Thallium in Organic Synthesis. 59. Alkaloid Synthesis via Intramolecular Nonphenolic Oxidative Coupling. Preparation of (±)-Ocoteine, (±)-Acetoxyocoxylonine, (±)-3-Methoxy-*N*-acetylnornantenine, (±)-Neolitsine, (±)-Kreysigine, (±)-*O*-Methylkreysigine, and (±)-Multifloramine[1-3]

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Abstract: Reaction of 1,2-bis(3,4-dimethoxyphenyl)ethane, 1,3-bis(3,4-dimethoxyphenyl)propane, diveratryl ether, *N*-methyl-*N*-veratrylveratramide, and *N*-methylbis(3,4-dimethoxybenzyl)amine with thallium(III) trifluoroacetate (TTFA) and $BF_3{\cdot}Et_2O$ in CH_2Cl_2/TFA resulted in intramolecular nonphenolic coupling to give the respective bridged biaryl systems. Extensions of this intramolecular aryl coupling procedure to appropriately substituted 1-benzyl- and 1-phenethyl-1,2,3,4-tetrahydroisoquinolines have resulted in effective syntheses of the aporphine alkaloids (±)-ocoteine, (±)-acetoxyocoxylonine, and (±)-neolitsine, the noraphorphine (±)-3-methoxy-*N*-acetylnornantenine, and the homoaporphine alkaloids (±)-kreysigine, (±)-*O*-methylkreysigine, and (±)-multifloramine.

Many different types of natural products contain a biaryl subunit, and for many years the classical approach to the total synthesis of such compounds has involved as a key step one or the other of a number of intramolecular biaryl coupling reactions. This approach has proved to be particularly effective with respect to various classes of alkaloids, where both older and more modern methods of biaryl synthesis have been widely exploited. Thus, the Ullmann, Pschorr, and photo-Pschorr reactions, photochemical dehydrohalogenation, and anodic and cathodic electrochemical oxidation have been successfully used for construction of the essential biaryl subunit. In many instances, however, yields in the biaryl coupling reactions are very low, while formation of mixtures of products is by no means uncommon; in other cases, the reactions may fail because particular subunit groups are incompatible with the reaction conditions. Regiospecific introduction of substituent groups which must eventually be eliminated in the coupling process can be an added complication, especially in syntheses where the Ullmann, Pschorr, or photo-Pschorr reactions are used.

Phenol oxidative coupling procedures have also been employed extensively in alkaloid synthesis for intramolecular carbon–carbon bond formation between two aromatic rings. Yields of coupled products, however, are generally poor and tend to vary erratically depending on the nature of the substrate and/or the reagent employed. While efforts continue to identify all of the reasons for these unsatisfactory results and to design substrate structural features more carefully,[5] a recently introduced alternative approach is the development of specific and selective reagents for *nonphenolic* coupling. We now report that thallium(III) trifluoroacetate (TTFA) is an efficient and versatile reagent for intramolecular nonphenolic coupling and describe its use in the total synthesis of a number of representative isoquinoline alkaloids.

Discussion

It has been established during the last few years that vanadium(IV) chloride, vanadium(V) oxychloride, and vanadium(V) oxyfluoride can function as powerful reagents for both inter- and intramolecular biaryl coupling, especially of substrates which contain hydroxy or alkoxy substituents. Vanadium(IV) chloride[6] and vanadium(V) oxychloride[7-14] have been used almost exclusively to couple mono- and diphenols, whereas the more reactive vanadium oxyfluoride has been applied primarily to nonphenolic oxidative coupling;[15-22] yields with the latter reagent are generally moderate to good. Vanadium(V) oxyfluoride induced intramolecular nonphenolic coupling has seen extensive recent use in the

(1) For the previous paper in this series, see: McKillop, A.; Turrell, A. G.; Young, D. W.; Taylor, E. C. *J. Am. Chem. Soc.*, preceding paper in this issue.

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(3) For preliminary details on the synthesis of (±)-ocoteine and (±)-acetoxyocoxylonine, see: Taylor, E. C.; Andrade, J. G.; McKillop, A. *J. Chem. Soc., Chem. Commun.* **1977**, 538-539.

(4) (a) Princeton University. (b) On leave of absence from the University of the Orange Free State, Bloemfontein, South Africa; financial assistance from the C.S.I.R., Pretoria, is gratefully acknowledged. (c) University of East Anglia.

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(18) Damon, R. E.; Schlessinger, R. H.; Blount, J. F. *J. Org. Chem.* **1976**, *41*, 3772-3773.

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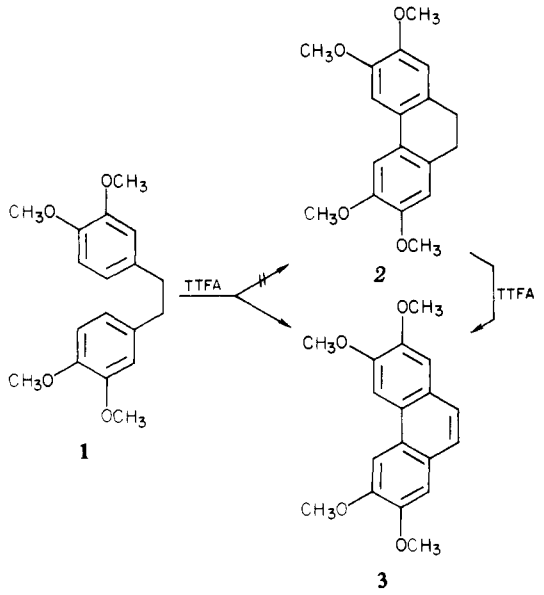
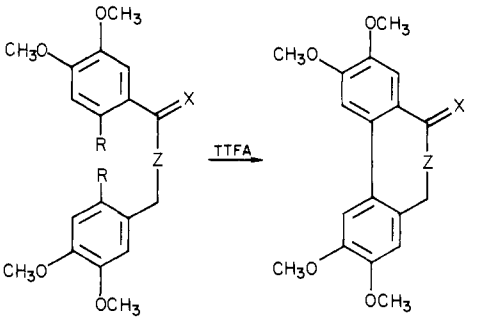
synthesis of alkaloids and other natural products; although the scope and limitations of the method have not been defined, it is already clear that use of this very powerful oxidant can lead to overoxidation, rearrangement and oxidative demethylation of aryl methyl ether substrates.

Model Studies. In the accompanying paper[1] we describe the use of TTFA for the regiospecific intermolecular nonphenolic oxidative coupling of electron-rich aromatic substrates to biaryls via radical cation intermediates. Initial attempts to extend the method to intramolecular coupling reactions were not very encouraging. Thus, oxidation of 1,2-bis(3,4-dimethoxyphenyl)ethane (**1**) with TTFA under a wide variety of conditions gave mainly tarry, intractable products; the only identifiable product which could be isolated (4–15%) was the phenanthrene **3**. The dihydrophenanthrene **2** is known to be an intermediate in the anodic oxidation of **1** to **3**; its oxidation potential is, however, lower than that of **1** and hence the electrochemical method, like the TTFA reaction, results only in formation of **3**.[23,24]



In contrast to the result obtained with **1**, treatment of 1,3-bis(3,4-dimethoxyphenyl)propane (**4a**) with TTFA in carbon tetrachloride containing a catalytic amount of boron trifluoride etherate resulted in smooth oxidative coupling to give the bridged biphenyl **5a**[25] in 81% yield. The ether **4b** was also smoothly coupled to 5,7-dihydro-2,3,9,10-tetramethoxydibenzo[*c*,*e*]oxepin (**5b**) in 80% yield by treatment with TTFA in acetonitrile at −40 °C in the presence of a small amount of boron trifluoride etherate. Attempts to obtain **5b** by Ullmann coupling of the dibromide **4c** have been reported to be unsuccessful.[26]

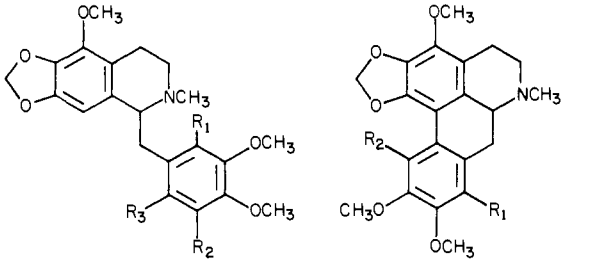
Even more encouraging from the point of view of potential extrapolations to alkaloid synthesis were the observations that both the amide **4d**[27] and the tertiary amine **4e** were smoothly coupled



a, R = H; X = H_2; Z = CH_2
b, R = H; X = H_2; Z = O
c, R = Br; X = H_2; Z = O
d, R = H; X = O; Z = NCH_3
e, R = H; X = H_2; Z = NCH_3

by TTFA to the corresponding tricyclic systems **5d** and **5e**. In the former case, use of carbon tetrachloride as solvent gave **5d** in 41% yield, together with 17% of *N*-methylveratramide; when the reaction was run in methylene chloride containing trifluoroacetic acid (TFA), however, **5d** was isolated in 58% yield. Under the same conditions the tricyclic amine **5e** was obtained in 43% yield from **4e**. The coupling reaction therefore accommodates the presence of two of the commonly encountered alkaloid functional groups.

Synthesis of (±)-Ocoteine and (±)-Acetoxyocoxylonine. The aporphine alkaloid (±)-ocoteine (**7a**) (also called thalicmine) has been prepared in low yield from **6a** by a standard Pschorr cyclization.[28] Reaction of the much more readily accessible precursor **6b** (see Experimental Section) with TTFA, by contrast, gave **7a** directly in 46% yield. During the study of the conditions for this cyclization, various attempts were made to minimize the amount of tarry byproduct which is formed during oxidation, and one of these led to an unusual reaction. Treatment of the benzylisoquinoline **6b** with thallium(III) acetate instead of the more reactive TTFA gave a 35% yield of the acetoxyaporphine **7b**. The structure of **7b** was readily assigned on the basis of analytical and spectroscopic properties, full details of which are given in the Experimental Section. That the acetoxy group is located at C_8 rather than C_{11} is particularly clear from the NMR spectrum. Thus, it has been shown for a series of aporphine alkaloids possessing a 1,2-methylenedioxy group that the chemical shift of the C_{11} proton lies in the range δ 7.47–7.86,[29] while that of the C_8 proton is in the range δ 6.8–7.1. The aromatic proton in **7b** resonates at δ 7.59, and hence the isomeric structure **7c** can be excluded. Interestingly, Ahmad and Cava have recently reported the isolation and characterization of the alkaloid ocoxylonine (**7d**);[30] the transformation **6b** → **7b** therefore represents the

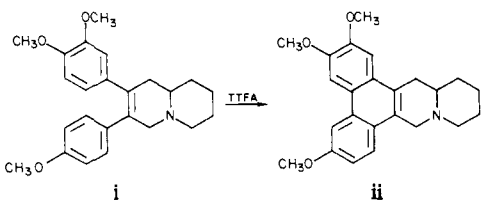


6a, $R_1 = R_2 = H$; $R_3 = NH_2$
b, $R_1 = R_2 = R_3 = H$

7a, $R_1 = R_2 = H$
b, $R_1 = OCOCH_3$; $R_2 = H$
c, $R_1 = H$; $R_2 = OCOCH_3$
d, $R_1 = OH$; $R_2 = H$

(23) (a) Ronlan, A.; Parker, V. D. *Chem. Commun.* **1970**, 1567–1568. (b) Ronlan, A.; Hammerich, O.; Parker, V. D. *J. Am. Chem. Soc.* **1973**, *95*, 7132–7138.

(24) Cryptopleurine (ii) has recently been synthesized in 69% yield by TTFA-induced intramolecular cyclization of julandine (i) (Herbert, R. B. *J. Chem. Soc., Chem. Commun.* **1978**, 794–795).



(25) Forbes, E. J.; Gray, C. J. *Tetrahedron* **1968**, *24*, 2795–2800.

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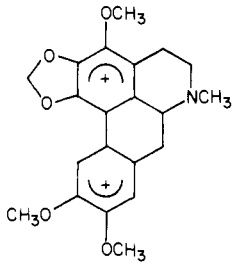
synthesis of (±)-acetoxyocoxylonine.

We believe that the mechanism of these intramolecular coupling reactions is similar to that postulated for the TTFA-induced intermolecular biaryl coupling reaction, i.e., via radical cation intermediates. The different reactions observed on treatment with TTFA and with thallium(III) acetate are a consequence of the relative nucleophilicities of the trifluoroacetate and acetate anions. The latter, being the more nucleophilic, can react efficiently with either the dication **8** or the radical cation **9** formed in the coupling



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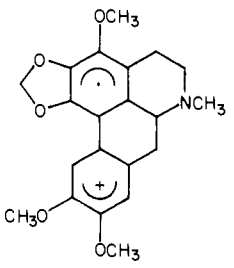

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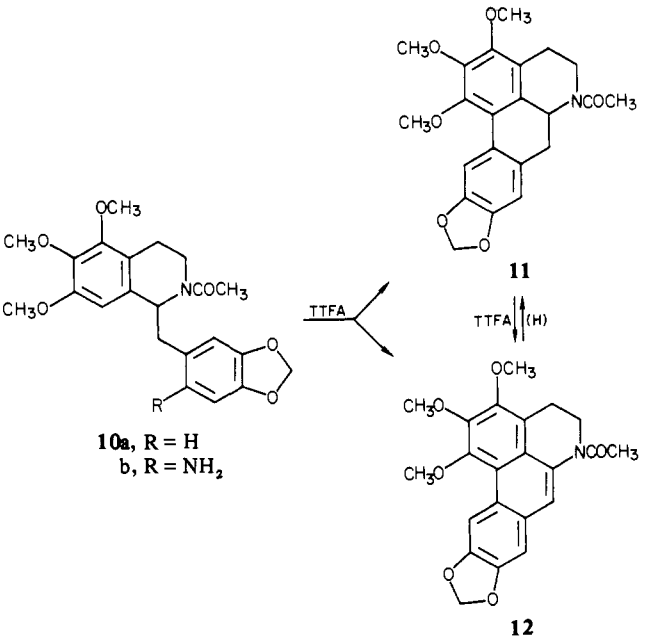
reaction. Aromatic nuclear acetoxylation has been observed previously with other metal acetates, and radical cation intermediates have been shown to be involved, for example, with manganese(III)[31] and cobalt(III) acetate,[32] cobalt(III) trifluoroacetate,[33] and silver(II) complexes in acetic acid.[34] The preparation of acetoxyocoxylonine represents another, albeit rare,[35,36] example of aromatic nuclear acetoxylation with a thallium(III) salt, and the synthetic potential of this process is currently under investigation.

Synthesis of (±)-3-Methoxy-*N*-acetylnornantenine and (±)-6a,7-Dehydro-3-methoxy-*N*-acetylnornantenine. The basicity of the nitrogen atom can play an important role in the oxidation of 1-benzyltetrahydroisoquinolines; deactivation by acylation, for example, has been shown to have a dramatic influence on the course of both anodic[37] and chemical[16] oxidation reactions. It was therefore of interest to investigate whether acylation at nitrogen would have any significant effect on the cyclization of a 1-benzyl-2-acetyltetrahydroisoquinoline to a noraporphine.

Oxidation of **10a** with TTFA in TFA at 0 °C gave two products (TLC) which were readily separated chromatographically. The major product (40%) was shown by comparison of its spectroscopic properties with those of an authentic sample to be (±)-3-methoxy-*N*-acetylnornantenine (**11**), a nonbasic noraporphine alkaloid recently isolated (as the (+) enantiomer) from the heartwood of *Liriodendron tulipifera*.[38] Structure **12** was assigned to the minor component, isolated in 31% yield, on the basis of analytical and spectroscopic data (Experimental Section). Reduction of **12** with amalgamated zinc in ethanol/hydrochloric acid gave **11**, while oxidation of the latter with TTFA gave **12**. Oxidation of **10a** with TTFA consistently gave mixtures of **11** and **12**, even when the amount of oxidant was reduced by half.

Acylation on nitrogen does not therefore have any significant effect on the TTFA-induced intramolecular cyclization reaction.



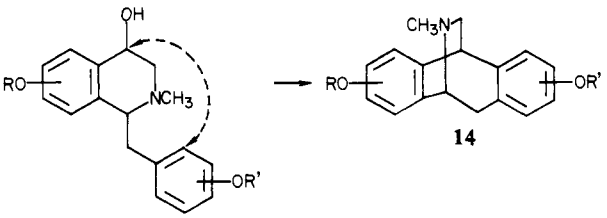
10a, R = H
b, R = NH_2

11

12

It does, on the other hand, apparently affect the redox potential of the initially formed noraporphine such that oxidative dehydrogenation at C-6a,7 is facile. Even so, it is noteworthy that, by comparison with the combined yield of 71% of cyclized products obtained from the TTFA reaction, **11** was obtained in only 13% yield via the Pschorr reaction from the 6-amino derivative **10b**.[39]

Attempted Preparation of (±)-Reframidine. Synthesis of (±)-Neolitsine. The isopavine alkaloids **14** are also derived from 1-benzyltetrahydroisoquinoline precursors; one of the postulated biosynthetic pathways involves benzyl-to-aryl coupling of a 1-benzyl-4-hydroxytetrahydroisoquinoline (e.g., **13** → **14**).[40] In



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view of the many similarities between TTFA and electrochemical oxidative coupling reactions, and the often-observed formation of benzyl radicals and/or cations under the latter conditions, we were interested in the possibility that simpler 1-benzyltetrahydroisoquinolines (i.e., with fewer activating alkoxy substituents) might undergo benzyl-to-aryl coupling in place of, or in addition to, coupling to the aporphine system upon treatment with TTFA. Thus, the 1-benzyltetrahydroisoquinoline **15** was oxidized with TTFA under a wide variety of conditions (−40 to 20 °C; use of TFA, TFA/BF_3·$O(C_2H_5)_2$, TFA/CH_3COOH, TFA/CH_3COOH/BF_3·$O(C_2H_5)_2$, CH_3CN/CCl_4, or CH_3CN/CCl_4/BF_3·$O(C_2H_5)_2$ as solvent) and the reaction course monitored both by TLC and by UV spectroscopy. The latter technique was used as a specific probe for the two possible oxidation products, namely, (±)-neolitsine (**16**), which shows λ_{max} at 218 and 287 nm, and (±)-reframidine (**17**), the UV spectrum of which has an additional absorption maximum at 248 nm.[41] No evidence was obtained for the formation of reframidine (**17**) under any of the conditions studied; only the UV absorptions characteristic of neolitsine (**16**) were observed. Preparative scale oxidation of **15** with TTFA in TFA/CH_2Cl_2 containing a catalytic amount of boron trifluoride

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(34) See, e.g., Nyberg, K.; Wistrand, L.-G. *J. Org. Chem.* **1978**, *43*, 2613–2617.
(35) Sullivan, P. D.; Menger, E. M.; Reddoch, A. H.; Paskovich, D. H. *J. Phys. Chem.* **1978**, *82*, 1158–1160.
(36) The direct conversion of magnesium or zinc porphyrins into *meso*-trifluoroacetoxyporphyrins on treatment with TTFA is reported to proceed via a radical process and is probably analogous to this acetoxylation reaction (Barnett, G. H.; Hudson, M. F.; McCombie, S. W.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 691–696).
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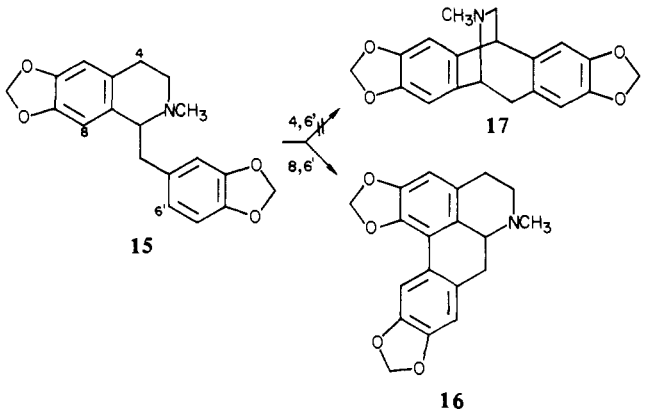
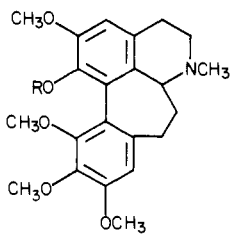
(41) Slavik, J.; Slavikova, L.; Dolejs, L. *Collect. Czech. Chem. Commun.* **1968**, *33*, 4066–4082.



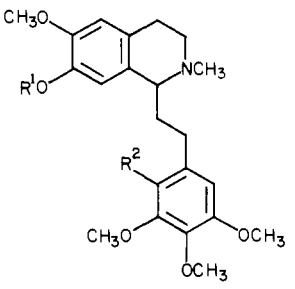
etherate at 0 °C gave (±)-neolitsine in 68% yield. Addition of thallium(I) acetate to the reaction mixtures did not alter the course of oxidation of **15** with TTFA, in contrast to the situation which pertains with the anodic oxidation of alkylbenzenes, where addition of nucleophiles results in proton abstraction at the benzylic position of the radical cation.[42]

Synthesis of (±)-Kreysigine and (±)-*O*-Methylkreysigine. Having demonstrated the utility of TTFA as a reagent for aporphine synthesis, attention was turned to its use in the synthesis of homoaporphines. It should be noted in this context that, while electrochemical oxidation methods have been widely applied to the intramolecular coupling of 1-benzyltetrahydroisoquinolines, attempts to extrapolate these techniques to 1-phenethyltetrahydroisoquinolines have proved unsuccessful.[43]

(±)-Kreysigine (**18a**) has previously been synthesised (yield) by the photo-Pschorr reaction of the diazonium salt **19a** (5%),[44] by photolysis of the bromo derivative **19b** (3%),[45] by hydrolysis of **18c** (56%)[46] (prepared in turn in 18% yield by rearrangement of the *p*-quinol acetate obtained from **19c**), and by monophenolic coupling of **19a** with vanadium(V) oxyfluoride (16%).[47] The first



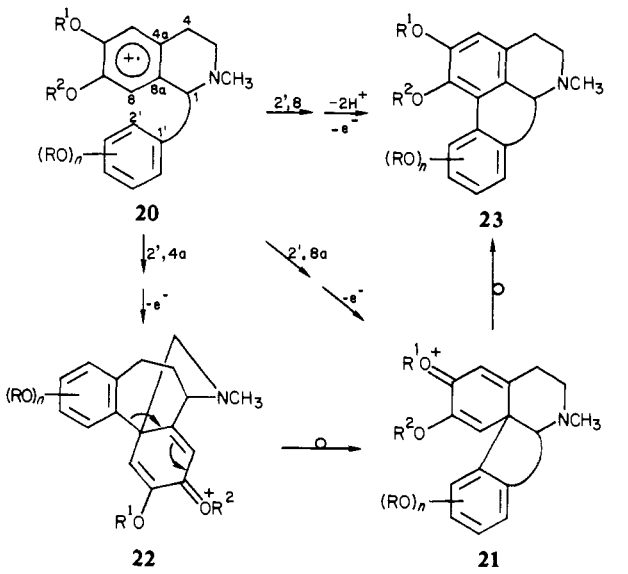
18a, R = H
b, R = CH_3
c, R = CH_3CO
d, R = $C_6H_5CH_2$



19a, R^1 = H; R^2 = N_2^+
b, R^1 = H; R^2 = Br
c, R^1 = R^2 = H
d, R^1 = $C_6H_5CH_2$; R^2 = H
e, R^1 = CH_3; R^2 = H

two methods suffer from the dual disadvantages that yields are extremely low and an extra substituent must be introduced into the penultimate precursor which, however, is subsequently lost in the intramolecular cyclization step. The third method involves a discouragingly cumbersome synthesis of **18c**, while all attempts to improve the yield in the vanadium(V) oxyfluoride oxidative coupling have been unsuccessful. (±)-*O*-Methylkreysigine has

Scheme I



not been synthesized directly, but has been prepared by prolonged treatment of kreysigine with diazomethane.[48]

Oxidation of the benzyl ether **19d** with TTFA in TFA/methylene chloride containing a catalytic amount of boron trifluoride etherate was allowed to proceed at 0 °C for 8 h, and then for a further 20 h at room temperature. Isolation and purification of the crude product by thick layer chromatography gave pure (±)-kreysigine (**18a**) in 40% yield. Under analogous conditions, the methyl ether **19e** was oxidatively coupled with TTFA to (±)-*O*-methylkreysigine (**18b**) in 46% yield.

The first step in all of the above TTFA-mediated coupling reactions is probably a one-electron oxidation to a radical cation (i.e., **20**).[49] However, the question of direct[1] vs. bridgehead coupling (followed by rearrangement)[50] of **20** to give **23** (see Scheme I) has not been resolved. We tend to favor direct 2',8 coupling, at least in the case of *O*-methylkreysigine (and presumably kreysigine as well), since no demethylation products were observed (i.e., no phenolic homoaporphine products could be detected); it seems improbable, therefore, that homoproerythrinadienone, homoneospirinedienone, or homoproaporphine intermediates could have been involved. The absence of demethylated products in these TTFA couplings contrasts with the ubiquitous demethylations observed with vanadium(V) oxyhalide oxidative couplings,[14,17] which are probably due, at least in part, to a competitive reaction involving a one-electron transfer methylation to the VOX_3 reagent by the aromatic substrate.[51] Finally, in view of the absence of dienone–phenol rearrangement products in the conversion of **19d** to **18a**, it seems reasonable to suggest that kreysigine is formed by in situ debenzylation of **18d**, i.e., at the last stage in the overall conversion of **19d** to **18a**.[52]

Synthesis of (±)-Multifloramine. (±)-Multifloramine (**24**) occurs together with kreysigine (**18a**) in *Kreysigia multiflora*, and its synthesis was undertaken in order to test the generality of the two key reactions involved in the synthesis of **18a**, namely, in-

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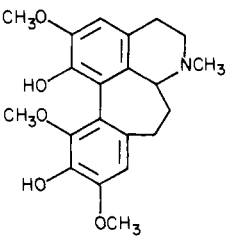
(48) Battersby, A. R.; Bradbury, R. B.; Herbert, R. B.; Munro, M. H. G.; Ramage, R. *Chem. Commun.* **1967**, 450–451.
(49) For precedents for the preferential formation of radical cations in ring A, see: Miller, L. L.; Stermitz, F. R.; Falk, J. R. *J. Am. Chem. Soc.* **1971**, *93*, 5941–5942, and references cited therein.
(50) Homomorphinanedienones are known to rearrange to homoaporphines in acidic media (see, for example, Kametani, T.; Fukumoto, K.; Satoh, F.; Yagi, H. *Chem. Commun.* **1968**, 1001–1002).
(51) For the formation of CH_3VOCl_2 from $VOCl_3$ and $(CH_3)_4Sn$, and its subsequent capture by further reaction with $VOCl_3$, see: Thiele, K. H.; Schumann, W.; Wagner, S.; Brüser, W. *Z. Anorg. Allg. Chem.* **1972**, *390*, 280–288.
(52) It has been demonstrated that the benzyloxy group can be cleaved by TFA at room temperature in 10–18 h (Marsh, J. P. Jr.; Goodman, L. *J. Org. Chem.* **1965**, *30*, 2491–2492. Kotani, E.; Tobinaga, S. *Tetrahedron Lett.* **1973**, 4759–4762).



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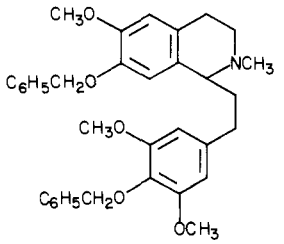
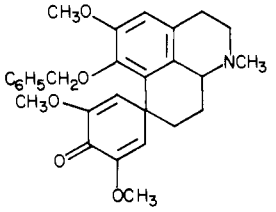
tramolecular oxidative coupling with TTFA combined with in situ debenzylation. Accordingly, the bis benzyl ether **25** was treated with TTFA in TFA containing a catalytic amount of boron trifluoride etherate. In contrast to the rather slow rate of oxidation observed for the phenethyltetrahydroisoquinolines **19d** and **19e**, **25** was very rapidly oxidized by TTFA at 0 °C, and only tars were obtained if the reaction was allowed to proceed for more than a few minutes. The reaction mixture was therefore quenched with water when a test for Tl(III) was negative (ca. 3 min); under these conditions the homoproaporphine **26** was isolated in 70% yield.

The IR, UV, and NMR spectra of **26**, which is not especially



25



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stable, are fully consistent with the assigned structure. The NMR spectrum in particular clearly shows the presence of only one benzyl ether grouping; the observed transannular coupling (J = 2 Hz) of the two olefinic hydrogen atoms is typical of homoproaporphines (see Experimental Section).[53] Treatment of **26** with sulfuric acid resulted in smooth dienone–phenol rearrangement, with concomitant debenzylation, to give an 81% yield of (±)-multifloramine (**24**), characterized by comparison of its properties with those of an authentic sample.[54a,b]

Experimental Section

Melting points were determined with a Mettler FP1 or Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained using Perkin-Elmer 237 B or 467 spectrophotometers; ultraviolet spectra were obtained using Perkin-Elmer 201 or Cary 11 spectrophotometers; NMR spectra were recorded on Varian A-60 or XL-100 spectrometers. Mass spectra were obtained on an MS-9 instrument. Elemental analyses were carried out by Hoffmann-La Roche Inc., Nutley, N.J., or by Eli Lilly & Co., Indianapolis, Ind. Thin layer chromatography was done in silica gel; routine examination was carried out on Whatman PK6F and preparative work on Whatman PK1F low-polarity plates. Solvents used in TTFA oxidations were degassed by entrainment with nitrogen for 0.5 h prior to use.

TTFA Coupling of 1,2-Bis(3,4-dimethoxyphenyl)ethane (1) to 2,3,6,7-Tetramethoxyphenanthrene (3). To a stirred suspension of 5.5 g (10 mmol) of TTFA in 120 mL of CCl_4 at 0 °C were added simultaneously 3.0 g (0.01 mol) of 1,2-bis(3,4-dimethoxyphenyl)ethane (**1**)[55] in 50 mL of CCl_4 and 10 mL of $BF_3{\cdot}Et_2O$. Stirring was continued overnight at room temperature; excess aqueous potassium iodide solution was then added, the mixture stirred for an additional 30 min, and the pH then adjusted to 9 with sodium carbonate. Sodium metabisulfite (2.0 g) was added, and the thallium(I) iodide which had separated was removed by filtration and washed thoroughly with $CHCl_3$. The organic layer was dried ($MgSO_4$), concentrated to ca. 5 mL, and passed through a short column of neutral alumina using $CHCl_3$ as eluant. Evaporation of the solvent and crystallization of the residue from benzene/hexane gave 124 mg (4.1%) of 2,3,6,7-tetramethoxyphenanthrene (**3**), mp 179.8 °C (lit.[23b] mp 180–181 °C).

TTFA Coupling of 1,3-Bis(3,4-dimethoxyphenyl)propane (4a) to 4′,4″,5′,5″-Tetramethoxy-1,2,3,4-dibenzocyclohepta-1,3-diene (5a). To a cooled suspension of 5.5 g (10 mmol) of TTFA in 120 mL of CCl_4 were added 3.16 g (0.01 mol) of **4a**[56] and 10 mL of $BF_3{\cdot}Et_2O$, and the reaction was conducted as described above under the preparation of **3**, yield 2.55 g (81%), mp 154.5 °C (lit.[25] mp 153–155 °C).

TTFA Coupling of Diveratryl Ether (4b) to 5,7-Dihydro-2,3,9,10-tetramethoxydibenzo[*c*,*e*]oxepin (5b). To a cooled (−40 °C) solution of 300 mg (0.55 mmol) of TTFA in 120 mL of acetonitrile was added in one portion 159 mg (0.5 mmol) of **4b**.[26] The mixture was allowed to come to room temperature and poured into water after a starch–iodide test for the presence of Tl(III) was negative (30 min). The reaction mixture was extracted with $CHCl_3$, and the extracts were washed with water and then with saturated sodium bicarbonate solution, dried ($MgSO_4$), and evaporated. Recrystallization of the residue from a mixture of methanol and ethanol gave 128 mg (80%) of pure **5b**: mp 248.1 °C (lit.[57] mp 249 °C); ^1H NMR ($CDCl_3$) δ 7.1, 7.0 (2 s, 4 H, 4 ArH), 4.0, 3.95 (2 s, 12 H, 4-OCH_3), 4.3 (s, 4 H, 2-OCH_2Ar).

***N*-Methyl-*N*-veratrylveratramide (4d).** A solution of 7.0 g of 3,4-dimethoxybenzoyl chloride in 10 mL of CH_2Cl_2 was added dropwise to a stirred solution of 6.0 g of *N*-methylveratrylamine[58] in a mixture of 30 mL of CH_2Cl_2 and 20 mL of pyridine during a period of 30 min. After 3 h at room temperature, the reaction mixture was poured into a mixture of ice and 5% HCl and extracted with benzene. The benzene extracts were dried (Na_2SO_4) and evaporated to leave a residue which was crystallized from ethanol to give 9.3 g (79%) of pure **4d**: mp 108–110 °C; IR (KBr) 1635 cm^{-1}. Anal. ($C_{19}H_{23}NO_5$) C, H, N.

TTFA Coupling of *N*-Methyl-*N*-veratrylveratramide (4d) to 6,7-Dihydro-2,3,9,10-tetramethoxy-6-methyldibenzo[*c*,*e*]azepin-5-one (5d). To a stirred, cooled mixture of 200 mg (0.37 mmol) of TTFA in 120 mL of TFA was added all at once a solution of 115 mg (0.33 mmol) of **4d** in 5 mL of CH_2Cl_2 and 1.5 mL of $BF_3{\cdot}Et_2O$. The mixture was allowed to come to room temperature and then stirred for an additional 3 h. Excess TFA was removed by evaporation under reduced pressure, water was added to the residue, and the mixture was extracted with $CHCl_3$. The extracts were concentrated to a small volume and filtered through a short column of neutral alumina; evaporation of the filtrate then gave a dark oil which was purified by preparative TLC ($CHCl_3/CH_3OH$, 10:1) to give 16 mg (14%) of **4d**, R_f 0.7, and 56 mg (58%) of **5d**, R_f 0.59, mp 221.8 °C (lit.[27] mp 220–221 °C).

TTFA Coupling of *N*-Methylbis(3,4-dimethoxybenzyl)amine (4e) to 2,7-Dihydro-2′,3′,2″,3″-tetramethoxy-1-methyldibenzo[*c*,*e*]azepine (5e). To a stirred mixture of 550 mg of TTFA (1.0 mmol) and 1.5 mL of $BF_3{\cdot}Et_2O$ in 100 mL of TFA at −30 °C was added a solution of 331 mg (1.0 mmol) of *N*-methylbis(3,4-dimethoxybenzyl)amine (**4e**)[59] in 15 mL of CH_2Cl_2. After 3 min, 50 mL of water was added and the reaction mixture was extracted with six 76-mL portions of $CHCl_3$. The combined extracts were shaken well with 20% aqueous ammonium hydroxide solution, dried (K_2CO_3), and evaporated to a small volume which was then filtered through a short column of neutral alumina. Evaporation of the filtrate gave a residue which was separated by preparative TLC ($CHCl_3/CH_3OH$, 9.5/0.5) to give 141 mg (43%) of **5e**, R_f 0.37, mp 160–161 °C (from acetone/ether) (lit.[57] mp 160–162 °C).

***N*-(2-Methoxy-3,4-methylenedioxyphenethyl)(3′,4′-dimethoxyphenyl)acetamide.** A mixture of 5.5 g of 2-(2-methoxy-3,4-methylenedioxyphenyl)ethylamine[60] and 5.5 g of methyl 3,4-dimethoxyphenylacetate was heated in a nitrogen atmosphere at 160 °C for 5 h. The reaction mixture was then cooled, the residue was taken up in $CHCl_3$, washed with 5% aqueous HCl, and dried (K_2CO_3), and the solvent was removed by distillation under reduced pressure. Crystallization of the residue from acetone/ether gave 7.6 g (83%) of pure product: mp 114 °C; IR (KBr) 3300, 1640 cm^{-1}. Anal. ($C_{20}H_{23}NO_6$) C, H, N.

1-(3′,4′-Dimethoxybenzyl)-2-methyl-5-methoxy-6,7-methylenedioxy-3,4-dihydroisoquinolinium Iodide. A mixture of 4.0 g of the above amide, 50 mL of acetonitrile, and 12 mL of phosphorus oxychloride was heated under reflux for 2.5 h. The mixture was then evaporated under reduced pressure and the residue was dissolved in 2% HCl. The pH of the re-

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sulting solution was adjusted to 9 with aqueous ammonium hydroxide and extracted with $CHCl_3$ (under N_2). The $CHCl_3$ extracts were washed well with water, dried (K_2CO_3), and evaporated to give 3.5 g of 1-(3′,4′-dimethoxybenzyl)-5-methoxy-6,7-methylenedioxy-3,4-dihydroisoquinoline as an unstable oil (IR 1640 cm^{-1})[61] which was immediately dissolved in 50 mL of methanol. To this solution was added 12 mL of methyl iodide and the reaction mixture was heated under gentle reflux for 1 h. Removal of the solvent by evaporation under reduced pressure and crystallization of the residue from ether/methanol gave 3.8 g (71%) of the isoquinolinium methiodide as yellow platelets, mp 183 °C. Anal. ($C_{21}H_{24}INO_5$) C, H, I, N.

1-(3′,4′-Dimethoxybenzyl)-2-methyl-5-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (6b). To an ice-cooled, stirred suspension of 3.5 g of the above methiodide in 100 mL of methanol was added portionwise, over a 30-min period, 2.0 g of sodium borohydride. The mixture was stirred at room temperature for 1 h and the solvent was removed by evaporation under reduced pressure. Water was added to the residue and the mixture was extracted with ether; the extracts were washed with aqueous sodium chloride solution and the ether layer was dried over anhydrous potassium carbonate. Evaporation then gave 2.55 g (97%) of **6b** as an oil: IR (neat) 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.7 (m, 3 H, 3ArH), 6.1 (s, 1 H, ArH), 5.82 (s, 2 H, OCH_2O), 3.97, 3.8, 3.75 (3 s, 9 H, $3OCH_3$), 3.6–2.2 (m, 7 H, $2CH_2$ + 1CH), 2.50 (s, 3 H, N–CH_3); hydrochloride, mp 206 °C (from acetone/ethanol). Anal. ($C_{21}H_{26}NO_5Cl·H_2O$): C, H, Cl, N.

TTA Coupling of 1-(3′,4′-Dimethoxybenzyl)-2-methyl-5-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (6b) to (±)-Acetoxyocoxylonine (7b). A solution of 250 mg (0.65 mmol) of TTA in 20 mL of acetonitrile and 20 mL of CCl_4 was cooled to 0 °C and a solution of 186 mg (0.5 mmol) of **6b** in 5 mL of CCl_4 and 1 mL of $BF_3·Et_2O$ added all at once. The reaction mixture was allowed to come to room temperature and then stirred for 2 h. Solvent was removed under reduced pressure and the solution adjusted to pH 9 with 5% aqueous ammonium hydroxide and then extracted with $HCCl_3$ until no color was apparent in the extracts. The combined $HCCl_3$ extracts were then dried (K_2CO_3) and evaporated and the residual oil purified by preparative TLC (acetone) to give 43.1 mg (21.2%) of the starting isoquinoline **6b**, R_f 0.32, and 58.5 mg (35%) of (±)-acetoxyocoxylonine, R_f 0.63: mp 161–163 °C; UV λ_{max} (EtOH) (log ε) 225 (4.49), 285 (4.22), 303 (4.1), 311 nm (405); IR (KBr) 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (s, 1 H, ArH), 6.08, 5.92 (d, 2 H, OCH_2O), 4.01, 3.91, 3.85 (3 s, 9 H, $3OCH_3$), 2.51 (s, 3 H, N–CH_3), 2.38 (s, 3 H, $ArOCOCH_3$), 3.25–2.20 (m, 7 H, $3CH_2$ + 1CH). Anal. ($C_{23}H_{25}NO_3$): C, H, N.

TTFA Coupling of 1-(3′,4′-Dimethoxybenzyl)-2-methyl-5-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (6b) to (±)-Ocoteine (7a). This compound was obtained in 46% yield from 280 mg of TTFA in 40 mL of acetonitrile and 40 mL of CCl_4 and 186 mg of **6b** in 5 mL of CCl_4 and 1.5 mL of $BF_3·Et_2O$ at −40 °C. The workup procedure was identical with that described above for the preparation of **7b**, except that the mixture was stirred for only 1.5 h and $CHCl_3/CH_3OH$ (9:1) was used in the purification step. Spectral data for the product **7a** were identical with those reported for the natural product:[28] hydrochloride, mp 259.5 °C (lit.[65] mp 258–260 °C).

1-(3′,4′-Methylenedioxybenzyl)-2-acetyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (10a). A mixture of 2.5 g of the above hydrochloride, 40 mL of pyridine, and 2 mL of acetic anhydride was stirred overnight at room temperature. Solvents were removed under reduced pressure, the residue was dissolved in $CHCl_3$, and the resulting solution was washed with water, dried (K_2CO_3), and evaporated to dryness. Crystallization of the residue from 2-propanol gave 2.66 g (95%) of **10a**: mp 123–125 °C; IR (KBr) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60 (m, 3 H, 3 ArH), 6.37, 6.13 (2 s, 1 H, ArH), 5.94, 5.83 (2 s, 2 H, OCH_2O), 5.60, 4.75 (2 t, 1 H, CH), 3.88, 3.82, 3.68 (3 s, 9 H, $3OCH_3$), 3.50–2.40 (m, 6 H, $3CH_2$), 2.13, 1.67 (s, 3 H, NAc). Anal. ($C_{22}H_{25}NO_6$) C, H, N.

TTFA Coupling of 1-(3′,4′-Methylenedioxybenzyl)-2-acetyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (10a) to (±)-3-Methoxy-*N*-acetylnornantenine (11) and (±)-3-Methoxy-*N*-acetyl-6a,7-dehydronornantenine (12). A solution of 280 mg (0.52 mmol) of TTFA in 120 mL of TFA was cooled to 0 °C and a solution of 200 mg (0.5 mmol) of **10a** in 5 mL of CH_2Cl_2 and 1 mL of $BF_3·Et_2O$ was added all at once. The reaction mixture was stirred at 0 °C for 3 h, and the solvent was removed under reduced pressure; water was added to the residue, and the pH adjusted to 9 with 5% aqueous ammonium hydroxide solution. The solution was extracted with $CHCl_3$ until no color was apparent in the extract; the combined extracts were dried (K_2CO_3) and evaporated, and the residual oil was purified by preparative TLC (benzene/acetone, 8:1) to give 81 mg (40%) of **11**, R_f 0.39, mp 175–177 °C (lit.[39] mp 174–175 °C), and 62 mg (31%) of **12** [R_f 0.50; mp 235 °C; UV λ_{max} (EtOH) (log ε) 206 (4.31), 263 (4.63), 284 (4.26), 324 nm (3.89); IR (KBr) 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.99, 8.54, 7.91 (3 s, 3 H, 3 ArH), 6.08 (s, 2 H, OCH_2O), 4.10, 3.95, 3.90 (3 s, 9 H, $3OCH_3$), 3.23 (m, 4 H, $2CH_2$), 2.41 (s, 3 H, NAc). Anal. ($C_{22}H_{21}NO_6$) C, H, N].

***N*-(3,4-Methylenedioxyphenethyl)(3′,4′-methylenedioxyphenyl)acetamide.** This compound was obtained by heating a mixture of 3.3 g of 3,4-methylenedioxyphenethylamine and 3.6 g of 3,4-methylenedioxyphenylacetic acid at 195 °C for 3 h, as described above: yield 5.4 g (76%); mp 120.9 °C; IR (KBr) 3300, 1650 cm^{-1}. Anal. ($C_{18}H_{17}NO_5$) C, H, N.

1-(3′,4′-Methylenedioxybenzyl)-2-methyl-6,7-methylenedioxy-3,4-dihydroisoquinolinium Iodide. A mixture of 5.0 g of the above amide in 50 mL of dry toluene and 7 mL of phosphorus oxychloride was heated under reflux for 1 h. The residue obtained on evaporation of the reaction mixture to dryness was washed twice with petroleum ether and then dissolved in water. The pH of the resulting aqueous solution was adjusted to 9 with 5% aqueous ammonium hydroxide solution and the solution rapidly extracted with ether; evaporation of the ether extracts gave the intermediate dihydroisoquinoline (4.2 g) as an oil. This was converted to its methiodide by stirring overnight with 15 mL of methyl iodide in 50 mL of ethanol. Crystallization of the resulting crude produce from 2-propanol/ether gave 3.1 g (45%) of the pure methiodide, mp 233–235 °C. Anal. ($C_{19}H_{18}INO_4$) C, H, N.

***N*-(2,3,4-Trimethoxyphenethyl)(3′,4′-methylenedioxyphenyl)acetamide.** This compound was prepared from 3.1 g of 2,3,4-trimethoxyphenethylamine[66] and 2.7 g of 3,4-methylenedioxyphenylacetic acid as described above for the preparation of *N*-(2-methoxy-3,4-methylenedioxyphenethyl)(3′,4′-dimethoxyphenyl)acetamide: yield 4.8 g (87%); mp 94–96 °C; IR (KBr) 3320, 1640 cm^{-1}. Anal. ($C_{20}H_{23}NO_6$) C, H, N.

1-(3′,4′-Methylenedioxybenzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinolinium Chloride. The above acetamide was converted in 89% yield to 1-(3′,4′-methylenedioxybenzyl)-5,6,7-trimethoxy-3,4-dihydroisoquinoline as described above under the preparation of 1-(3′,4′-dimethoxybenzyl)-2-methyl-5-methoxy-6,7-methylenedioxy-3,4-dihydroisoquinolinium iodide. Reduction with sodium borohydride in methanol as previously described under the preparation of **6b**, followed by addition of dry HCl, gave the desired product, mp 192–196 °C (from acetone). Anal. ($C_{20}H_{24}ClNO_5$) C, H, N.

1-(3′,4′-Methylenedioxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (15). This was obtained as an oil from 3.0 g of the above methiodide, 2.0 g of sodium borohydride, and 60 mL of methanol as previously described for the preparation of **6b**: yield 1.9 g (88%); ^1H NMR ($CDCl_3$) δ 6.7–6.2 (m, 5 h, 5 ArH), 5.80, 5.75 (2 s, 4 H, 2 OCH_2O), 3.65–2.4 (m, 7 H, 3 CH_2 + 1 CH), 2.38 (s, 3 H, NCH_3). Anal. ($C_{19}H_{19}NO_4$) C, H, N.

TTFA Coupling of 1-(3′,4′-Methylenedioxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline to (±)-Neolitsine (16). Using the procedure described for the preparation of **10a** and **12**, the above tetrahydroisoquinoline was converted in 68% yield to (±)-neolitsine, mp 193–195 °C, using the following conditions and reagents: TTFA (105 mg), TFA (60 mL), 0 °C, the above tetrahydroisoquinoline (62 mg), CH_2Cl_2 (5 mL), and $BF_3·Et_2O$ (0.5 mL). When the reaction mixture reached room temperature, solvents were removed under reduced pressure and the product was purified by preparative TLC ($CHCl_3/CH_3OH$, 9:1): R_f 0.56; IR ($CHCl_3$) 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50, 6.65, 6.38 (3 s, 3 H, 3 ArH), 5.96–5.80 (m, 4 H, 2 OCH_2O), 3.30–2.20 (m, 7 H, 3 CH_2 + 1 CH), 2.5 (s, 3 H, NCH_3). Anal. ($C_{19}H_{17}NO_4$) C, H, N.

TTFA Coupling of 1-(3′,4′,5′-Trimethoxyphenethyl)-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (19d) to (±)-Kreysigine (18a). A solution of 239 mg of **19d**[46] in 5 mL of CH_2Cl_2 was added to a cold (0 °C) solution of 280 mg of TTFA in 120 mL of TFA, followed by rapid addition of 1 mL of $BF_3·Et_2O$. The reaction mixture was stirred under a nitrogen atmosphere for 8 h at 0 °C and then for a further 20 h at room temperature. The solvent was removed under reduced pressure, 20 mL of water was added, and the resulting solution was neutralized with 5% aqueous ammonium hydroxide solution. Ex-

(61) The instability of this dihydroisoquinoline in basic solution is presumably due to rapid air oxidation of the benzylic methylene group to a carbonyl. Similar instability has been noted for other isoquinoline and dihydroisoquinoline systems.[62-64]

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traction with 4 × 40 mL of $CHCl_3$, followed by concentration of the combined, dried (K_2CO_3) extracts to a small volume and filtration through a short column of neutral alumina, gave, after final evaporation, a brown oil which was purified by preparative TLC ($CHCl_3/CH_3OH$, 9:1) to give 78.5 mg (41%) of pure (±)-kreysigine: R_f 0.36; mp 185–186 °C (lit.[47] mp 185–186 °C); UV λ_{max} (CH_3OH) (log ϵ) 220 (4.63), 260 (4.16), 291 nm (3.87); IR ($CHCl_3$) 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.72, 6.69 (2 s, 2 H, 2 ArH), 3.90 (s, 9 H, 3 OCH_3), 3.65 (s, 3 H, OCH_3), 3.2–2.0 (m, 10 H, 4 CH_2 + 1 CH + 1 OH), 2.39 (s, 3 H, NCH_3).

1-(3′,4′,5′-Trimethoxyphenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (19e). This compound was prepared in 95% yield from 1-(3′,4′,5′-trimethoxyphenethyl)-2-methyl-3,4-dihydroisoquinolinium iodide[67] as described for the preparation of **6b**: mp 76.5 °C (from hexane/ether); ^1H NMR ($CDCl_3$) δ 6.60, 6.40 (2 s, 4 H, 4 ArH), 3.87 (s, 15 H, 5 OCH_3), 3.50–1.90 (m, 9 H, 4 CH_2 + 1 CH), 2.50 (s, 3 H, NCH_3). Anal. ($C_{23}H_{31}NO_5$) C, H, N.

TTFA Coupling of 1-(3′,4′,5′-Trimethoxyphenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (19e) to (±)-*O*-Methylkreysigine (18b). The oxidative coupling of **19e** to **18b** was carried out as described above for the preparation of **18a**. Preparative TLC ($C_6H_6/CH_3OH/CHCl_3$, 1:4:10) then gave 58 mg (28%) of recovered **19e**, R_f 0.91, and 65 mg (46%) of pure (±)-*O*-methylkreysigine as an oil [R_f 0.86; UV λ_{max} (CH_3OH) (log ϵ) 220 (4.54), 260 (4.01), 296 nm (3.54); IR ($CHCl_3$) 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.72, 6.59 (2 s, 2 H, 2 ArH), 3.90, 3.67, 3.58 (3 s, 15 H, 5 OCH_3), 3.40–2.00 (m, 9 H, 4 CH_2 + 1 CH), 2.41 (s, 3 H, NCH_3); methiodide mp 152.3 °C (from acetone–ether) (lit.[68] mp 150–153 °C)].

1-(4′-Benzyloxy-3′,5′-dimethoxyphenethyl)-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline (25). This compound was prepared in quantitative yield as an oil from the corresponding dihydroisoquinolinium iodide[67] as described above for the preparation of **6b**: IR (neat) 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (m, 10 H, 10 ArH), 6.60, 6.30 (2 s, 4 H, 4 ArH), 5.08, 4.95 (2 s, 4 H, 2 OCH_2Ar), 3.82, 3.75 (2 s, 9 H, 3 OCH_3), 3.40–1.90 (m, 9 H, 4 CH_2 + 1 CH), 2.43 (s, 3 H, NCH_3). Anal. ($C_{35}H_{39}NO_5$) C, H, N.

1-Methyl-3′,5′,5-trimethoxy-6-benzyloxy-1,2,3,8,9,9a-hexahydro-7*H*-benzo[*d*,*e*]quinoline-7-spiro[cyclohexa-2′,5′-dien]-4′-one (26) and (±)-Multifloramine (24). A solution of 100 mg (0.2 mmol) of **25** in 5 mL of CH_2Cl_2 was added to a stirred mixture of 118 mg (0.21 mmol) of TTFA in 100 mL of TFA at 0 °C, followed by rapid addition of 1 mL of $BF_3 \cdot Et_2O$. After the intense green color had faded (ca. 3 min; by this time a starch–iodide test for Tl(III) was negative), the mixture was extracted with 4 × 100 mL of $CHCl_3$. The extracts were washed with 5% aqueous ammonium hydroxide solution, dried (K_2CO_3), and evaporated and the residue was purified by preparative TLC ($CHCl_3/CH_3OH$, 10:1) to give 58 mg (70%) of **26** as an amorphous powder: *m/e* M^+ 461; R_f 0.52; IR ($CHCl_3$) 1665, 1621 cm^{-1}; UV λ_{max} (CH_3OH) (log ϵ) 222 (4.6), 278 nm (4.12); ^1H NMR ($CDCl_3$) δ 7.25 (m, 5 H, 5 ArH), 6.65 (s, 1 H, ArH), 6.12, 6.00 (d, 2 H, J = 2 Hz, olefinic), 4.75 (q, 2 H, OCH_2Ar), 3.82, 3.55 (2 s, 9 H, 3 OCH_3), 3.20–1.90 (m, 9 H, 2 CH_2 + 1 CH), 2.42 (s, 3 H, NCH_3). Without further purification, 40 mg of **26** was added portionwise under nitrogen to 10 mL of ice-cold, degassed, concentrated H_2SO_4 over a period of 30 min. The reaction mixture was then stirred at 4 °C for 7 h and for a further 16 h at room temperature. It was then poured into 100 mL of ice water and the pH of the solution adjusted to 3 with aqueous sodium hydroxide solution, and then to 8 with a mixture of $NaHCO_3/Na_2CO_3$. The resulting solution was extracted with 4 × 100 mL of $CHCl_3$. Evaporation of the dried (K_2CO_3) $CHCl_3$ extracts gave 26 mg (81%) of pure (±)-multifloramine, mp 206–208 °C (from methanol) (lit.[48] mp 209–212 °C). This synthetic product, and an authentic sample of the natural material, had the same R_f values in three different solvent systems and superimposable IR, ^1H NMR, and UV spectra.

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Reaction of 1-Chloro-2-alkylcycloalkenes with Organolithium Reagents. A Novel Cyclopropanation Reaction Involving the Generation of Carbenes from Vinyl Halides[1]

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Abstract: The reactions of 1-chloro-2-alkylcycloalkenes with organolithium reagents have been investigated in detail. It has been demonstrated that six-, seven-, and eight-membered cyclic olefins yield bicyclo[4.1.0]heptanes, bicyclo[5.1.0]octanes, and bicyclo[6.1.0]nonanes, respectively. The mechanism of this transformation has been examined in detail and has been shown to involve a multistep process which includes (a) extraction of the allylic proton by the organolithium, (b) α elimination of lithium chloride to yield an allylic carbene, (c) intramolecular addition of the carbene to the double bond to produce a cyclopropene, (d) addition of the organolithium to the cyclopropene, and (e) neutralization. As part of the mechanistic investigation, 2-chloro-3-methylbicyclo[2.2.1]heptene was shown to yield 3-methylenetricyclo[2.2.1.$0^{2,6}$]heptane.

The reaction of vinyl halides with organolithium reagents has been investigated in detail because of the possibility of generating unusual alkynes by this path.[3-5] As part of our general interest in highly strained molecules of all types, we have explored the use of such reactions, especially for the synthesis of highly distorted alkynes such as bicyclo[2.2.1]hept-2-yne.[4] It was in connection with these interests that we first explored the reaction of 1-chloro-2-alkylcycloalkenes with organolithium reagents.[1] We now wish to report the details of this study, which demonstrated that a variety of 1-chloro-2-alkylcycloalkenes react with organolithium reagents to yield fused-ring cyclopropanes.

Our initial exploration of this area was prompted by the 1967 report of Montgomery and Applegate[3] that a mixture of 1-

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