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Total Synthesis of dl-Metaphanine

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In the series of our investigations on total syntheses of hasubanan alkaloids, we have reported synthesis of dl-cepharamine[1] and dl-hasubanonine[2]. Among hasubanan alkaloids, metaphanine[3] is remarkable for possessing a hemiketal ring in the molecule, and we wish to report total synthesis of dl-metaphanine in this communication.

Oxidation of the compound (3)*1, m.p. 235-7°*2 prepared via ketalization of the previously reported acetoxy ketone (2b)[2] with chromic anhydride in aqueous acetic acid afforded quantitatively the C_{10}-oxo derivative (4), m.p. 232-3°, ν_{max} 1768, 1755, 1690 and 1599 cm^{-1}. Hydrolysis of 4 under the basic condition, followed by treatment with diazomethane gave the ketal-alcohol (6), m.p. 253-4°, ν_{max} 3560, 1682 and 1590 cm^{-1}, in a 92% yield. In our synthetic approach, it is necessary to introduce a 10-hydroxy group trans to the ethanamine bridge via the 10-oxo derivatives for the intramolecular hemiketal ring formation. Reduction of 6 with $NaBH_4$ in MeOH, followed by acetylation afforded the cis-hydroxy derivative (7)*3, m.p. 235-6°, ν_{max} 3580, 1726, and 1677 cm^{-1}, n.m.r. τ 7.92 (3H, s.), 6.48 (1H, d., J=1.5 Hz, >C<u>H</u>-OH), and 3.97 (1H, q., J=3 Hz, δ_{AB}=2 Hz, >C<u>H</u>-OAc), in the highly selective manner (75%) and a very small amount of the desired trans-alcohol (8), (< 6%), m.p. 138-9°, ν_{max} 3580, 1730, and 1678 cm^{-1}, n.m.r. τ 7.72 (3H, s.), 6.48 (1H, d., J=1.5 Hz, >C<u>H</u>-OH), 4.25 (1H, q., J=7 Hz, δ_{AB}=3 Hz, >C<u>H</u>-OAc), was isolated from the column chromatography of the mother liquor from filtration of 7. Using i-PrOH or aqueous t-BuOH-i-PrOH as the solvent in this reduction was observed the slight improvement of the yield of 8 (<35%). Reduction of 6 with $LiAlH_4$

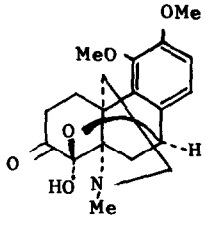
in ether or with $NaAlH_2(OCH_2CH_2OCH_3)_2$ in benzene also exclusively gave the undesired cis-amino-alcohol (9), m.p. 194-5°, ν_{max} 3550 cm^{-1}, n.m.r. τ 6.45 (1H, d., J=1.5 Hz, >C<u>H</u>-OH) and 5.50 (1H, q., J=2.5 Hz, δ_{AB}=2 Hz, >C<u>H</u>-OH). Treatment of 6 with Na in amyl alcohol or t-BuOH, followed by acetylation yielded 8, 7, and 6 in 2:1:1 ratio but the yield was rather poor. Finally, Meerwein-Ponndorf reduction in which 6 was refluxed with aluminum isopropoxide in toluene and i-PrOH was successfully employed, wherein the desired trans alcohol (10), m.p. >300°, was obtained stereoselectively and quantitatively. The diol (10) was then transformed into monopyranyl ether (11), m.p. 184-5°, ν_{max} 3540, 3400, and 1673 cm^{-1}, m/e 489 (M^+), by treatment with p-TsOH and dihydropyran in CH_2Cl_2. Subsequently, the compound (11) was reduced to the oily amine (12), ν_{max} 3540 cm^{-1}, with $LiAlH_4$ and oxidation of C_8-OH of 12 was then examined but all trials were unfruitful.

At this point, we directed our attention to construct the hemiketal ring prior to reduction of the amide group. Thus, oxidation of 11 with Collins' bispyridine-chromium (VI) oxide reagent, followed by acidic hydrolysis in aqueous acetic acid at 50-55° afforded the hemiketal derivative (13), m.p.> 300°, ν_{max} 3540 and 1675 cm^{-1}, in a 68% yield. All attempts to protect the C_8-hemiketal hydroxy group by various procedures, however, were unsuccessful and P_2S_5-Raney Ni reduction[4] of 13 also failed. Reduction of 13 itself with $LiAlH_4$ in ether under mild condition gave the desired product (15), m.p. 215°, ν_{max} 3550 cm^{-1}, n.m.r. τ 7.15 (1H, O<u>H</u>) and 5.08 (1H, d., J=6.5 Hz, C_{10}-<u>H</u>), in a low yield (< 18%) and the diol amine (14), m.p. 127-9°, ν_{max} 3540 cm^{-1}, n.m.r. τ 6.45 (1H, d., J=1.5 Hz, C_8-<u>H</u>) and 5.26 (1H, q., J=6.5 Hz, δ_{AB}=3 Hz, C_{10}-<u>H</u>) in a 52% yield but the yield of 15 was unfixed. The selective reduction of the amide group by the Borch's procedure[5] was then made on the γ-lactam (13). Thus, treatment of 13 with one equivalent of $Et_3O^+ \cdot BF_4^-$ in CH_2Cl_2 at room temperature resulted in the imino ether fluoborate which without isolation was reduced with excess $NaBH_4$ in EtOH to give the amine (15) in a 50% yield (28% of 13 was recovered).

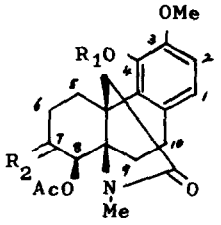
Finally, deketalization of 15 with c-HCl-MeOH afforded dl-metaphanine (16), m.p. 205-6°, (Anal. Calcd. for $C_{19}H_{23}O_5N$; C, 66.07; H, 6.71; N, 4.06.

Found: C, 65.87; H, 6.76; N, 4.11), in a 53 % yield.

The synthetic dl-metaphanine was proved to be completely identical with natural metaphanine in terms of their i.r., n.m.r., and mass spectra, and t.l.c. behabior.



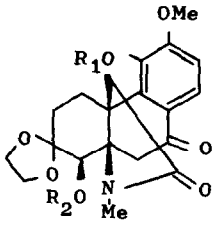
(1)



(2a) R_1=Me, R_2=O

(2b) R_1=Ac, R_2=O

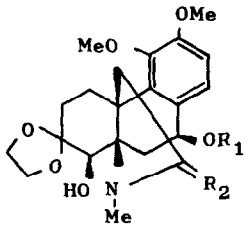
(3) R_1=Ac, R_2=



(4) R_1=R_2=Ac

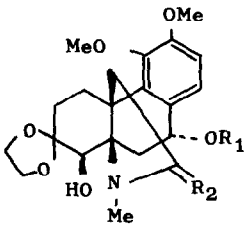
(5) R_1=R_2=H

(6) R_1=Me, R_2=H



(7) R_1=Ac, R_2=O

(9) R_1=H, R_2=H_2



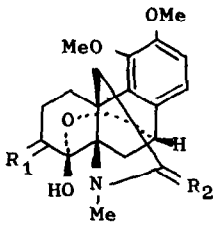
(8) R_1=Ac, R_2=O

(10) R_1=H, R_2=O

(11) R_1=THP, R_2=O

(12) R_1=THP, R_2=H_2

(14) R_1=H, R_2=H_2



(13) R_1=, R_2=O

(15) R_1=, R_2=H_2

(16) R_1=O, R_2=H_2

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REMARKS and REFERENCES

*1 Oxidation of the compound (2a) did not give the compound (6: R_1=Me, R_2=Ac) in satisfactory yield. Stereochemistry with regard to the C_8-hydroxy group will be stated in a full paper.

*2 All compounds reported in this communication gave satisfactory analyses.

*3 Stereochemistry with regard to the C_{10}-hydroxy group was estimated by comparing the n.m.r. signal coupling patterns of a methine proton geminal to the C_{10}-acetoxy group in synthetic compounds with those of compounds derived from natural metaphanine. The conclusive evidence came from the hemiketal ring formation in the subsequent synthetic step.

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