

spatol to **4** is assumed, the C-17 stereochemistry in **1** must be *S*. The cyclobutane ring has both cyclopentane rings joined in a *cis* fashion, and each ring is oriented *anti* in a manner identical with that found in bourbonene.

Epoxides, and diepoxides in particular,⁹ have long been known to possess cytotoxic activity resulting from protein binding via displacement reactions with sulfhydryl groups.¹⁰ In the case of spatol, the unsaturation in proximity to the epoxide groups may enhance the reactivity of this metabolite to nucleophilic addition.

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Supplementary Material Available: Details of the X-ray crystallographic experiment, tables of fractional coordinates, thermal parameters, bond distances, bond angles, and observed and calculated structure factors for compound **4** (16 pages). Ordering information is given on any current masthead page.

(9) (a) J. L. Everett and G. A. R. Kon, *J. Chem. Soc.*, 3131 (1950); (b) S. M. Kupchan, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, 33, 2288 (1974).
 (10) E. Fujita and Y. Nagao, *Bioorg. Chem.* 6, 287 (1977).

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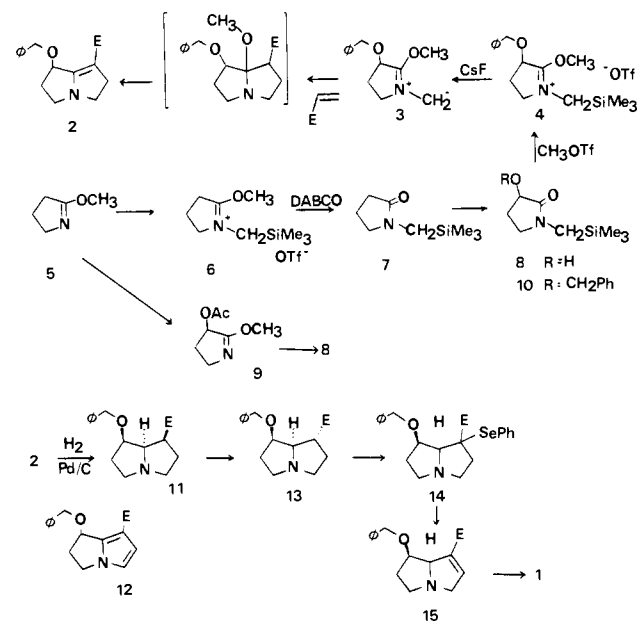
Stereospecific Synthesis of Retronecine by Imidate Methylide Cycloaddition

Sir:

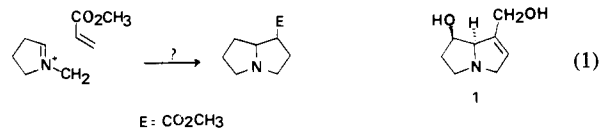
We have recently described the first synthetically viable route to nonstabilized iminium ylides, as well as their 1,3-dipolar cycloadditions to give pyrrolines.¹ This study is now extended to construction of the pyrrolizidine nucleus, culminating in an efficient, stereospecific synthesis of retronecine (**1**).^{2,3} Derivatives of retronecine are of some interest as antitumor agents.⁴

Although the simplest conceivable route to pyrrolizidines appeared to involve cycloadditions such as eq 1,⁵ stereochemical considerations in the context of the retronecine problem suggested than an alternative oxidation state of the cycloadduct would be more desirable. Specifically, our plans were based on the as-

Scheme 1



sumption that an ester-conjugated enamine **2** could be reduced from the least hindered side to control stereochemistry.



For preparation of **2**, we envisioned a cycloaddition between methyl acrylate and the imidate methylide **3**, a member of a hitherto unknown class of nonstabilized nitrogen ylides.⁵⁻⁷ As in our previous study,¹ the crucial ylide intermediate can be generated by CsF desilylation from the (trimethylsilyl)methyl salt **4**.

The retronecine sequence depends on the hydroxy lactam **8** as the first nontrivial intermediate. Two routes to **8** have been developed. The shortest route starts with alkylation of imidate **5** by $\text{CF}_3\text{SO}_3\text{CH}_2\text{SiMe}_3$ (20 °C, 0.5 h, CH_2Cl_2) to give a salt **6** (not isolated) which can be demethylated with Dabco (18 h, 20 °C, CH_2Cl_2) to give the lactam **7** (mp 30–32 °C). Enolate hydroxylation of **7** using the LDA, $\text{MoO}_5\cdot\text{Py}\cdot\text{HMPA}$ method⁸ (–78 °C, 1.5 h; allow to warm to 20 °C) affords **8**, mp 71–72 °C (60%). An alternative route which has some advantages on a large scale is based on the known conversion of **5** into **9** via bromination (NBS) and nucleophilic displacement with $(\text{C}_2\text{H}_5)_4\text{N}^+\text{OAc}^-$.⁹ Treatment of **9** with $\text{Me}_3\text{SiCH}_2\text{OSO}_2\text{CF}_3$ and Dabco as before, followed by acetate hydrolysis (NaOCH_3 in 2% aqueous ethanol, room temperature, 18 h), gives hydroxy lactam **8** in 70% yield overall from **9**.

After a brief survey of other hydroxyl protecting groups,¹⁰ the benzyl ether **10** (PhCH_2Br ; NaH ; DME, 20 °C; 90% after Kugelrohr distillation, 115–120 °C at 0.1 mm) was selected for conversion to retronecine. The cycloaddition sequence begins with O-alkylation of **10** by treatment with $\text{CH}_3\text{OSO}_2\text{CF}_3$ (CH_2Cl_2 , 20 °C, 18 h). The crude salt **4** is then dissolved in DME and is stirred

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 (2) Review: Bull, L. B.; Culvenor, C. C.; Dick, A. T. "The Pyrrolizidine Alkaloids"; North-Holland Publishing Co.: Amsterdam, 1968.

(3) Recent work on total synthesis of retronecine: (a) Tufariello, J. J.; Lee, G. E. *J. Am. Chem. Soc.* 1980, 102, 373. (b) Keck, G. E.; Nickell, D. G. *Ibid.* 1980, 102, 3634. (c) First total synthesis: Geissman, T. A.; Weiss, A. C., Jr. *J. Org. Chem.* 1962, 27, 139.

(4) Kugelman, M.; Lin, W. C.; Axelrod, M.; McBride, T. J.; Rao, K. V. *Lloydia* 1976, 39, 125. Powis, G.; Ames, M. M.; Kovach, J. S. *Cancer Res.* 1979, 39, 3564. Kovach, J. S.; Ames, M. M.; Powis, G.; Moertel, C. G.; Hahn, R. G.; Creagan, E. T. *Ibid.* 1979, 39, 4540.

(5) The conceptually similar cycloaddition of ylides generated in situ from *N*-acylamino acids + acetic anhydride can be used to prepare aromatized pyrrolizidines,⁶ which can then be hydrogenated to saturated analogues. This approach has not yet been demonstrated for substrates having an oxygen function as required for retronecine.

(6) (a) Pizzorno, M. T.; Albonico, S. M. *J. Org. Chem.* 1974, 39, 731. *Ibid.* 1977, 42, 909. (b) Robins, D. J. *J. Chem. Soc., Perkin Trans. 1*, 1979, 1734. (c) *J. Chem. Soc., Chem. Commun.* 1979, 1181.

(7) Related, stabilized azomethine ylides are well-known. Reviews: (a) Lown, J. W. *Rec. Chem. Prog.* 1971, 32, 51. (b) Kellogg, R. M. *Tetrahedron* 1976, 32, 2165. (c) Huisgen, R. *J. Org. Chem.* 1976, 41, 403. See also: Hermann, H.; Huisgen, R.; Mader, H. *J. Am. Chem. Soc.* 1971, 93, 1779 and references therein.

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(10) The pivalate was unsatisfactory due to apparent elimination during ylide generation; other ethers such as CH_2OCH_3 gave lower yields in the cycloaddition step.

at 20 °C with $\text{CH}_2=\text{CHCO}_2\text{CH}_3$ and anhydrous CsF (dried, vacuum desiccator) to effect the 1,3-dipolar cycloaddition. After 24 h, a 51% yield of cycloadduct **2** can be isolated based on starting lactam **10**. Some loss of material in the cycloaddition step is to be expected since the initially formed adduct loses a molecule of methanol under the reaction conditions. According to our previous experience, α -trimethylsilyl "onium" salts are sensitive to protiodesilylation by hydroxylic agents, and other complications involving the sensitive imidate salt **4** may also arise.

Catalytic reduction of **2** (10% Pd/C, atmospheric pressure, EtOAc) gave a single reduction product (83%), assigned stereochemistry as in **11** based on subsequent transformations. The only side product detected was the aromatized compound **12** (pyrrole hydrogens at 6.66 and 6.60 ppm), 8% after chromatography. The oily reduction product **11** spontaneously epimerized (48 h, 20 °C, neat) to a crystalline isomer **13** (mp 48–50 °C). Similar endo \rightarrow exo isomerizations have been reported previously¹¹ among pyrrolizidine alkaloids.

Final transformations of **13** to retronecine involve a selenium-based elimination similar to that used by Robins for synthesis of supinidine.^{6b} Generation of the enolate (–78 °C, LDA in THF + 5% HMPA) followed by reaction with diphenyl diselenide at –35 °C affords the selenide **14** in >95% yield. Oxidation of **14** (2 equiv of MCPBA, –78 °C, 2 h, CH_2Cl_2 ; add 5 equiv of Me_2S at –78 °C to destroy excess oxidant) followed by selenoxide elimination (cold selenoxide transferred dropwise into refluxing CCl_4 by cannula) gives the unsaturated ester **15** (oil, 90% from **13** after chromatography). Finally, Dibal reduction (–78 °C to room temperature; $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ workup, 85%) and benzyl ether cleavage with 3 equiv of Li in liquid ammonia (5 h, –33 °C; quench with isoprene followed by solid NH_4Cl) results in crystalline *d,l*-retronecine,¹² 70% yield after sublimation.

Even though the key 1,3-dipolar cycloaddition proceeds in only 51% yield, the sequence from hydroxy lactam **8** to retronecine is quite efficient (ca. 20% overall). Related applications of nonstabilized imidate methylide cycloadditions to synthesis of five-membered nitrogen rings are being investigated.

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(11) Likhoshesterov, A. M.; Kulkov, V. N.; Kochetkov, N. K. *Zh. Obshch. Khim.* **1964**, *34*, 2798.

(12) Mp 129–130 °C, twice recrystallized from acetone (lit.^{3b,c} mp 130 °C).

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Thermal Reactions of 2,3-Diazabicyclo[2.2.0]hex-2-ene. The First Example of a Disrotatory Diazacyclobutene Ring Opening

Sir:

2,3-Diazabicyclo[2.2.0]hex-2-ene¹ (**1**) belongs to two important classes of compound, the diazabicyclo[2.2.*n*]alkenes^{2,3} and the

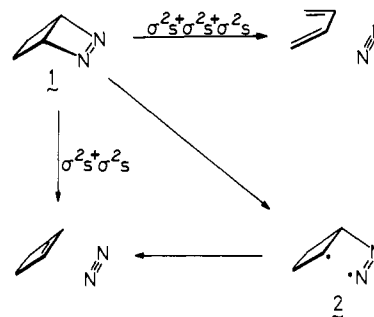


Figure 1. Possible deazetation reactions of 2,3-diazabicyclo[2.2.0]hex-2-ene.

diazetines.⁴⁻⁶ We report here that **1** undergoes two thermal reactions, a deazetation process which has an important bearing on the formally similar reaction of other cyclic azo compounds and a ring opening which is, to our knowledge, without precedent in diazetine chemistry.

Thermal deazetation of **1** could, in principle, give cyclobutene or butadiene as the hydrocarbon product. Unlike the deazetation of the other members of the diazabicyclo[2.2.*n*]alkene series, the concerted nitrogen extrusion from **1** is thermally forbidden⁷ unless accompanied by cleavage of the C5–C6 bond (Figure 1). As always, a stepwise C–N bond cleavage could occur to afford a biradical (**2**) which would presumably lead to cyclobutene.⁸

Experimentally, pyrolysis of **1** at 90–130 °C in cyclooctane or benzene was found to give cyclobutene as the exclusive (>98%) deazetation product.⁹ Some butadiene was observed at long reaction times but this could be ascribed to the known ring opening of cyclobutene.¹⁰

Apparently **1** eschews the $\sigma_2s + \sigma_2s + \sigma_2s$ fragmentation, a rather surprising result when compared with pyrolysis of 3,4,5,6-tetrahydropyridazine for which the analogous three-bond cleavage comprises 46% of the reaction.¹¹ One might have expected that cyclobutene ring strain would have weakened the C5–C6 bond in **1** and would thereby have made the three-bond fragmentation more favorable. Possibly the higher temperature of the tetrahydropyridazine study¹¹ and the (presumably) positive ΔS^\ddagger for fragmentation to three components combined to make the $\sigma_2s + \sigma_2s + \sigma_2s$ reaction more prominent in that case.

In fact deazetation was found to be only a minor reaction of **1** (~10%) in the temperature range of our investigation (90–130 °C). The main reaction was a ring opening leading, we believe, to 4,5-dihydropyridazine (**3**) as the primary product. Under the reaction conditions **3** apparently dimerized and, eventually, trimerized¹² (Figure 2) as it has been shown to do in an earlier investigation.¹³

The ¹H NMR spectrum of the reaction mixture during pyrolysis

(2) Boyd, R. J.; Bunzli, J. C.; Synder, J. P.; Heyman, M. L. *J. Am. Chem. Soc.* **1973**, *95*, 6478.

(3) Heyman, M. L.; Bandurco, V. T.; Synder, J. P. *Chem. Commun.* **1971**, 297.

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(5) Engel, P. S.; Hayes, R. A.; Keifer, L.; Szilagyi, S.; Timberlake, J. W. *J. Am. Chem. Soc.* **1978**, *100*, 1876.

(6) White, D. K.; Greene, F. D. *J. Am. Chem. Soc.* **1978**, *100*, 6760.

(7) White and Greene⁶ have raised the possibility of a fragmentation which is antarafacial on nitrogen. We do not believe that **1** would be able to undergo such a reaction because of its rigidity.

(8) Formation of butadiene from **2** would require the intermediacy of a second biradical whereas formation of cyclobutene simply involves C–N bond cleavage.

(9) Cyclobutene was identified by comparison of its ¹H NMR spectrum and GC retention time with those of an authentic sample and by its quantitative conversion to butadiene on extended pyrolysis.

(10) Cooper, W.; Walters, W. D. *J. Am. Chem. Soc.* **1958**, *80*, 4220.

(11) Dervan, P. B.; Santilli, D. S. *J. Am. Chem. Soc.* **1980**, *102*, 3863.

(12) The trimer was identified by X-ray crystallographic analysis.¹³ The dimer was unstable and could not be fully characterized but it did have a chemical ionization mass spectrum with the correct molecular ion.

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