drastines was the isolation of the novel white crystalline oxidation dimer oxybisberberine, mp 215–216 °C dec (pyridine), in 60% yield from the ferricyanide oxidation of **1**.[3] This photosensitive dimer, which shows no carbonyl absorption in the ir, is stable in base, but rapidly and irreversibly cleaves in acid. When this breakdown is effected with methanolic hydrogen chloride, the products are berberine chloride (**1**), and orange colored 8-methoxyberberinephenolbetaine (**2**): $C_{21}H_{19}NO_6$; mp 175–176 °C (ether); λ_{max}^{EtOH} 230, 262, 313, 359, 374, and 455 nm (log ϵ 4.50, 4.11, 4.09, 3.81, 3.80, and 3.83); NMR δ 2.90 (t, 2 H, C-5 CH_2), 3.86 (s, 3 H, OCH_3), 3.98 (s, 6 H, 2 × OCH_3), 4.58 (t, 2 H, C-6 CH_2), 5.86 (s, 2 H, OCH_2O), 6.51 (s, 1 H, C-4 H), 7.35 (d, 1 H, $J_{11,12}$ = 9 Hz), 9.28 (d, 1 H, $J_{11,12}$ = 9 Hz, C-12 H), and 8.80 (s, 1 H, C-1 H).

Phenolbetaine **2** has the requisite oxygen function at C-13 as well as the potential carboxylic ester at C-8 for transformation to a phthalideisoquinoline. The unmasking of the C-8 carboxyl was achieved by simple hydration whereby a solution of **2** in water saturated ether at room temperature slowly decolorizes to furnish upon workup in 80% yield the hydrochloride salt of dehydronorhydrastine methyl ester (**3**): $C_{21}H_{21}NO_7 \cdot HCl \cdot CH_3OH$; mp HCl salt 144–145 °C (MeOH–ether); ν_{max}^{KBr} 1670 and 1735 cm^{-1}; λ_{max}^{EtOH} 210, 228, 280, and 308 nm (log ϵ 4.50, 4.37, 4.20, and 4.19). The NMR spectrum of the free base (enol form) with δ 2.73 and 3.81 (2 t, 2 × 2H, CH_2–CH_2), 3.84, 3.92, and 3.96 (3 s, 3 × 3 H, 3 OCH_3), 5.98 (s, 2 H, OCH_2O), 6.70 and 7.03 (2 s, 2 × 1H, C-5 and C-8 H), and 7.04 (ABq, 2 H, J = 9 Hz, ics = 10 Hz, C-2′ and C-3′ H) fully supported the structural assignment.[4] N-Alkylation of the free base **3** with methyl iodide in refluxing acetonitrile afforded, in quantitative yield, dehydrohydrastine methyl ester (**4**); $C_{22}H_{23}NO_7$; HI salt mp 167–168 °C (MeOH–ether); $\nu_{max}^{CHCl_3}$ 1670 and 1735 cm^{-1}. The free base (keto form) of **4** exhibited mp 125–127 °C (MeOH); NMR δ 2.22 (s, 3 H, N–CH_3), 2.5–3.4 (m, 4 H, CH_2–CH_2), 3.45 (s, 1 H, C-1 H), 3.81, 3.83, and 3.97 (3 s, 3 × 3H, 3 OCH_3), 5.83 (s, 2 H, OCH_2O), 6.32 and 6.60 (2 s, 2 × 1H, C-8 and C-5 H), and 7.30 (ABq, 2 H, J = 9 Hz, ics = 74 Hz, C-3′ and C-2′ H).

Direct sodium borohydride reduction of **4** in ethanol, followed by acid workup provided a 1:2 mixture of (±)-α-hydrastine (**5**) and (±)-β-hydrastine (**6**) in 90% yield, spectrally identical with semisynthetic (−)-α-hydrastine and natural (−)-β-hydrastine, respectively.[5]

Two pathways, therefore, are now available in the laboratory for cleavage of the critical N-7 to C-8 bond of berberinoids under conditions which could approximate in part the processes of nature. The first of these, namely, the quinone methide route, starts with a phenolic *N*-methyldihydroprotoberberine salt and leads to spirobenzylisoquinolines.[6] The second route, described herein, involves direct oxidation of an N-7 to C-8 immonium bond of a berberinoid salt to lead eventually to phthalideisoquinolines.[7]

References and Notes

(1) This research was supported by Grant HL-12971 from the National Institutes of Health. Acceptable combustion elemental analyses were obtained for compounds **2–4**. NMR spectra were at 60 MHz in $CDCl_3$.

(2) W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 305 (1910). See also R. Robinson, "Structural Relations of Natural Products", Clarendon Press, Oxford, 1955, p 88.

(3) The exact structure of oxybisberberine is in the process of being determined by x-ray crystallography.

(4) We have found that the known compound berberinephenolbetaine (J. Iwasa and S. Naruto, *J. Pharm. Soc. Jpn.*, **86**, 534 (1966); *Chem. Abstr.*, **65**, 12247b (1966)) also decolorizes when subjected to these same hydrolytic conditions. However, hydration does not proceed in a straightforward manner, and numerous highly oxidized products are obtained. These will be discussed at a later date.

(5) R. D. Haworth and A. R. Pinder, *J. Chem., Soc.*, 1776 (1950); R. D. Haworth, A. R. Pinder, and R. Robinson, Nature (*London*), **165**, 529 (1950); see also W. H. Perkin, Jr., J. N. Rây, and R. Robinson, *J. Chem. Soc.*, **127**, 740 (1925).

(6) M. Shamma and C. D. Jones, *J. Am. Chem. Soc.*, **92**, 4943 (1970); M. Shamma and J. F. Nugent, *Tetrahedron*, **29**, 1265 (1973).

(7) Attention should be called, however, to the important finding that in *Papaver somniferum* the tetrahydroprotoberberine base (−)-scoulerine labeled at C-14 leads to the phthalideisoquinoline (−)-α-narcotine also mostly labeled at the corresponding site (A. R. Battersby, M. Hirst, D. J. McCaldin, R. Southgate, and J. Staunton, *J. Chem. Soc. C*, 2163 (1968); A. R. Battersby and M. Hirst, *Tetrahedron Lett.*, 669 (1965); and A. R. Battersby, R. J. Francis, M. Hirst, R. Southgate, and J. Staunton, *Chem. Commun.*, 602 (1967)). It follows that in the plant (−)-scoulerine must suffer oxidation of the N-7 and C-8 bond while the integrity of the C-14 asymmetric center is essentially maintained.

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Reactions of Silyl Enol Ethers and Lactone Enolates with Dimethyl(methylene)ammonium Iodide. The Bis-α-methylenation of Pre-Vernolepin and Pre-Vernomenin

Sir:

Recently we described the synthesis of bisnorvernolepin (**1**) and bisnorvernomenin (**2**) in 17 steps from 1,3-butadiene.[1] Since the first total synthesis of *dl*-vernolepin (**3**)[2] and *dl*-vernomenin (**4**)[2] of Grieco and co-workers[3,4] had involved transformation of a mixture of **1** and **2** into **3** and **4**, which was then separated into individual components, our preparation of homogeneous **1** and **2** constituted a technical total synthesis of the racemates **3** and **4**.

Although the α-methylenation of lactones has received considerable study,[5a–c] culminating in the bis-α-methylenation of bisnordeoxyvernolepin[7] and thence of **1** and **2**,[3] we were desirous of augmenting this capability in the context of converting a vicinal hydroxybutylrolactone such as **5** into its α-methylene derivative **6** *without protection of the hydroxyl.*

This objective arose from practical considerations. Preliminary efforts to convert **1** into its OTHP derivative afforded only a 70% yield of relatively pure product.[8] A 71% yield was recorded for the conversion of the OTHP derivatives of **3** and **4** into the final products.[3] Thus, this type of protection, deprotection maneuver appears to result in the loss of ca. one-half of the difficulty won tricyclic material, *apart* from the less than ideal efficiency of the bis-α-methylenation process.

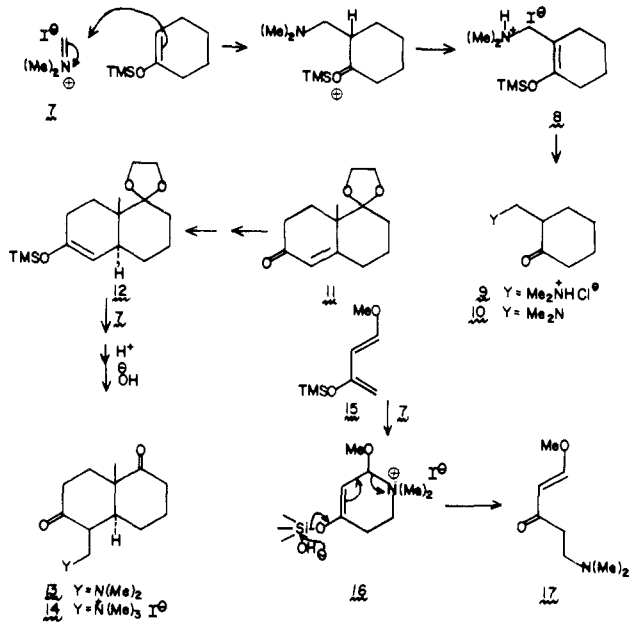
Our attentions focused on a Mannich approach. Such a route would avoid differentiating between a hydroxyl group[9] that must be retained and one which must be used for further functionalization. The specific[10] Mannich agent used was dimethyl(methylene)ammonium iodide (**7**), a nicely crystalline salt first prepared and used by Eschenmoser in another context.[11] Before relating the successful application of **7** to the stated objective, we describe some new chemistry which should serve to stimulate other applications of this highly reactive and interesting reagent.

Compound **7**, which is insoluble in methylene chloride, reacts instantaneously with a solution of 1-trimethylsilyloxycyclohexene in this solvent to produce a salt which must be formulated as **8** on the basis of its spectral properties: δ $CDCl_3$ 0.25 (s, 9), 3.03 (s, 3), 3.70 (s, 2) (no vinylic hydrogens); $\lambda_{max}^{CHCl_3}$ 6.02 μ (silyl enol ether). Reaction of **8** with aqueous HCl gives Mannich salt **9**, which affords the well known **10** (87% overall yield) after neutralization. The ability to perform a Mannich reaction on a silyl enol ether[12,13] without catalysis and with restoration of the double bond to its original site is a valuable observation in terms of trapping possibilities.

We have demonstrated the utility of this chemistry as a route to steroids. Reductive silylation[14a] of **11**[14b] affords **12**. This reacts at room temperature with **7** to afford a silyl enol ether

Mannich salt, which upon treatment with aqueous acid and neutralization affords Mannich base **13**. Oily **13** gives a crystalline methiodide **14**, mp 224–225 °C dec (>95% overall yield). The potential utility of systems such as **13** and related precursors of α-methylene ketones has been skillfully demonstrated by Hajos[15a] and Stork.[15b] *It will be noted that the method described here avoids the need for regeneration of a kinetic enolate by means of alkyl lithium reagent such as is required in the formaldehyde method of Stork and D'Angelo.*[15b]

Cycloaddition of **7** with diene **15** occurs instantaneously at room temperature to afford **16**, [16a] which is cleaved with aqueous sodium hydroxide to give Mannich base **17**[16a] in 95% overall yield. Cycloaddition of **7** with siloxydienes followed by basic unravelling is a route to otherwise difficulty accessible Mannich bases of unsaturated carbonyl systems.



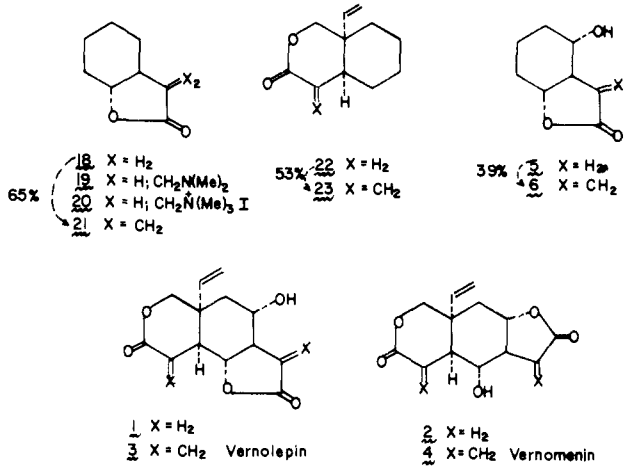
Dimethylaminomethylation of lactones via their enolates can be achieved directly with compound **7**.[6] For instance, treatment of 1 equiv of lactone **18**[17] with 1.2 equiv of lithium diisopropylamide (LDA, derived from the reaction of *n*-butyllithium with isopropylamine) in dry THF at −78 °C was followed by addition of 3 equiv of a suspension of **7** in THF. After 10 min at −78 °C, the system was stirred at −42 °C for 20 min and quenched with aqueous sodium bicarbonate. Workup afforded crude **19**, which was converted to the crude methiodide **20**.[6] Treatment of **20** with 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU) in dioxane followed by chromatography furnished a 65% yield (overall) of crystalline **21**.[6] Similarly, vinyllactone **22**[18-21] was converted to **23** in 53% yield.

The feasibility of methylenating **5** without hydroxyl group protection was then demonstrated. Reaction of **5**[22] (−78 °C, THF) with 3 equiv of LDA in the presence of 2.5 equiv of hexamethylphosphoramide (HMPA) followed by reaction of the presumed dianion with 6.5 equiv of **7** for 10 min at −78 °C and for 30 min at −42 °C, afforded a crude dimethylaminomethylated product. Treatment with methyl iodide and thence with DBU in THF gave, after acidic workup,[23] a 39% yield overall of **6**, mp 61–62 °C.[16a,b]

In a similar way, the conversion of **1** to *dl*-vernolepin (**3**), mp 209–211 °C (lit.[3] 210–211 °C), was achieved. In this conversion, a large excess of LDA (5.5 equiv) was employed to generate the presumed trianion and 6 equiv of HMPA were employed to maintain a virtually homogeneous solution throughout. The excess LDA was quenched with excess **7** (15 equiv). The yield was 31% (overall). The yield achieved via the OTHP using compound **7** was 18% overall, while that reported[3] via the OTHP using hydroxymethylation was 11%. The infrared ($CHCl_3$), NMR (250 MHz, pyridine-d_5), and mass spectra of *dl*-**3** were identical with those obtained from an authentic sample kindly provided by Professor S. M. Kupchan.

Finally, compound **2** was converted (20% overall)[24] to *dl*-vernomenin (**4**), mp 183–184 °C (lit.[3] 186–188 °C). The infrared spectrum of *dl*-**4** was identical with a spectrum furnished by Professor Kupchan. Its NMR spectrum (250 MHz, pyridine-d_5) closely corresponded to a 100-MHz spectrum (furnished by Professor Kupchan) of natural vernomenin obtained in pyridine–acetone. All protons in the 250-MHz spectrum are virtually resolved. A total synthesis of **3** and **4** is thus achieved. *Parenthetically, we note that these results provide the first definitive proof of the structure of pre-vernolepin* (**1**) *and pre-vernomenin* (**2**), *hitherto surmised by spectral analyses of the mixture*[3] *and the individual compounds.*[1,25]

Studies employing compound **7** in a variety of new situations are in progress and their results will be described in due course.



Acknowledgment. This study was supported by PHS Grant CA-12107-12 and by an unrestricted Grant from the Ciba-Geigy Corp. NMR spectra were obtained on facilities supported by RR-00296. A valuable discussion with Professor Paul Dowd (ref 11) is gratefully acknowledged. We also thank Professor S. M. Kupchan for providing a sample of natural vernolepin and spectra of vernomenin.

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(21) J. A. Marshall and D. E. Seitz, *J. Org. Chem.*, **40**, 534 (1975).
(22) Prepared by Mei-Yuan Tsai of this Laboratory: S. Danishefsky, M. Tsai, and T. Kitahara, manuscript in preparation.
(23) In several cases it was shown that the hydroxyl group is not liberated until aqueous acid workup. We have not yet properly investigated the status of this oxygen or the precise nature of the functional group (or mixtures of systems) which is present after the methyl iodide–DBU sequence. Conceivably, a fuller understanding of this situation might allow for yield improvements in the unprotected α-hydroxy series.
(24) This reaction was conducted once on 28 mg of **2**. Thus, the rather disappointing yield reported here may well be subject to improvement. Such efforts will be made.
(25) Since the overall yields are quite low, it need not follow that the major compound of the **3**, **4** mixture arises from the major component of its precursor 1, **2** mixture.

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Synthetic Methods and Reactions. 17.[1] Uranium Hexafluoride, a Convenient New Oxidizing Agent for Organic Synthesis

Sir:

Uranium hexafluoride, depleted of fissionable ^{235}U, is abundantly available.[2] In spite of its availability and remarkable properties, the study of the reactions of UF_6 with organic compounds remained virtually unexplored. The highly covalent nature of UF_6 makes it particularly suitable for reaction in nonaqueous solvents. Stable solutions of UF_6 in chlorofluorocarbons (Freons) or chlorohydrocarbons (methylene chloride or chloroform), can be used conveniently as they do not attack glass and are generally easy to handle. We wish to report our observation of the facile and selective oxidation of several classes of organic compounds with UF_6, which promises to make it a useful oxidizing agent in organic synthesis.

Ethers undergo oxidative cleavage to form carbonyl compounds and alcohols. Furthermore, the direction of cleavage is predictable, thus the utility of ethers (such as benzyl or benzhydryl ethers) as protecting groups for alcohols is broadened. The oxidation of methyl ethers is regiospecific. Trapping experiments with phenyllithium suggest the intermediacy of methoxycarbenium ions in the reaction. Results of the oxidation of alkyl (cycloalkyl) methyl ethers are summarized in Table I.

Table I. Oxidative Cleavage of Alkyl (Cycloalkyl) Methyl Ethers

Alkyl (cycloalkyl) methyl ether	Carbonyl product	Yield, %
Cyclohexyl	Cyclohexanone	86
Cycloheptyl	Cycloheptanone	83
Benzyl	Benzaldehyde	78
p-Tolyl	4-Tolualdehyde	73
4-Bromobenzyl	4-Bromobenzoaldehyde	67
Benzhydryl	Benzophenone	57
4-Nitrobenzyl	4-Nitrobenzaldehyde	77
4-Cyanobenzyl	4-Cyanobenzaldehyde	71
α-Phenethyl	Acetophenone	75

Table II. Oxidative Cleavage of Benzyl and Benzhydryl Ethers

Ether	Alcohol product	Yield, %
n-Hexyl benzyl	*n*-Hexanol	44
Cyclohexyl benzyl	Cyclohexanol	66
Cycloheptyl benzyl	Cycloheptanol	56
n-Octyl benzhydryl	*n*-Octanol	63
Cyclohexyl benzhydryl	Cyclohexanol	61
2-Octyl benzhydryl	2-Octanol	69
2-*o*-Nitrophenethyl benzhydryl	2-*o*-Nitrophenethyl alcohol	64

$$RR'CHOMe + UF_6 \longrightarrow RR'\overset{+}{C}HOMe\ F^- \quad (UF_5) \xrightarrow[-HF]{-UF_4} RR'C{=}\overset{+}{O}Me \xrightarrow{H_2O} RR'C{=}O$$

Benzyl and benzhydryl ethers are cleaved to the corresponding alcohols and benzaldehyde or benzophenone, respectively. The usefulness of the present method is further demonstrated by the cleavage of 2-*o*-nitrophenethyl benzhydryl ether to benzophenone and the parent alcohol by UF_6. Hydrogenolytic procedures would be untenable due to the presence of an easily reducible nitro group. No attempt has been made to optimize yields of the products summarized in Table II, which clearly can be improved.

$$ROCHR'Ph \xrightarrow[2.\ H_2O]{1.\ UF_6} ROH + PhR'CO$$

R = alkyl, cycloalkyl

R′ = H or Ph

In a typical procedure for the oxidative cleavage of ethers, an ice-cooled magnetically stirred solution of 3.52 g (0.01 mol) of UF_6 in 100 ml of 1,1,2-trichlorotrifluoroethane (Freon 113) was reacted with 1.28 g (0.01 mol) of cycloheptyl methyl ether, added dropwise in 10 ml of the same solvent. The reaction was allowed to proceed for 1 h and was quenched with 25 ml of water and the resulting uranyl salts were filtered. The filtrate was worked up in the usual manner to give 0.93 g (83% yield) of pure cycloheptanone, characterized as the 2,4-dinitrophenylhydrazone (mp 145 °C).

Benzylic alcohols are readily oxidized to the corresponding

$$PhCHROH + UF_6 \longrightarrow PhCH\overset{+}{R}OH\ F^- \quad (UF_5) \xrightarrow[-UF_4]{-HF} PhCR{=}\overset{+}{O}H\ F^- \xrightarrow{-HF} PhCR{=}O$$