days. A very slow formation of less polar product (A-type metabolite) is observed. In the freezer, the dehydration occurs considerably slower. The δ-lactone–hydroxy acid, **8a**, by standing at room temperature, forms additional polar spot on TLC. It appears that the equilibrium mixture of δ-lactone–hydroxy acid and dihydroxy diacid is formed.[4]

Acknowledgment. The author wishes to thank Mr. J. R. Boal for running the GC–mass spectra and also Dr. R. C. Kelly and Dr. H. A. Karnes for making the starting material available. Helpful discussions with Dr. J. E. Pike of these laboratories are also acknowledged.

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(4) Treatment of **8a** with base followed by reaction with diazomethane gave **9b**. However, it always resulted in equilibrium mixture of lactone (**8b**) and hydroxy ester (**9b**). (Observation by Dr. W. P. Schneider of these laboratories.)
(5) The synthesis of this versatile intermediate (with natural prostaglandin configuration) will be published shortly by Dr. R. C. Kelly of these laboratories.
(6) 1-Dimethyl-*tert*-butylsilyloxy-4-pentynyllithium was obtained in situ by reacting the corresponding alkyne with methyllithium at −20∼−10 °C for 10 min. The alkyne, 1-dimethyl-*tert*-butylsilyloxy-4-pentyne [bp 65 °C (9 mm)] was easily obtained by silylation[9] of 4-pentyn-1-ol (Farchan Co.).
(7) A similar result was obtained when 1-trimethylsilyloxy-1-pentyne was used (**1** → **2b**). Hydrolysis of trimethylsilyl group gave lactone–diol (**2c**) in 85% overall yield.
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(10) Because of the similar solubility of both the tetraol, **6a**, and the reagent toward solvent and water, it became very difficult to remove the excess reagent. One solution to this problem was to prepare the TMS derivative directly from the reaction mixture. Extraction with hexane followed by aqueous washing removed the reagent. TMS groups were easily removed by stirring in 5% potassium carbonate in methanol–water (4:1).
(11) We thank Dr. E. G. Daniels of these laboratories for providing the GC–mass spectrum of the authentic sample for the comparison. He has identified this metabolite from the urine of single dose injection of PGE_2 into rats and rhesus monkeys: private communication from Dr. E. G. Daniels.
(12) We thank Dr. F. F. Sun and Dr. W. P. Schneider of these laboratories for providing us with the GC–mass spectrum of the authentic sample for the comparisons. See also F. F. Sun, *Biochim. Biophys. Acta*, **348**, 249 (1974); F. F. Sun and J. E. Stafford, *ibid.*, **369**, 95 (1974).
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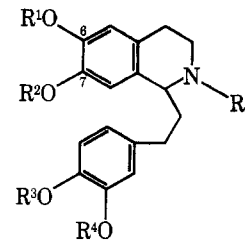
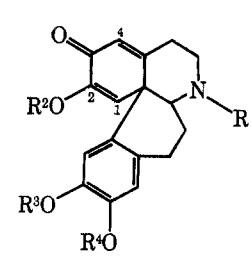
Novel Nonphenol Oxidative Coupling of Phenethylisoquinolines[1]

Summary: Oxidative coupling of nonphenolic phenethylisoquinolines **1a–c** with VOF_3–TFA gave homoaporphines **4a,g,h** in high yields via homoproerythrinadienone intermediates (e.g., 8).

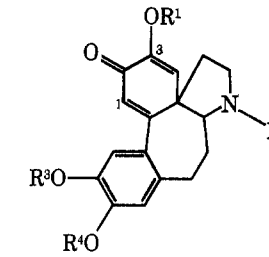
Sir: Nonphenol oxidative coupling reactions which yield spirodienone intermediates and products are currently subjects of great interest.[2-8] The first practical syntheses of this type involved electrooxidative coupling of benzylisoquinolines to morphinandienones.[2-4] Recent reports have also described the chemical intramolecular coupling of nonphenolic benzylisoquinolines with vanadium oxytrifluoride in trifluoroacetic acid (TFA) and demonstrated that the oxidations proceed via morphinandienone intermediates.[6-8] We report herein novel nonphenol oxidative coupling reactions



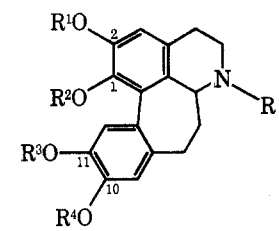
1a, $R^1 = R^2 = R^3 = R^4 = CH_3$; $R = COCF_3$
b, $R^1 = CH_2Ph$; $R^2 = R^3 = R^4 = CH_3$; $R = COCF_3$
c, $R^2 = CH_2Ph$; $R^1 = R^3 = R^4 = CH_3$; $R = COCF_3$
d, $R^1 = R^4 = H$; $R^2 = R^3 = CH_3$; $R = COCF_3$
e, $R^2 = R^3 = H$; $R^1 = R^4 = R = CH_3$
f, $R^1 = R^2 = R^3 = R^4 = R = CH_3$



2a,c,d



3a,b

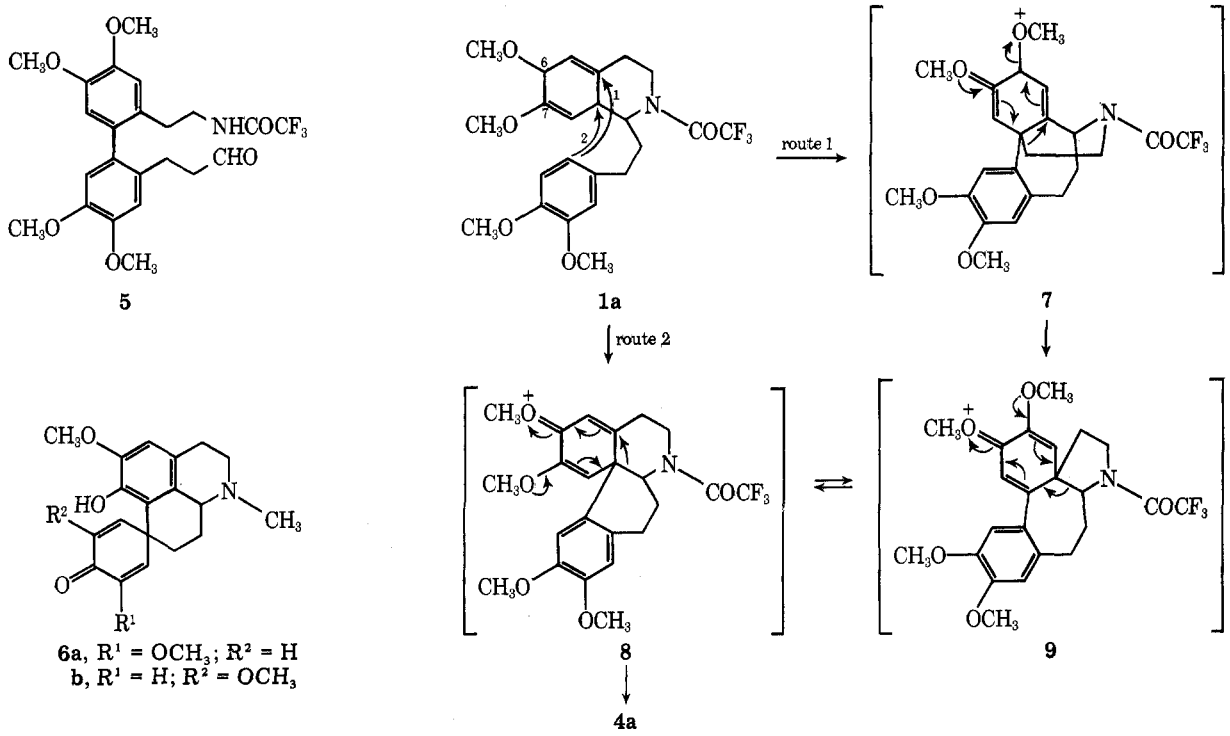


4a,e,f

4g, $R^1 = H$; $R^2 = R^3 = R^4 = CH_3$; $R = COCF_3$
h, $R^2 = H$; $R^1 = R^3 = R^4 = CH_3$; $R = COCF_3$

of phenethylisoquinolines **1a–c** using VOF_3–TFA which yield homoaporphines **4a,g,h** via homoproerythrinadienone intermediates (e.g., 8).

Treatment of a solution of (±)-*N*-trifluoroacetylhomonorlaudanosine (**1a**)[9,10] in CH_2Cl_2 and TFA[11] at −10 °C with VOF_3 in TFA for 10 min followed by aqueous workup gave homoproerythrinadienone **2a** (5%, mp 161–162 °C), homoneospirinedienone **3a** (64%, mp 171.5–172 °C), homoaporphine **4a** (2%, mp 167–169 °C), and aldehyde **5** (22%, mp 143–144 °C). To confirm the structure of **2a**, diphenolic precursor **1d** was first oxidized with VOF_3–TFA to homoproerythrinadienone **2d**[12] (78%); subsequent O-methylation of **2d** with diazomethane gave **2a**. In contrast to the acid-catalyzed rearrangement of proerythrinadienones to neospirinedienones,[13] homoproerythrinadienone[14] **2a** and homoneospirinedienone **3a** rearranged to homoaporphines **4g** (87%, mp 221–222 °C) and **4h** (84%, mp 200–201 °C), respectively, upon treatment with BF_3–Et_2O in CH_2Cl_2 at room temperature for 24 h. Treatment of **4g** and **4h** with diazomethane yielded **4a**. The structure of 1,2,10,11-tetrasubstituted homoaporphine **4a** was confirmed by an unambiguous synthesis. Thus oxidation of **1e** with VOF_3–TFA gave diastereoisomeric homoproaporphines[15] **6a** (38%, mp 193–194 °C dec; melting point, ir, uv, and NMR in good agreement with those of (±)-kreysiginone[16a]) and **6b** [30%, mp 198–200 °C dec (lit.[16a] mp 202 °C dec)]. Treatment of **6a** with BF_3–Et_2O in CH_2Cl_2 afforded diphenolic homoaporphine **4e** [87%, mp 185.5–187 °C (lit.[17] 185–187 °C)], which on methylation with diazomethane gave tetramethoxyhomoaporphine **4f**[18] (70% as the hydrochloride; mp 222–224 °C dec; melting point, mixture melting point, TLC, uv, NMR, and mass spectrum identical with those of a sample prepared by alkaline hydrolysis of **4a** followed by N-methylation with HCHO–$NaBH_4$).



The rearrangement of homoneospirinedienone **3a** to 1,2,10,11-tetrasubstituted homoaporphine **4h** indicates the intermediacy of a homoproerythrinadienone (e.g., 8), a route supported by the observed facile rearrangement of homoproerythrinadienone **2a** to homoaporphine **4g.** The demonstrated conversions[7] of (±)-*N*-acylnorlaudanosines to (±)-*N*-acylmorphinandienones and thence to (±)-*N*-acylneospirinedienones in nonphenol oxidative coupling of benzylisoquinolines with VOF_3–TFA led us to consider also the possibility that the conversion of phenethylisoquinoline **1a** to homoaporphine **4a** might proceed via route 1: **1a** → **7** → **9** → **8** → **4a.** To investigate this possibility the 6-benzyloxy (**1b**) and 7-benzyloxy (**1c**) analogues of (±)-*N*-trifluoroacetylhomonorlaudanosine (**1a**) were oxidized with VOF_3–TFA for 10 min. Thus **1b** gave **2a** (50%) and **3b** (42%, mp 169–170 °C, 3-benzyloxy analogue of **3a**), whereas **1c** gave **2b** (3%, mp 134–134.5 °C, 2-benzyloxy analogue of **2a**) and **3a** (60%). These results preclude route 1, via homomorphinandienone-type intermediates (e.g., **7**), and confirm route 2, via homoproerythrinadienone-type intermediates (e.g., 8), for the formation of homoneospirinedienones **3a,b** from phenethylisoquinolines **1a–c.** Furthermore, the homoproerythrinadienone-type intermediates (e.g., 8) and homoneospirinedienone-type intermediates (e.g., **9**) appear to be in equilibrium in the reaction medium. It was thought that isolation of **2a** and **3a** in high yields in the oxidations of **1b** and **1c**, respectively, could indicate shifts of equilibria due to easy cleavage of the benzyl groups from the corresponding benzyloxonium ions. This was confirmed by isolation of **2a** (71%, no appreciable amount of **3b**) and **3a** (65%, no appreciable amount of **2b**) upon treatment of **1b** and **1c**, respectively, with VOF_3–TFA for ~1 h.

The foregoing mechanistic considerations and demonstrated facile rearrangement of homoproerythrinadienone **2a** and homoneospirinedienone **3a** to homoaporphines **4g** and **4h**, respectively, suggested that homoaporphines might be obtained directly from the phenethylisoquinolines if enough time were allowed for rearrangement of the corresponding homoproerythrinadienone-type (e.g., 8) and homoneospirinedienone-type intermediates (e.g., **9**). Indeed, the phenethylisoquinolines **1a, 1b,** and **1c** gave homoaporphines **4a** (84%), **4g** (80%), and **4h** (65%), respectively, upon treatment with VOF_3–TFA for several hours.

The conversion of homoproerythrinadienone **2d** to dibenz[*d,f*]azecine, a key homoerythrina alkaloid precursor, has recently been reported.[19] In view of the close similarity in structure of homoproerythrinadienones and homoneospirinedienones, the latter may as well be a precursor of dibenz[*d,f*]azecine. Studies aimed at efficient synthetic routes to homoerythrina alkaloids using homoproerythrinadienones and homoneospirinedienones are in progress.

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(10) All new compounds were characterized by concordant analytical and spectral data. The structural formulas containing asymmetric atoms refer to racemic mixtures.
(11) In a typical oxidation 1 mmol of the substrate [0.05 M solution in methylene chloride containing 20% TFA–TFAA (20:1 by weight)] was treated with 2.5 molar equiv of VOF_3 [dissolved in a minimum volume of a 1:1 solution of ethyl acetate and TFA–TFAA (20:1 by weight)].
(12) The homoproerythrinadienone **2d** was previously obtained in 35% yield by oxidation of **1d** using $VOCl_3$ in CH_2Cl_2.[14]
(13) T. Kametani, R. Charubala, M. Ihara, M. Koizumi, K. Takahashi, and K. Fukumoto, *J. Chem. Soc. C,* 3315 (1971); T. Kametani, K. Takahashi, T. Honda, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.*, **20,** 1793 (1972).
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(15) The homoproaporphines **6a,b** were previously obtained in 31% and 36.6% overall yield by oxidation of **1e** using potassium ferricyanide[16a] and ferric chloride,[16b] respectively.
(16) (a) A. R. Battersby, E. McDonald, M. H. G. Munro, and R. Ramage, *Chem. Commun.*, 934 (1967); A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro, and R. Ramage, *J. Chem. Soc., Perkin Trans. 1,* 1394 (1974). (b) T. Kametani, K. Fukumoto, H. Yagi, and F. Satoh, *Chem. Commun.*, 878 (1967); *J. Org. Chem.*, **33,** 690 (1968).

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(18) The tetramethoxyhomoaporphine **4f** was also obtained in 40% yield by treatment of **1f** in FSO_3H, CH_2Cl_2, and TFA with VOF_3 in TFA.
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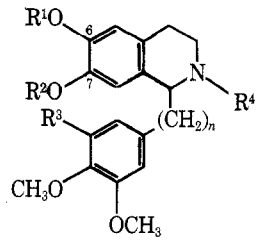
Efficient Intramolecular Monophenol Oxidative Coupling[1]

Summary: The remarkably efficient intramolecular oxidative couplings of monophenolic benzyltetrahydroisoquinolines **1a,b** to aporphines **4a,b** and of monophenolic phenethyltetrahydroisoquinolines **1c–g** to homoaporpines **4c–f,** spirodienones **2c–f,** and **6** are described.

Sir: The important role played by diphenol oxidative coupling in the biosynthesis of alkaloids has been well documented and reviewed.[2] In general, laboratory attempts to effect intramolecular oxidative coupling of diphenols have suffered from low yields, mainly attributable to overoxidation. Recently, attention has been directed toward utilization of monophenolic substrates in an attempt to develop effective intramolecular oxidative coupling methods for use in alkaloid synthesis.[3–5] We report herewith the remarkable efficiency of the monophenol oxidative coupling method using VOF_3 for the syntheses of aporphines **4a,b,** homoproaporphines **2c–f,** homoaporphines **4c–f,** and homoproerythrinadienone **6.**

Treatment of a solution of (±)-*N*-trifluoroacetylnorcodamine (**1a**)[6,7] in CH_2Cl_2 with VOF_3 in trifluoroacetic acid (TFA)[8] at −10 °C for 10 min followed by aqueous workup gave (±)-*N*-trifluoroacetylwilsonirine[9] (**4a,** 70%, mp 196.5–197 °C) along with morphinandienone **5a**[10,11] (8%, mp 179.4–181.5 °C). Under the same conditions, oxidation of (±)-codamine (**1b**) gave a complex mixture of products from which only (±)-thalicmidine [**4b,** 38%, mp 191–193 °C dec (lit.[12] 190–192 °C)] was isolable. In contrast, an 80% overall yield of (±)-thalicmidine (**4b**) was obtained upon treatment of the borane complex[13] of **1b** with VOF_3–TFA (15 min at −10 °C) and subsequent removal of the blocking group by heating with anhydrous Na_2CO_3 in methanol under reflex. Morphinandienone **5b** could not be detected by thin layer chromatography in either of the latter experiments. The facile and high-yield conversions of **1a,b** to **4a,b** constitute the most efficient reported route to 1,2,9,10-tetrasubstituted aporphines.

To evaluate the potential of the monophenol oxidative coupling method for the syntheses of homoaporphines and of homomorphinandienones such as the colchicine precursor *O*-methylandrocymbine,[14] 7-hydroxy-1-phenethyltetrahydroisoquinolines **1c–f** were prepared[7] and oxidized with VOF_3–TFA at −10 to −15 °C for 5–10 min. Thus the oxidation of **1c** yielded homoaporphine **4c**[15] (40%) along with homoproaporphine **2c** (18%, mp 192.5–193.5 °C), and **1d** gave homoproaporphine **2d** [42%, mp 200–201 °C dec (lit.[16] 200–202 °C)] along with homoaporphine **4d** [14%, mp 190–192 °C (lit.[17] 195–196 °C)]. Only one isomer of homoproaporphine **2c** or **2d** was obtained, in contrast to the diasteroisomeric mixture obtained by oxidation of diphenolic precursor **1d.**[15,16,18] Similarly, oxidation of **1e** yielded homoaporphine **4e** (46%, mp 161–162 °C) along with homoproaporphine **2e** (4%, mp 207–210 °C dec), and **1f** gave homoproaporphine **2f** [54%, mp



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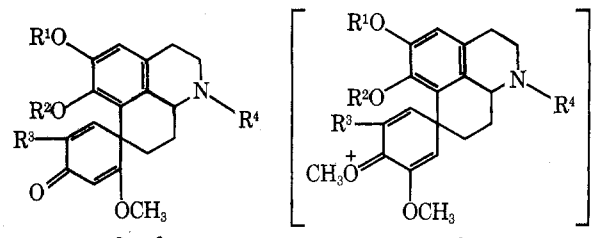
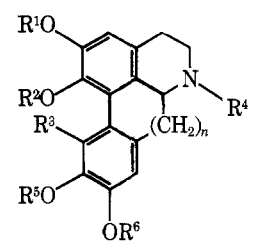
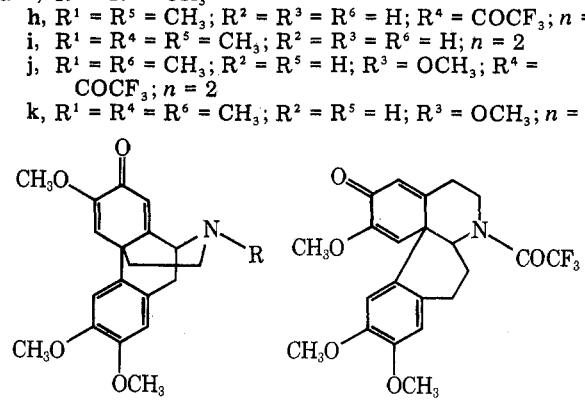
b, $R^1 = R^4 = CH_3$; $R^2 = R^3 = H$; $n = 1$
c, $R^1 = CH_3$; $R^2 = R^3 = H$; $R^4 = COCF_3$; $n = 2$
d, $R^1 = R^4 = CH_3$; $R^2 = R^3 = H$; $n = 2$
e, $R^1 = CH_3$; $R^2 = H$; $R^3 = OCH_3$; $R^4 = COCF_3$; $n = 2$
f, $R^1 = R^4 = CH_3$; $R^2 = H$; $R^3 = OCH_3$; $n = 2$
g, $R^1 = R^3 = H$; $R^2 = CH_3$; $R^4 = COCF_3$; $n = 2$



2c–f **3c–f**



4a–f, $R^5 = R^6 = CH_3$
h, $R^1 = R^5 = CH_3$; $R^2 = R^3 = R^6 = H$; $R^4 = COCF_3$; $n = 2$
i, $R^1 = R^4 = R^5 = CH_3$; $R^2 = R^3 = R^6 = H$; $n = 2$
j, $R^1 = R^6 = CH_3$; $R^2 = R^5 = H$; $R^3 = OCH_3$; $R^4 = COCF_3$; $n = 2$
k, $R^1 = R^4 = R^6 = CH_3$; $R^2 = R^5 = H$; $R^3 = OCH_3$; $n = 2$



5a, R = $COCF_3$
b, R = CH_3 **6**

174–176 °C (lit.[16] 176–178 °C)] along with (±)-kreysigine [**4f,** 16%, mp 185–186 °C (lit.[16] 187–189 °C)]. No homomorphinandienone could be detected by thin layer chromatography in any of the above experiments. Homoproaporphines **2c, 2d, 2e,** and **2f** underwent smooth dienone–phenol rearrangements[16,19] upon treatment with BF_3–Et_2O in CH_2Cl_2 at room temperature[20] and afforded homoaporphines **4h** (93%, mp 167–168 °C), **4i** [70%, mp 241–242 °C dec (lit.[19] 241–242 °C)], **4j** (87%, mp 208–208.5 °C), and **4k** [(±)-multifloramine, 72%, mp 185–188 °C dec (lit.[16] 190–192 °C dec)], respectively. The formation of homoproaporphines **2c–f** and of homoaporphines **4c–f** in the oxidations of phenethyltetrahydroisoquinolines **1c–f,** and the demonstrated facile acid-catalyzed rearrangements of homoproaporphines **2c–f** to homoaporphines **4h–k** suggested that the formation of homoaporphines **4c–f** from monophenolic phenethyltetrahydroisoquinolines **1c–f** may proceed via homoproaporphine-type intermediates (**3c–f**)