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TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of the *trans*-2,6-dialkylpiperidine alkaloids (2*R*,6*R*)-lupetidine and (2*R*,6*R*)-solenopsin A

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Abstract

The enantioselective synthesis of the *trans*-2,6-dialkylpiperidine alkaloids (2*R*,6*R*)-lupetidine and (2*R*,6*R*)-solenopsin A from 6-methyl-2-piperidone **1** is described. The key step of this synthesis consists of the addition of a dialkylcopper derivative to the thioimidate salt **3** followed by sodium borohydride reduction of the resulting iminium salt.

The stereoselective synthesis of substituted piperidines, which are widespread skeletal fragments of important biologically active natural products, has attracted considerable attention in the last few decades[1]. In particular, the 2,6-disubstituted piperidine ring structure has been found in certain members of the pine and fire ant species. However, although *cis*-2,6-dialkylpiperidines are easily accessible, efficient stereoselective methods for the synthesis of *trans*-2,6-disubstituted piperidines are relatively scarce. Solenopsin A [(2*R*,6*R*)-2-methyl-6-undecylpiperidine][2] and solenopsin B [(2*R*,6*R*)-2-methyl-6-tridecylpiperidine],[2] isolated from the venom secreted by the fire ant *Solenopsis invicta*, have been a vehicle for the testing of several different synthetic methods.[3] These methods include: (i) hydride reduction of 1-piperideines[4] or the corresponding iminium salts;[5] (ii) intramolecular aminomercuration;[6] (iii) alkene nitrone cycloadditions;[7] (iv) alkylation of α-lithiated piperidine derivatives;[8] (v) addition of organocerium reagents to 6-alkyl-1-piperideines;[9] (vi) reductive decyanation of 2,6-dialkyl-2-cyanopiperidines;[10] (vii) intramolecular addition of allylsilanes to nitrones;[11] (viii) isomerization of *N*-nitroso-*cis*-2,6-dialkylpiperidines;[12] and (ix) nucleophilic amine substitution of mesylates.[13,14] Some of these procedures have been extended to the enantioselective synthesis of solenopsins.[15]

In a previous paper[16] we reported the enantioselective synthesis of the *cis*-2,6-dialkylpiperidine alkaloid (2*R*,6*S*)-dihydropinidine from 6-methyl-2-piperidone **1** (Scheme 1). The key step was the addition of propylmagnesium bromide to the iminium salt **A** (R=H), generated by partial reduction of the amide carbonyl of **1**. The observed stereoselectivity is a consequence of the stereoelectronically preferred axial approach[17] of the nucleophile to the most stable half chair conformation of **A** (Scheme 2), which

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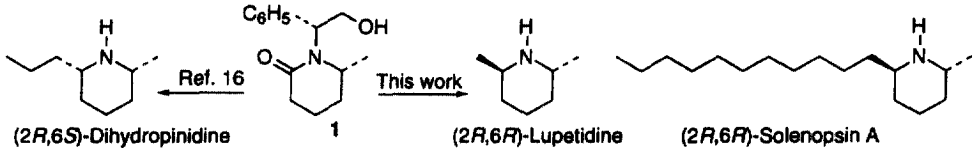
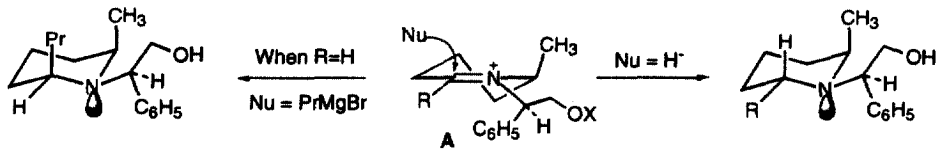
incorporates a methyl group in a pseudoaxial orientation to relieve the $A^{(1,2)}$ strain.[18] Reversal of this sequence, i.e. addition of an organometallic reagent to the lactam **1**, followed by hydride addition to the resulting iminiun salts **A** (R=Me or R=*n*-$C_{11}H_{23}$), also under stereoelectronic control, would lead to the *trans*-2,6-dialkylpiperidine alkaloids (2*R*,6*R*)-lupetidine and (2*R*,6*R*)-solenopsin A, respectively.

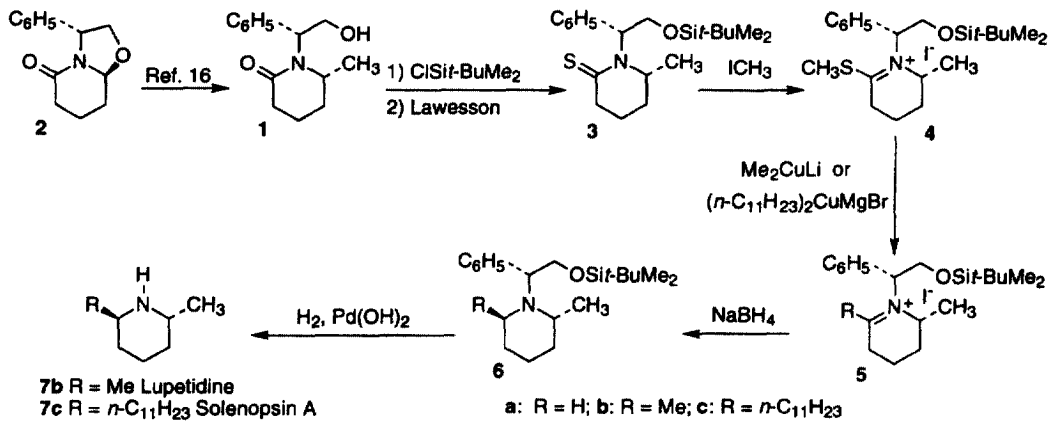


Scheme 1.



Scheme 2.

Our initial attempts to prepare *trans*-2,6-dialkylpiperidines by treatment of lactam **1** (easily prepared[16] from the chiral non-racemic bicyclic lactam **2**, Scheme 3) with Grignard, organolithium,[19] or organocerium[20] reagents, followed by reduction with lithium aluminium hydride or sodium borohydride, resulted in failure. These results prompted us to use the more reactive thioimidate salt **4**:[21] addition of an organometallic reagent to the iminium moiety of **4**, followed by elimination of the methylsulfanyl group, would also lead to the desired iminium salts **5** (i.e. **A**, R=alkyl).



Scheme 3.

Compound **4** was obtained in good yield by protection of the hydroxyl group of lactam **1**, followed by treatment with Lawesson reagent and subsequent alkylation of the resulting thioamide **3** with methyl iodide. However, treatment of **4** with methyllithium or methylmagnesium bromide, followed by addition of $NaBH_4$, afforded the reduced piperidine **6a** as the only identifiable product. This result can be attributed to the basicity of the above organometallic reagents, which deprotonate the α position of thioimidate **4** yielding the corresponding ketene *S,N*-acetal;[22] subsequent addition of a hydride affords piperidine **6a**. However, addition of the less basic[23] organometallic derivative lithium dimethylcuprate to the salt **4** at 0°C, followed by treatment of the reaction mixture with $NaBH_4$, afforded the desired 2,6-dimethylpiperidine **6b** (92:8 *trans*:*cis* ratio) in 55% overall yield from thioamide **3**. Piperidine **6a** was also formed in about 17% yield in all cases. Finally, hydrogenolysis of the benzylic substituent of **6b**

gave *trans*-2,6-dimethylpiperidine **7b**, whose hydrochloride showed mp 243–244°C and $[\alpha]_D$ +12.4 (*c* 3.0, EtOH) {lit.[24] mp 247–249°C and $[\alpha]_D$ +12.8 (*c* 3.06, EtOH)} and possessed data identical to those reported for the alkaloid (2*R*,6*R*)-lupetidine,[24] isolated from *Nanophyton erinaceum*.[25]

The above methodology provides a general synthetic entry to enantiopure *trans*-2,6-dialkylpiperidines. This was exemplified by an enantioselective synthesis of the fire ant venom solenopsin A. Thus, treatment of the thioimidate salt **4** with di-*n*-undecylcopper(I)-magnesium bromide, followed by reduction with $NaBH_4$, afforded the corresponding 2-methyl-6-undecylpiperidine in 54% overall yield from thioamide **3** as a 7:3 mixture of *trans*-**6c** and its *cis*-isomer,[26] which could be separated by column chromatography after desilylation (*n*-Bu_4NF). Debenzylation of the major isomer afforded (2*R*,6*R*)-solenopsin A **7c**, which was isolated as the hydrochloride {mp 141–142°C and $[\alpha]_D$ −7.0 (*c* 1.3, $CHCl_3$); lit.[8b] mp 141–142°C and $[\alpha]_D$ −7.6 (*c* 0.5, $CHCl_3$)}. The spectral data (^{1}H-NMR and ^{13}C-NMR) of our synthetic solenopsin A were identical with those reported.[5g]

The above results expand the potential of chiral non-racemic bicyclic lactam **2** for the enantioselective synthesis of diversely substituted piperidines.[27]

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References

1. (a) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp. 1–90. (b) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1985; Vol. 26, pp. 89–183. (c) Wang, C.-L. J.; Wuonola, M. A. *Org. Prep. Proced. Int.* **1992**, *24*, 585–621. (d) Angle, S. R.; Breitenbucher, J. G. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science: Amsterdam, 1995; Vol. 16, pp. 453–502. (e) Schneider, M. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996; Vol. 10, pp. 155–299.
2. (a) MacConnell, J. G.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1971**, *26*, 1129–1139. (b) Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982**, *38*, 1949–1958. (c) Leclercq, S.; Thirionet, I.; Broeders, F.; Daloze, D.; Vander Meer, R.; Braekman, J. C. *Tetrahedron* **1994**, *50*, 8465–8478.
3. For a review, see: Leclercq, S.; Daloze, D.; Braekman, J.-C. *Org. Prep. Proced. Int.* **1996**, *28*, 501–543.
4. (a) Hill, R. K.; Yuri, T. *Tetrahedron* **1977**, *33*, 1569–1571. (b) Sakane, S.; Matsumura, Y.; Yamamura, Y.; Ishida, Y.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 672–674. (c) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831–2843. (d) Meyers, A. I.; Edwards, P. D.; Bailey, T. R.; Jagdmann, G. E. *J. Org. Chem.* **1985**, *50*, 1019–1026. (e) Yamaguchi, R.; Nakazono, Y.; Matsuki, T.; Hata, E.; Kawanisi, M. *Bull. Chem. Soc. Jpn* **1987**, *60*, 215–222. (f) Ryckman, D. M.; Stevens, R. V. *J. Org. Chem.* **1987**, *52*, 4274–4279. (g) Taber, D. F.; Deker, P. B.; Fales, H. M.; Jones, T. H.; Lloyd, H. A. *J. Org. Chem.* **1988**, *53*, 2968–2971. (h) Bacos, D.; Célérier, J. P.; Marx, E.; Rosset, S.; Lhommet, G. *J. Heterocyclic Chem.* **1990**, *27*, 1387–1392. (i) Fukuda, Y.; Utimoto, K. *Synthesis* **1991**, 975–978. (j) Fukuda, Y.; Matsubara, S.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 5812–5816. (k) Ukaji, Y.; Watai, T.; Sumi, T.; Fujisawa, T. *Chem. Lett.* **1991**, 1555–1558.
5. (a) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 3369–3372. (b) Takahashi, K.; Kurita, H.; Ogura, K.; Iida, H. *J. Org. Chem.* **1985**, *50*, 4368–4371. (c) Grierson, D. S.; Royer, J.; Guerier, L.; Husson, H.-P. *J. Org. Chem.* **1986**, *51*, 4475–4477. (d) Wasserman, H. H.; Rusiecki, V. *Tetrahedron Lett.* **1988**, *29*, 4977–4980. (e) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1991**, *56*, 2506–2512. (f) Kotsuki, H.; Kusumi, T.; Inoue, M.; Ushio, Y.; Ochi, M. *Tetrahedron Lett.* **1991**, *32*, 4159–4162. (g) Jefford, C. W.; Bo Wang, J. *Tetrahedron Lett.* **1993**, *34*, 2911–2914.
6. (a) Moriyama, Y.; Doan-Huynh, D.; Monneret, C.; Khuong-Huu, Q. *Tetrahedron Lett.* **1977**, 825–828. (b) Adams, D. R.; Carruthers, W.; Williams, M. J.; Crowley, P. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1507–1513. (c) Mundy, B. P.;

Bjorklund, M. *Tetrahedron Lett.* **1985**, *26*, 3899–3902. (d) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100–3109.
7. (a) Carruthers, W.; Williams, M. J. *J. Chem. Soc., Chem. Commun.* **1986**, 1287–1288. (b) Chackalamannil, S.; Wang, Y. *Tetrahedron* **1997**, *53*, 11203–11210.
8. (a) Beak, P.; Koo Lee, W. *J. Org. Chem.* **1993**, *58*, 1109–1117. (b) Comins, D. L.; Radi Benjelloun, N. *Tetrahedron Lett.* **1994**, *35*, 829–832.
9. Oppolzer, W.; Bochet, C. G.; Merifield, E. *Tetrahedron Lett.* **1994**, *35*, 7015–7018.
10. Nagasaka, T.; Hayashi, H.; Kumakawa, M.; Sakamoto, M.; Mizuno, M.; Hamaguchi, F. *Heterocycles* **1989**, *29*, 2157–2166. See also Refs. 2c and 5a.
11. Wuts, P. G. M.; Jung, Y.-W. *J. Org. Chem.* **1988**, *53*, 1957–1965.
12. Fuji, K.; Ichikawa, K.; Fujita, E. *Chem. Pharm. Bull.* **1979**, *27*, 3183–3185.
13. (a) Takahata, H.; Inose, K.; Araya, N.; Momose, T. *Heterocycles* **1994**, *38*, 1961–1964. (b) Solladié, G.; Huser, N. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 153–156.
14. Lupetidine [(2*R*,6*R*)-2,6-dimethylpiperidine] has also been synthesized following this method: Najdi, S.; Kurth, M. J. *Tetrahedron Lett.* **1990**, *31*, 3279–3282.
15. See Refs. 2c, 4g, 4k, 5c, 5f, 5g, 7b, 8b, 9, 13a and 13b.
16. Amat, M.; Llor, N.; Hidalgo, J.; Hernández, A.; Bosch, J. *Tetrahedron: Asymmetry* **1996**, *7*, 977–980.
17. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; p. 211.
18. (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–412. (b) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.
19. Cervinka, O. In *The Chemistry of Enamines, Part I*; Rappoport, Z., Ed. In *The Chemistry of Functional Groups*; Patai, S.; Rappoport, Z., Eds.; Wiley: Chichester, 1994; p. 489.
20. (a) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904–3912. (b) Denmark, S. E.; Edwards, J. P.; Nicaise, O. *J. Org. Chem.* **1993**, *58*, 569–578.
21. Kantlehner, W. In *Iminium Salts in Organic Chemistry*; Böhme, H.; Viehe, H. G., Eds.; Wiley: New York, 1979; Part 2, p. 279.
22. Gompper, R.; Elser, W. *Org. Synth.* **1968**, *48*, 97–101.
23. For the alkylation of the α-position of cyclic amines via thioimidate salts with lithium acetylides, see: (a) Takahata, H.; Yamazaki, T. *Heterocycles* **1988**, *27*, 1953–1973. (b) Takahata, H.; Takahashi, K.; Wang, E.-C.; Yamazaki, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1211–1214.
24. Najdi, S.; Kurth, M. J. *Tetrahedron Lett.* **1990**, *31*, 3279–3282.
25. (a) Kuzovkov, A. D.; Menshikov, G. P. *Zhur. Obshchei Khim.* **1950**, *20*, 1524 [*Chem. Abstr.* **1951**, *45*, 2485g]. (b) Hill, R. K.; Morgan, J. W. *J. Org. Chem.* **1966**, *31*, 3451–3452. (c) Perrone, R.; Tortorella, V. *Tetrahedron* **1978**, *34*, 2533–2536.
26. The lower stereoselectivity in the hydride reduction of the R–C=N bond of related 1-piperidinium salts when R is an alkyl group larger than CH_3 has previously been observed.[4c,d,k]
27. (a) 2-Alkyl: Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223–2226. (b) 3-Alkyl: Amat, M.; Pshenichnyi, G.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron: Asymmetry* **1996**, *7*, 3091–3094. (c) *cis*-2,6-Dialkyl: see Ref. 16. (d) *trans*-3,4-Dialkyl: Amat, M.; Hidalgo, J.; Bosch, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1591–1594 and 1845. See also (e) Amat, M.; Llor, N.; Bosch, J.; Solans, X. *Tetrahedron* **1997**, *53*, 719–730. (f) Amat, M.; Llor, N.; Hidalgo, J.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron: Asymmetry* **1996**, *7*, 2501–2504.