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STEREOSELECTIVE SYNTHESES OF SOLENOPSIN A AND B

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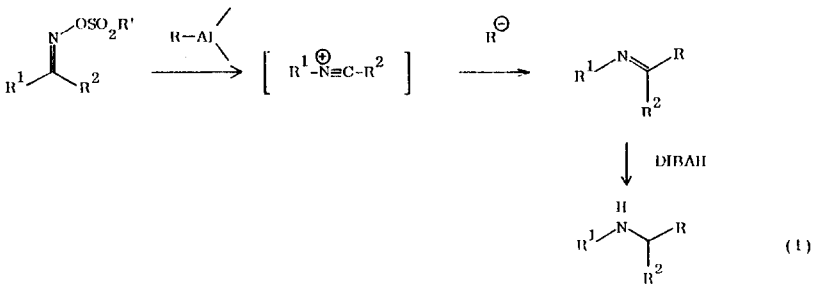
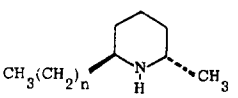
Summary: Effective and convenient syntheses of solenopsin A and B have been developed which involve the Beckmann rearrangement-alkylation reaction promoted by organoaluminum reagents and a new stereoselective reduction of imino functional group.

The recent discovery of the aluminum method for the direct synthesis of α-alkylated amines from the simple oxime sulfonate (eq. 1) has substantially simplified the task of the synthesis in this area.[1] Thus,



(1)

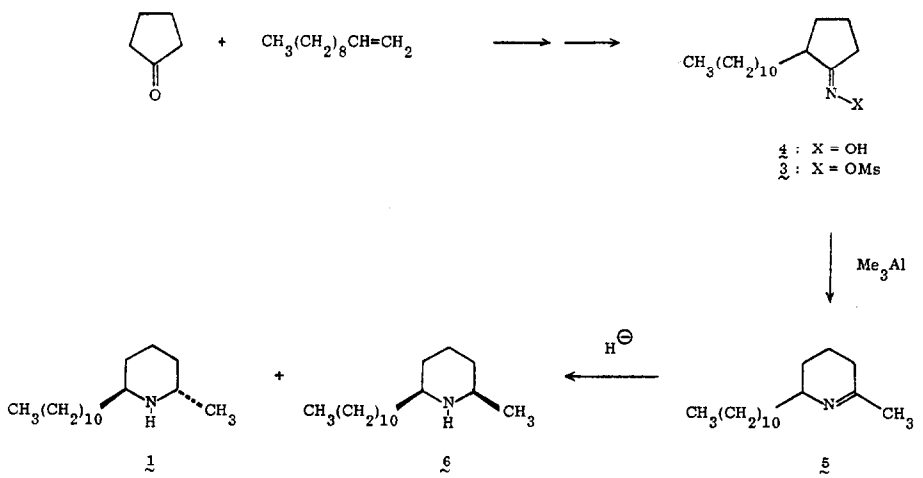
the method should be especially useful in the field of alkaloid synthesis: for example, it provides a simple approach to the structure of 2,6-dialkylated piperidines from α-alkylcyclopentanones. Solenopsin A (1) and B (2), naturally occuring piperidine alkaloids isolated from the venom of the fire ant, Solenopsis savissima,[2] are members of these class of compounds which exhibit pronounced hemolytic,[3] insecticidal, and antibiotic[4] activity. As far as we know there were no known synthetic methods capable of generating stereospecifically trans-2,6-disubstituted piperidine structure, characteristic of 1 and 2.[5] This fact, together with the occurrence of the same structural unit in other natural products,[6] led us to study the stereospecific route to solenopsin A and B.



1 : SOLENOPSIN A (n = 10)
2 : SOLENOPSIN B (n = 12)

The starting oxime sulfonate 3 was synthesized from cyclopentanone in three steps: Reaction of excess cyclopentanone (10 equiv) with 1-undecene (1 equiv) in the presence of silver oxide (1 equiv) at 130°C for 5 h[7] produced after isolation in the usual way α-undecylcyclopentanone which was treated with hydroxylamine hydrochloride (1.5 equiv)-sodium acetate (2 equiv) in methanol at 25°C for 5 h. Chromatography of the crude product on silica gel with 20% ether in hexane led to the isolation of pure anti-oxime 4[8] in 73% overall yield from 1-undecene as a semi-solid, which was converted to the corresponding mesylate 3 with methanesulfonyl chloride (1.1 equiv)-triethylamine (1.5 equiv) in methylene chloride at -20°C for 40 min (~95-100%). Treatment of the oxime mesylate 3 in dry methylene chloride with 2 equiv of trimethylaluminum (a 2 M toluene solution)[10] at -78°C for 5 min and at 25°C for 1 h resulted in formation of the imine 5 in 54% yield[11] after work up by NaF-H_2O method.[1]

Completion of the synthesis requires reduction of the C=N double bond of 5 with correct configurations. Unfortunately, however, it was soon apparent from examination of the literature that existing methodology was totally inadequate for the selective reduction of 5 into trans-2,6-disubstituted piperidine structure.[12] Thus, the reduction of 5 using usual aluminum- or borohydride type reagents[13] in different solvents at low temperature afforded solenopsin A (1) and its cis isomer 6 in the range of <1/99 to 80/20 (GC analysis) as illustrated in Table I (Entry 1~10). Excellent stereoselectivity was finally attained in the formation of the trans form 1 by adding trimethylaluminum (1 equiv to $LiAlH_4$) into the reaction mixture at low temperature, and solenopsin A (1) was obtained almost exclusively (>95%, Entry 17).[14] The spectral data (^1H NMR and IR) of synthetic solenopsin A was identical with the reported ones.[2]



In a similar manner, solenopsin B (2) was prepared with high stereoselectivity (~95% by GC assay) using procedures which exactly paralleled those described above for the synthesis of solenopsin A.

Table I. Stereoselectivity of the Reduction of the Imine 5 with Hydride Reagents.[a]

Entry	Hydride Reagent	Solvent	Product Ratio[b] (6 : 1)
1	DIBAH (4 eq)	CH_2Cl_2	99 : 1
2	$LiAlH_4$ (7 eq)-NaOMe (14 eq)[c]	THF	99 : 1
3	$NaBH_3CN$ (3 eq)-HCl[d]	MeOH	98 : 2
4	$LiAlH_4$ (7 eq)-$Ti(OPr^i)_4$ (7 eq)	THF	90 : 10
5	n-BuLi (5 eq)-DIBAH (5 eq)[c]	Ether	83 : 17
6	$LiAlH_4$ (25 eq)-LiCl (50 eq)[c]	THF	80 : 20
7	$LiAlH_4$ (7 eq)-$NiCl_2$ (7 eq)[c]	THF	75 : 25
8	$LiAlH_4$ (5 eq)-$TiCl_3$ (10 eq)[c]	THF	67 : 33
9	$LiAlH_4$ (25 eq)	CH_2Cl_2 or THF	67 : 33
10	$LiAlH_4$ (25 eq)	Ether	20 : 80
11	$Mg(AlH_4)_2$ (25 eq)	Ether	33 : 67
12	$LiAlH_4$ (7 eq)-BF_3OEt_2 (7 eq)	Ether	33 : 67
13	$LiAlH_4$ (7 eq)-$TiCl_4$ (7 eq)	THF	25 : 75
14	$LiAlH_4$ (7 eq)-Me_3Al (7 eq)[e]	Ether	13 : 87
15	$LiAlH_4$ (7 eq)-Bu^i_3Al (7 eq)	THF	6 : 94
16	$LiAlH_4$ (7 eq)-Me_3Al (7 eq)	DME	6 : 94
17	$LiAlH_4$ (7 eq)-Me_3Al (7 eq)	THF	5 : 95

a) All reactions were carried out on a 0.3-1 mmol scale. Unless specified, the imine 5 was added to hydride reagents at -78°C under argon, and then additives were introduced. The reaction mixture was stirred at -78°C for 30 min, at -45°C for 1 h, at -20°C for 1 h, and finally at 0°C for 1 h. After work-up by NaF-H_2O method, the crude product was purified by column chromatography to give a mixture of cis and trans isomers in 94-97% yield. b) Isomeric ratio was determined by GLC (OV-101, 210°C): t_r(6) = 3.91 min, t_r(1) = 4.31 min. c) The imine was added to a mixture of hydride reagents and additives at -78°C. d) The imine was reduced at 25°C for 20 h, and worked up in a usual manner. e) The use of excess $LiAlH_4$ (7 eq of $LiAlH_4$ to 4 eq of Me_3Al) or excess Me_3Al (10 eq of Me_3Al to 5 eq of $LiAlH_4$) did not affect the ratio of 6 to 1.

ACKNOWLEDGMENT

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6. For example, see: a) pseudo-Carpaine: Govindachari, T. R.; Pai, B. R.; Narasimhan, M. S. J. Chem. Soc., 1954, 1847. Govindachari, T. R.; Nagarajan, K.; Viswanathan, N. Tetrahedron Lett., 1965, 1907. b) Himberline, Himandravine, and Himgravine: Pinhey, J. T.; Ritchie, E.; Taylor, W. C. Austral. J. Chem., 1961, 14, 106. Fridrichsons, J.; Mathieson, A. M. Acta Cryst., 1962, 15, 119. c) Lythranine and Lythranidine: Fujita, E.; Fuji, K.; Bessho, K.; Sumi, A.; Nakamura, S. Tetrahedron Lett., 1967, 4595.
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8. ^{1}H NMR (CCl_4) δ9.09 (1H, br s, OH), 2.20-2.61 (3H, m, N=C-CH, N=C-CH_2), 0.88 (3H, br t, CH_3).
9. The crude oxime mesylate 3 was used without purification for the following rearrangement with trimethylalumimum. Satisfactory spectral (^{1}H NMR and IR) data were obtained for this compound.
10. Purchased from Aldorich Chemical Company, Inc.
11. ^{1}H NMR (CCl_4) δ3.87-3.40 (1H, m, NCH), 1.81 (3H, d, J = 2.0 Hz, N=C-CH_3), 0.89 (3H, br t, CH_3); IR (liquid film) 2920, 2850, 1660, 1460, 1370 cm^{-1}.
12. Methods and selectivities for previous syntheses of solenopsin A: a) Reduction of 2,6-disubstituted pyridine with sodium in ethanol (cis/trans = 85:15).[5a] b) Mundy N-acyllactam rearrangement followed by reduction of the imine with $NaBH_4$ (cis/trans = 80:20).[5b] c) Nitrosation, equilibrium by t-BuOK, and denitrosation of the cis-isomer (cis/trans = 50:50), which permit the full conversion to the trans isomer after repetition of this process.[5d]
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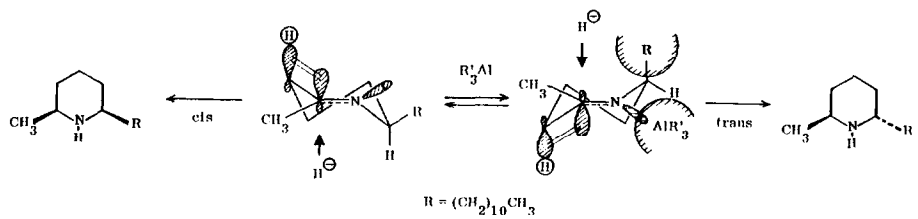
14. The stereochemical outcome arising from the reduction of the imine in the presence of trialkylaluminum is tentatively rationalized by a theory of charge-transfer stabilization of the transition state for nucleophilic addition to a carbonyl group (Cieplak, A. S. J. Am. Chem. Soc., 1981, 103, 4540.). In the hydride reduction of the imine 5, the rear-side approach of the hydride toward the molecule is preffered by the stabilization of the $\sigma^*_{\ddagger}$ orbital (low-lying vacant orbital of the imine) through electron delocalization from the σ_{C-H} bond into the $\sigma^*_{\ddagger}$ orbital, producing the cis isomer. On the other hand, by the addition of Lewis acid (R'_3Al), the R group of 5 would occupy the axial position because of the steric interaction between R and R'_3Al ($A^{(1,2)}$-Strain: see Nalua, A. S. Tetrahedron Lett., 1981, 22, 2017.). This facilitates the front-side approach of the hydride toward the molecule to furnish the desired trans isomer



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