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Syntheses of (–)-(2*R*,3*R*,6*S*)-Irnigaine and (+)-(2*R*,3*R*,6*S*)-N-Methylirnigaine

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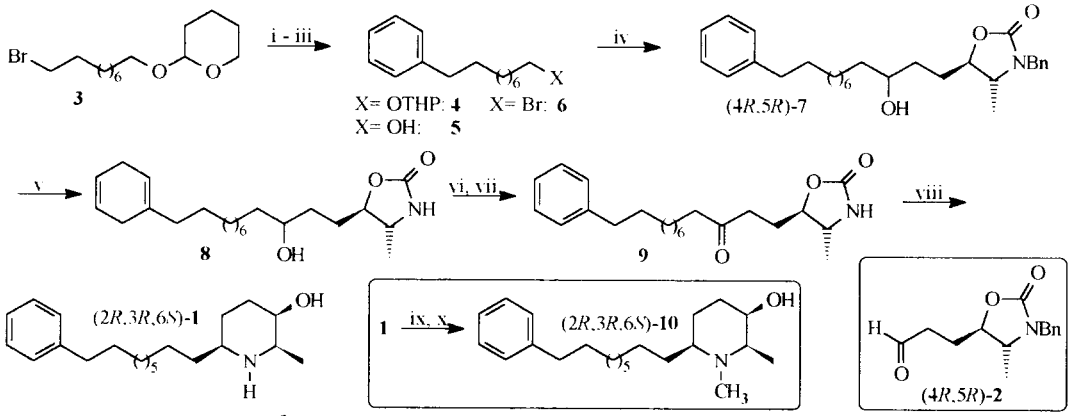
Abstract: Syntheses of irnigaine **1** and the N-methyl derivative **10** were performed starting from chiral building block **2**. Synthetic and spectroscopic data are given including the absolute structure of **1** by an X-ray structure of the hydrochloride. © 1998 Elsevier Science Ltd. All rights reserved.

The alkaloid irnigaine **1** was first described in 1995 by Melhaoui and Bodo and is a recent representative of the group of 2,6-disubstituted 3-piperidinols. It was isolated in small amounts from the tubers of *Arisarum vulgare* (Araceae). The biological activity was examined, its structure and relative configuration were elucidated and the absolute configuration was proposed on the basis of its optical rotation.[1]

Since the assignment of the absolute configuration was in contradiction to previous results from our group regarding this class of all-cis-piperidinols[2,3] we decided to synthesize (2*R*,3*R*,6*S*)-**1**[4] and also (2*R*,3*R*,6*S*)-**10** according to Scheme 1.



i) 0.2 eq LiCl, 0.1 eq $CuCl_2$, 1 eq **3**,[5] 2.5 eq PhMgBr, THF, 0°C → rt, 24h, FC, 93%. ii) MeOH, cat. HCl, RF, 1h, FC, 99%. iii) 1.1 eq CBr_4, 1.15 eq PPh_3, DCM, 0°C, 1h, FC, 100%. iv) 1.4 eq **6**, Mg, THF, 1h RF → rt, 1.0 eq (4*R*,5*R*)-**2**,[2] rt, 45min, FC, 87%. v) 12 eq ^{t}BuOH, 10 eq Li, $EtNH_2$, 1h -78°C → rt, FC, 96%. vi) 1.5 eq DDQ, $PhCH_3$, 100°C, 24h, FC (Alox N, then SiO_2), 78% (contains ~12% **9**). vii) 0.67 eq Jones' reagent, acetone, 0°C, 5min, FC, 91%. viii) 10 eq 2N NaOH, EtOH, RF, 3.5h; 10% Pd/C, MeOH, H_2, 14h, rt, 90% (2 steps), 1.43g. ix) 3 eq Et_3N, 2 eq Boc_2O, DMF, 60°C, 2h, FC, 88%. x) 5 eq $LiAlH_4$, RF, 14h, FC, 60%.

Scheme 1. Syntheses of (2*R*,3*R*,6*S*)-irnigaine **1** and of N-methylirnigaine (2*R*,3*R*,6*S*)-**10**.[6]

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Whereas the natural occurring alkaloids have often been isolated on a mg scale we obtained (2*R*,3*R*,6*S*)-**1** on a gram scale (1.43g, 6 steps, 53% overall yield starting from **2**). The X-ray structure of the hydrochloride of **1**[7] (Figure 1) represents the correct absolute configuration of the molecule and is independent evidence for the (–)-(2*R*,3*R*,6*S*)-configuration of **1** and, respectively, for the (+)-(2*R*,3*R*,6*S*)-configuration of **10**. With these results at hand, the (2*S*,3*S*,6*R*)-configuration suggested in the literature for the isolated alkaloids seems to be questionable. The Table shows that derivatives of irnigaine display great varieties in their optical rotations. A determination of absolute configuration of the free base irnigaine **1** by correlation of its optical rotation to that of the hydrochloride of the piperidinol cassine[8] is clearly not possible, and leads to the questionable results. Inconsistently the rotatory data of the natural derivatives would have suggested that irnigaine and N-methylirnigaine belong to different stereochemical families, which is unlikely for biogenetic reasons.

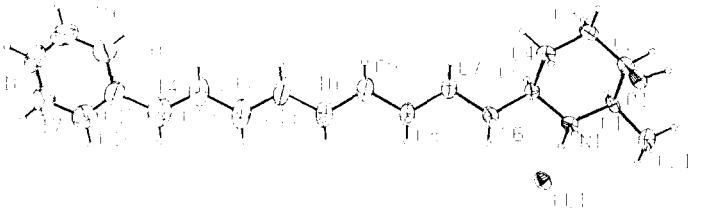

Figure 1. X-ray crystal structure of (2*R*,3*R*,6*S*)-**1** · HCl.

	$[\alpha]_D^{20}$ ($CHCl_3$)	
	synthesized (2*R*,3*R*,6*S*)	isolated from natural source
1	-9.2° (c= 1.085)	-14° (c= 0.3)
1 · HCl	+2.84 (c= 0.95)	—
10	+15.41 (c= 1.22)	-8.0 (c= 5.0)
10 · HCl	+6.53 (c= 1.01)	—

This is probably a result of the difficulties of isolating pure natural materials in small amounts, so these inconsistencies can only be resolved after isolation of further material. Consequently a clearcut assignment of absolute configurations to the natural products is not possible at present.

References and Notes

1. Melhaoui, A.; Bodo, B. *Natural Prod. Lett.* **1995**, 7, 101.
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3. Oetting, J.; Holzkamp, J.; Pahl, A.; Meyer, H.H. *Tetrahedron Asymm.* **1997**, 8(3), 477.
4. Spectroscopic data for **1**: 2-Methyl-6-(9'-phenyl-nonyl)-piperidin-3-ol $C_{21}H_{35}NO$ (317.51). ^1H NMR (400MHz, $CDCl_3$): δ= 1.09 (d, ^3J= 6.4Hz; 3H, 2-CCH_3), 1.21–1.39, 1.41–1.53 (2m; 17H, 4-CH_{ax}, 5-CH_2, 1'–7'-CH_2), 1.60 (quint, ^3J= 7.2Hz; 2H, 8'-CH_2), 1.89 (dq, ^2J= 14.7Hz, ^3J= 2.9Hz; 1H, 4-CH_{eq}), 2.47–2.56 (m; 1H, 6-$CH_{ax}N$), 2.60 (t, ^3J= 7.7Hz; 2H, 9'-CH_2), 2.74 (dq, ^3J= 1.5, 6.6Hz; 1H, 2-$CH_{ax}N$), 3.54 (sb; 1H, 3-$CH_{eq}O$), 7.14–7.20, 7.24–7.30 (2m; 5H, Ar-CH) ppm. ^{13}C NMR (100MHz, DEPT, $CDCl_3$): δ= 18.78 (4-CCH_3), 25.83, 26.24, 29.32, 29.49, 29.51, 29.57, 29.81, 31.51, 32.11, 37.10 (4–5-CH_2, 1'–8'-CH_2), 35.99 (9'-CH_2), 55.77 (6-CHN), 57.20 (2-CHN), 68.07 (3-CHO), 125.55, 128.21, 128.39 (Ar-CH), 142.92 (Ar-C_q) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3460, 3024, 2928, 2856, 1496, 1464, 1436, 1392, 1264, 1116, 1092 cm^{-1}. MS (50°C): m/e= 317 (1), 316 (5, M^+), 258 (2), 114 (100), 96 (10), 91 (22). HRMS: calc. for $C_{21}H_{35}NO$: 317.2719; found: 317.2720.
5. Side chain building block **3** was synthesized according to lit.[2] and reference cited therein.
6. All synthetic intermediates were fully characterized and gave satisfactory analytical and spectroscopic data.
7. Crystal data for **1**: $C_{21}H_{36}ClNO$ (353.96); monoclinic; space group: P 21(no. 4); a, b, c [Å]: 7.912(2), 8.097(2), 17.130(3); β: 92.77(2)°; V= 1096.1(4)Å^3; Z= 2; D_c= 1.072g/cm^3; T= 300K; 2θ range: 4.7 to 48.1°; data observed ($I_0>2\sigma(I_0)$): 1682; R_1= 0.0375; wR_2= 0.0548; Flack x: -0.10(6); Complete crystallographic data were deposited as supplementary publication no. CCDC-101053 and can be obtained under the following address from the Cambridge Crystallographic Data Centre in Great Britain: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +(1223) 336-033; deposit@ccdc.cam.ac.uk.
8. Rice, W.Y.jr.; Coke J.L. *J. Org. Chem.* **1966**, 31, 1010.