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NOVEL STEREOSELECTIVE SYNTHESIS OF CHIRAL NONRACEMIC *cis*- AND *trans*-3-ALKYL-4-AMINOPIPERIDINES

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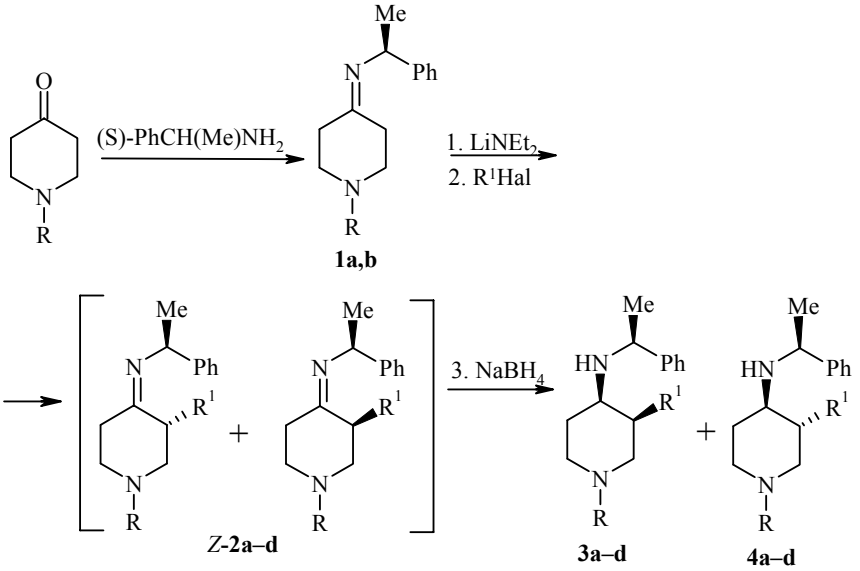
We have shown that previously unknown optically pure *trans*-(*3R,4R*) isomers **4a-d** with diastereomeric excess *de* > 99% and the diastereomeric pair of *cis*-(*3S,4R*),-(*3R,4S*) isomers **3a-d** with *de* < 71% of N-[(1*S*)-1-phenylethyl]-4-amino-1,3-dialkylpiperidine are formed in 46%-90% yield by sequential lithiation and alkylation by alkyl halides of the chiral imines **1a,b,** with formation of *Z*-(3*S*)-3-alkyl- and *Z*-(*3R*)-3-alkylimines **2a-d** followed by their reduction by sodium borohydride in ethanol. The entire reaction sequence is carried out with no isolation of intermediates.

The *cis* isomers **3a-d** and the *trans* isomers **4a-d** were separated by column chromatography on aluminum oxide; their structure and diastereomeric purity were established from elemental analysis, chromato-mass spectrometry, and ^{1}H, ^{13}C NMR spectra. The *cis* and *trans* structure of isomers **3a-d** and **4a-d** was established by analysis of the vicinal spin–spin coupling constants for the 3-H and 4-H protons of the piperidine ring, using high-resolution one-dimensional and two-dimensional ^{1}H NMR spectroscopy. Formation of only the



1a R = Bn, **b** R = Me; **2–4 a** R = Bn, R^1 = Me; **b** R = Me, R^1 = Me; **c** R = Me, R^1 = Allyl; **d** R = Me, R^1 = CH_2OMe

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Z-form of the diastereomeric imines **2a-d** is supported by the presence in the ^{13}C NMR spectra of reaction samples (after completion of the alkylation process) of signals from the $C_{(4)}$ atoms of only the *Z*-form of the (3*S*)- and (3*R*)-isomers of imine **2b**; signals from the *E*-form of these isomers appear after these samples have been held for 10 h at room temperature, which is quite consistent with the data in [1-3]. Key factors determining the diastereoselectivity of the process are the ratio of the *Z*-(3*S*)- and *Z*-(3*R*)-imines **2a-d** formed and the subsequent preference for hydride attack on one side of the prochiral C=N bond. The absolute configuration of the target 1,3-dialkyl-4-aminopiperidines was determined by the stereochemical correlation method, in line with the configuration of (*3R,4S*)-*cis*-N-[(1*S*)-1-phenylethyl]-4-amino-1-methyl-3-(4-methylbenzyl)piperidine, as established by X-ray diffraction.

The stereoselective synthesis we developed is the first general approach to optically pure *trans* isomers and enriched *cis* isomers of 3-alkyl-4-aminopiperidines, which are chiral synthons for obtaining next-generation analgesics.

Synthesis of the Compounds 3a-d and 4a-d, Using as an Example the *cis* and *trans* Isomers of N-[(1*S*)-1-phenylethyl]-4-amino-1,3-dimethylpiperidine (3b, 4b) (General Procedure). The reaction was carried out under an argon atmosphere using a septum and a syringe procedure. (1*S*)-N-(1-Methylpiperidin-4-ylidene)-1-phenylethylamine (3 g, 13.9 mmol) in absolute THF (5 ml) was added to a solution of lithium diethylamide, obtained at -10°C by stirring for 10 min a mixture of solutions of $HNEt_2$ (1.32 g, 18 mmol) in absolute THF (20 ml) and a 1.6 N BuLi solution in hexane (11.3 ml, 18 mmol). The reaction mixture was stirred for 30 min at -10°C, then cooled down to -80°C; then MeI (2.56 g, 18 mmol) was added and the mixture was stirred for 1 h at -80°C. Then in sequence we added absolute ethanol (2 ml) and $NaBH_4$ (0.68 g, 18 mmol) and then stirred this mixture for another hour at -80°C. Then the reaction mixture was allowed to stand with vigorous stirring in order to warm up to room temperature. The solvents were evaporated off, the residue was decomposed by careful addition of 6 N HCl until evolution of hydrogen stopped; then water (10 ml) was added, and a 20% NaOH solution was added up to pH 12-13 and it was extracted with CH_2Cl_2 (2 × 30 ml). The organic extracts were combined and dried with anhydrous Na_2SO_4, and then the solvent was evaporated off. The residue was chromatographed on a column with Al_2O_3 in the hexane–EtOAc system with a gradient from 30:1 to 1:1. We obtained 1.42 g (44%) of the *cis*-(*3S,4R*) and (*3R,4S*) diastereomeric pair **3b** and 1.45 g (45%) of the *trans*-(*3R,4R*) diastereomer **4b** of N-[(1*S*)-1-phenylethyl]-4-amino-1,3-dimethylpiperidine. (*3S,4R*),(*3R,4S*)-**3b**: *de* 29%, R_f 0.6 (Alufol, hexane–acetone 1:1), $[\alpha]_D^{20}$ -59° (*c* 2.0, benzene). Chromato-mass spectrum (retention time), *m/z* (I_{rel}, %): (*3R,4S*)-**3b**: (12.08 min) 232 $[M]^+$ (1); 127 $[M - CH(CH_3)C_6H_5]^+$ (100); 105 $[CH(CH_3)C_6H_5]^+$ (49); 96 (64); (*3S, 4R*)-**3b**: (12.20 min) 232 $[M]^+$ (1); 127 $[M - CH(CH_3)C_6H_5]^+$ (100); 105 $[CH(CH_3)C_6H_5]^+$ (61); 96 (88); (*3R,4R*)-**4b**: *de* > 99%, R_f 0.2 (Alufol, hexane–acetone 1:1), $[\alpha]_D^{20}$ -108° (*c* 2.0, benzene). ^1H NMR spectrum (400 MHz, $CDCl_3$, TMS), δ, ppm (*J,* Hz): 0.89 (3H, d, *J* = 6.2, 3-CH_3); 1.04 (1H, br. s, N<u>H</u>); 1.26 (1H, m, *J* = 4.0, *J* = 11.0, *J* = 12.4, *J* = 12.6, 5*a*-H); 1.31 (3H, d, *J* = 6.4, $CH(CH_3)C_6H_5$); 1.49 (1H, t, *J* = 10.8, *J* = 10.8, 2*a*-H); 1.53 (1H, m, *J* = 2.1, *J* = 10.8, *J* = 6.2, *J* = 12.0, 3*a*-H); 1.71-1.78 (2H, m, *J* = 11.8, *J* = 12.4, *J* = 3.0, *J* = 11.0, *J* = 4.1, *J* = 11.1, 4*a*-,6*a*-H); 2.04 (1H, d of pseudo q, *J* = 3.0, *J* = 12.7, *J* = 4.1, *J* = 2.9, 5*e*-H); 2.17 (3H, s, 1-CH_3); 2.69 (1H, dd, *J* = 7.3, *J* = 2.1, 2*e*-H); 2.78 (1H, m, *J* = 4.0, *J* = 4.1, *J* = 11.1, *J* = 1.0, 6*e*-H); 3.95 (1H, q, *J* = 6.4, C<u>H</u>$(CH_3)C_6H_5$); 7.19-7.33 (5H, m, $CH(CH_3)C_6$<u>H</u>$_5$). ^{13}C spectrum ($CDCl_3$, 100 MHz, TMS), δ, ppm: 16.3; 25.7; 31.9; 37.2; 46.1; 54.1; 55.1; 57.3; 63.0; 126.6, 126.6, 128.2, 146.0. Chromato-mass spectrum (retention time), *m/z* (I_{rel}, %): (12.09 min) 232 $[M]^+$ (1); 127 $[M\text{-}CH(CH_3)C_6H_5]^+$ (44); 105 $[CH(CH_3)C_6H_5]^+$ (48), 96 (100). Found, %: C 47.10; H 4.37; N 16.06. $C_{15}H_{24}N_2 \cdot 2C_6H_3N_3O_7$ (dipicrate). Calculated, %: C 46.96; H 4.38; N 16.23.

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