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LIGAND ASSISTED HYDRIDE DELIVERY : AN EXPEDITIOUS STEREOSELECTIVE TOTAL SYNTHESIS OF (±) NOR-SEDAMINE AND ITS PYRROLIDINO ANALOG

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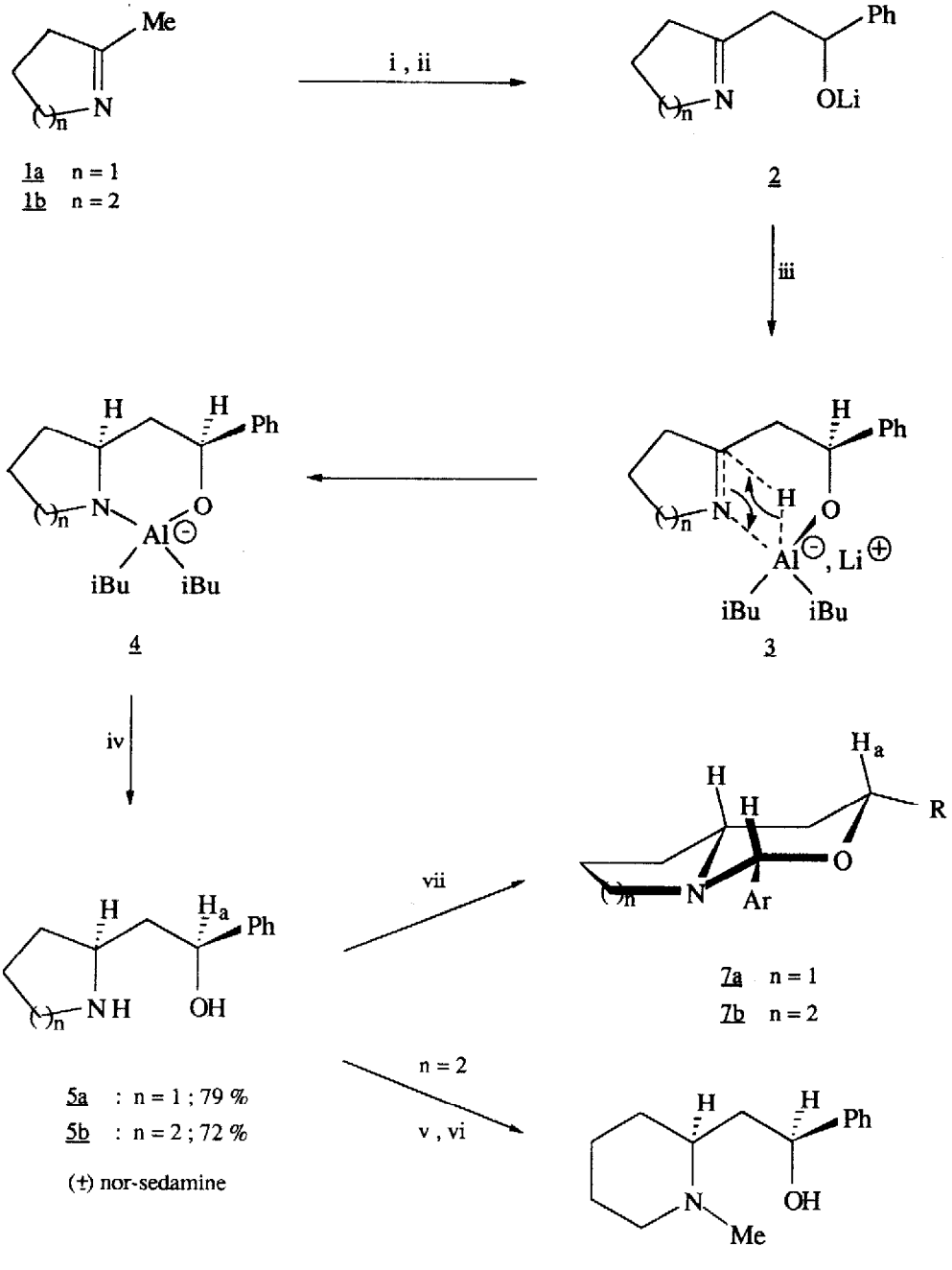
Summary - The principle of an efficient stereoselective one pot synthesis of γ–aminoalcohols is reported and applied to the total synthesis of (±) nor-sedamine and its pyrrolidino analog.

The well-recognized advantages of intramolecularity and the common chelate and complexation effects embody proximity as an important factor for controlling the course of chemical reactions. These complex induced proximity effects (CIPE) constitute a well established and general principle [1]. A subset of this area namely the ligand assisted nucleophilic additions has been recently illustrated, in particular, by spectacular examples of internal hydride delivery via the intermediacy of alkoxide-aluminum hydride complexes [2,3]. In this note, we report the application of these principles to a highly stereoselective total synthesis of the γ-aminoalcohols (±) nor-sedamine and its five membered ring analog.

The sequence which we used is depicted in the scheme : Addition of the imines **1a** [4] or **1b** [5] to a THF solution of LDA (1.2 eq.) at -20°C gave, after two hours, a yellow solution of the corresponding azaenolates [6] which faded upon dropwise addition at -78°C of one equivalent of freshly distilled benzaldehyde. After 0.5 h, the lithium iminoaldolates **2** thus obtained were quenched by the addition of DIBAL (1M in hexane, 1.2 eq., -78°C to R.T., 18 h). After hydrolysis with an aqueous solution of NaF and filtration, the aminoalcohols **5** were purified by kugelrohr distillation [7].

Several points are worthy of note. The aminoalcohols **5** were obtained by a one pot sequence and isolated in good yields, thus showing the efficiency of each step (metallation,



Reagents and conditions : i LDA, THF, -20°C ; ii PhCHO, - 78°C ; iii DIBAL (1M in hexane), -78°C to R.T. ; iv NaF, H_2O, then kugelrhor purification ; v $ClCO_2Me$, saturated Na_2CO_3, CH_2Cl_2 ; vi $LiAlH_4$, then H_2O ; vii $pNO_2C_6H_4CHO$, Δ C_6H_6, Dean and Stark trap.

aldolisation and reduction). We could not obtain any evidence for products arising from an endocyclic metallation of the imines, in agreement with the literature data [8]. Only one diastereomer could be detected by ^1H and ^{13}C NMR of the crude reaction mixture (within a detection limit of 3 %) thus indicating an excellent 1,3 asymmetric induction in the reduction step. The stereochemistry of **5b** was determined after its transformation into **6b** via the reduction by LAH of the corresponding carbamate (two steps, 70 % overall yield). **6b** is identical in all respects with the (±) sedamine known to be the erythro diastereoisomer [9,10] : **6b** : m.p. 90°C (4/1 mixture of benzene/light petroleum ether) (lit. [9] 89-90°C) ; ^1H NMR ($(CDCl_3)$, 300 MHz) : $\delta C\underline{H}OH$ = 4.90, dd, J = 10.6 and 2.7 Hz (lit. [10] : δCHOH = 4.84, dd, J = 9.5 and 2.5 Hz). The following observations led us to assume that **5b** and **5a** have the same stereochemistry. The NMR data of these two aminoalcohols are very similar [7] : ^1H NMR δH_a : **5a** : 4.86 (dd, J = 10.2 and 2.1 Hz) ; **5b** : 4.92 (dd, J = 10.6 and 2.6 Hz). Furthermore, the reaction of **5a** and **5b** with p.nitrobenzaldehyde led to the oxazines **7a** and **7b** [11] respectively which show very similar δH_a and δC_a [**7a**, δH_a = 4.6 - 4.8 (m) ; δC_a = 79.7 (d). **7b**, δH_a = 4.6 - 4.9 (m) ; δC_a = 79.2 (d)].

From a mechanistic stand point, the internal delivery of hydride to the carbon nitrogen double bond in the chelates **3** leading to **4** should occur from the opposite side of the phenyl group. The transition state proposed by Narasaka and co-workers [12] for the reduction of γ-hydroxyoxime ethers and the examination of molecular models suggest a preferred conformation with a phenyl group in a pseudo-equatorial position, thus minimizing its 1.3 interaction with an isobutyl group on the aluminum and leading to the erythro diastereoisomer. This is corroborated by the observation that if $H_3B : SMe_2$ was used instead of DIBAL, we obtained a 7/3 mixture of erythro and threo diastereomers.

In conclusion, the sequence depicted in this note constitutes an efficient and simple diastereoselective access to 1,3 γ-aminoalcohols which complements those already existing in the literature [13]. The generality of this scheme is under active investigation.

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7 **5a** : B.p.$_{0.01}$ = 100-105°C (oven temperature) ; yield = 79 % (from **1a**), ^{1}H NMR ($CDCl_3$, 300 MHz) δ : 1.3 - 2.0 (m, 6H), 2.8 - 3.0 (m, 2H), 3.5 - 3.6 (m, 1H), 4.68 (br s, 2H exchangeable with D_2O), 4.86 (dd, J = 10.2 and 2.1 Hz, 1H), 7.1 - 7.5 (m, 5H). ^{13}C n.m.r. ($CDCl_3$, 20.1 MHz) : δ:25.7 (t), 32.8 (t), 43.6 (t), 45.7 (t), 59.1 (d), 74.7 (d), 125.7 (d), 126.9 (d), 128.3 (d), 145.6 (s). M.s. : m/z 191 ($M^{+\cdot}$). **5b** : B.p.$_{0.01}$ = 110-115°C, m.p. 92-93°C (pentane) (lit. [8] 94-96°C) ; yield = 72 % (from **1b**) ; ^{1}H n.m.r. ($CDCl_3$, 300 MHz) δ : 1.0 - 1.9 (m, 8H), 2.6 - 2.7 (m, 1H), 2.8 - 2.9 (m, 1H), 3.0 - 3.2 (m, 1H), 4.92 (dd, J = 10.6 and 2.6 Hz, 1H), 5.05 (br s, 2H exchangeable with D_2O), 7.1 - 7.5 (m, 5H). ^{13}C n.m.r. ($CDCl_3$, 20.1 MHz) : δ 24.5 (t), 27.2 (t), 34.1 (t), 45.3 (t), 46.1 (t), 58.0 (d), 75.2 (d), 125.7 (d), 127.0 (d), 128.3 (d), 145.6 (s).

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