

Rapid Access to *trans*-2,6-Disubstituted Piperidines: Expedient Total Syntheses of (–)-Solenopsin A and (+)-*epi*-Dihydropinidine

Adrian P. Dobbs,* Sebastien J. J. Guesné

Department of Chemistry, University of Exeter, Stocker Road, Exeter, EX4 4QD, UK
 Fax +44(1392)263434; E-mail: A.Dobbs@exeter.ac.uk

Received 4 May 2005

Abstract: Expedient syntheses of (–)-solenopsin A and (+)-*epi*-dihydropinidine are reported, the key step in both being the one-pot multicomponent aza-silyl-Prins condensation reaction to yield a *trans* dihydropyridine.

Key words: total synthesis, (–)-solenopsin A, (+)-*epi*-dihydropinidine, multicomponent condensation, aza-silyl-Prins reaction, *trans* dihydropyridine

The piperidine ring system is one of the most common motifs found in numerous natural products, drugs and drug candidates. Accordingly, the important bioactivities of piperidines have stimulated the development of new synthetic approaches and considerable efforts have been devoted to the enantioselective preparation of these compounds. An excellent review of the synthesis of piperidines has recently appeared.¹ *Trans*-2,6-disubstituted piperidines represent a subclass of naturally occurring alkaloids that have also been the targets of many synthetic efforts, not only due to their range of pharmacological activities but also the difficulty in establishing the *trans* substitution pattern across the nitrogen atom. Notable examples include (–)-solenopsin A (**1**), a constituent of fire-ant venom from *Solenopsis* species, the venom of which is characterised by a predominance of 2-alkyl-6-methylpiperidines.² These have appeared as novel drug candidates for the treatment of Alzheimer's disease. The structurally related (+)-*epi*-dihydropinidine has been isolated from pine and spruce species such as *Picea pungens* or *Pinus ponderosa* (Figure 1).³

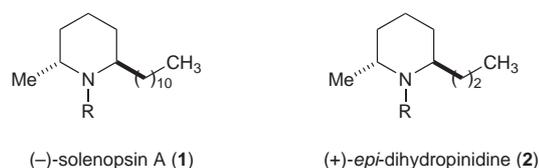
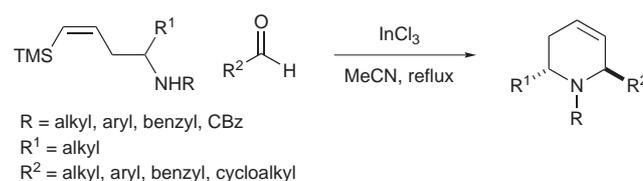


Figure 1

There are too many synthetic approaches to these and other *trans*-2,6-disubstituted piperidines to be able to report them all here, so the reader is directed to several recent reviews for a comprehensive coverage.^{1,4}

We have previously reported the aza-silyl-Prins reaction (ASPR; Scheme 1) as an efficient method for the preparation of tetrahydropyridines.⁵ The ASPR involves the reaction of an aldehyde with a silylated homoallylic amine in the presence of a mild Lewis acid; the easy-to-handle and moisture-tolerant indium trichloride being the one of choice in the majority of our work. Furthermore, the reaction is completely diastereoselective and gives only the 2,6-*trans*-substituted product when a R¹ substituent is introduced in the homoallylic amine component. Given this complete diastereocontrol, it occurred to us that (–)-solenopsin A and (+)-*epi*-dihydropinidine would be excellent targets to showcase this novel methodology in total synthesis and hence reduce the number of steps in the overall synthesis of these important synthetic targets.

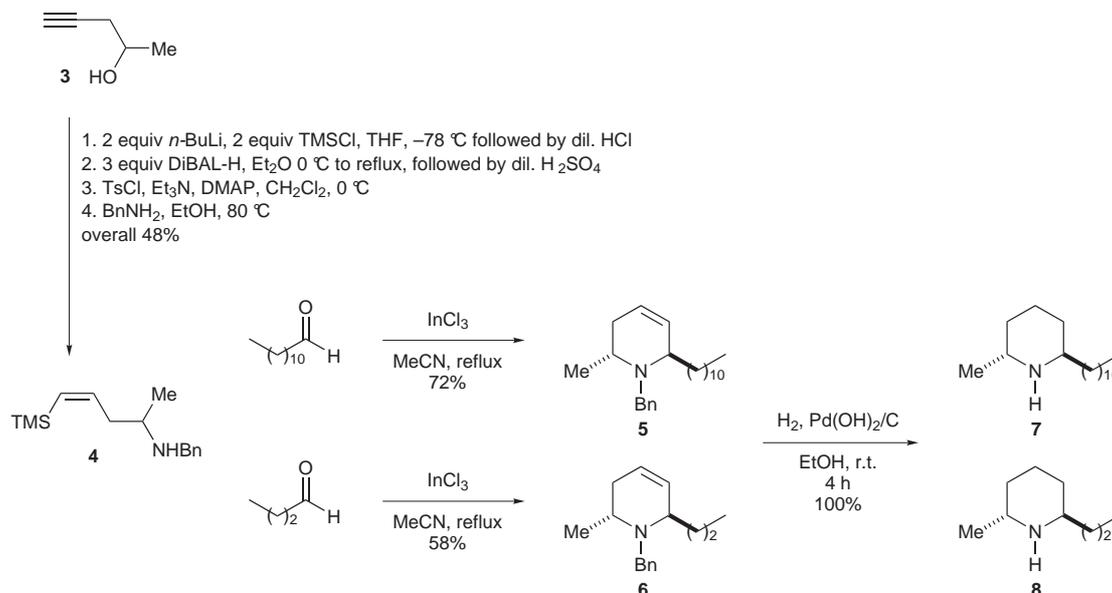


Scheme 1 The aza-silyl-Prins reaction

We envisaged efficient total syntheses of **1** and **2** using a common strategy from an intermediate tetrahydropyridine, prepared via the ASPR.

Racemic syntheses of both compounds were first performed. The two aldehydes required were dodecyl aldehyde and butyraldehyde, both of which are commercially available. The required *N*-benzyl-substituted secondary amine was prepared in four steps from 4-pentyn-2-ol: silylation, DiBAL-H reduction, tosylation and displacement with benzylamine, to give **4** in 48% yield over the four steps.⁵ The ASPR reaction proceeded in good yields to give the *trans*-substituted tetrahydropyridines **5** and **6** in 72% and 58% yield, respectively. The *trans*-configuration of both compounds was determined by NOE studies, with enhancement observed between the axial methyl group and axial hydrogen atom.

Having carefully chosen the benzyl protecting group, it was now possible, in one step, both to deprotect the benzyl group and hydrogenate the double bond using catalytic hydrogenation on a palladium hydroxide catalyst in quantitative yield after four hours. Thus, it was possible



Scheme 2 Total syntheses of racemic solenopsin A and epi-dihydropinidine

to obtain both racemic solenopsin A and racemic *epi*-dihydropinidine in six linear steps and 35% and 28% overall yields, respectively.⁶

The racemic syntheses described were readily modified to enantiospecific ones simply by the introduction of an additional step at the start of the synthetic schemes: commencing with the ring opening of either (*R*)-(+)- or (*S*)-(–)-propylene oxide with trimethylsilylacetylene and boron trifluoride etherate afforded enantiomerically pure samples of both stereoisomers of **4**. Completion of the reaction sequence as described gave enantiopure samples of both the natural and unnatural isomers of **7** and **8** (Scheme 2). No racemisation was observed during the reaction sequence.⁷

In summary, we have reported the first successful application of the ASPR reaction in enantioselective total synthesis and have completed the syntheses of both racemic, natural and unnatural solenopsin A and *epi*-dihydropinidine.

Typical Experimental Procedure for the Indium Trichloride Mediated ASPR

The secondary amine (1.0 mmol) was added dropwise to a solution of indium trichloride (221 mg, 1.0 mmol) and an aldehyde (1.0 mmol) in anhydrous MeCN (20 mL) at reflux temperature. Once the reaction was completed (monitored by TLC) the solution was cooled, concentrated and the residue obtained was partitioned between CH₂Cl₂ (20 mL) and 1 M NaOH (20 mL). The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with 1 M NaOH, H₂O, dried (MgSO₄) and concentrated under reduced pressure. The residue obtained was then purified by flash chromatography to give the corresponding tetrahydropyridine.

(±)-*trans*-1-Benzyl-2-methyl-6-undecyl-1,2,3,6-tetrahydropyridine (**5**)

Following the general procedure, (±)-*N*-benzyl-*N*-(*Z*)-(1-methyl-4-trimethylsilylbut-3-enyl)amine (**4**) (250 mg, 1.00 mmol) and dodecyl aldehyde (244 μL, 1.00 mmol), were reacted and TLC indicated full consumption of starting materials after 24 h of stirring at reflux temperature. The work up gave a yellow oil, which was purified by flash column chromatography (95% hexane, 4% EtOAc, 1% Et₃N) to give the title compound (243 mg, 0.71 mmol, 72%) as a colourless oil. IR (neat) ν_{\max} = 2925, 1602 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.40–7.36 (2 H, m, ArH), 7.31–7.26 (2 H, m, ArH), 7.23–7.19 (1 H, m, ArH), 5.79–7.75 (1 H, m, H-C4), 5.61–5.57 (1 H, m, H-C5), 3.69 (1 H, d, *J* = 13.8 Hz, CHH-Ph), 3.48 (1 H, d, *J* = 13.8 Hz, CHH-Ph), 3.16–3.11 (1 H, m, H-C2), 2.91 (1 H, br s, H-C6), 2.04–1.91 (1 H, m, H-C3), 1.90–1.80 (1 H, m, H-C3), 1.50–1.36 (2 H, m, H-C9), 1.34–1.13 (18 H, m, H-C10–C18), 1.12 (3 H, t, *J* = 6.7 Hz, H-C8), 0.89 (3 H, t, *J* = 6.6 Hz, H-C19). ¹³C NMR (75.5 MHz, CDCl₃): δ = 141.4 (ArC), 129.9 (C5), 128.9 (ArCH), 128.1 (ArCH), 126.5 (ArCH), 124.8 (C4), 56.8 (C6), 50.8 (C7), 46.7 (C2), 33.9 (C9), 32.1 (C10), 29.8 (C11–C16), 29.5 (C3), 26.0 (C17), 22.8 (C18), 16.8 (C8), 14.3 (C19). MS (CI): *m/z* (%) = 342 (100) [MH⁺], 186 (54). HRMS: *m/z* calcd for C₂₄H₄₀N: 342.3161; found [MH⁺]: 342.3155. Anal. Calcd for C₂₄H₃₉N: C, 84.39; H, 11.51; N, 4.10. Found: C, 84.45; H, 11.36; N, 4.19. For (–)-(2*R*,6*R*)-*trans*-1-benzyl-2-methyl-6-undecyl-1,2,3,6-tetrahydropyridine: [α]_D³⁰ –40.9 (*c* 1.1, CHCl₃).

(±)-*trans*-1-Benzyl-2-methyl-6-propyl-1,2,3,6-tetrahydropyridine (**6**)

Following the general procedure, (±)-*N*-benzyl-*N*-(*Z*)-(1-methyl-4-trimethylsilylbut-3-enyl)amine (250 mg, 1.00 mmol) and butyraldehyde (89 μL, 1.00 mmol) were reacted and TLC indicated full consumption of starting materials after 24 h of stirring at reflux temperature. The work up gave a brown oil, which was purified by flash column chromatography (97% hexane, 2% EtOAc, 1% Et₃N) to give the title compound (133 mg, 0.57 mmol, 58%) as a yellow oil. IR (neat) ν_{\max} = 2959, 1601 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.38–7.36 (2 H, m, ArH), 7.31–7.29 (2 H, m, ArH), 7.23–7.21 (1 H, m, ArH), 5.81–5.74 (1 H, m, H-C4), 5.62–5.56 (1 H, m, H-C5), 3.69 (1 H, d, *J* = 14.0 Hz, CHH-Ph), 3.47 (1 H, d, *J* = 14.0, CHH-Ph), 3.14 (1 H, br s, H-C2), 2.92 (1 H, br s, H-C6), 2.05–1.94

(1 H, m, H-C3), 1.94–1.82 (1 H, m, H-C3), 1.47–1.18 (4 H, m, H-C9, H-C10), 1.12 (3 H, d, $J = 6.4$ Hz, H-C8), 0.77 (3 H, t, $J = 7.2$ Hz, H-C11). ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 141.4$ (ArC), 129.8 (C5), 128.8 (ArCH), 128.1 (ArCH), 126.5 (ArCH), 124.8 (C4), 56.7 (C6), 50.7 (C7), 46.7 (C2), 36.3 (C9), 39.5 (C3), 19.2 (C10), 16.9 (C8), 14.3 (C11). MS (CI): m/z (%) = 230 (42) $[\text{MH}^+]$, 186 (100), 91 (10). HRMS (CI): m/z calcd for $\text{C}_{16}\text{H}_{24}\text{N}$: 230.1908; found $[\text{MH}^+]$: 230.1917. Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{N}$: C, 83.79; H, 10.11; N, 6.11. Found: C, 83.88; H, 9.98; N, 6.14.

Acknowledgment

We gratefully acknowledge the EPSRC (studentship to SJJG) and the Royal Society (small equipment grant) for funding of this project.

References

- (1) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.
- (2) (a) Isolation of solenopsin A: Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982**, *38*, 1949. (b) Potential for treatment of Alzheimer's disease: Takadoi, M.; Yamaguchi, K.; Terashima, S. *Bioorg. Med. Chem.* **2003**, *11*, 1169.
- (3) Todd, F. G.; Stermitz, F. R.; Blokhin, A. V. *Phytochemistry* **1995**, *40*, 401.
- (4) (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781.
(b) Felpin, F. X.; Lebreton, J. *Curr. Org. Chem.* **2004**, 83.
- (5) (a) Dobbs, A. P.; Guesné, S. J. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880.
(b) Dobbs, A. P.; Guesné, S. J. J.; Coles, S. J.; Hursthouse, M. B. *Synlett* **2003**, 1740.
- (6) All compounds gave satisfactory analytical and spectroscopic data. Data for **7** and **8** in agreement with previously reported values.^{2,3}
- (7) The absence of racemisation of compounds **4–8** was judged by NMR experiments using $\text{Eu}(\text{hfc})_3$ doping at each stage and comparison with the racemic series, where separation occurred.