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STEREOSPECIFIC SYNTHESIS AND STEREOCHEMICAL STRUCTURE CONFIRMATION OF DUMETORINE[1].

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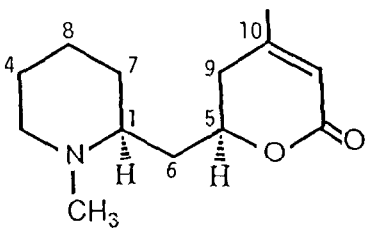
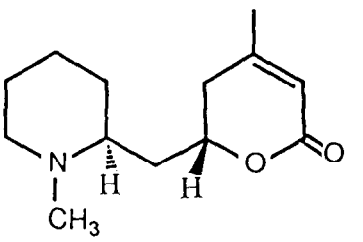
Abstract. A short stereospecific route to the alkaloid dumetorine 1 and its 5-epimer 2 is presented. This provides the first reported synthesis of this new alkaloid as well as stereochemical confirmation of its structure.

(+)Dumetorine, an alkaloid accompanying dioscorine, was recently isolated from tubers of *Dioscorea dumetorum* Pax, a plant used by natives in Africa for medicinal purposes[2]. Based on extensive NMR studies, dumetorine was identified as 1 and the indicated syn (erythro) configuration was proposed on the basis of optical rotation additivities[2]. We now confirm structure 1 for dumetorine by unequivocal stereospecific synthesis of (±)1 and its epimer 2.

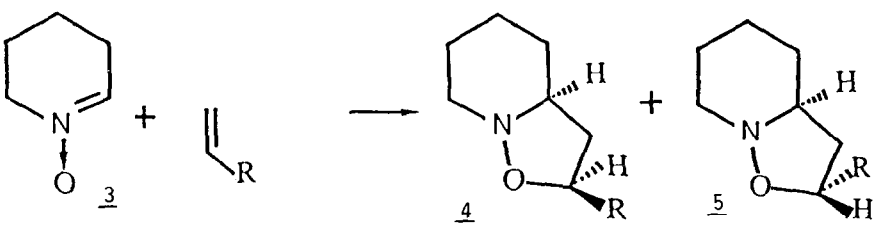


Dumetorine 1

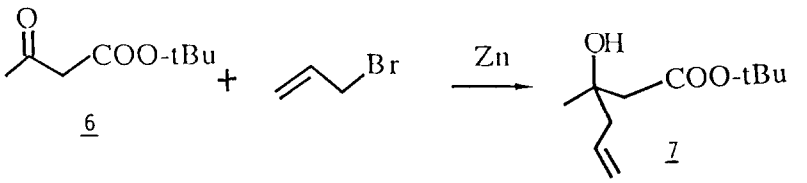


2

Our interest in stereospecific 1,3-dipolar cycloadditions[1,3] led us to consider a nitrone-olefin cycloaddition as an approach to the regiospecific and stereospecific introduction of the two stereochemical centers in 1. It had been shown[4] that dipolar cycloaddition of cyclic nitrone 3 with α,β-unsaturated carbonyl compounds leads to a mixture of 4 and 5 (e.g. R = CO_2Me) in which the syn adduct 4 predominates. The latter could be a useful building block of dumetorine. Nevertheless, we decided in favor of a more convergent approach (see Scheme 1). This has the advantage of utilizing the completely stereospecific cycloaddition[4,5] of non-conjugated terminal olefins to nitrone 3 leading to 5 with the opposite stereochemistry (anti) to that found in dumetorine, even though it requires an epimerization step at the CH-O center. At the same time 5-epidumetorine 2 became accessible for comparison.

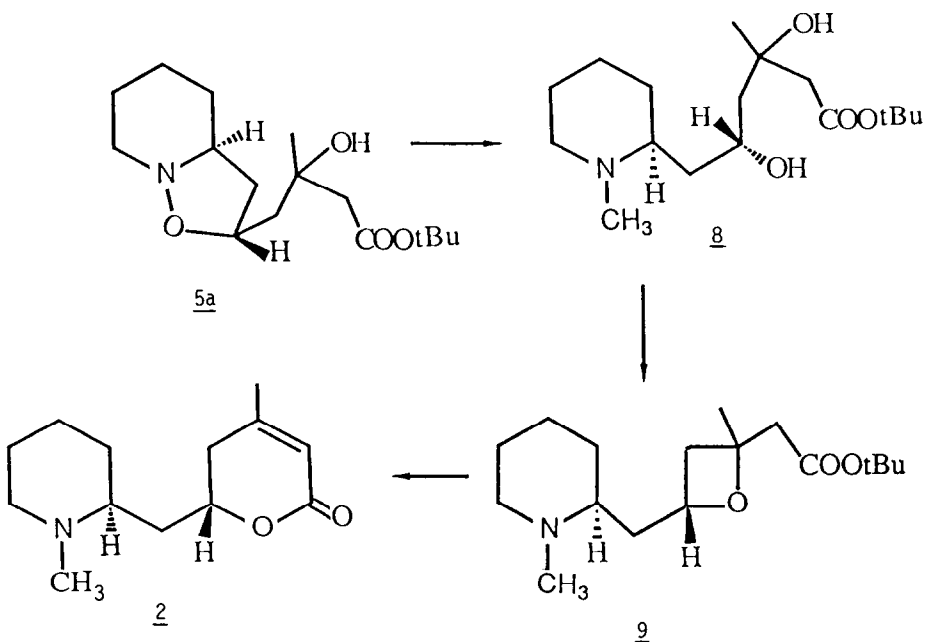


Reaction of allyl bromide with Zn in the presence of t-butyl acetoacetate 6 at room temperature provided in 70% yield the olefin 7, [6] which underwent regio- and stereospecific cycloaddition to 3 to give exclusively the anti adduct 5a as two diastereomers[7] in 72% yield.



6 7

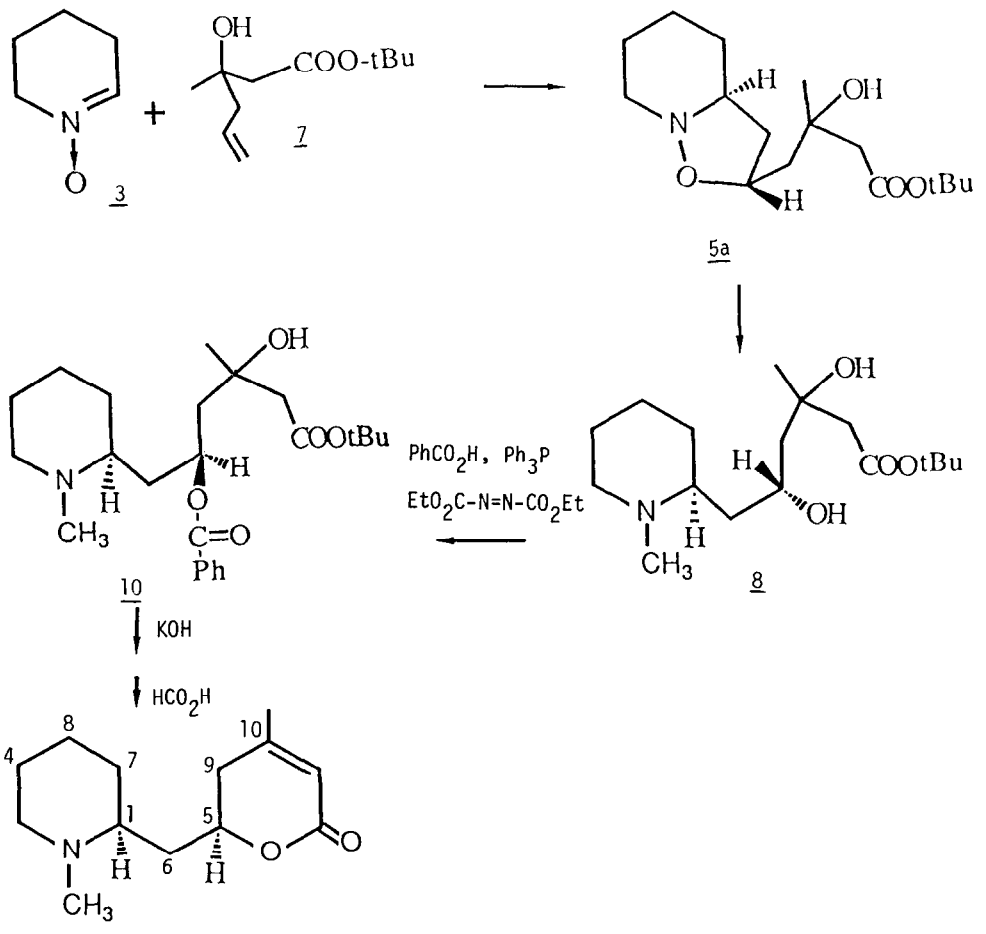
Methylation with methyl iodide followed by zinc, reduction in 50% aqueous acetic acid led to amino diol 8 in 78% as a mixture of diastereomers due to the tertiary hydroxyl center but containing carbons 1 and 5 in the stereospecific array indicated.[2] Attempts to remove the t-butyl protecting group under standard conditions (HCO_2H at room temperature) led to formation of oxetane 9 as a single isomer. Apparently 9 resulted from internal trapping of a tertiary carbocation by the secondary alcohol. Further heating of oxetane 9 in formic acid proceeded via hydrolysis of the t-butyl ester, ring opening with elimination and lactonization to afford 5-epidumetorine 2 in 65% yield.



5a 8 2 9

(±)Dumetorine 1 was obtained from diol 8 by an inversion of C-5 according to the Mitsunobu procedure[8]. The resulting benzoate 10 (57%) which already contained the desired stereochemistry, was saponified (82%) and converted to dumetorine 1 in 50% yield by heating with formic acid. The product was identical by ^{1}H and ^{13}C-NMR to natural dumetorine[9]. 5-Epidumetorine 2 exhibited almost identical spectra except for a few characteristic differences[7]. For instance, C-5 absorbs at 73.3 ppm in dumetorine 1 and at 75.96 in the 5-epimer 2. In the ^{1}H-NMR the C-5 proton appears at 4.53 as an 8 line signal in 1, whereas it is found at 4.50 as a 6-line multiplet in 2. Our short and stereospecific approach to 1 and 2 provides the first reported synthesis of dumetorine, as well as confirmation of its stereochemical assignment.

Scheme 1



Dumetorine 1

Acknowledgement: This research was supported by a grant from the Israel Academy of Sciences and Humanities.

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5. E. Gössinger, Tetrahedron Lett. 2229 (1980).
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7. Characteristic NMR data (in $CDCl_3$, ^1H-300 MHz, ^{13}C-75 MHz):
   5a (1:1 mixture) ^1H-1.28 and 1.31 (2s,Me), 1.46 (brs, ^tBu) 3.43 (brd, J=10 Hz, C-6, 2H), 3.87 (m,C-1,1H), 4.28 (m,C-5,1H). ^{13}C-23.84, 24.75, 27.07, 27.38, 28.10, 29.28, 41.38, 46.18, 46.41, 46.88, 47.30, 55.22, 66.18, 70.64, 70.79, 72.78, 73.05, 80.98, 81.12, 172.01.
   8 (1:1 mixture) ^1H-1.29 (s,Me), 1.45 and 1.46 (2s,^tBu) 2.34 (s,Me), 2.90 (brd, J=12 Hz, C-1,1H), 4.48 (m,C-5,1H). ^{13}C-24.27, 25.47, 28.08, 28.28, 29.56, 37.39, 46.57, 46.83, 57.09, 62.54, 67.08, 71.68, 80.39, 171.86.
   10 ^1H (1:1 mixture) ^1H-1.28 and 1.29 (2s,Me), 2.61 (s,Me) 3.13 (brd,J=12 Hz, C-1;1H), 5.42 (m,C-5,1H), 7.45 and 8.05 (m,Ph).
   2 ^1H-1.98 (s,C-13 Me), 2.28 (s,N-Me), 2.86 (t,d,J=4,12 Hz, C-1H) 4.50 (6 line multiplet, C-5H), 5.80 (brs,C-11,1H), 1.26-2.30 (m, remaining H's). ^{13}C-22.96(q), 23.84(t), 24.92(t), 31.51(t) 35.27(t), 38.54(t), 42.58(q), 56.23(t), 60.08(d), 75.96(d), 116.53(d), 156.82(s), 165.14(s).
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9. We thank Dr. M.S. Tempesta for detailed spectra of dumetorine used in the comparison.

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