

POLYENE CYCLIZATION TERMINATED BY THIOL

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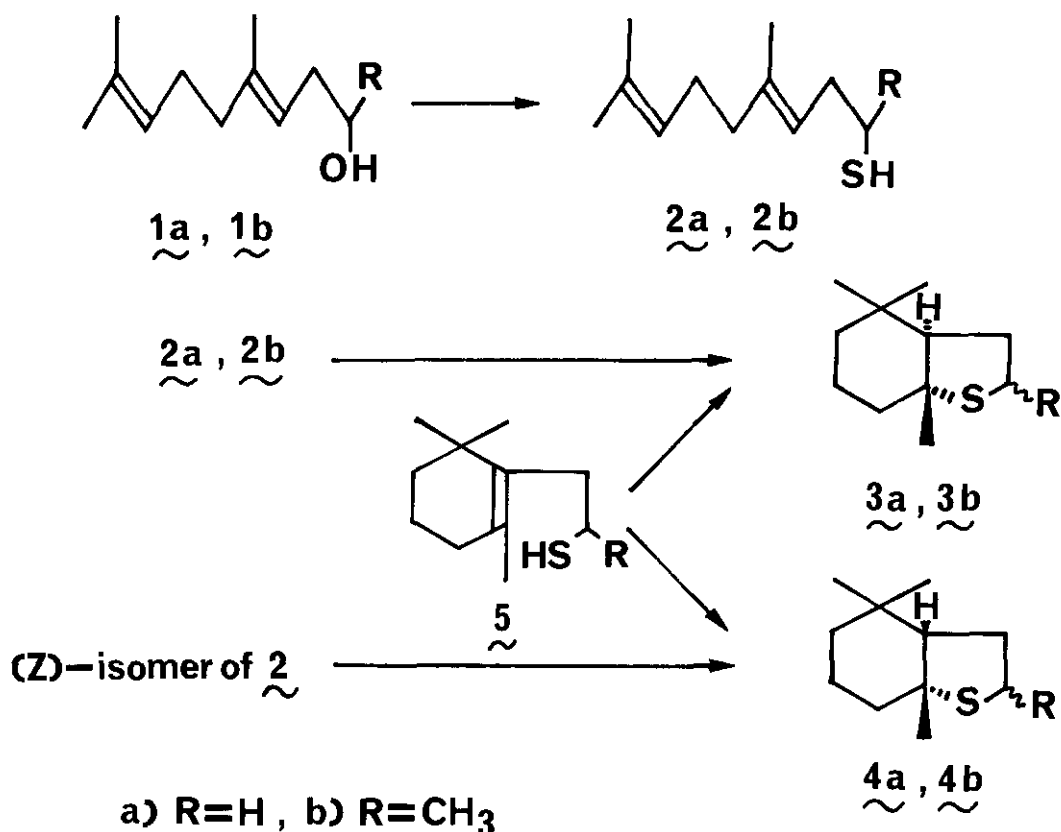
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Abstract — Acid-catalyzed cyclization of geranyl and neryl derivatives was effectively terminated by thiol, and afforded trans- and cis-fused alkyl substituted thiahydrindanes stereoselectively.

Polyene cyclization has been well-known to be one of the efficient methods for the stereoselective synthesis of polycyclic compounds.¹ We have already synthesized several polycyclic lactones stereoselectively by the acyclic polyene cyclization terminated by carboxylic acid.² Though various functional groups have been investigated as the terminator for the polyene cyclization,³ little attention has been paid for thiol.⁴ Here we report the effective termination by thiol in the acid-catalyzed cyclization of geranyl and neryl derivatives which enables the selective formation of the thiahydrindanes with the stereocontrolled ring junction.

Homogeraniol (1a) was quantitatively obtained by reduction of homogeranic acid ethyl ester with lithium aluminium hydride. After bromination of 1a, the corresponding bromide was converted via the thiuronium salt to homogeranyl thiol (2a) in 67% yield (1. PBr₃/hexane, rt, 2 h; 2. (NH₂)₂CS/H₂O, reflux, 40 min; 3. 2M-NaOH, reflux, 1 h). Thiol (2a) was purified by silica gel column chromatography (hexane:AcOEt=99.8:0.2).

Cyclization was carried out by dropwise addition of boron trifluoride etherate to a dichloromethane solution of 2a at room temperature followed by stirring at this temperature for 20 min. The usual work-up afforded trans-octahydro-4,4,7a-trimethylbenzo(b)thiophene (3a) in 68% yield as a single GC-detectable



product. The sulfide (3a) was purified by silica gel column chromatography (hexane:AcOEt=99.5:0.5) (3a: MS (m/z) 184 (M^+), $^1\text{H-NMR}(\text{CDCl}_3)$ δ =0.88(CH_3 ,s), 0.96(CH_3 ,s), 1.37(CH_3 ,s)). The trans ring fusion of 3a was characterized by the chemical shift of the two axial (at the C-4 and C-7a position) and one equatorial (at the C-4 position) methyl group in $^{13}\text{C-NMR}$ spectra ($^{13}\text{C-NMR}(\text{CDCl}_3)$ δ =20.5, 25.2, and 33.9 respectively). In contrast, the cyclization of (3Z)-isomer of 2a afforded the cis isomer (4a) stereoselectively in 55% yield under the same conditions (4a: MS (m/z) 184 (M^+), $^1\text{H-NMR}(\text{CDCl}_3)$ δ =0.90(CH_3 ,s), 0.98(CH_3 ,s), 1.43(CH_3 ,s), $^{13}\text{C-NMR}(\text{CDCl}_3)$ δ =28.5, 28.8, and 30.2 (due to three methyl groups)).

Cyclization of the monocyclic derivative was also examined. Under the same reaction conditions, cyclization of 5 (R=H) proceeded nonstereoselectively to afford a 7:3 mixture of 3a and 4a in 52% yield. Therefore, it was shown that the cyclization of 2a and its (3Z)-isomer proceeded without forming 5 as an intermediate and the cyclization of acyclic polyenic thiol was apparently more

efficient for stereoselective synthesis of the bicyclic sulfide than that of monocyclic one.

Termination by the secondary thiol was also investigated. Dienol (1b) was quantitatively obtained by reduction with lithium aluminium hydride of the corresponding ketone which was prepared by the coupling of geranyl cyanide with methyl lithium, or by the alkylation of 2-methyl-1,3-dithiane with geranyl chloride followed by oxidative hydrolysis. Thiol (2b) was obtained in 79% yield by mesylation of 1b followed by thioetherification and reduction (1. $\text{MsCl}/\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$, -10°C , 20 min; 2. $\text{C}_6\text{H}_5\text{CH}_2\text{SNa}/\text{THF}$, reflux, 40 min; 3. Na/NH_3 , -78°C , 20 min). The purification and the cyclization of 2b were carried out by the same manner as the case of 2a. As a result, 3b was obtained in 53% yield as a 3:2 mixture of the epimers at the C-2 position. Two epimers were separated by silica gel column chromatography (hexane:AcOEt=99.5:0.5) (the major epimer of 3b: MS (m/z) 198 (M^+), $^1\text{H-NMR}(\text{CDCl}_3)$ $\delta=0.85(\text{CH}_3, \text{s})$, $0.94(\text{CH}_3, \text{s})$, $1.29(\text{CH}_3, \text{d}, J=6 \text{ Hz})$, $1.38(\text{CH}_3, \text{s})$; the minor one: MS (m/e) 198 (M^+), $^1\text{H-NMR}(\text{CDCl}_3)$ $\delta=0.87(\text{CH}_3, \text{s})$, $0.94(\text{CH}_3, \text{s})$, $1.40(\text{CH}_3, \text{d}, J=6 \text{ Hz})$, $1.43(\text{CH}_3, \text{s})$. The trans ring fusion of the two epimers was also characterized by the chemical shift of the three methyl groups at the C-7a and C-4 position ($^{13}\text{C-NMR}(\text{CDCl}_3)$ the major epimer: $\delta=20.4$, 25.1 , and 33.8 ; the minor epimer: $\delta=20.8$, 27.1 , 33.9). The cyclization of the (4Z)-isomer of 2b also afforded the cis-fused bicyclic sulfide 4b in 44% yield as a 3:2 mixture of the epimers at the C-2 position (the major epimer of 4b: MS (m/z) 198 (M^+), $^1\text{H-NMR}(\text{CDCl}_3)$ $\delta=0.95(\text{CH}_3, \text{s})$, $1.05(\text{CH}_3, \text{s})$, $1.30(\text{CH}_3, \text{d}, J=6 \text{ Hz})$, $1.50(\text{CH}_3, \text{s})$; the minor one: MS (m/z) 198 (M^+), $^1\text{H-NMR}(\text{CDCl}_3)$ $\delta=0.92(\text{CH}_3, \text{s})$, $1.06(\text{CH}_3, \text{s})$, $1.27(\text{CH}_3, \text{d}, J=6 \text{ Hz})$, $1.49(\text{CH}_3, \text{s})$). It was shown that the termination by the secondary thiol was also efficient for the synthesis of the bicyclic sulfides (3a) and (4b) with the stereocontrolled ring fusion, but could not control the stereochemistry at the C-2 substituent.

In this work it was proved that thiol behaves as an effective cation trapping nucleophile, and the acid-catalyzed cyclization of acyclic polyene terminated by thiol is one of the useful synthetic methods for the trans- and cis-fused alkyl substituted bicyclic sulfides which have often been found in mineral resources.^{5,6}

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Received, 29th July, 1985