkaloid Synthesis. Facile Total Syntheses of (±)-O-Methyljoubertiamine and (±)-Mesembrine[1]

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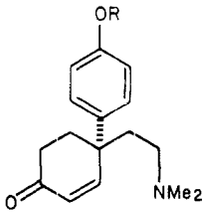
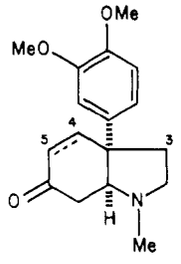
A general strategy for the construction of quaternary carbon atoms via geminal alkylation operations has been successfully employed in the facile total syntheses of the *Sceletium* alkaloids (±)-*O*-methyljoubertiamine (**2**) and (±)-mesembrine (**3**). The key step in these syntheses features the direct homologation of the monoprotected 1,4-diones **14** and **23** into the enamine **15** and the metallo enamine **26**, respectively, using variants of the Wittig reaction. The subsequent reaction of the enamine **15** with allyl bromide resulted in the generation of a fully substituted carbon atom that was suitably functionalized for transformation to (±)-*O*-methyljoubertiamine (**2**). On the other hand, alkylation of the metallo enamine **26** with *N*-(2-bromoethyl)-*N*-methylcarbamate (**27**) allowed the eventual construction of the 4,4-disubstituted cyclohexenone **29** which was readily elaborated into (±)-mesembrine (**3**). The efficiency of this new entry to the *cis*-3a-aryloctahydroindole alkaloids is underscored by the synthesis of (±)-mesembrine (**3**) from veratraldehyde in 40% overall yield. An alternative synthesis of the cyclohexenone **29** is also described which exploits an improved procedure for the spiroannelation of a cyclohexenone at a carbonyl center. This useful synthetic method features the alkylation of the metallo enamines that are generated by homologation operations with 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, **31** → **32** → **33** → **29**.

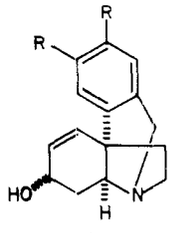
The alkaloids which are found in the various *Sceletium* species of plants (family *Aizoaceae*)[2] have continued to arouse the interests of synthetic organic chemists, and a number of investigations have culminated in the total syntheses of several representative members, including joubertiamine (**1**),[3] *O*-methyljoubertiamine (**2**),[1,3,4] mesembrine (**3**),[5] and mesembrenone (**4**).[5b] Although some derivatives of the octahydroindole alkaloid mesembrine exhibit central nervous system activity,[6] its prime significance as an attractive synthetic target may be more fully appreciated upon the recognition of its close structural relationship with the more complex *Amaryllidaceae* alkaloids crinine (**5**),[7] martidine (**6**),[5j,8] and pretazettine (**7**).[9] Each of these alkaloids possesses a functionalized, *cis*-3a-aryloctahydroindole nucleus, and any general synthetic entry to the *Sceletium* and *Amaryllidaceae* alkaloids must, therefore, incorporate an efficient methodology for the construction of this archetypal structural unit.



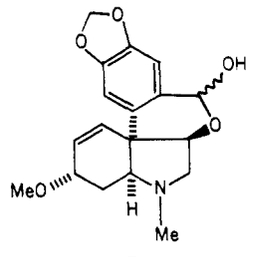
1, R = H
2, R = Me



3, 4,5-dihydro
4, $\Delta^{4,5}$



5, R = OCH_2O
6, R = OMe



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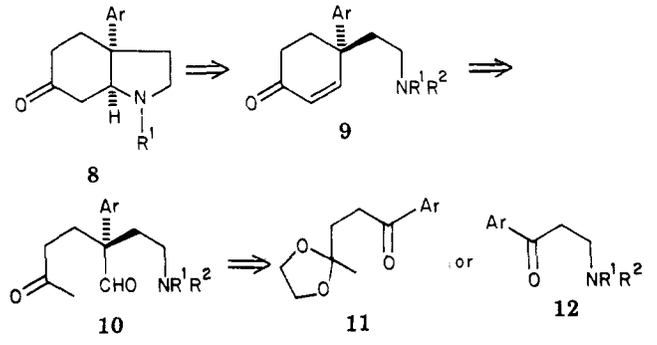
Although a retrosynthetic analysis of the generalized *cis*-3a-aryloctahydroindole **8** allows the formulation of a variety of feasible pathways for its construction,[5] one eminently attractive strategy emerges as depicted in Scheme I. The initial functional group disconnection involves a retro conjugate addition that leads inexorably

Scheme I



(1) For a preliminary account of a portion of this work, see S. F. Martin and T. A. Puckette, *Tetrahedron Lett.*, 4229 (1978).

(2) Cf., (a) P. W. Jeffs, G. Ahmann, H. F. Campbell, D. S. Farrier, G. Ganguli, and R. L. Hawks, *J. Org. Chem.*, **35**, 3512 (1970); (b) R. R. Arndt and P. E. J. Kruger, *Tetrahedron Lett.*, 3237 (1970); (c) F. O. Snyckers, F. Strelow, and A. Wiechers, *Chem. Commun.*, 1467 (1971); (d) P. W. Jeffs, T. Capps, D. B. Johnson, J. M. Karle, N. H. Martin, and B. Rauckman, *J. Org. Chem.*, **39**, 2703 (1974); and (e) T. M. Capps, K. D. Hargrave, P. W. Jeffs, and A. T. McPhail, *J. Chem. Soc., Perkin Trans 2*, 1098 (1977).

(3) R. V. Stevens and J. T. Lai, *J. Org. Chem.*, **37**, 2138 (1972).

(4) H. F. Strauss and A. Wiechers, *Tetrahedron*, **34**, 127 (1978).

(5) (a) M. Shamma and H. R. Rodriguez, *Tetrahedron*, **24**, 6583 (1968); (b) T. J. Curphey and H. L. Kim, *Tetrahedron Lett.*, 1441 (1968); (c) T. Ohishi and H. Kugita, *ibid.*, 5445 (1968); (d) R. V. Stevens and M. P. Wentland, *J. Am. Chem. Soc.*, **90**, 5580, (1968); (e) S. L. Keely, Jr., and F. C. Tahk, *ibid.*, **90**, 5584 (1968); (f) T. Oh-ishi and H. Kugita, *Chem. Pharm. Bull.*, **18**, 299 (1970); (g) H. Taguchi, T. Oh-ishi, and H. Kugita, *ibid.*, **18**, 1008 (1970); (h) G. Otani and S. Yamada, *ibid.*, **21**, 2130 (1973); (i) R. V. Stevens, P. M. Lesko, and R. Lapalme, *J. Org. Chem.*, **40**, 3495 (1975); and (j) J. B. P. A. Wijnberg and W. N. Speckamp, *Tetrahedron*, **34**, 2579 (1978).

(6) A. Ohishi and H. Kugita, Japanese Patents 7143538 (*Chem. Abstr.*, **76**, 59442t (1972)) and 7143539 (*Chem. Abstr.*, **76**, 59443u (1972)).

(7) For the total synthesis of crinine and related alkaloids, see inter alia: (a) H. Muxfeldt, R. S. Schneider, and J. B. Mooberry, *J. Am. Chem. Soc.*, **88**, 3670 (1966); (b) H. W. Whitlock, Jr., and G. L. Smith, *ibid.*, **89**, 3600 (1967); (c) T. Kametani, T. Kohno, R. Charubala, S. Shibuya, and K. Fukumoto, *Chem. Pharm. Bull.*, **20**, 1488 (1972); (d) R. V. Stevens, L. E. Du Pree, Jr., and P. L. Loewenstein, *J. Org. Chem.*, **37**, 977 (1972); (e) M. A. Schwartz, B. F. Rose, and B. Vishnuvajjala, *J. Am. Chem. Soc.*, **95**, 612 (1973); and (f) S. M. Kupchan, O. P. Dhingra, and C.-K. Kim, *J. Org. Chem.*, **43**, 4076 (1978).

(8) For the total synthesis of maritidine and related alkaloids, see inter alia: (a) M. A. Schwartz and R. A. Holton, *J. Am. Chem. Soc.*, **92**, 1090 (1970); (b) E. Kotani, N. Takeuchi, and S. Tobinaga, *J. Chem. Soc., Chem. Commun.*, 550 (1973); (c) E. Kotani, N. Takeuchi, and S. Tobinaga, *Tetrahedron Lett.*, 2735 (1973); and (d) S. Yamada, K. Tomioka, and K. Koja, *Chem. Pharm. Bull.* **25**, 2681 (1977); (e) see also ref 5j.

(9) (a) W. C. Wildman and D. T. Bailey, *J. Org. Chem.*, **33**, 3749 (1968); (b) W. C. Wildman and D. T. Bailey, *J. Am. Chem. Soc.*, **91**, 150 (1969).

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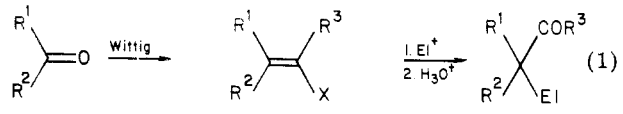
to the 4-(2-aminoethyl)-4-arylcyclohexenone **9**, which is closely related to *O*-methyljoubertiamine (**2**), as the crucial synthetic intermediate. Significantly, the cyclization of amino enones related to **9** (R^2 = H) had previously been shown to produce the requisite *cis*-octahydroindole nucleus.[5a] The formation of the 4,4-disubstituted cyclohexenone **9** by the intramolecular aldol condensation of the δ-keto aldehyde **10** is straightforward. However, the elaboration of compound **10**, which possesses a quaternary carbon atom bearing disparately functionalized alkyl substituents, represents a significant synthetic challenge since the methodology for the creation of fully substituted carbon atoms is one of the most restricted in organic synthesis. One particularly appealing approach to compound **10** merely requires the net replacement of both of the carbon–oxygen bonds of the carbonyl moiety of the precursor ketones **11** and **12** by an operation involving initial carbonyl homologation, followed by an alkylation step in which an additional carbon–carbon bond was formed at the original electrophilic center.

Indeed, we have recently developed several effective, one-pot procedures for the geminal dialkylation at a carbonyl carbon which feature the regiospecific conversion of carbonyl compounds into the enamines[10] and metallo enamines[11] of the homologous aldehydes or ketones using variants of the Wittig reaction (eq 1). The subsequent



(1)

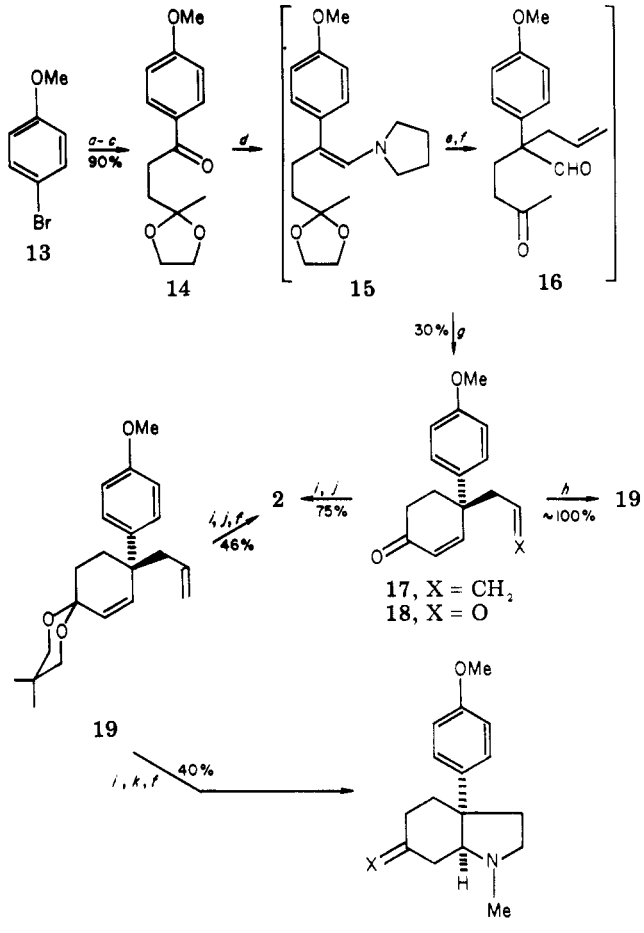
X = NR^4_2, $N(Li)R^4$

alkylation of these nucleophilic carbonyl derivatives thus generated in situ, followed by a hydrolytic workup, completed the construction of the quaternary carbon atom. Since a wide variety of electrophilic reagents may be employed in the alkylation step, it is feasible to elaborate fully substituted carbon atoms that bear alkyl appendages containing differentiated functionality. We now wish to describe the expeditious application of this useful methodology to the total syntheses of (±)-*O*-methyljoubertiamine (**2**) and (±)-mesembrine (**3**) according to the retrosynthetic format depicted in Scheme I.

Synthesis of (±)-*O*-Methyljoubertiamine (2). The monoprotected 1,4-dione **14** which was required for the synthesis of *O*-methyljoubertiamine (**2**) (Scheme II) was readily prepared. Thus, addition of the Grignard reagent derived from *p*-bromoanisole (**13**) to 2-(2-cyanoethyl)-2-methyl-1,3-dioxolane[12] and then controlled, acid-catalyzed hydrolysis of the resulting imine gave **14** in 90% yield. The olefination of the monoprotected dione **14** employing diethyl pyrrolidinolithiomethylphosphonate followed by alkylation of the enamine **15** thereby produced with allyl bromide[10a] and acid-catalyzed hydrolysis of the intermediate iminium salt, afforded the δ-ketoaldehyde **16**. The subsequent conversion of **16** to the key intermediate 4-allyl-4-arylcyclohexenone **17** was then easily effected by base-catalyzed cycloaldolization and dehydration. The overall yield for the transformation **14** → **17**, which may be conveniently executed without the isolation of any intermediates, was an acceptable 30%.

In order to complete the synthesis of *O*-methyljoubertiamine, it was then merely necessary to convert the

Scheme II



[a] $Mg/Et_2O/\Delta$. [b] $NC(CH_2)_2C(OCH_2CH_2O)CH_3$. [c] NH_4Cl/H_2O. [d] $(CH_2)_4NCHLiP(O)(OEt)_2/THF/-78 \rightarrow 25\,^\circ C$. [e] $CH_2{=}CHCH_2Br$/dioxane/Δ. [f] H_3O^+. [g] KOH/H_2O/MeOH. [h] $Me_2C(OCH_2CMe_2CH_2O)/TsOH/\Delta$. [i] $O_3/CH_2Cl_2/-78\,^\circ C$. [j] $Me_2NH_2Cl/NaBH_3CN/t$-BuOH. [k] $MeNH_3Cl/NaBH_3CN/MeOH$.

allyl substituent of the 4,4-disubstituted cyclohexenone **17** into a 2-(*N*,*N*-dimethylaminoethyl) side chain. One eminently attractive strategy for achieving this critical transformation required the oxidative excision of one carbon atom to give the enone aldehyde **18** followed by the reductive amination of the formyl group with dimethylamine. Although the selective cleavage of the double bond of the allyl moiety was easily effected using osmium tetroxide/sodium metaperiodate,[13] the product aldehyde **18** was moderately unstable, thereby precluding its reproducible isolation in an acceptable fashion. However, the selective ozonolysis[14] of the allyl group with 1 equiv of ozone in methylene chloride at −78 °C and immediate treatment of the intermediate ozonide with sodium cyanoborohydride[15] and dimethylamine hydrochloride in anhydrous *tert*-butyl alcohol proceeded smoothly to afford *O*-methyljoubertiamine (**2**) in 75% overall yield. Alternatively, *O*-methyljoubertiamine could be prepared from the protected cyclohexenone **19** by a similar sequence of reactions. In this event, acid-catalyzed transketalization

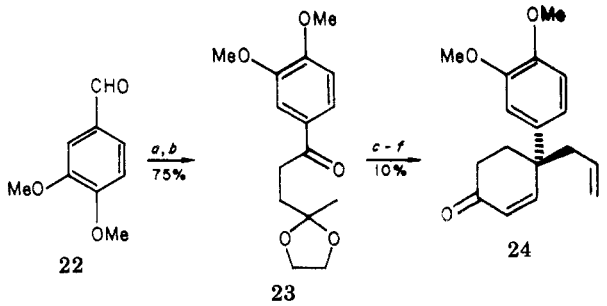
(10) (a) S. F. Martin and R. Gompper, *J. Org. Chem.*, **39**, 2814 (1974); (b) S. F. Martin, *ibid.*, **41**, 3337 (1976); (c) S. F. Martin, T. S. Chou, and C. W. Payne, *ibid.*, **42**, 2520 (1977).
(11) S. F. Martin and G. W. Phillips, *J. Org. Chem.*, **43**, 3792 (1978).
(12) E. Brown and R. Dhal, *Bull. Soc. Chim. Fr.*, 4292 (1972).
(13) R. Pappo. D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).
(14) For an excellent review of ozonation see P. S. Bailey, "Ozonation in Organic Chemistry", Vol. 1 , W. Trahanovsky, Ed., Academic Press, New York, 1978.
(15) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).

of the 4-allyl-4-aryl-2-cyclohexenone **17** with 2,2,5,5-tetramethyl-1,3-dioxane[16] provided a virtually quantitative yield of the ketal **19** which also suffered selective scission of the monosubstituted double bond of the allyl unit upon ozonolysis in methylene chloride at −78 °C. The resulting ozonide was then dissolved in anhydrous methanol and allowed to react with sodium cyanoborohydride in the presence of dimethylamine hydrochloride. Subsequent hydrolytic removal of the ketal moiety provided *O*-methyljoubertiamine (**2**) in 46% overall yield from **17**.

The construction of the *cis*-3a-aryloctahydroindole ring system is an objective of paramount importance to the syntheses of mesembrine (**3**), mesembrenone (**4**), and the more complex *Amaryllidaceae* alkaloids **5**–**7**, and it was, therefore, a matter of utmost concern to ascertain whether the 4-allyl-4-arylcyclohexenone **17** might also serve as a viable intermediate for the preparation of the *cis*-octahydroindole **20**. Since compound **20** had been previously converted to joubertiamine (**1**) and *O*-methyljoubertiamine (**2**),[3] the successful transformation of **17** into **20** would then provide yet another synthetic pathway to these two alkaloids. Unfortunately, all attempts to prepare the *cis*-octahydroindole **20** directly from the allyl cyclohexenone **17** by sequential ozonolysis and reductive amination with methylamine hydrochloride/sodium cyanoborohydride were frustrated by the inescapable obtention of the methylamino octahydroindole **21** as the major product, regardless of the reaction conditions. Whereas the α,β-unsaturated ketone function present in *O*-methyljoubertiamine was stable to the conditions required for the reductive amination of the aldehyde function, the saturated carbonyl group of the octahydroindole **20** apparently suffered facile and unavoidable reductive amination. A modification of the synthetic plan which did not involve the intermediacy of a saturated ketone moiety during the critical reductive amination step was therefore required. Although a number of possible pathways were explored, the problem was most effectively resolved by the expeditious use of the ketal **19** as the substrate for the ozonolysis–reductive amination sequence. Thus, compound **19**, which was prepared from **17** by transketalization as previously described, was dissolved in methylene chloride and allowed to react with 1 equiv of ozone at −78 °C. After the ozonide thus produced was treated with sodium cyanoborohydride and methylamine hydrochloride in anhydrous methanol, hydrolytic removal of the ketal moiety and spontaneous cyclization of the resulting amino enone afforded the desired *cis*-3a-aryloctahydroindolone **20** in 40% overall yield from **17**.

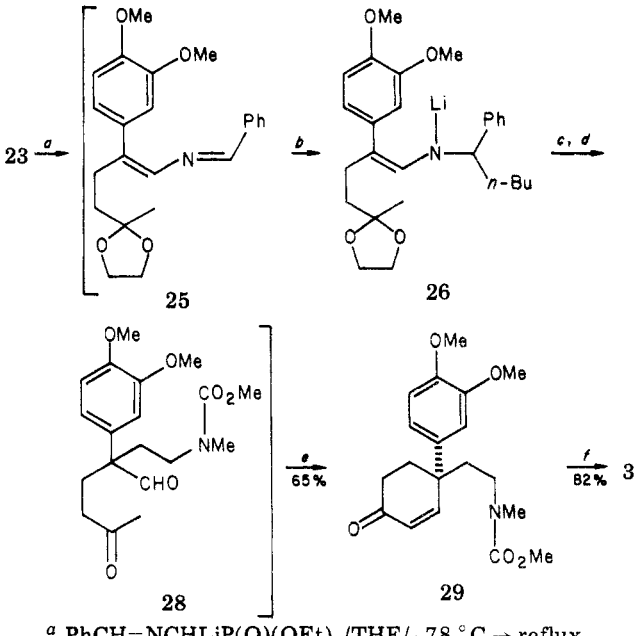
Synthesis of (±)-Mesembrine (3). After the efficacy of the general synthetic strategy depicted in Scheme I for the construction of the *cis*-3a-aryloctahydroindole nucleus via intermediate enamines was successfully demonstrated, efforts were then directed toward the seemingly trivial extension of this methodology to the synthesis of mesembrine (**3**). Thus, the requisite monoprotected 1,4-dione **23** was conveniently prepared in 75% overall yield by the addition of the Grignard reagent derived from 2-methyl-2-(2-bromoethyl)-1,3-dioxolane[18] to veratraldehyde

Scheme III



[a] $BrMg(CH_2)_2C(OCH_2CH_2O)CH_3$/THF. [b] $HCrO_4^-$. [c] $(CH_2)_4NCHLiP(O)(OEt)_2$/THF/−78 → 25 °C. [d] $CH_2=CHCH_2Br$/dioxane/Δ. [e] H_3O^+. [f] KOH/H_2O/MeOH.

Scheme IV



[a] PhCH=NCHLiP(O)$(OEt)_2$/THF/−78 °C → reflux. [b] *n*-BuLi/−78 °C. [c] $Br(CH_2)_2NMeCO_2Me$/−78 → 25 °C. [d] H_3O^+. [e] KOH/H_2O/MeOH/25 °C. [f] KOH/H_2O/EtOH/Δ.

(**22**) followed by the Jones oxidation[19] of the intermediate benzyl alcohol. Unfortunately, the sequential treatment of **23** with diethyl pyrrolidinolithiomethylphosphonate, allyl bromide, aqueous acid, and then aqueous base in a manner reminiscent of the previous transformation **14** → **17** provided the desired allyl cyclohexenone **24** in a disappointing 10% overall yield (Scheme III).

At this juncture, it became painfully clear that the procedures for the construction of quaternary carbon atoms via enamines were subject to unfortunate limitations. On the other hand, our recently developed methodology for the highly efficient elaboration of fully substituted carbon atoms from carbonyl compounds via intermediate metallo enamines[11] seemed to be worthy of attention. Since metallo enamines are inherently more nucleophilic than the corresponding enamines, their use in carbon–carbon bond-forming reactions allows vastly greater flexibility in the choice of the electrophilic reagent. For example, in the present instance the judicious choice of an alkylating agent might result in the *direct* introduction of the essential 2-(*N*-methylamino)ethyl side chain at the quaternary center, thereby obviating the trouble-

(16) Neither the 1,3-dioxolane nor unsubstituted 1,3-dioxane protecting groups were sufficiently stable to survive the conditions of the reductive amination. Although the corresponding 1,3-dithiolane and 1,3-dithiane protecting groups were stable under these conditions, considerable difficulty was encountered in the efficient dethioketalization of the intermediate amino dithioketals.[17]

(17) Cf. (a) T. Oishi, H. Takechi, K. Kamemoto, and Y. Ban, *Tetrahedron Lett.*, 11 (1974); (b) L. Duhamel, P. Duhamel, and N. Mancelle, *Bull. Soc. Chim., Fr.*, 331 (1974); (c) H. Muxfeldt, W. D. Unterweger, and G. Helmchen, *Synthesis*, 694 (1976).

(18) A. A. Ponaras, *Tetrahedron Lett.*, 3105 (1976).

(19) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

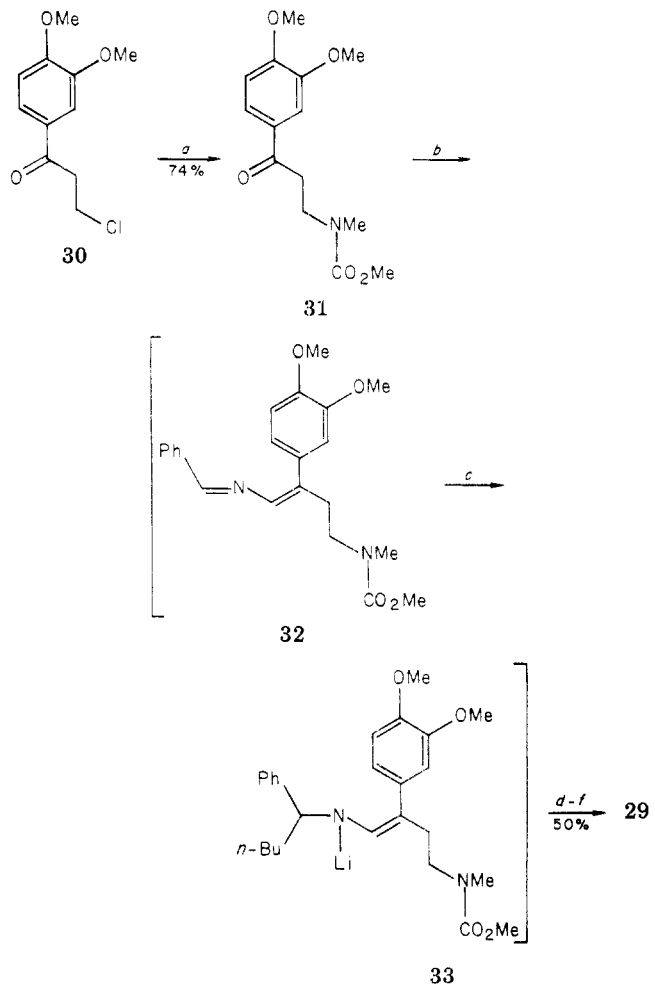
some functional group manipulation of the allyl moiety as previously described for the synthesis of the *cis*-octahydroindole **20**. Reduction of this strategy to practice has resulted in an extraordinarily facile and efficient synthesis of racemic mesembrine from the monoprotected 1,4-dione **23** (Scheme IV).

In this event, olefination of **23** with diethyl *N*-benzylideneaminolithiomethylphosphonate[20] afforded the 2-azadiene **25** which cleanly suffered regioselective 1,2-addition of *n*-butyllithium generating the metallo enamine **26** in situ. When the metallo enamine **26** was alkylated with *N*-(2-bromomethyl)-*N*-methylcarbamate (**27**) and aqueous acid was added to the resulting mixture, the δ-ketoaldehyde **28** was produced. Subsequent treatment of the crude δ-ketoaldehyde **28** with aqueous potassium hydroxide/methanol resulted in facile cycloaldolization and dehydration to give the key intermediate 4,4-disubstituted cyclohexenone **29** in 65% overall yield. After the hydroxide-induced *N*-decarbomethoxylation of **29**, spontaneous cyclization of the intermediate amino enone ensued, and (±)-mesembrine (**3**) was isolated in 82% yield. The racemic mesembrine thus obtained was identical (IR, NMR, TLC) with natural (−)-mesembrine.[21]

The general utility of our procedure for the facile construction of quaternary carbon centers by geminal dialkylation operations using regiospecifically generated metallo enamines as intermediates is further substantiated by a simple, alternative synthesis of the enone urethane **29**. This route, which commences with a protected β-amino ketone related to **12**, is outlined in Scheme V. The requisite β-(*N*-methyl-*N*-carbomethoxy) ketone **31** was easily prepared in 74% yield by the reaction of the known β-chloro ketone **30**[22] with methyl *N*-methylcarbamate in the presence of a catalytic amount of *p*-toluenesulfonic acid.[23] Subsequent olefination of the ketone **31** with diethyl *N*-benzylideneaminolithiomethylphosphonate produced the 2-azadiene **32** which suffered regioselective attack by *n*-butyllithium to give the metallo enamine **33**. Alkylation of **33** with 2-(2-bromoethyl)-2-methyl-1,3-dioxolane,[12] followed by the addition of aqueous acid, produced the δ-keto aldehyde **28** which was smoothly converted by base-catalyzed cycloaldolization–dehydration to the 4,4-disubstituted cyclohexenone **29** in 50% overall yield from **31**. The effective utilization of the relatively unreactive 2-(2-bromoethyl)-2-methyl-1,3-dioxolane as a masked 3-oxobutyl synthon in this annelation sequence is noteworthy.

The application of this general strategy for alkaloid synthesis which is outlined in Scheme I to the total syntheses of the more complex *Amaryllidaceae* alkaloids is under active investigation, and these results will be reported independently.

Scheme V



[a] MeNHCO$_2$Me/toluene/TsOH/Δ. [b] PhCH=NCHLiP(O)(OEt)$_2$/THF/−78 °C → reflux. [c] *n*-BuLi/−78 °C. [d] Br(CH$_2$)$_2$C(OCH$_2$CH$_2$O)CH$_3$/THF/HMPA/−78 → 25 °C. [e] H_3O^+. [f] KOH/H$_2$O/MeOH.

Experimental Section

General. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. All boiling points are uncorrected. ^{1}H NMR spectra were determined on a Varian A-60A or HA 100 spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in δ units downfield from the internal reference tetramethylsilane. The infrared spectra (IR) were recorded on a Beckman IR-5A spectrophotometer, using chloroform as a solvent. Low-resolution mass spectra were obtained on a DuPont (CEC) 21-491 instrument, and the high-resolution mass spectra were obtained on a DuPont (CEC) 21-110 instrument. Preparative liquid chromatography was performed on a Waters Prep LC 500 instrument using two Prep PAK columns. Glassware was oven dried prior to use, and all reactions were executed under dry nitrogen. The tetrahydrofuran (THF) was freshly distilled from potassium–benzophenone, and the ether was freshly distilled from sodium–benzophenone. Hexamethylphosphoric triamide (HMPA) was distilled from potassium under reduced pressure.

1-(2-Methyl-1,3-dioxolan-2-yl)-3-oxo-3-(4-methoxyphenyl)propane (14). To a mechanically stirred mixture of magnesium turnings (4.89 g, 0.21 mol) suspended in anhydrous ether (300 mL) was added *p*-bromoanisole (**13**) (29.84 g, 0.16 mol). Upon completion of the addition, the reaction mixture was heated at reflux for 2.5 h and then cooled to 0 °C. A solution of 2-(2-cyanoethyl)-2-methyl-1,3-dioxolane[12] (15.0 g, 0.11 mol) in anhydrous ether (100 mL) was then slowly added, and the resulting mixture was stirred at room temperature for 18 h, whereupon saturated ammonium chloride (150 mL) and 1 N HCl (210 mL) were added. The two-phase mixture was then stirred vigorously at room temperature for about 1 h to effect hydrolysis of the intermediate imine. The layers were separated, and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ (1 × 75 mL) and dried ($MgSO_4$). After the excess solvents were removed under reduced pressure, the crude product was purified by vacuum distillation to give 23.90 g (90%)) of **14**: bp 156–157 °C (0.05 mm); mp 46–48 °C; IR 1642, 1597 cm^{-1}; NMR δ 8.02 (d, 2 H, J = 9 Hz), 6.97 (d, 2 H, J = 9 Hz), 3.95 (s, 4 H), 3.86 (s, 3 H), 3.05 (t, 2 H, J = 7.5 Hz), 2.12 (t, 2 H, J = 7.5 Hz) 1.36 (s, 3 H); mass spectrum m/e 250, 235, 135, 87 (base).

(20) R. W. Ratcliff and B. G. Christensen, *Tetrahedron Lett.*, 4645 (1973).

(21) We wish to thank Professors P. W. Jeffs and M. Shamma for generous samples of authentic (−)-mesembrine.

(22) K. Freudenberg and H. Fikentscher, *Justus Liebigs Ann. Chem.*, **440**, 36 (1924).

(23) H. Mohrle and R. Engelsing, *Monatsh. Chem.*, **102**, 233 (1971).

An analytical sample was prepared by recrystallization from hexane, mp 46–48 °C. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.02; H, 7.27.

4-Allyl-4-(4-methoxyphenyl)-2-cyclohexenone (17). To a well-stirred solution of diethyl pyrrolidinomethylphosphonate[10a] (25.3 g, 0.11 mol) in anhydrous THF (400 mL) was slowly added *n*-butyllithium (0.11 mol, 2.6 N hexane) at −78 °C. After the completion of the addition, the solution was stirred 1 h at −78 °C, and then the monoprotected 1,4-dione **14** (23.8 g, 0.095 mol) in anhydrous THF (175 mL) was slowly added. The solution was stirred at −78 °C for 10 h and then at room temperature for 18 h. The resulting solution of enamine **15** was concentrated under reduced pressure, and dry dioxane (100 mL) and allyl bromide (69.1 g, 0.57 mol) were added to the residue. The resulting mixture was then heated at reflux for 48 h, whereupon the excess solvents were removed under reduced pressure. The residual oil was dissolved in methanol (200 mL), and the solution was acidified to pH 1 with 1 N HCl. Then the solution was stirred at room temperature overnight, whereupon it was cooled to 0 °C. To this solution of δ-ketoaldehyde **16** was added slowly solid potassium hydroxide until pH ≃12, and the stirring was continued at room temperature for 1 h. After the methanol was removed under reduced pressure, the aqueous mixture was saturated with NaCl and extracted with ether (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), and the excess solvents were removed under reduced pressure to give crude **17**, which was purified by preparative liquid chromatography using ethyl acetate–hexane (1:4) as the eluent. Subsequent vacuum distillation afforded 6.9 g (30%) of **17**: bp 149–150 °C (0.04 mm); IR 1678, 1610 cm^{-1}; NMR δ 7.32 (d, 2 H, J = 9 Hz), 7.15 (d, 1 H, J = 10 Hz), 6.94 (d, 2 H, J = 9 Hz), 6.22 (d, 1 H, J = 10 Hz), 4.90–5.80 (complex, 3 H), 3.82 (s, 3 H), 2.65 (m, 3 H), 2.27 (br s, 4 H); exact mass (calcd for $C_{16}H_{18}O_2$, 242.1307), found 242.1304. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.58; H, 7.55.

***O*-Methyljoubertiamine (2). Method A.** A solution of allyl cyclohexenone **17** (181 mg, 0.75 mmol) in anhydrous methylene chloride (5 mL) at −78 °C was treated with 1 equiv of ozone. The excess solvent was removed under reduced pressure, and the residue was dissolved in anhydrous *tert*-butyl alcohol (5 mL) containing sodium cyanoborohydride (151 mg, 0.81 mmol). The heterogeneous mixture was stirred at room temperature for 0.5 h at which time dimethylamine hydrochloride (122 mg, 1.50 mmol) was added, and the resulting mixture was stirred for 20 h. The reaction was quenched by addition of 1 N HCl (5 mL), and the *tert*-butyl alcohol was removed under reduced pressure. Saturated brine (10 mL) was added to the residue, and the aqueous mixture was washed with ether (2 × 10 mL). The aqueous phase was then cooled in an ice bath, made alkaline by the addition of solid KOH, and extracted with ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give 150 mg (75%) of chromatographically pure *O*-methyljoubertiamine (**2**). The IR and NMR spectra of this material were identical with those previously recorded:[24] mass spectra m/e 273, 149, 84, 58 (base).

Method B. A mixture of the allyl cyclohexenone **17** (98 mg, 0.41 mmol), 2,2,5,5-tetramethyl-1,3-dioxane (2 mL), and a catalytic amount of *p*-toluenesulfonic acid (ca 5 mg) was heated at 80 °C under reduced pressure (100 mm) for 3 h, and the resulting oil was dissolved in dry methylene chloride (10 mL). The solution of crude ketal **19** thus obtained was cooled to −78 °C and treated with 1 equiv of ozone. The excess methylene chloride was then removed under reduced pressure, and to the crude ozonide was added a solution of sodium cyanoborohydride (22.0 mg, 0.35 mmol) in anhydrous methanol (0.5 mL) followed by the addition of dimethylamine hydrochloride (133 mg, 1.63 mmol) in anhydrous methanol (1.5 mL). The resulting cloudy suspension was stirred at room temperature for 24 h, 3 N HCl (5 mL) was added, and the stirring was continued for an additional 4 h. The methanol was removed under reduced pressure, the aqueous mixture was extracted with ether (3 × 10 mL), and the organic layers were discarded. The aqueous layer was then cooled to 5 °C, made alkaline with solid KOH, and extracted again with ether (3 × 15 mL). The combined ether layers were dried ($MgSO_4$), and the excess solvents were removed under reduced pressure to give crude *O*-methyljoubertiamine (**2**) which was purified by column chromatography on basic alumina (5 g), using 3% $MeOH/CH_2Cl_2$ as the eluting solvent. The pure *O*-methyljoubertiamine thus obtained (51 mg, 46%) was identical (IR, NMR, and TLC) with the sample prepared by method A.

***cis*-*N*-Methyl-3a-(4-methoxyphenyl)octahydroindol-6-one (20).** A mixture of the allyl cyclohexanone **17** (94.5 mg, 0.39 mmol), 2,2,5,5-tetramethyl-1,3-dioxane (2.5 mL), and a catalytic amount of *p*-toluenesulfonic acid (ca 5 mg) was heated at 85 °C under reduced pressure (100 mm) for 3 h, and the resulting oil was dissolved in dry methylene chloride (10 mL). The resulting solution of crude ketal **19** was then cooled to −78 °C and treated with 1 equiv of ozone. After removal of the excess methylene chloride under reduced pressure, solutions of sodium cyanoborohydride (21.2 mg, 0.34 mmol) in anhydrous methanol (0.5 mL) and methylamine hydrochloride (105 mg, 1.56 mmol) in anhydrous methanol (1.5 mL) were added. The reaction mixture was then stirred at room temperature for 24 h, 3 N HCl (5 mL) was added, and the stirring was continued for an additional 4 h. After the removal of the methanol under reduced pressure, the aqueous mixture was extracted with ether (3 × 10 mL), and the organic layers were discarded. The aqueous layer was cooled, made alkaline with solid KOH, and extracted again with ether (3 × 10 mL). The combined organic layers were then dried ($MgSO_4$), and the excess solvents were removed under reduced pressure. The crude *cis*-octahydroindolone **20** thus obtained was purified by column chromatography on basic alumina (5 g), using 3% $MeOH/CH_2Cl_2$ as the eluting solvent to give 41 mg (40%) of pure **20** which gave IR and NMR spectra that were identical with those previously recorded:[24] mass spectrum m/e 259, 188, 95, 70 (base).

1-(2-Methyl-1,3-dioxolan-2-yl)-3-oxo-3-(3,4-dimethoxyphenyl)propane (23). To a stirred suspension of magnesium turnings (3.60 g, 150.0 mmol) in anhydrous THF (25 mL) was added 1,2-dibromoethane (1.97 g, 10.5 mmol). After the initial exothermic reaction had subsided and the magnesium had a tarnished appearance, a solution of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[12] (9.75 g, 50.0 mmol) and 1,2-dibromoethane (1.97 g, 10.5 mmol) in anhydrous THF (25 mL) was added slowly dropwise over 45 min while maintaining the reaction temperature at 25 °C with a water bath. Upon the completion of the addition, the reaction mixture was stirred at room temperature for 0.5 h and then transferred via cannula to a solution of veratraldehyde **22** (5.54 g, 33.3 mmol) in anhydrous THF (15 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 24 h, whereupon saturated NH_4Cl (75 mL) was added. Sufficient water was added to dissolve the salts (ca. 50 mL), and the aqueous mixture was extracted with ether (3 × 30 mL). The combined organic layers were washed with water (1 × 30 mL) and saturated brine (1 × 30 mL) and dried ($MgSO_4$). The excess solvents were removed under reduced pressure, the crude alcohol was immediately dissolved in acetone (150 mL) at 0 °C, and aqueous chromic acid [prepared from chromium trioxide (2.22 g, 22.2 mmol), concentrated H_2SO_4 (3.26 g, 33.3 mmol), and water (20 mL)] was slowly added (ca. 45 min) with vigorous stirring. The reaction was then quenched by the addition of saturated $NaHCO_3$ (10 mL), and the solids were removed by vacuum filtration through a Celite pad. The aqueous mixture was extracted with ether (3 × 100 mL), and the combined organic layers were washed with water (1 × 50 mL) and saturated brine (1 × 50 mL) and then dried ($MgSO_4$). Removal of the excess solvents under reduced pressure and vacuum distillation of the crude product afforded 6.98 g (75%) of **23** which solidified upon standing: bp 165 °C (0.05 mm); mp 90–91 °C; IR 1670, 1590 cm^{-1}; NMR δ 7.58 (d, 1 H, J = 8.5 Hz), 7.52 (s, 1 H), 6.86 (d, 1 H, J = 8.5 Hz), 3.92 (s, 4 H), 3.90 (s, 6 H), 3.01 (t, 2 H, J = 7 Hz), 2.09 (d, 2 H, J = 7 Hz), 1.35 (s, 3 H); mass spectrum m/e 280, 236, 165, 87 (base).

An analytical sample was prepared by recrystallization from hexane, mp 90–91 °C. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.49; H, 6.91.

4-[2-(*N*-Carbomethoxy-*N*-methylamino)ethyl]-4-(3,4-dimethoxyphenyl)-2-cyclohexenone (29). Method A. To a well-stirred solution of *n*-butyllithium (7.5 mmol, 2.7 N hexane) in anhydrous THF (50 mL) at −78 °C was added slowly dropwise a solution of diethyl *N*-benzylideneaminomethylphosphonate[20]

(24) We wish to thank Professors R. V. Stevens and A. Wiechers for supplying the necessary IR and NMR spectra for this comparison.

(1.91 g, 7.5 mmol) in anhydrous THF (5 mL). After 1 h, a solution of monoprotected 1,4-dione **23** (1.40 g, 5.0 mmol) in anhydrous THF (10 mL) was added dropwise, and the solution was allowed to warm to room temperature (ca. 1 h) and then heated at reflux for 2 h. The resulting solution of 2-azadiene **25** was cooled to −78 °C, *n*-butyllithium (7.5 mmol, 2.7 N hexane) was added, and the stirring was continued at −78 °C for an additional 1 h. A solution of methyl *N*-(2-bromoethyl)-*N*-methylcarbamate (**27**) (4.15 g, 21.2 mmol) was then added, and the stirring was continued at −78 °C for 8 h and then at room temperature for 16 h. Then the mixture was acidified to pH 1 with 1 N HCl, and the resulting mixture was stirred vigorously at room temperature for 8 h, whereupon ether (75 mL) was added. The layers were separated, and the aqueous layer was extracted with ether (3 × 75 mL). The combined organic layers were washed with 1 N HCl (1 × 50 mL), water (2 × 50 mL), and saturated brine (1 × 50 mL) and dried ($MgSO_4$). Removal of the excess solvents under reduced pressure afforded the crude δ-ketoaldehyde **28** which was dissolved in methanol (50 mL) at 0 °C. To this solution of **28** was added with stirring 10% KOH (10 mL), and the resulting mixture was stirred at room temperature for 1 h. The methanol was removed under reduced pressure and saturated brine (25 mL) was added; the aqueous mixture was extracted with ether (3 × 50 mL). The combined organic layers were washed with saturated brine (2 × 50 mL) and dried ($MgSO_4$). After the evaporation of the excess solvents under reduced pressure, the crude product mixture was purified by high-performance liquid chromatography using ethyl acetate–hexane (2:1) as the eluent to give 1.13 g (65%) of pure **29**. An analytical sample was prepared by Kugelrohr distillation at 220 °C (bath temperature) (0.01 mm): IR 1675, 1595 cm^{-1}; NMR δ 7.22 (d, 1 H, J = 10 Hz), 6.85 (s, 3 H), 6.18 (d, 1 H, J = 10 Hz), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.68 (s, 3 H), 3.19 (t, 2 H, J = 8.5 Hz), 2.83 (s, 3 H), 2.35–1.85 (complex, 6 H); mass spectrum m/e 347, 231 (base), 102. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.85; H, 7.43; N, 3.76.

Method B. A solution of diethyl *N*-benzylideneaminomethylphosphonate[20] (1.50 g, 6.0 mmol) in anhydrous THF (3 mL) was added to a stirred solution of *n*-butyllithium (6.0 mmol, 2.7 N hexane) in anhydrous THF (40 mL) at −78 °C. After 1 h, a solution of ketourethane **31** (1.40 g, 5.0 mmol) in anhydrous THF (5 mL) was added, and the reaction mixture was allowed to warm to room temperature (ca. 1 h) and then heated at reflux for an additional 2 h. The resulting solution of the 2-aza diene **31** was cooled to −78 °C, *n*-butyllithium (9.0 mmol, 2.7 N hexane) was added, and the stirring was continued at −78 °C for 1 h. After the addition of freshly distilled hexamethylphosphoramide (10 mL), a solution of pure 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[12] (2.92 g, 15.0 mmol) in anhydrous THF (5 mL) was added. The reaction mixture was then stirred at room temperature for 18 h, whereupon 1 N hydrochloric acid (50 mL) was added, and the stirring was continued at room temperature for 6 h. Saturated brine (50 mL) was added, and the resulting mixture was extracted with ether (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), and the excess solvents were removed under reduced pressure to provide the crude δ-ketoaldehyde **28** as a dark oil. This δ-ketoaldehyde was dissolved in methanol (30 mL), 10% aqueous potassium hydroxide (20 mL) was added, and the resulting mixture was stirred at room temperature for 1 h, whereupon the methanol was removed under reduced pressure. The aqueous mixture was extracted with ether (5 × 25 mL), and the combined organic layers were dried ($MgSO_4$). Evaporation of the excess solvents under reduced pressure followed by purification of the crude cyclohexenone **29** by high-performance liquid chromatography, using ethyl acetate–hexane (2:1) as the eluent, afforded pure **29**, 0.88 g (50%), which was identical with that prepared by method A above.

Methyl *N*-(2-Bromoethyl)-*N*-methylcarbamate (27). A solution of *N*-methylethanolamine (27.5 g, 0.5 mol) in 48% HBr (169.0 g, 1.05 mol) was heated at 160–180 °C (oil bath) for 9 h, during which time water (ca. 90 mL) was slowly removed by distillation at a head temperature less than 110 °C. The reaction mixture was cooled and then poured into cold acetone (200 mL), whereupon 1-(*N*-methylamino)-2-bromoethane hydrobromide crystallized (81.3 g). Concentration of the mother liquors yielded a second crop to give a total of 94.8 g (87%) of crude salt which was used without purification. A portion of the crude 1-(*N*-methylamino)-2-bromoethane hydrobromide (15.0 g, 0.069 mol) was dissolved in 2 N NaOH (35 mL) at 0 °C, and then methyl chloroformate (7.77 g, 0.082 mol) and 4 N NaOH (17 mL) were added simultaneously with vigorous stirring. The reaction mixture was stirred at 0 °C for an additional 0.5 h, the aqueous mixture was then extracted with ether (3 × 50 mL), and the combined organic layers were dried ($MgSO_4$). Removal of the excess solvents under reduced pressure followed by bulb-to-bulb (Kugelrohr) vacuum distillation at 80 °C (bath temperature) and 0.1 mm afforded 9.34 g (70%) of pure **27**: IR 1689 cm^{-1}; NMR δ 3.70 (s, 3 H), 3.65–3.47 (complex, 4 H), 2.99 (s, 3 H); mass spectrum m/e 197, 195, 107, 102 (base), 58; exact mass (calcd for $C_5H_{10}BrNO_2$) 194.9895, found 194.9905.

Methyl *N*-Methyl-*N*-[3-(3,4-dimethoxyphenyl)-3-oxopropyl]carbamate (31). A mixture containing methyl *N*-methylcarbamate (11.3 g, 0.12 mol), 3,4-dimethoxy-3′-chloropropiophenone (**30**) (14.4 g, 0.06 mol), and a catalytic amount of *p*-toluenesulfonic acid (ca. 50 mg) in toluene (250 mL) was heated at reflux for about 48 h. The mixture was then washed with saturated brine (1 × 100 mL) and dried ($MgSO_4$), and the excess solvents were removed under reduced pressure. The crude ketourethane **31** thus obtained was then recrystallized from ether–hexane to give 12.9 g (74%) as a white crystalline solid: mp 66–67 °C; IR 1678, 1582 cm^{-1}; NMR δ 7.60 (d, 1 H, J = 8.5 Hz), 7.51 (br s, 1 H), 6.88 (d, 1 H, J = 8.5 Hz), 5.93 (s, 6 H), 3.90 (s, 3 H), 3.66 (t, 2 H, J = 7 Hz), 3.18 (t, 2 H, J = 7 Hz), 2.97 (s, 3 H); mass spectrum m/e 281, 192, 165 (base), 102. Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.81; N, 4.98. Found: C, 59.72; H, 6.96; N, 4.85.

Mesembrine (3). A solution of **29** (1.07 g, 3.08 mmol) in a mixture of degassed ethanol (10 mL) and 10% KOH (10 mL) was heated at reflux for 24 h under nitrogen. The mixture was then cooled to 0 °C and acidified with 3 N HCl. After the evaporation of the ethanol under reduced pressure, saturated brine (25 mL) was added, and the aqueous mixture was washed with ether (3 × 25 mL). The aqueous solution was then cooled to 0 °C and made alkaline (pH 10–12) with solid KOH, and the resulting mixture was extracted with ether (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), and the excess solvents were evaporated under reduced pressure to give 0.73 g (82%) of chromatographically pure, racemic mesembrine (**3**). The IR, NMR, and mass spectra and TLC of this material were identical with those obtained from natural (−)-mesembrine.[21]

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Registry No. (±)-**2**, 34603-52-6; (±)-**3**, 6023-73-0; **13**, 104-92-7; **14**, 70068-11-0; **15**, 70503-55-8; (±)-**16**, 71171-80-7; (±)-**17**, 70503-57-0; (±)-**19**, 70503-58-1; (±)-**20**, 70503-69-4; **22**, 120-14-9; **23**, 71171-81-8; **25**, 71171-82-9; **27**, 71171-83-0; (±)-**28**, 71171-84-1; (±)-**29**, 71171-85-2; **30**, 4693-38-3; **31**, 71171-86-3; 2-(2-cyanoethyl)-2-methyl-1,3-dioxolane, 40159-07-7; allyl bromide, 106-95-6; 2,2,5,5-tetramethyl-1,3-dioxane, 767-55-5; dimethylamine hydrochloride, 506-59-2; 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, 37865-96-6; diethyl *N*-benzylideneaminomethylphosphonate, 50917-73-2; *N*-methylethanolamine, 109-83-1; 1-(*N*-methylamino)-2-bromoethane hydrobromide, 40052-63-9; methyl chloroformate, 79-22-1; methyl *N*-methylcarbamate, 6642-30-4.