Suprafaciality of Thermal *N*-4-Alkenylhydroxylamine Cyclizations: Syntheses of (±)-α-Lycorane and (+)-Trianthine

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The thermal cyclizations of *N*-alkenylhydroxylamines (**I** → **IV**, Scheme 1), first reported by House et al.[1] and independently discovered by us,[2] have also been described by others.[3] This reaction was initially proposed to occur *via* a radical-chain mechanism.[1] More recently, Ciganek has postulated the retro-Cope elimination pathway **I** → **II** → **III** → **IV** in analogy to the thermal conversion of *N*-alkenyl-*N*-methylhydroxylamines to cyclic *N*-oxides.[4] However, compelling proof of either a radical or a concerted mechanism for cyclizations **I** → **IV** has not yet been presented.

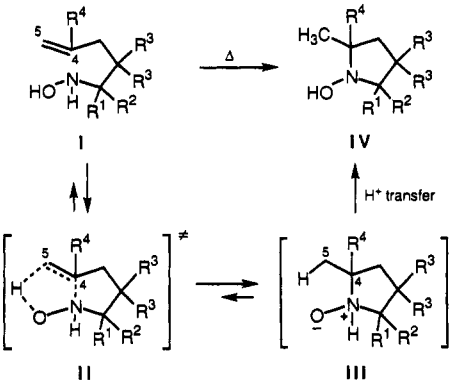
We report here that the thermally induced cyclization of *N*-4-alkenylhydroxylamines (**I** → **IV**) proceeds stereospecifically in a suprafacial manner and illustrate the relevance of this result in alkaloid synthesis.

To study the alkene faciality of this process, the (*E*)- and (*Z*)-5,5-disubstituted 4-alkenylhydroxylamines **2** and **4** were prepared *via* *C*-alkylation of thiazoline **1**[5] with (*E*)- and (*Z*)-1-chloro-3-phenyl-2-butene,[6] respectively, followed by thiazoline reduction, thiazolidine hydrolysis, aldehyde oximation, and oxime reduction (Scheme 2).

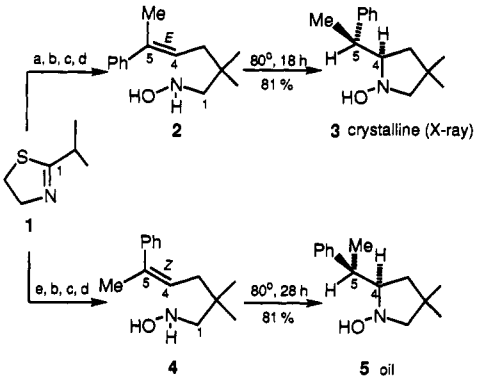
It was gratifying to find that both hydroxylamines **2** and **4** cyclized smoothly when heated in degassed benzene at reflux (18–28 h), providing *N*-hydroxypyrrolidines **3** and **5**, respectively, in 81% yield and without cross-contamination (^{1}H-NMR). The configurations of cyclization products **3** and **5** were assigned unambiguously by X-ray diffraction analysis of the crystalline isomer **3** (mp 85–86 °C).[7] The relative C(4)/C(5) configurations of **3** and **5** correspond to suprafacial formation of the C(4)–N and C(5)–H bonds in the ring closure. This lends strong support to Ciganek's retro-Cope elimination hypothesis and militates against a radical-chain mechanism for intramolecular alkene/hydroxylamine additions.

Having settled this mechanistic question, we set out to exploit this newly found stereospecificity in organic synthesis.

Scheme 1



Scheme 2[a]



[a] (a) LDA, (*E*)-1-chloro-3-phenyl-2-butene, THF, room temperature, 16 h; (b) (i) Al–Hg, Et_2O/H_2O, room temperature, 3 h; (ii) Hg_2Cl_2, $MeCN/H_2O$, 4:1, room temperature, 1.5 h; (c) NH_2OH, EtOH, reflux, 13 h; (d) $NaBH_3CN$, aqueous MeOH, pH = 3; (e) LDA, (*Z*)-1-chloro-3-phenyl-2-butene, THF, room temperature, 16 h.

We selected as a first target (±)-α-lycorane (**9**),[8] several syntheses of which have appeared in the literature (Scheme 3).[9]

Cyclohexenylacetaldehyde **6**,[10] readily available by reduction of the corresponding ethyl ester[11] with *i*-Bu_2AlH (1 molar equiv, –78 °C, toluene), was condensed with hydroxylamine, and the resulting oxime was reduced ($NaBH_3CN$, pH = 3) to give alkenylhydroxylamine **7** (70% from **6**, mp 75–80 °C). Heating **7** in rigorously degassed mesitylene under argon at 140 °C for 17 h provided the expected retro-Cope elimination product **8** (mp 116–118 °C) as a single isomer (^{1}H-NMR) in 83% yield. *N,O*-Hydrogenolysis of **8** (Raney-Ni, wet Et_2O[12a]) and modified Pictet–Spengler ring closure[12b] (Eschenmoser's salt, THF, 40 °C, 15 h) of the resulting secondary amine afforded (±)-α-lycorane (**9**, mp 95–97 °C, 74% from **8**). Hence (±)-α-lycorane (**9**) has been prepared from ester **6** by a sequence of six steps in overall 43% yield (36% overall from 4-bromo-1,2-(methylenedioxy)benzene), which compares very favorably with previous syntheses of **9**.[9]

More ambitiously, we then addressed the enantiospecific synthesis of (+)-trianthine (**18**) (Scheme 3).[13] Following the

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(3) (a) Black, D. St. C.; Doyle, J. E. *Aust. J. Chem.* **1978**, *31*, 2317. (b) Lamanec, T. R.; Bender, D. R.; DeMarco, A. M.; Karady, S.; Reamer, R. A.; Weinstock, L. M. *J. Org. Chem.* **1988**, *53*, 1768. (c) Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *J. Chem. Soc., Chem. Commun.* **1993**, 169.

(4) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007. For analogous cyclizations of acetylenic hydroxylamines to nitrones, see: Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393. Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M. *Tetrahedron Lett.* **1992**, *33*, 7421.

(5) Meyers, A. I.; Durandetta, J. L. *J. Org. Chem.* **1975**, *40*, 2021.

(6) (*E*)- and (*Z*)-1-chloro-3-phenyl-2-butene were prepared by treatment of (*E*)- and (*Z*)-3-phenyl-2-buten-1-ol with CCl_4/PPh_3 in CH_2Cl_2 at room temperature for 8 h. (*E*)-3-Phenyl-2-buten-1-ol: Bussas, R.; Muensterer, H.; Kresze, G. *J. Org. Chem.* **1983**, *48*, 2828. (*Z*)-3-Phenyl-2-buten-1-ol was prepared by *syn*-hydromagnesiation/methylation of 3-phenyl-2-propyn-1-ol following the procedure of Sato et al.: Sato, F.; Ishikawa, H.; Watanabe, H.; Miyake, T.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1981**, 718.

(7) Bernardinelli, G.; Oppolzer, W.; Spivey, A. C. *Acta Crystallogr.*, submitted for publication.

(8) (–)-α-Lycorane, obtained by degradation of naturally occurring lycorine, has the absolute configuration opposite to that depicted in **9**: Fales, H. M.; Wildman, W. C. *J. Am. Chem. Soc.* **1958**, *80*, 4395. Takeda, K.; Kotera, K.; Mizukami, S.; Kobayashi, M. *Chem. Pharm. Bull.* **1960**, *8*, 483.

(9) Bäckvall, J. E.; Andersson, P. G.; Stone, G. B.; Gogoll, A. *J. Org. Chem.* **1991**, *56*, 2988 and references mentioned therein. *Cf.*: Martin, S. F. The Amaryllidaceae Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, p 251.

(10) The lycorane skeleton numbering is used for all intermediates in our syntheses of (±)-α-lycorane and (+)-trianthine.

(11) Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 6783.

(12) (a) Murahashi, S.-I.; Sun, J.; Tsuda, T. *Tetrahedron Lett.* **1993**, *34*, 2645. (b) Keck, G. E.; Webb, R. R., II. *J. Am. Chem. Soc.* **1981**, *103*, 3173.

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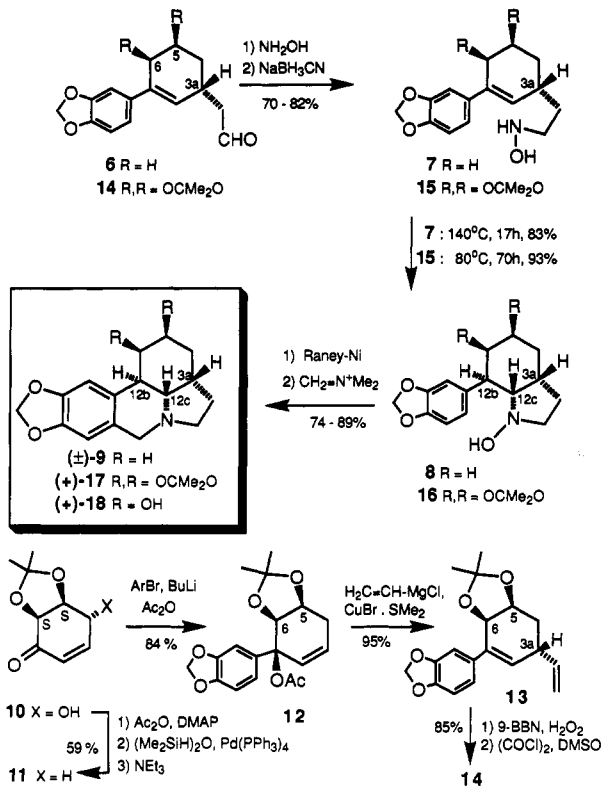
Scheme 3



pioneering work of Hudlicky et al.,[14] commercially available (1*S*,2*S*)-3-chlorocyclohexa-3,5-diene-1,2-diol was converted to enantiomerically pure 4-hydroxycyclohexenone **10** (60% overall). *O*-Acetylation of **10** (90%) and efficient deacetoxylation with 1,1,3,3-tetramethyldisiloxane in the presence of $Pd(PPh_3)_4$ (2.5 mol %, CH_2Cl_2, reflux, 27 h)[15] gave a mixture of α,β- and β,γ-unsaturated enones; *in situ* isomerization with Et_3N (1 equiv, CH_2Cl_2, reflux, 1 h), flash chromatography (FC), and crystallization (pentane/AcOEt) yielded pure (*S*,*S*)-enone **11** (66%, mp 82–83 °C). Enone **11** underwent smooth 1,2-addition/alkoxide trapping by successive treatment with (3,4-(methylenedioxy)phenyl)lithium (Et_2O/THF, −78 °C → 0 °C) and Ac_2O (0 °C → room temperature) to give, after FC and crystallization (Et_2O), allylic acetate **12** as a single stereoisomer (84%, mp 115–116 °C). *Anti*-selective S_N2' substitution of allylic acetate **12** with vinylmagnesium chloride/CuBr·SMe_2 afforded exclusively *trans*-vinylcyclohexene **13** (95%). Hydroboration/oxidation of the vinyl group in **13** gave cyclohexenylacetaldehyde **14** (85%), which after oximation and oxime reduction ($NaBH_3CN$, pH = 3) furnished (*trans*-cyclohexenylethyl)hydroxylamine **15** (82% from crude **14**).

Hydroxylamine **15** was then subjected to the crucial retro-Cope elimination step. Heating a 0.01 M solution in degassed benzene under argon at reflux for 70 h provided cyclization product **16** as the only stereoisomer in 93% yield.[16] Cleavage of the N–O bond in **16** (Raney-Ni, wet Et_2O[12a]), followed by Pictet–Spengler cyclization[12b] (Eschenmoser's salt, THF, 40 °C, 15 h), gave the isopropylidene-protected alkaloid **17** (89% from **16** (Et_2O/pentane): mp 155–157 °C; lit.[13b] di-*O*-isopropylidene zephyranthine mp 156–157 °C). Finally, *O*-deprotection of **17** (AcCl, MeOH[17]) provided (+)-trianthine (**18**) (56%, 89% based on recovered **17**): mp (MeOH) 179–180 °C; lit.[13a] mp 205–206 °C; $[\alpha]_D$ = 49° ($CHCl_3$, *c* = 0.26, 20 °C; lit.[13a] $[\alpha]_D$ = 51.2°).[18]

This first enantioselective synthesis of (+)-trianthine (24% overall from **10**) features the use of a microbiologically derived chiral cyclohexadiene diol and a new γ-hydroxy enone deoxygenation. Moreover, it highlights the preparative potential of suprafacial alkenylhydroxylamine cyclizations which will be further explored in our laboratory.

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Supplementary Material Available: Details of preparation and analytical data including mp, IR, ^{1}H-NMR, ^{13}C-NMR, MS and $[\alpha]$ values (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) (a) (+)-Trianthine was isolated from Amaryllidaceae *Pancratium triathum* and found to be antipodal to (−)-zephyranthine: Frederik, D. M.; Murav'eva, D. A. *Khim. Prir. Soedin.* **1982**, *4*, 534. (b) (−)-Zephyranthine was isolated from *Zephyranthes candida*: Ozeki, S. *Chem. Pharm. Bull.* **1964**, *12*, 253. (c) Racemic zephyranthine/trianthine has been synthesized by Tsuda et al.: Tsuda, Y.; Sano, T.; Taga, J.; Isobe, K.; Toda, J.; Takagi, S.; Yamaki, M.; Murata, M.; Irie, H.; Tanaka, H. *J. Chem. Soc., Perkin Trans 1* **1979**, 1358.

(14) Hudlicky, T.; Luna, H.; Olivo, H. F.; Andersen, C.; Nugent, T.; Price, J. D. *J. Chem. Soc., Perkin Trans 1* **1991**, 2907.

(15) This γ-acetoxy enone deoxygenation protocol is without direct precedent. Polymethylhydrosiloxane/$Pd(PPh_3)_4$ reduces allylic acetates faster than cinnamaldehyde: Keinan, E.; Greenspoon, N. *J. Org. Chem.* **1983**, *48*, 3545.

(16) The C(3a)-epimer of **15** cyclized significantly faster (benzene, reflux, 14 h), affording the (3a*R*,12b*S*,12c*R*)-isomer of **16** in 91% yield.

(17) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131.

(18) Reported for (−)-zephyranthine: mp (dec, $C_{16}H_{19}NO_4 \cdot {}^1/_2H_2O$) 201–202 °C; $[\alpha]_D$ = −43.17 (*c* 0.47, $CHCl_3$).[13b] The ^{1}H-NMR (400 MHz) and ^{13}C-NMR spectra of synthetic **18** are identical with those of (±)-zephyranthine.[13c]