step in eq 1) was also followed via pyrrolidine formation in the NMR.

As seen in Table I, no ester hydrolysis was observed after 312 h at pD 8.2 in the absence of pig liver esterase. On the other hand, under the NMR conditions mentioned above, addition of the enzyme gave ester hydrolysis in a >95% yield after 50 h at pD 7.4. The rate of amine release following this ester hydrolysis depended strongly upon the pD. For example, amide cleavage (i.e. the second step in eq 1) has half-lives of 10.5 min at pD 6.50, 19 min at pD 6.90, and 2.7 h at pD 7.40. Intramolecular acid-catalyzed amide hydrolysis clearly diminishes in rate as the carboxyl ionizes.[4] Overall generation of amine has an optimal half-life of about 12 h near pD 7.4. Below that pD, the PLE-catalyzed esterolysis begins to slacken; above pD 7.4, amide cleavage becomes rate-determining under our standard conditions.[9]

(9) The kinetic behavior is similar to that described for a Kemp's triacid derivative detailed in ref 4 except that the cross-over point for the rate-determining step is shifted somewhat to more basic pH values. The cyclohexyl byproduct (visible in the NMR) is either the anhydride at lower pH's or the dicarboxylate at higher pH's.

When a primary amine, tryptamine, was used instead of pyrrolidine, the same mechanism applied although the overall rate of amine cleavage was an order of magnitude less. Obviously, primary amine release is too slow for a workable drug therapy, a problem that could, possibly, be rectified via a more reactive ester functionality. Structural optimization has not been attempted, so that at this stage we can only present the general concept and offer a prototypical example. One encouraging point with regard to potential practicality, however, relates to the chymotrypsin data in Table I. Since chymotrypsin, a pancreatic protease, was found incapable of catalyzing ester or amide hydrolysis in our compounds, a drug masked as in eq 1 could likely survive passage through the intestinal tract.

In summary, we have developed a new type of prodrug in which biochemical and chemical "demasking" processes are sequentially linked via an enforced 1,3-diaxial disposition.

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Reverse Cope Eliminations. Pyrrolidine and Piperidine *N*-Oxides by Intramolecular Addition of N,N-Disubstituted Hydroxylamines to Unactivated Double Bonds

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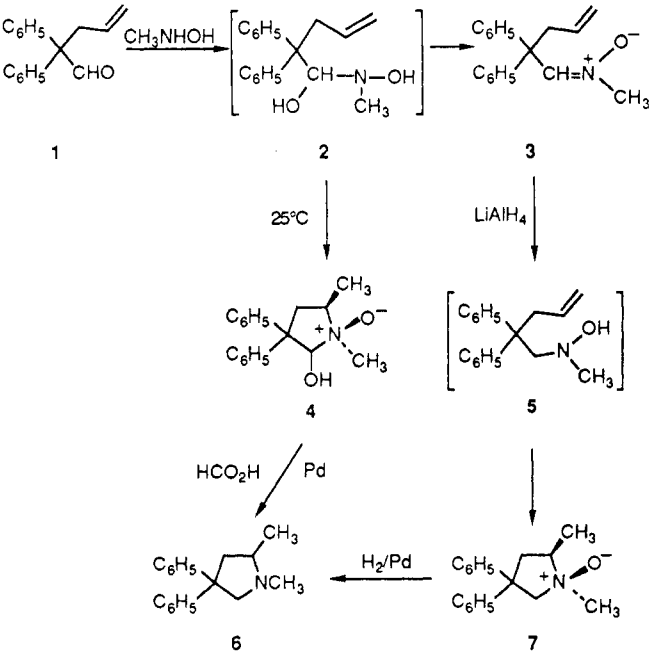
Summary: *N*-(4-Pentenyl)- and *N*-(5-hexenyl)-*N*-methylhydroxylamine and some of their derivatives cyclize under mild conditions in a concerted reverse Cope elimination to give 2-alkylpyrrolidine and 2-alkylpiperidine *N*-oxides.

In 1976, House and co-workers reported the cyclization of substituted *N*-(4-pentenyl)- and *N*-(5-hexenyl)-hydroxylamines to 1-hydroxy-2-methylpyrrolidines and 1-hydroxy-2-methylpiperidines, respectively,[1-3] and suggested a radical-chain mechanism for this reaction. We report here some preliminary observations on the scope and mechanism of the analogous transformation of unsaturated N,N-disubstituted hydroxylamines into cyclic *N*-oxides.[4]

When 2,2-diphenyl-4-pentenal (1) was allowed to react with *N*-methylhydroxylamine in ethanol at room temperature, the desired nitrone **3** was obtained in only 45% yield (Scheme I). The second product, formed in 51% yield, was shown to be 1,5-dimethyl-3,3-diphenyl-2-pyrrolidinol 1-oxide (**4**) by elemental analysis, ^{1}H NMR spectroscopy, and reduction to 1,2-dimethyl-4,4-diphenylpyrrolidine (**6**). *N*-Oxide **4** is the product of a formal reverse Cope elimination[5] of intermediate **2**. Reduction

Scheme I



(1) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

(2) The reaction was independently discovered by Oppolzer, W.; Siles, S.; Snowden, R.; Bakker, B. H.; Petrzilka, M. *Tetrahedron Lett.* **1979**, 4391, footnote 5.

(3) For additional examples of this cyclization, see: (a) Black, D. St. C.; Doyle, J. E. *Aust. J. Chem.* **1978**, *31*, 2317. (b) Yamada, F.; Makita, Y.; Suzuki, T.; Somei, M. *Chem. Pharm. Bull.* **1985**, *33*, 2162. (c) Yamada, F.; Hasegawa, T.; Wakita, M.; Sugiyama, M.; Somei, M. *Heterocycles* **1986**, *24*, 1223. (d) Lamanec, T. R.; Bender, D. R.; DeMarco, A. M.; Karady, S.; Reamer, R. A.; Weinstock, L. M. *J. Org. Chem.* **1988**, *53*, 1768 and references cited there. Karady, S.; Corley, E. G.; Abramson, N. L.; Weinstock, L. M. *Tetrahedron Lett.* **1989**, *30*, 2191. (e) Carling, R. W.; Leeson, P. D. *Tetrahedron Lett.* **1988**, *29*, 6985. (f) Leeson, P. D.; James, K.; Baker, R. *J. Chem. Soc., Chem. Commun.* **1989**, 433.

(4) For a transformation in which one of the steps was proposed to involve a reverse Cope elimination of an N,N-disubstituted hydroxylamine, see: Takahashi, S.; Kusumi, T.; Sato, Y.; Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1777.

(5) For a review of the Cope elimination, see: Cope, A. C.; Trumbull, E. R. *Org. React.* **1960**, *11*, 317.

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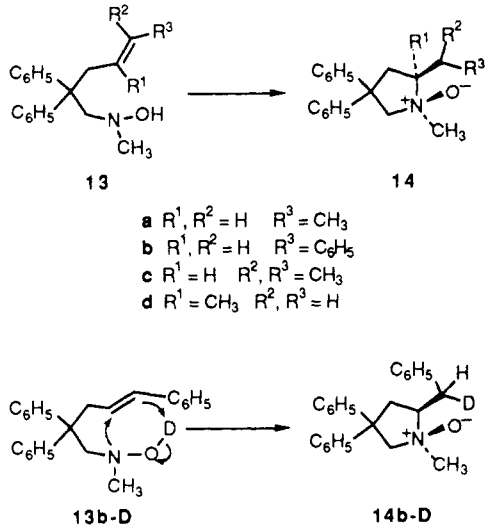
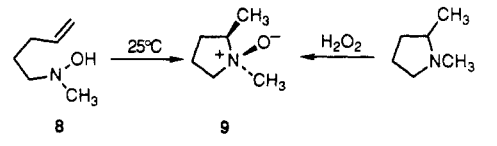
Scheme II



of nitrone **3** with lithium aluminum hydride at 0 °C and isolation at 25 °C gave a single *N*-oxide **7** (89% yield) which crystallized from acetonitrile as a monohydrate. X-ray crystallographic structure determination[6] showed the two methyl groups to be trans. The water molecule was attached to the *N*-oxide oxygen by a hydrogen bond of 1.646 Å length; the O–H–O bond angle was 177.4°. There was no evidence for the presence, in the crude product, of the intermediate unsaturated hydroxylamine **5**, which must have cyclized at or below room temperature. Catalytic hydrogenation of *N*-oxide **7** gave pyrrolidine **6**.

To determine the scope of this remarkably facile cyclization, the thermal behavior of a number of N,N-disubstituted unsaturated hydroxylamines was studied. Cyclization of *N*-(4-pentenyl)-*N*-methylhydroxylamine (**8**), prepared from 4-pentenal via lithium aluminum hydride reduction of the corresponding nitrone, proceeded at room temperature to give a single *N*-oxide (**9**) which was identical with the major oxidation product of 1,2-dimethylpyrrolidine. On distillation, *N*-oxide **9** partially reverted to hydroxylamine **8**, but on standing at room temperature it was completely regenerated. The cyclization is thus reversible. The homologous *N*-(5-hexenyl)-*N*-methylhydroxylamine, **11**, prepared[7] by a Cope elimination of 1-methylhexahydroazepine 1-oxide (**10**), cyclized to *N*-oxide **12** only very slowly at room temperature. The rate



of cyclization was accelerated by dissolution in chloroform, which appears to be the optimum solvent for reverse Cope eliminations. Heating hydroxylamine **11** under reflux in this solvent (bp 61 °C) caused complete conversion into *N*-oxide **12** with a half-life of about 2 h. *N*-Oxide **12** was identical with the major oxidation product[7] of 1,2-dimethylpiperidine. *cis*-1,2-Dimethylpiperidine 1-oxide and *N*-oxide **10** were absent within limits of detection by ^{1}H NMR spectroscopy.

(6) We thank Dr. J. C. Calabrese and W. J. Marshall for this determination.

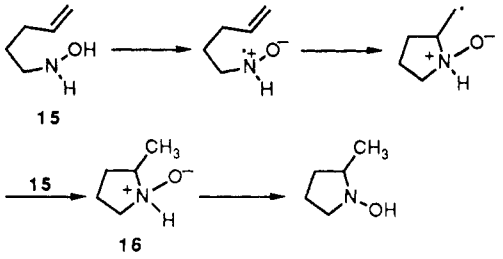
(7) Cope, A. C.; LeBel, N. A. *J. Am. Chem. Soc.* **1960**, *82*, 4656.

Table I. Solvent Dependence of the Equilibrium 13b ⇌ 14b at 25 °C

solvent	% 13b	% 14b
$CDCl_3$	0	100
CD_3OD	0	100
$(CD_3)_2CO$	<5	>95
CD_3CN	15	85
C_6D_6[a]	44	56
$(CD_3)_2SO$	55	45
$(CD_3)_2SO$ + CF_3CO_2H	0	100
THF-d_8	60	40
DMF-d_7	67	33
pyridine-d_5	74	26

[a] These numbers may not represent the true equilibrium since **14b** started to precipitate before the ^{1}H NMR spectrum could be determined for a second time.

Scheme III



To determine the influence of double bond substitution on the rate of cyclization, hydroxylamines **13a–d** were prepared by reduction of the appropriate nitrones with lithium aluminum hydride at 0 °C and isolation at 25 °C. Under these conditions, hydroxylamines **13b** (100% *E*) and **13d** cyclized completely to single *N*-oxides **14b** and **14d**, respectively (Scheme II), whereas the crotyl derivative **13a** (85:15% *E*:*Z*) cyclized to *N*-oxide **14a** to the extent of 74%; conversion was complete after 24 h at room temperature in chloroform. The dimethylallyl analogue **13c**, on the other hand, cyclized only very slowly. When the lithium aluminum hydride reduction of the nitrone precursor of hydroxylamine **13b** was quenched with D_2O, deuterium was introduced into only one of the two diastereotopic benzylic positions of **14b** as determined by ^{1}H NMR spectroscopy (**13b**-D → **14b**-D).[8]

In solvents at room temperature, hydroxylamine **13b** and *N*-oxide **14b** (as the monohydrate) are in equilibrium. The equilibrium constant depends strongly on the nature of the solvent (Table I). The *Z* isomer of **13b** was not detected. Chloroform and methanol probably stabilize the *N*-oxide by formation of hydrogen bonds; dimethyl sulfoxide and tetrahydrofuran are known to dramatically accelerate the Cope elimination as a consequence of desolvation of the *N*-oxide oxygen.[9] Removal of the solvent from the tetrahydrofuran solution at room temperature and dissolution in $CDCl_3$ caused complete reversion of **13b** to **14b**.

The Cope elimination is a concerted syn elimination involving a five-membered transition state.[5,10] The data

(8) We thank Prof. Barry M. Trost for suggesting this experiment.

(9) Cram, D. J.; Sahyun, M. R. V.; Knox, G. R. *J. Am. Chem. Soc.* **1962**, *84*, 1734. Sahyun, M. R. V.; Cram, D. J. *J. Am. Chem. Soc.* **1963**, *85*, 1263.

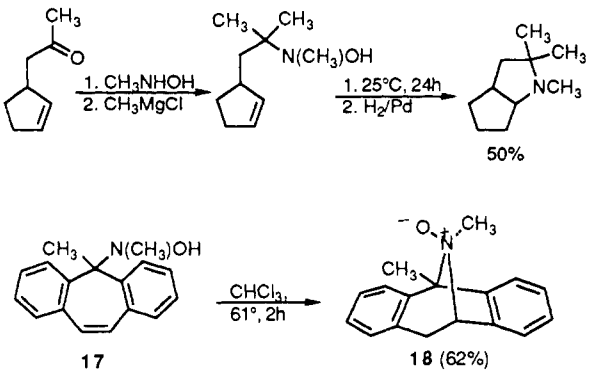
(10) Cram, D. J.; McCarty, J. E. *J. Am. Chem. Soc.* **1954**, *76*, 5740. Bach, R. D.; Andrzejewski, D.; Dubold, L. R. *J. Org. Chem.* **1973**, *38*, 1742. Chiao, W.-B.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 2802. Kwart, H.; George, T. J.; Louw, R.; Ultee, W. *J. Am. Chem. Soc.* **1978**, *100*, 3927. Kwart, H.; Brechbiel, M. *J. Am. Chem. Soc.* **1981**, *103*, 4650.

given above indicate that the reverse reaction proceeds by the same mechanism (shown in **13b**-D, Scheme II) rather than by the radical-chain mechanism proposed by House and co-workers[1] for the cyclization of N-monosubstituted unsaturated hydroxylamines to cyclic hydroxylamines (Scheme III). Pertinent observations are: (1) Only one of two possible *N*-oxides is formed; for *N*-oxide **7**, the newly formed methyl group and the *N*-oxide oxygen were shown to be cis as required by the concerted mechanism. It is reasonable to assume that the same stereochemical relationship holds for all other *N*-oxides as well. (2) In suitably substituted substrates the reaction is reversible at room temperature. (3) The observed influence of double bond substitution on the rate of cyclization is inconsistent with a radical mechanism, particularly the rapid cyclization of the internally substituted hydroxylamine **13d** as compared to the very slow cyclization of the terminally disubstituted hydroxylamine **13c**. (4) The specific transfer of deuterium in the transformation of **13b**-D to **14b**-D (Scheme II) is consistent only with a concerted mechanism.

The rate of cyclization of monosubstituted hydroxylamines (Scheme III) has been shown subsequently[3a] to be unaffected by radical inhibitors. We propose that it proceeds by a concerted reverse Cope elimination as well, the only difference being that the secondary *N*-oxide **16** (Scheme III) formed initially rearranges irreversibly[11] to the *N*-hydroxy isomer.

(11) In this connection we have found that no 1-decene is formed when *N*-decyl-*N*-methylhydroxylamine is heated, either neat at 200 °C or in dimethyl sulfoxide at 180 °C.

Scheme IV



The potential use of the reverse Cope elimination in synthesis is under investigation. Two examples are shown in Scheme IV.[12] The reverse Cope elimination discussed here has an analogy in the recently reported[13] intramolecular addition of certain oximes to double bonds to give derivatives of 3,4,5,6-tetrahydropyridine *N*-oxide.

(12) The transformation of **17** into **18** is analogous to the cyclization of *N*-[5-(5-methyl-5*H*-dibenzo[*a*,*d*]cycloheptenyl)]hydroxylamine to 5-methyl-12-hydroxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine, which is the key step in the synthesis of the *N*-methyl-D-aspartate receptor antagonist MK-801.[3d]

(13) Pradhan, S. K.; Akamanchi, K. G.; Divakaran, P. P. *Tetrahedron Lett.* **1982**, *24*, 5017. Pradhan, S. K.; Akamanchi, K. G.; Divakaran, P. P.; Pradhan, P. M. *Heterocycles* **1989**, *28*, 813. Bishop, R.; Brooks, P. R.; Hawkins, S. C. *Synthesis* **1988**, 997. Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron Lett.* **1990**, *31*, 559.

Carbohydrates to Carbocycles: A Synthesis of (-)-α-Pipitzol[1]

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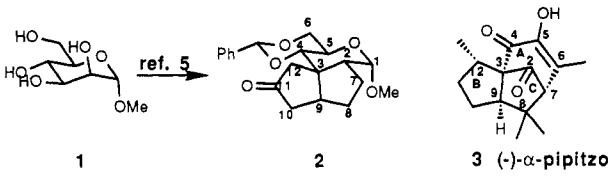
Summary: A 2-deoxy-3-keto sugar derived from methyl α-D-mannopyranoside has been processed to give a multibranched-chain sugar which undergoes serial radical cyclization, affording a pyranosidodiquinane as the key intermediate. The diquinane moiety represents the BC ring system of pipitzol, the A ring being obtained from the pyranosido moiety. A late intermediate is identified by comparison with the racemic modification prepared by Funk and Bolton, and, following their procedure, (-)-α-pipitzol was obtained spectroscopically identical with the racemic modification but with $[\alpha]_D = -141°$.

Studies in this laboratory have been concerned with the development of synthetic routes to complex polycyclic hydrocarbons from sugars,[4] and recently, radical cyclization avenues have been examined for preparation of the requisite annulated pyranoside precursors.[5,6] Central features of this approach are the use of the pyranoside core for several purposes: (i) easy stereocontrol in the creation of off-template stereocenters; (ii) for proof of structure via NMR analyses; (iii) as a source of varied latent functionalities; and, as a bonus, (iv) for its optical activity. In this paper, we exploit these attributes to achieve a stereospecific synthesis of (-)-α-pipitzol, **3**,[7-9] which makes this type

Scheme I



(1) This work was supported by a grant from the National Institutes of Health (GM 37380).

(2) Taken in part from Ph.D. Thesis of H.P., Duke University, 1989. Present address: Smith Kline Beecham, King of Prussia, PA.

(3) I.I.C. is grateful to the Government of Spain for a Post Doctoral Fellowship. Permanent address: Departmento de Quimica Organica, Universidad de Alcala, Madrid, Spain.

(4) Fraser-Reid, B.; Anderson, R. C. *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 1. Fraser-Reid, B.; Tsang, R. *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: New York, 1989; Vol. 2.

(5) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116.

(6) (a) Dickson, J. K., Jr.; Tsang, R.; Llera, J. M.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 5350. (b) Pak, H.; Dickson, J. K., Jr.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 5357.

(7) Isolation: Walls, F.; Padilla, J.; Joseph-Nathan, P.; Giral, F.; Romo, J. *Tetrahedron Lett.* **1965**, 1977. Walls, F.; Padilla, J.; Joseph-Nathan, P.; Giral, F.; Escobar, M.; Romo, J. *Tetrahedron* **1966**, *22*, 2387. Joseph-Nathan, P.; Roman, L. U.; Hernandez, J. D.; Taira, Z.; Watson, W. H. *Tetrahedron* **1980**, *36*, 731.

0022-3263/90/1955-3009$02.50/0