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The Preparation of α-Substituted, β-Hydroxy Piperidines and Pyrrolidines: The Total Synthesis of Febrifugine.

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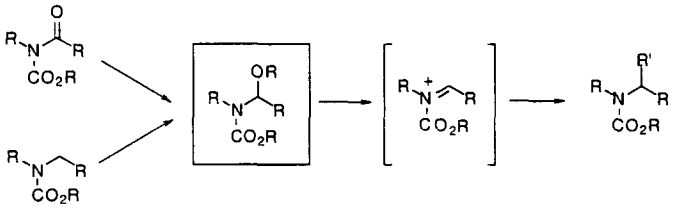
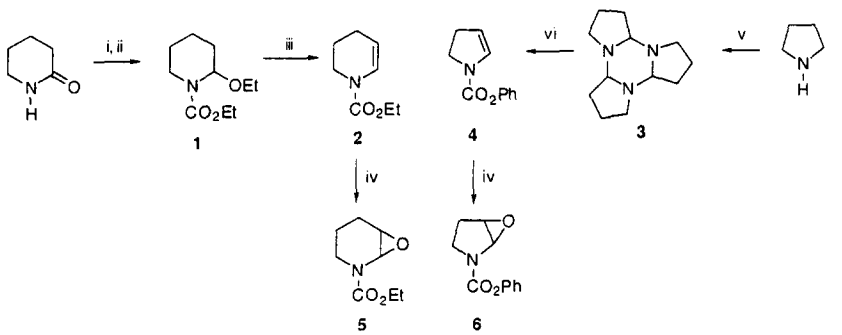
Abstract Epoxides generated from cyclic ene carbamates are effective N-acyl iminium ion precursors and allow for the preparation of β-hydroxy, α-substituted piperidines and pyrrolidines. The total synthesis of racemic Febrifugine is also described. Copyright © 1996 Elsevier Science Ltd

The use of α-alkoxy carbamates and amides as precursors to N-acyl iminium ions for the construction of carbon-carbon bonds is well documented.[1] Typically these versatile systems arise from the partial reduction of the corresponding carbonyl[2] or oxidation of the hydrocarbon under electrochemical[3] or transition metal-mediated[4] conditions.



Subsequent acyl iminium ion formation by Lewis or protic acids followed by trapping with various nucleophiles returns the amido-alkylation products in good to excellent yields. Often the judicious choice of a Lewis acid and the presence of proximal stereocenters can greatly influence the facial selectivity of these additions.[5] Because of an interest in α-substituted β-hydroxy piperidines and pyrrolidines for natural product synthesis and medicinal chemical research, we have investigated the use of epoxides derived from cyclic ene carbamates as N-acyl iminium ion precursors (see below). Furthermore, we have applied this methodology to the preparation of the hydrangea alkaloid Febrifugine.[6]

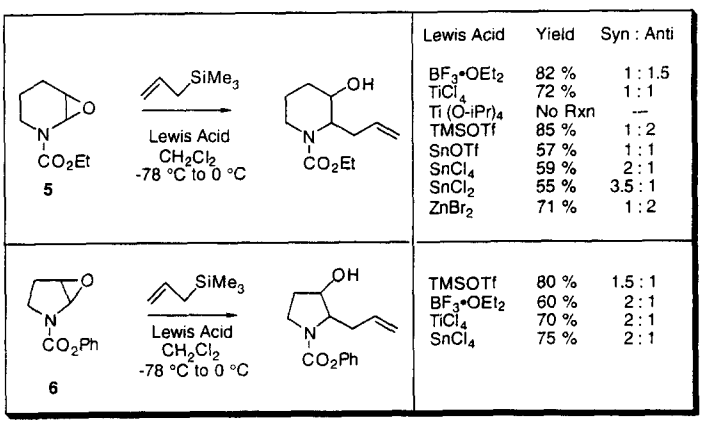
As a model system, the epoxides derived from N-carbethoxy-1,2,3,4-terahydropyridine and N-carbophenoxy-1,2-dihydropyrrole were chosen (Scheme 1). N-Acylation of δ-valerolactam followed by partial reduction with lithium triethylborohydride (acidic ethanol work-up) provided **1**. Simply heating **1** with magnesium sulfate in toluene returned the desired elimination product (**2**). The preparation of the pyrrolidine ene carbamate **4** via trimer **3** proceeded as described previously.[7] Under peracid conditions (meta-chloroperbenzoic or peracetic acid with or without buffer) a complex mixture of unstable products were obtained possibly derived from opening of the epoxide with the resultant carboxylate by-product. Ultimately, the application of dimethyl dioxirane[8] in acetone at low temperature returned the desired epoxides **5** and **6**[9] in excellent yields.[10]



Scheme 1. i) n-BuLi, THF, -78 °C then $ClCO_2Et$ (76%); ii) $LiB(H)Et_3$, THF, -78 °C then HCl in EtOH (94%); iii) $MgSO_4$, toluene, reflux (35%); iv) dimethyl dioxirane, acetone, 0 °C to RT (97%); v) $Na_2S_2O_8$, NaOH, H_2O, cat. $AgNO_3$ (25%); vi) distillation followed by $ClCO_2Ph$, TEA, -78 °C (30%).

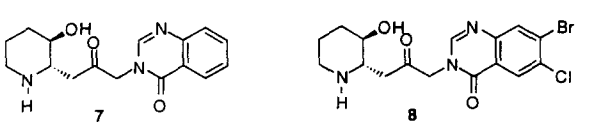
Upon treatment of **5** and **6** with a variety of Lewis acids, the N-acyl iminium ions were generated and readily trapped by allyltrimethyl silane in good yields (Table 1). While epoxides derived from cyclohexenes can be opened by nucleophiles with excellent stereoselectivity, the facial selectivity of these additions was low.[11] Although some related systems have been speculated to proceed via an S_N2-like mechanism, most seem to involve the planar N-acyl iminium ion. Based on the non-selective opening of **5** and **6**, the ionic intermediates are probably formed here and the α-alkoxy stereocenter provides little directing effect. Although we are currently investigating other means for improving this selectivity (such as the incorporation of directing groups into the carbamate or applying reagents with inherent diastereoselectivity), the present methodology remains useful for the preparation of α-substituted β-hydroxy pyrrolidines and piperidines and, to this end, we have prepared (±) Febrifugine by total synthesis.

Table 1

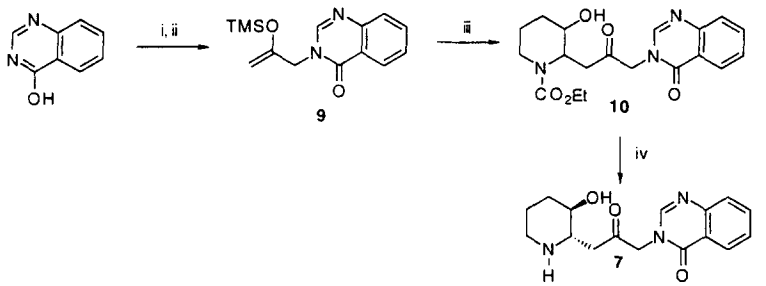


Lewis Acid	Yield	Syn : Anti
BF_3•OEt_2	82 %	1 : 1.5
$TiCl_4$	72 %	1 : 1
Ti (O-iPr)$_4$	No Rxn	---
TMSOTf	85 %	1 : 2
SnOTf	57 %	1 : 1
$SnCl_4$	59 %	2 : 1
$SnCl_2$	55 %	3.5 : 1
$ZnBr_2$	71 %	1 : 2
TMSOTf	80 %	1.5 : 1
BF_3•OEt_2	60 %	2 : 1
$TiCl_4$	70 %	2 : 1
$SnCl_4$	75 %	2 : 1

Febrifugine (**7**) is a hydrangea alkaloid that possesses antimalarial and anticoccidial properties[12] and a semi-synthetic derivative, Halofuginone (**8**), is a successful commercial anti-parasitic used in chicken feed.[13]



Previous synthetic work has established the relative and absolute configuration of the piperidine substituents.[14] The necessary nucleophilic partner (silyl enol ether **9** - see Scheme 2) for coupling with epoxide **5** was readily prepared from 4-hydroxyquinazoline by N-alkylation with chloroacetone followed by trimethylsilyl trifluormethane sulfonate trap of the corresponding enolate. Coupling of **5** and **9** was then accomplished by treatment with titanium tetrachloride to generate a mixture (1:1) of separable diastereomers (**10**).[15] After chromatography, deprotection of the basic amine with potassium hydroxide[16] yielded the natural product (**7**).[17]



Scheme 2. i) NaH, DMF, 0 °C then chloroacetone, 0 °C to RT (62%); ii) TMSOTf, Hunig's Base, CH_2Cl_2, RT (82%); iii) **5**, $TiCl_4$, CH_2Cl_2, 0 °C (40%); iv) separation by flash chromatography then KOH, diethylene glycol, H_2O, Δ (10%).

In summary, a new N-acyl iminium ion precursor has been devised that is particularly useful for the simultaneous introduction of β-hydroxy and α-substitution into piperidine and pyrrolidine templates.

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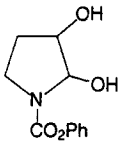
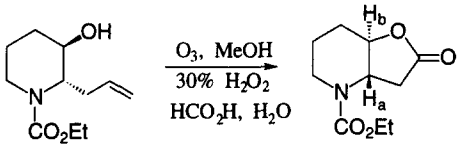
9. Depending on the dryness of the epoxidation solvent, compound **6** was isolated in the non-hydrated and hydrated form:



10. **General procedure for epoxidation of ene carbamates**: To a cooled (0 °C), stirred solution of freshly prepared dimethyl dioxirane (see Ref. 8) in dry acetone (250 mL; ~0.07 M; 17 mmol) was added the ene carbamate **2** (1.2 g; 7.7 mmol), neat, via pipette. The resulting solution was lightly capped and stirred at 0 °C for 0.5 hr. then carefully allowed to warm to room temperature and stir overnight. The reaction mixture was then concentrated at reduced pressure to provide epoxide **5** as a clear, colorless liquid (1.28 g; 97%). No further purification was necessary.
^{1}H NMR (250 MHz, $CDCl_3$, rotomers) δ 5.72 (d, 0.5H, J = 3.7 Hz), 5.55 (d, 0.5H, J = 2.7 Hz), 4.16 (q, 2H, J = 7.1 Hz), 3.91 (c, 1H), 3.61 (dt, 1H, J = 4.2, 10.8 Hz), 3.01 (td, 1H, J = 2.9, 10.3 Hz), 2.05-1.42 (m, 4H), 1.27 (t, 3H, J = 7.1 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$, rotomers) δ 14.3, 14.4, 18.5, 23.5, 24.8, 26.5, 37.8, 38.5, 61.7, 61.7, 66.8, 69.1, 76.3, 77.7, 156.0, 157.0. Exact mass calculated for $C_8H_{13}NO_3$: 171.0892; Found: 171.0904.

11. The assignment of stereochemistry was based on the conversion of **5** to a known lactone in which the coupling constants of the ring junction protons are distinctive (see Barringer, D. F.; Berkelhammer, G.; Wayne, R. S. *J. Org. Chem.* **1973**, *38*, 1937.):



J_{ab} = 8.4 Hz

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15. **Preparation of 10**: To a cooled (0 °C), stirred solution of epoxide **5** (73 mg; 0.43 mmol) and silyl enol ether **9** (134 mg; 0.49 mmol) in dry methylene chloride (2 mL) was added a titanium (IV) tetrachloride-methylene chloride solution (1.28 mL; 1.0 M; 1.28 mmol), dropwise, via syringe under nitrogen atmosphere. The resulting brown, cloudy solution was stirred at 0 °C for 1.5 hr. The reaction was then quenched with the addition of saturated, aqueous sodium bicarbonate (10 mL). After vigorous stirring for 10 min., this mixture was extracted with methylene chloride (3 x 15 mL). Combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo to provide 170 mg of a light yellow oil. Flash chromatography (5% methanol in methylene chloride on silica gel) returned two diastereomers as clear, colorless oils:
Diastereomer 1 (less polar product; anti stereochemistry; 35 mg; 22 %): ^{1}H NMR (300 MHz, $CDCl_3$, rotomers) δ 8.21-8.15 (m, 2H), 7.72-7.61 (m, 2H), 7.43 (c, 1H), 4.91 (c, 0.5H), 4.34-4.20 (m, 2.5H), 4.08-4.02 (m, 3H), 3.83-3.67 (m, 1H), 2.90-2.73 (m, 1H), 2.42 (dd, 0.5H, J = 8.1, 13.6 Hz), 2.26-2.00 (m, 1.5 H), 1.86-1.23 (m, 4H), 1.17 (t, 1.5H, J = 7.1 Hz), 1.09 (t, 1.5H, J = 7.1 Hz). Exact mass calculated for $C_{19}H_{23}N_3O_5$: 373.1638; found: 373.1632.
Diatereomer 2 (more polar product; syn stereochemistry; 29 mg; 18%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.24 (c, 1H), 8.01 (s, 1H), 7.79-7.69 (c, 2H), 7.48 (c, 1H), 5.09-4.81 (m, 2H), 4.72 (t, 1H, J = 6.4 Hz), 4.10 (q, 2H, J = 7.1 Hz), 3.96 (br d, 1H, J = 14.2 Hz), 3.87 (d, 1H, J = 2.7 Hz), 2.95 (br t, 1H, J = 13.2 Hz), 2.81 (d, 2H, J = 8.1 Hz), 2.65 (br s, 1H), 1.96-1.69 (m, 3H), 1.42 (c, 1H), 1.22 (t, 3H, J = 7.1 Hz). Exact mass calculated for $C_{19}H_{23}N_3O_5$: 373.1638; found: 373.1646
16. Acidic conditions resulted in significant amounts of dehydrated material. For a similar deprotection see Wenkert, E.; Hudlicky, T.; Showalter, H. D. H. *J. Am. Chem. Soc.* **1978**, *100*, 4893.
17. From this deprotection reaction, diastereomer 1 (**10**) provided a solid which had spectral properties characteristic of the natural product.

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