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

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The thermal cyclizations of N-alkenyldihydroxylamines (I → IV, Scheme 1), first reported by House et al. and independently discovered by us, have also been described by others. This reaction was initially proposed to occur via a radical-chain mechanism. More recently, Ciganek has postulated the retro-Cope elimination pathway I → II → III → IV in analogy to the thermal conversion of N-alkenylnaphthaquinones to cyclic N-oxides. 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-alkenyldihydroxylamines (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-alkenyldihydroxylamines 2 and 4 were prepared via C-alkylation of thiazolidine 1 with (E)- and (Z)-1-chloro-3-phenyl-2-butene, respectively, followed by thiazoline reduction, thioamidine 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-hydroxyoxypyrrolidines 3 and 5, respectively, in 81% yield and without cross-contamination (1H-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). The relative C(4)/C(5) configurations of the corresponding ethyl ester with i-Bu2AlH (1 molar equiv, −78 °C, toluene), was condensed with hydroxylamine, and the resulting oxime was reduced (NaBH3CN, pH 3) to give N-4-alkenyldihydroxylamine 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 (9H-NMR) in 83% yield. N-O-Hydrolysis of 8 (Raney-Ni, wet Et2O) and modified Pictet-Spengler ring closure (20) (E)-1-chloro-3-phenyl-2-butene, THF, room temperature, 16 h. We selected as a first target (±)-α-lycorane (9), several syntheses of which have appeared in the literature (Scheme 3).

Cyclohexenylacetaldehyde 6, readily available by reduction of the corresponding ethyl ester with (i-Bu)2AlH (1 mol equiv, −78 °C, toluene), was condensed with hydroxylamine, and the resulting oxime was reduced (NaBH3CN, pH 3) to give N-alkenyldihydroxylamine 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 (9H-NMR) in 83% yield. N-O-Hydrolysis of 8 (Raney-Ni, wet Et2O) and modified Pictet-Spengler ring closure (20) (E)-1-chloro-3-phenyl-2-butene, THF, room temperature, 16 h.

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More ambiguously, we then addressed the enantiospecific synthesis of (+)-triathianine (18) (Scheme 3).

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(10) The lycorane skeleton numbering is used for all intermediates in our syntheses of (α)-α-lycorane and (+)-triathianine.
Scheme 3

- 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.\(^\text{16}\) Cleavage of the N-O bond in 16 (Raney-Ni, wet Et\(_2\)O)\(^\text{15}\), followed by Pictet-Spengler cyclization\(^\text{12}\) (Erlenmeyer's salt, THF, 40 °C, 15 h), gave the isopropylidene-protected alkaloid 17 (89% from 16 (Et\(_2\)O/pentane): mp 155–157 °C; lit.\(^\text{13}\) di-O-isopropylidene zephyranthine mp 156–157 °C). Finally, O-deprotection of 17 (AcCl, MeOH)\(^\text{17}\) provided (+)-trianthine (18) (56%, 89% based on recovered 17): mp (MeOH) 179–180 °C; lit.\(^\text{13}\) mp 205–206 °C; [\(\alpha\)]\(_D\) = 49° (CHCl\(_3\), c = 0.26, 20 °C; lit.\(^\text{13}\) [\(\alpha\)]\(_D\) = 5.12°).\(^\text{18}\)

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

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Supplementary Material Available: Details of preparation and analytical data including mp, \(^1\)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.