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Synthesis of Pyranotropanes via Enantioselective Deprotonation Strategy

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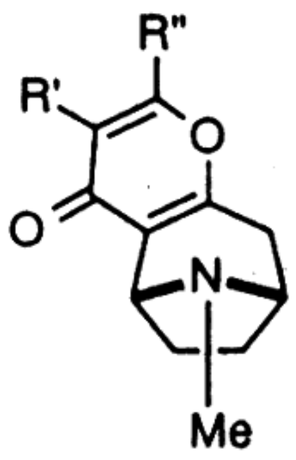
Abstract: Synthesis of tropane alkaloids darlingine, chalcostrobamine and isobellendine both in the racemic form and as unnatural enantiomers is described. Enantioselective deprotonation of tropinone, which proceeded with ca 90% ee, was the key step in each of the syntheses. Enantioselectivity was increased in the presence of LiCl.

Deprotonation of cyclic ketones with chiral lithium amide bases is a promising new synthetic tool. Several methodology studies have been published,[1] and the principle, that cyclic ketones of C_S symmetry can be deprotonated enantioselectively seems to be firmly established. The method has also been applied in several syntheses of natural products.[2] In this letter, we describe synthesis of pyranotropanes (**1**) via deprotonation of tropinone (**2**). This route offers a quick access to the tropane alkaloids isobellendine (**1a**) and darlingine (**1b**); both the racemates and the unnatural enantiomers (ent- forms of the natural products) were synthesized.[3]



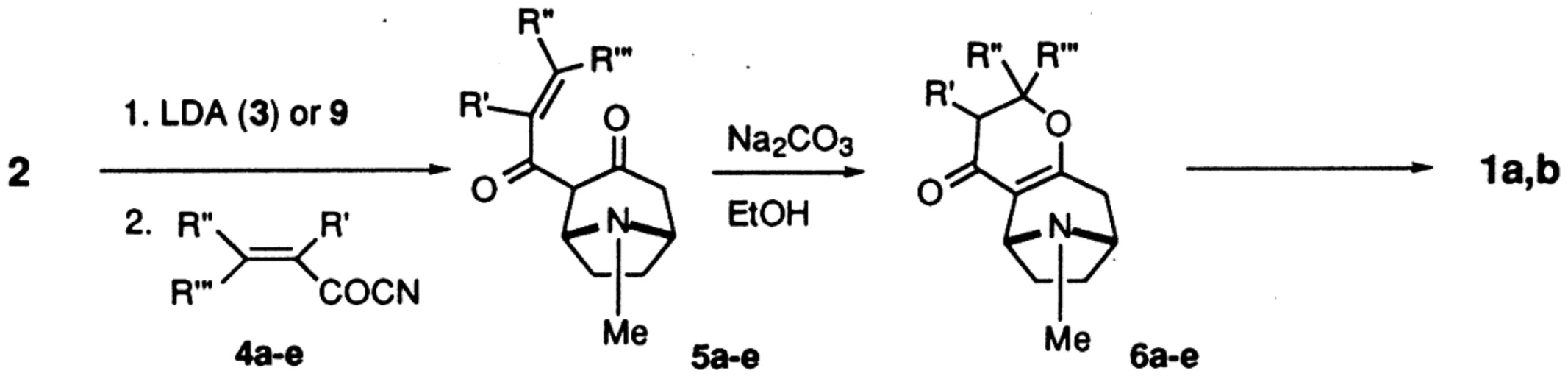
1a R' = H; R" = Me
1b R' = Me; R" = Me

2

Synthesis of racemic pyranotropanes: Tropinone (**2**) was deprotonated with lithium diisopropylamide (**3**; THF; -78°C) and the resulting solution, containing racemic tropinone Li-enolate, was treated with an acyl cyanide (**4a-d**, Scheme 1).[4] Senecioyl cyanide (**4d**) afforded the cleanest and highest yielding reaction (yield 91%) and furthermore, it turned out that the resulting compound **5d** cyclized readily under basic conditions to give the bicyclic product **6d** (96% yield). A brief investigation using HPLC proved that the two enantiomers of **6d** were detectable as two separate peaks on a chiral column (ChiraDex; Merck). Thus compound **6d** provided a good model for studies of enantioselectivity (*vide infra*).

Other acyl cyanides i.e. crotonyl cyanide (**4a**), tigloyl cyanide (**4b**) and cinnamoyl cyanide (**4c**) also reacted readily with lithium enolate of tropinone and yielded compounds **5a** (91%), **5b** (not isolated), and a natural product (±) chalcostrobamine **5c** (80% yield). Products **5a** and **5b** were cyclized *in situ* under basic conditions to give the bicyclic systems **6a** (81%) and **6b** (81% from tropinone) as mixtures of diastereoisomers in each case. In order to obtain tropane alkaloids isobellendine (**1a**) and darlinginine (**1b**) from these compounds it was necessary to introduce a double bond into the α,β position of the dihydropyranone ring. This was accomplished by subjecting compound **6b** to bromination using cupric bromide in refluxing AcOEt (yield 78%), followed by elimination of HBr (using 20% ammonia) which yielded (±) darlingine **1b** (96%).

SCHEME 1



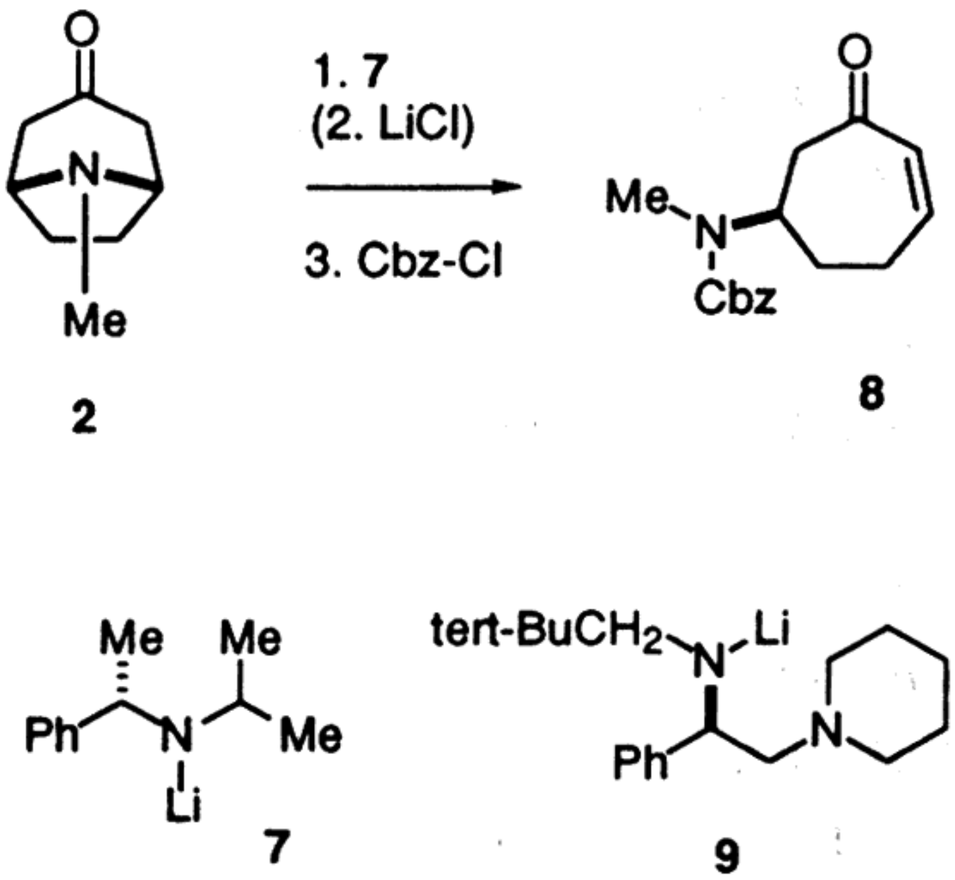
a R"= Me; R', R"'= H; **b** R', R"= Me; R"'= H; **c** R', R"'= H; R"= Ph; **d** R'= H; R"= R"' = Me; **e** R' = Br; R"= H; R"'= Me

Somewhat surprisingly, compound **6a** proved resistant to this approach (attempted bromination proceeded very slowly and the resulting bromide did not eliminate HBr, while attempted selenylation resulted in opening of the dihydropyranone ring) and an alternate method of producing isobellendine had to be devised. Ultimately, we made a different acyl cyanide reagent: 2-bromo-2-butenoyl cyanide (**4e**)[4] designed to give a cyclic intermediate **6e** which would be already set up for elimination. This strategy worked well and the "one pot" acylation-cyclization-elimination of HBr (the elimination step was accomplished with Et_3N) sequence starting with the reaction of **4e** with tropinone Li-enolate yielded (±) isobellendine **1a** (35%).

Enantioselective syntheses: The synthetic strategy described above should yield pure enantiomers of compounds **5a-e**, and, consequently, enantiomerically pure natural products, if a method allowing enantioselective deprotonation of tropinone was available. Previous studies done by our group,[5] and also by others,[6,7b] proved that tropinone can be deprotonated enantioselectively, but the selectivity was often modest. It was also observed that, certain additives can increase the enantioselectivity, sometimes substantially.[7]

Studying a novel reaction of tropinone ring opening via deprotonation with chiral base **7** followed by treatment with benzyl chloroformate (i.e. **2** to **8**),[5] we initially observed formation of the cycloheptenone product **8** having optical purity of 45%. When LiCl was added to the enolate the efficiency of the reaction varied with the amount of LiCl used and reached a maximum with 0.5 equivalent of LiCl (per amide; cf. Scheme 2 and Fig. 1). Other chiral bases tested behaved similarly; base **9** proved to work exceptionally well and, in the presence of 0.5 equivalent of LiCl, yielded the product **8** having optical purity of 92%.

SCHEME 2



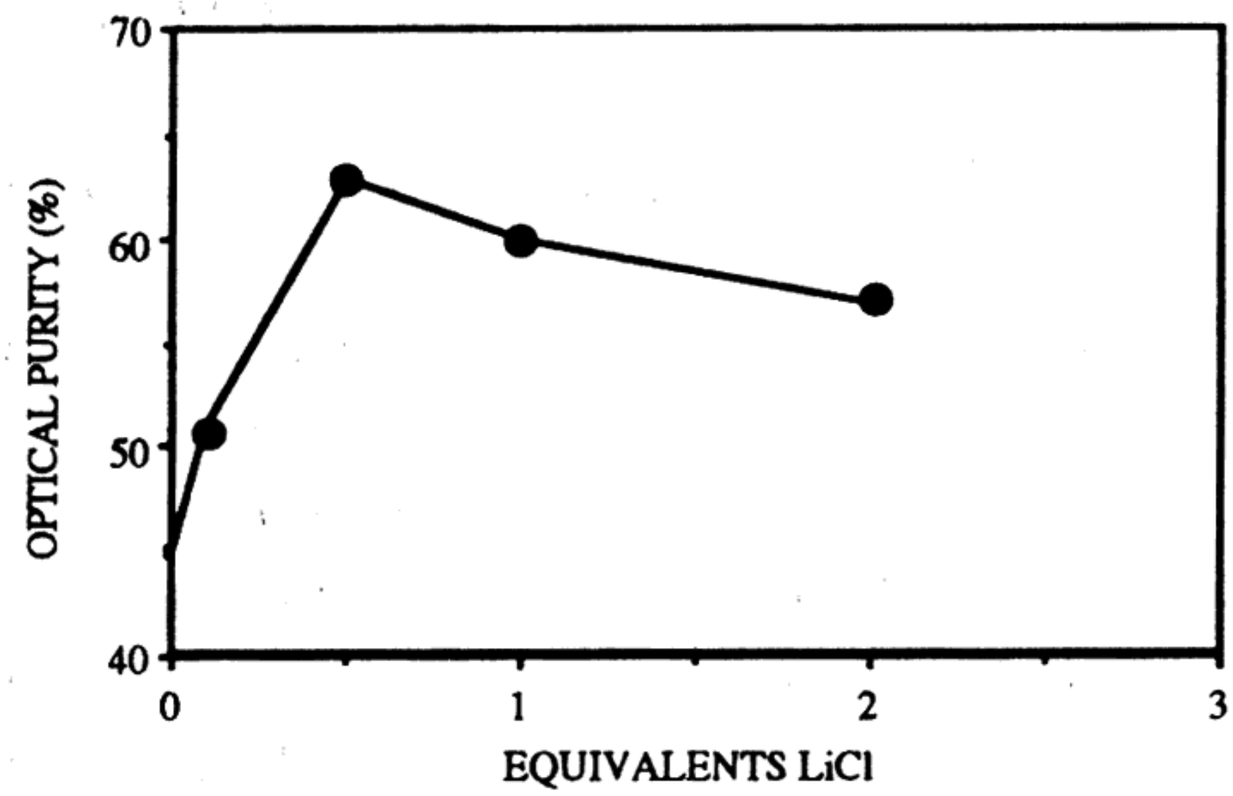


Fig. 1: Dependence of optical purity of **8** on the amount of LiCl additive (base **7**).

We then applied base **9** in the synthetic pathway depicted in Scheme 1 (in the presence of 0.5 equivalents of LiCl). This allowed us to synthesize the non-natural enantiomers of tropane alkaloids: *ent*-chalcostrobamine, *ent*-isobellendine and *ent*-darlingine; as well as compound **6d** in optically active form. The yields and selectivities are summarized in Table 1.

Table 1: Synthesis of ent-isobellendine (**1a**), ent-darlingine (**1b**), ent-chalcostrobamine (**5c**) and **6d**:

PRODUCT	YIELD (%)[a]	EE (%)
1a	45	88[b]
1b	53	-[c]
5c	75	90[b]
6d	90	92[d]

(a) All yields were calculated from tropinone and refer to chromatographically purified products (b) ee determined by NMR with chiral solvating agent[8] (c) no suitable method to measure ee was found (d) by HPLC (ChiraDex^{R}).

Thus, enantioselective deprotonation of tropinone, followed by reaction of the enolate with the appropriate acyl cyanide, followed by cyclization provides a concise synthetic approach to tropane alkaloids belonging to the pyranotropane group.[8]

REFERENCES AND NOTES

1. Review: Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1.
2. a. Greene, A. E.; Serra, A. A.; Barreiro, E. J.; Costa, P. R. R. *J. Org. Chem.* **1987**, *52*, 1170.
   b. Cain, C. N.; Simpkins, N. S. *Tetrahedron Lett.* **1987**, *28*, 3723.
   c. Leonard, J.; Ouali, D.; Raman, S. K. *Tetrahedron Lett.* **1990**, *31*, 739.
   d. Izawa, H.; Shirai, R.; Kawasaki, H.; Kim, H.-D.; Koga K. *Tetrahedron Lett.* **1989**, *30*, 7221.
   e. Cox, P. J.; Simpkins, N. S. *Synlett* **1991**, 321.
   f. Wild, H.; Born L. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1685.
   g. Honda, T.; Kimura, N.; Tsubuki, M. *Tetrahedron: Asymmetry* **1993**, *4*, 21.
   h. Bunn, B. J.; Cox, P. J.; Simpkins, N. S. *Tetrahedron* **1993**, *49*, 207.
3. Recent review on tropane alkaloids: Lounasmaa, M.; Tamminen, T. In *The Alkaloids*; Cordell, G. A. Ed.; Academic Press: Toronto, **1993**, vol. *44*, pp. 1-100.
4. a. Lounasmaa, M.; Holmberg, C.; Langenskiold, T. *Planta Medica* **1983**, *48*, 56. Acyl cyanides **4a-d** were synthesized as described: b. Hoffman, H. M. R.; Haase, T.; Ismail, Z. M.; Preftitsi, S.; Weber, A. *Chem. Ber.* **1982**, *115*, 3880. c. Normant, J. F.; Piechucki, C. *Bull. Soc. Chim. Fr.* **1972**, *6*, 2402. Compound **4e** was prepared by additon of Br_2 to crotonyl cyanide and elimination of HBr from the product (75% yield).
5. Majewski, M.; Zheng G.-Z. *Can. J. Chem.* **1992**, *70*, 2618.
6. a. Momose, T.; Toyooka, N.; Seki, S.; Hirai, Y. *Chem. Pharm. Bull.* **1990**, *38*, 2072.
   b. Momose, T.; Toyooka, N.; Hirai, Y. *Chem. Lett.* **1990**, 1319.
7. a. Majewski, M.; Gleave, D. M. *J. Org. Chem.* **1992**, *57*, 3599.
   b. Bunn, B. J.; Simpkins, N. S. J. Org. Chem. **1993**, *58*, 533.
8. The procedure used in synthesis of compound **6d** was typical: Lithium amide **9** was prepared by mixing n-BuLi (1.2 mmol; 0.60 mL of 2.0 molar soln. in hexanes) with the chiral amine (0.329 g, 1.2 mmol) in THF (3.5 mL) at 0°C. Lithium chloride in THF (0.48 mmol, 0.96 mL of 0.5 molar THF soln.) was added and the mixture was stirred for 15 minutes. After cooling to -78°C, tropinone (0.139 g, 1 mmol) in THF (1 mL) was added dropwise. After 2.5 h senecioyl cyanide **4d** (0.20 mL, 0.28 g, 2.6 mmol) was added and the resulting mixture was stirred at -78°C for 30 min followed by quenching with 40% K_2CO_3 (4 mL). After warming to r.t. the product was extracted out with ether (3x10 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed under vacuum to give the crude product **5d** which was refluxed for 1 hour in ethanol (2 mL) with anhydrous sodium carbonate (0.2 g). The resulting product **6d** was purified by flash chromatography on silica gel deactivated with triethylamine (50% AcOEt in hexane followed by 10% MeOH in CH_2Cl_2) which yielded the product **6d** as colourless oil (0.199 g, 90%) and the recovered chiral amine (0.312 g, 95% recovery). Compound **6d** had $[\alpha]_D^{22}$ -33° (c = 0.01 g/mL, MeOH) and 92% ee by HPLC (ChiraDex^R). The spectra (NMR, IR, MS) and the elemental analysis were in agreement with the proposed structure. NOTE: ee of the other products was also measured by ^{1}H-NMR in the presence of a chiral solvating agent [S-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol].