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SYNTHESIS OF (±)-ISOPROSOPININES A AND B

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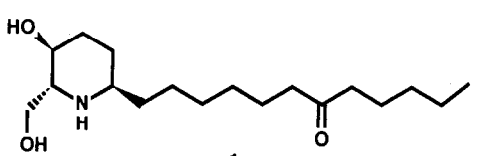
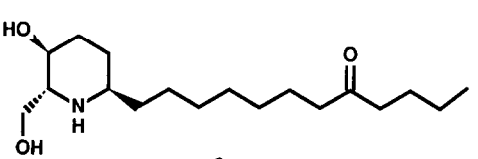
Summary: The total synthesis of the piperidine alkaloid isoprosopinine A (**1**) and an improved synthesis of isoprosopinine B (**2**) are reported. The key steps were alkylation of the anions of the sulphones (**5**) and (**6**) respectively with the common intermediate bromide (**4**) and the novel reductive cleavage of the sulphonamides (**7**) and (**8**) with sodium-amalgam.

The prosopis alkaloids form an interesting class of 2,3,6-trisubstituted piperidine derivatives exhibiting a range of biological activities.[1] We recently reported a synthesis of isoprosopinine B (**2**),[2] but comparison of the synthetic material with an authentic sample was complicated by the fact that (**2**) was isolated as an inseparable mixture with its isomer isoprosopinine A (**1**).[3] The previous synthesis of (**2**) relied on a relatively economical Wittig homologation reaction to introduce the side chain, but the yield was moderate. In this Letter we report a much improved method for side chain construction which has been applied to the first total synthesis of isoprosopinine A (**1**) and also to isoprosopinine B (**2**). During this synthesis a novel method for the reductive deprotection of N-tosylpiperidines has been discovered.



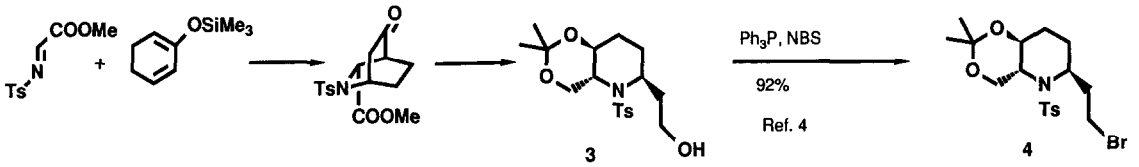
1



2

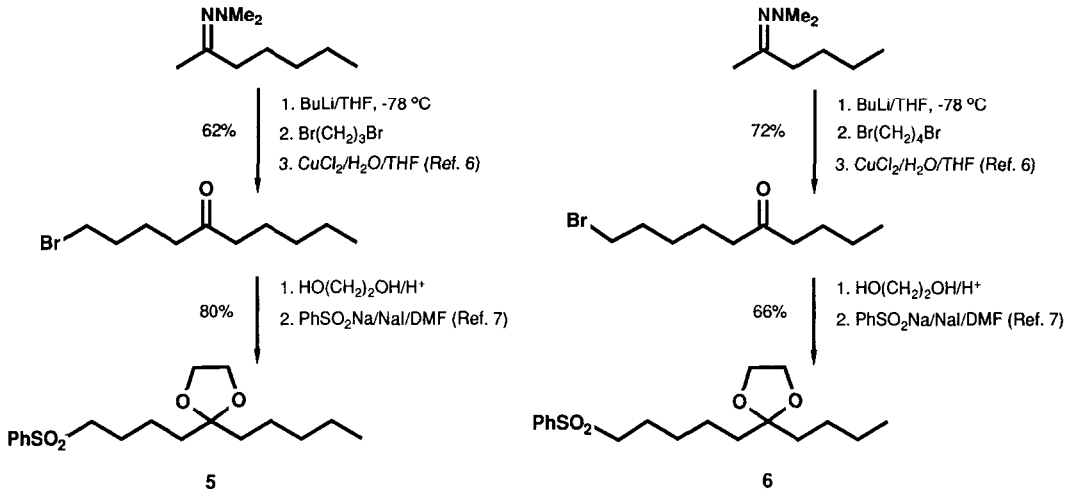
The common starting material for the syntheses is the bromide (**4**) which is readily prepared from the alcohol (**3**), itself available in five steps from simple starting materials (Scheme 1).[2]

SCHEME 1



The required side-chain sulphones (**5**) and (**6**) were prepared in good yield using Corey-Enders hydrazone alkylations of heptanone and hexanone respectively (Scheme 2).[5]

SCHEME 2

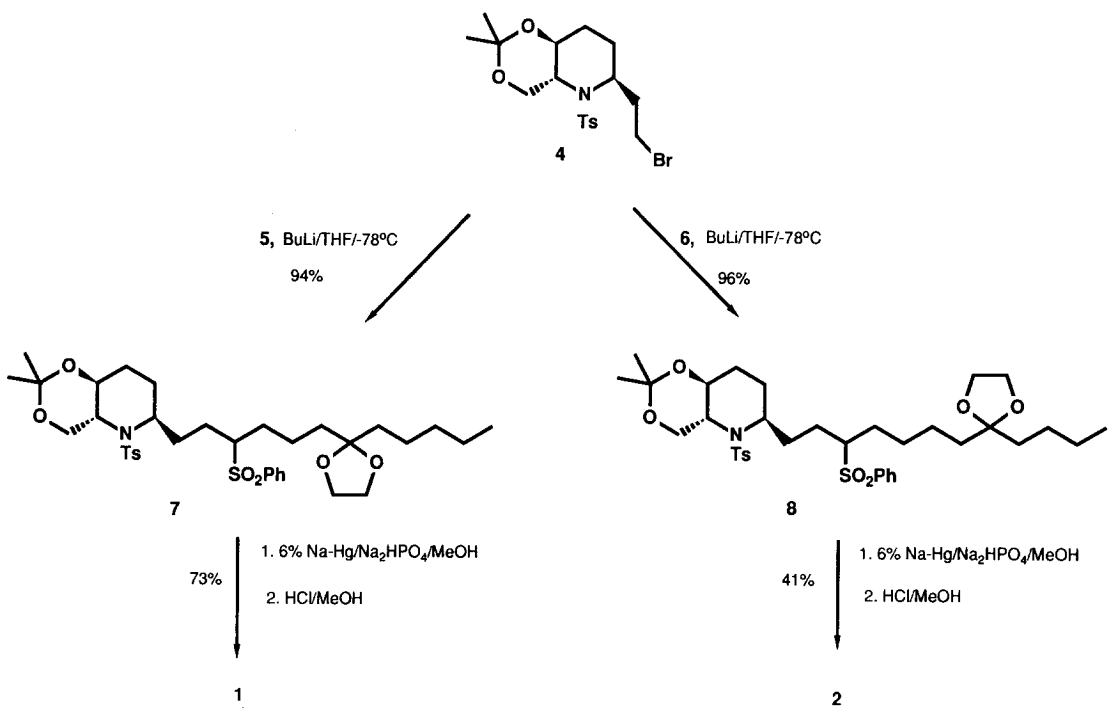


Coupling of the bromide (**4**) with the anions of the sulphones (**5**) and (**6**) gave the compounds (**7**) and (**8**) respectively, in high yield (Scheme 3). Attempts to remove the sulphone and N-tosyl groups from the piperidine (**7**) using either sodium in liquid ammonia[8] or sodium naphthalenide[9] gave complex mixtures. However the use of a large excess (20-30 eq.) of freshly prepared 6% sodium-amalgam in phosphate-buffered methanol removed (after two cycles) both the sulphone[10] and the N-tosyl protecting group cleanly, and the remaining protecting groups were removed with methanolic HCl to give (±)-isoprosopinine A (**1**) in good yield. This is, to our knowledge, the first report of the use of sodium-amalgam for sulphonamide cleavage, and may have wider application as a selective reagent for such deprotections. Similar treatment of the intermediate (**8**) gave, after removal of the other protecting groups (±)-isoprosopinine B (**2**) in slightly lower yield. This suggests that the success of the sodium-amalgam method for removal of N-tosyl groups is dependent on the age of the amalgam, and that optimum results require fresh

reagent.

The spectra of synthetic isoprosopinines A and B were very similar and resembled those of the mixed sample derived from natural sources.[3,11] The main difference between (**1**) and (**2**) can be detected in the ^{13}C NMR spectrum where methylene resonances in the side-chain differ slightly.[12]

SCHEME 3



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12. Data for (**4**): m.p., 93.5-94.5 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.8-7.2 (4H), 4.43 (1H, m), 4.31 (1H, dd, J 11.6, 10.8 Hz), 3.99 (1H, dd, J 11.6, 4.7 Hz), 3.61 (1H, ddd, J 10.6, 10.4, 4.4 Hz), 3.38 (2H, t, J 7.1 Hz), 3.17 (1H, ddd, J 10.8, 10.4, 4.7), 2.43 (3H, s), 2.41-1.4 (6H, m), 1.39 (3H, s), 1.34 (3H, s).
    Data for (**1**): m.p. 86-7 °C.
    ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.65 (1H, dd, J 10.6, 7.7 Hz), 3.60 (1H, dd, J 10.6, 5.5 Hz), 3.53 (1H, ddd, J 6.5, 5.5, 4.2 Hz), 2.82 (1H, dt, J 7.7, 5.5 Hz), 2.75 (1H, m), 2.37 (4H, t, J 7.5 Hz), 2.16 (3H, broad), 1.7-1.1 (20H, m), 0.87 (3H, t, J 6.8 Hz).
    ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 211.5, 68.0, 62.3, 58.2, 49.8, 42.8, 42.7, 33.7, 31.4, 29.4, 29.2, 28.6, 27.4, 26.1, 23.7, 23.6, 22.4, 13.8.
    IR ($CHCl_3$) 3610 (m), 3420 (m, broad) 2935 and 2860 (m), 1710 (s) cm^{-1}.
    Data for (**2**): m.p. 90-1 °C.
    ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.6 (1H, dd J 10.8, 7.6), 3.63 (1H, dd, J 10.8, 5.5 Hz), 3.55 (1H, ddd, J 6.5, 5.5, 4.2 Hz), 2.94 (1H, dt, J 7.7, 5.5 Hz), 2.83 (1H, m), 2.66 (3H, broad), 2.40 (4H, t, J 7.5 Hz), 1.8-1.1 (20H, m), 0.90 (3H, t, J 6.8 Hz).
    ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 211.4, 67.9, 62.9, 58.4, 49.9, 42.7, 42.5, 33.8, 29.4, 29.3, 29.2, 28.6, 27.3, 26.2, 26.1, 23.8, 22.4, 13.8.
    IR ($CHCl_3$) 3620 (m), 3460 (broad), 2930 and 2860 (s), 1710 (s) cm^{-1}.

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