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Synthesis of α-Hydroxy-Tetradehydrocularines

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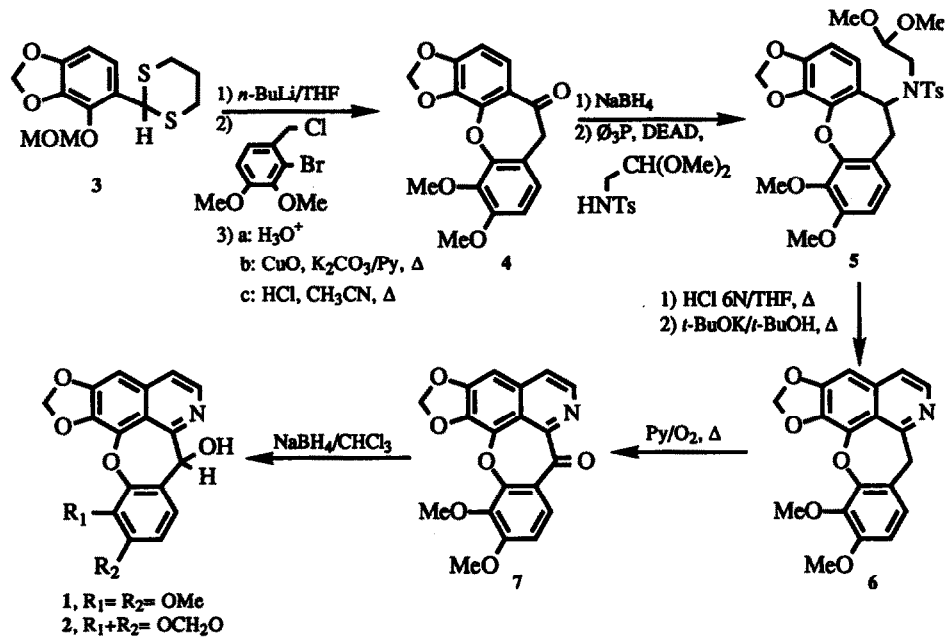
Abstract: The first total synthesis of an α-hydroxytetradehydrocularine is described. The synthesis was based on the construction of a dibenzoxepinone followed by assembly of the isoquinoline heteroring. As a result, the structure of the alkaloid linaresine should be revised.

Recently, the α-hydroxy-tetradehydrocularine structures **1** and **2** were respectively proposed for the alkaloids linaresine[1] and sauvagnine[2] on the basis of spectroscopic evidence. They not only have an anomalous substitution pattern, but also originate from different plant sources than current cularines.[3] Furthermore, a unique biogenetic origin from protoberberines (and thus differing from that of the usual cularines) was proposed for linaresine.[1]

In view of these novelties, we undertook the total synthesis of **1** using the dibenzoxepinone **4** as the key intermediate upon which the isoquinoline heteroring can be constructed.



The ketone **4**[4] was prepared in 29% overall yield using our recently reported method[5] based on the benzylation of the anion derived from dithiane **3**, followed by deprotection of the methoxymethyl ether, Ullmann reaction and hydrolysis of the dithiane.

The assembly of the isoquinoline heteroring on dibenzoxepinones has been previously carried out by a Pomerantz-Fritsch cyclisation, which takes place in very low yield (8%).[6] We have overcome this difficulty by preparing the ketal **5** by an alternative procedure based on the Mitsunobu reaction of the alcohol derived from **4** with $HN(Ts)CH_2CH(OMe)_2$.[7] Acid cyclisation of compound **5** (6N HCl/dioxane, reflux 1h) followed by basic treatment (*t*-BuOK/*t*-BuOH, reflux 3h) afforded **6** (33%) along with a large amount of the oxepine derived from elimination of the side chain (45%). Product **6** was refluxed for 23h in dry pyridine under O_2 to yield the oxoderivative **7** in 67% yield. Finally, compound **1**[8] was obtained by $NaBH_4$ reduction of **7** in anhydrous $CHCl_3$.

Comparision of the spectra of **1** (^1H NMR, MS, IR, UV) with those of linaresine[9] showed notable differences, thus proving that the proposed structure of linaresine should be revised. Furthermore, our synthetic α-hydroxy derivative **1** is rather unstable, being easily oxidized by air to the oxocompound **7**, which suggests that any α-hydroxy-tetradehydrocularines present in natural sources might not survive the isolation process. These findings also strongly suggest the necessity of revising the structure **2** proposed for sauvagnine.

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7. 0.5 gr of $Ø_3P$ and 0.41 gr of $HN(Ts)CH_2CH(OMe)_2$ are dissolved in 10 ml of dry THF under Ar; to this solution are sequentially added 0.2 g of the alcohol and 0.24 mL of DEAD, and the resulting mixture is stirred for 3h; then the solvent is concentrated and the residue is washed with 10% NaOH (5 x 15 mL) and water; the crude so obtained is chromatographed (SiO_2; 2:3, AcOEt: hexane), affording 0.21 g (60%) of compound **5**.
8. **1**: ^1H NMR (250 MHz, CD_3CN): 3.81 (s, 3H, OMe), 3.87 (s, 3H, OMe), 6.13 (s, 1H), 6.24 (s, 2H, O-CH_2-O), 6.47 (s, 1H), 6.88 (d, J= 8.6, 1H, Ar-H), 7.07 (s 1H, ArH), 7.32 (d, J= 8.6, 1H, Ar-H), 7.53 (d, J= 5.7, 1H, ArH), 8.20 (d, J= 5.7, 1H, ArH).
   ^{13}C NMR (62.83 Mz, $CDCl_3$): 56.3 (CH_3), 61.8 (CH_3), 69.2 (CH-OH), 99.6 (CH), 102.6 (CH_2), 109.3 (CH), 117.6 (C), 118.6 (CH), 120.5 (CH), 130.3 (C), 135.5 (C), 135.8 (C), 138.9 (CH), 141.3 (C), 142.7 (C), 147.7 (C), 152.3 (C), 152.9 (C), 154.6 (C). IR ($CHCl_3$), ν_{max}: 3300, 3010, 2940, 1500, 1455, 1275, 1200. UV ($CHCl_3$), λ_{max}: 284, 320, 332 nm. MS (m/z, %): 353 (M^+, 37), 352 (36), 324 (100), 322 (31), 308 (26), 280 (14).
9. We thank Prof. M. Shamma and Prof. H. Guinaudeau, who kindly supplied copies of the spectra of linaresine.

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