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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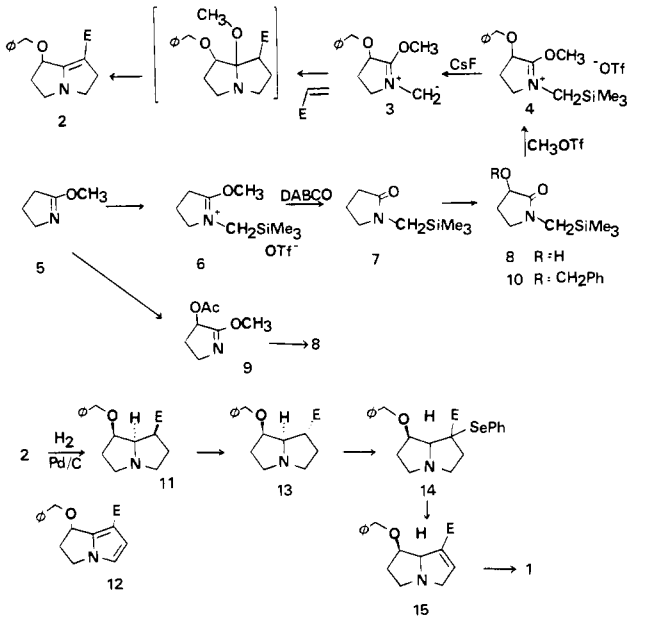
Stereospecific Synthesis of Retronecine by Imidate Methylide Cycloaddition

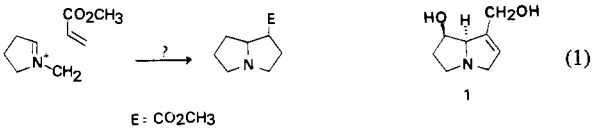
Sir:

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

Scheme I





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 $CF_3SO_3CH_2SiMe_3$[1] (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,MoO_5·Py·HMPA method[8] (−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 $(C_2H_5)_4N^+OAc^-$.[9] Treatment of **9** with $Me_3SiCH_2OSO_2CF_3$ 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 $CH_3OSO_2CF_3$ (CH_2Cl_2, 20 °C, 18 h). The crude salt **4** is then dissolved in DME and is stirred

(1) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452.
(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.
(8) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.
(9) Yamada, Y.; Okada, H. *Agric. Biol. Chem.* **1976**, *40*, 1437.
(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.

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at 20 °C with CH_2=$CHCO_2CH_3$ 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 → exo isomerizations have been reported previously[11] 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; $Na_2SO_4 \cdot 10H_2O$ 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) Likhosherstov, 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-ene[1] (**1**) belongs to two important classes of compound, the diazabicyclo[2.2.*n*]alkenes[2,3] and the 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.

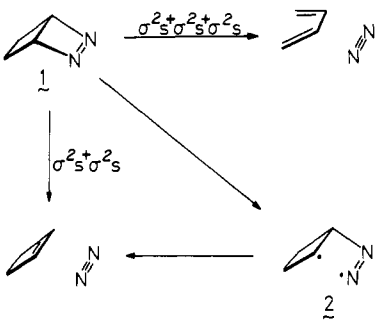

Figure 1. Possible deazetation reactions of 2,3-diazabicyclo[2.2.0]hex-2-ene.

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 extrustion from **1** is thermally forbidden[7] 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 ${}_\sigma2_s + {}_\sigma2_s + {}_\sigma2_s$ fragmentation, a rather suprising 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 cyclobutane 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 study[11] and the (presumably) positive $\Delta S^\ddagger$ for fragmentation to three components combined to make the ${}_\sigma2_s + {}_\sigma2_s + {}_\sigma2_s$ 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, trimerized[12] (Figure 2) as it has been shown to do in an earlier investigation.[13]

The ^1H NMR spectrum of the reaction mixture during pyrolysis

(1) Wildi, E. A.; Carpenter, B. K. *Tetrahedron Lett.* **1978**, 2469.
(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.
(4) Rieber, N.; Alberts, J.; Lipsky, J. A.; Lemal, D. M. *J. Am. Chem. Soc.* **1969**, *91*, 5668.
(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 Greene[6] 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.
(13) Bandlish, B. K.; Brown, J. N.; Timberlake, J. W.; Trefonas, L. M. *J. Org. Chem.* **1973**, *38*, 1102. We are grateful to a referee for bringing this obviously important reference to our attention.

0002-7863/80/1502-7994$01.00/0