Asymmetric Synthesis of (1*R*,8*S*)- and (1*S*,8*S*)-1-Hydroxypyrrolizidin-3-ones from Boc-L-Prolinal and (*S*)- and (*R*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)(Ac)], respectively

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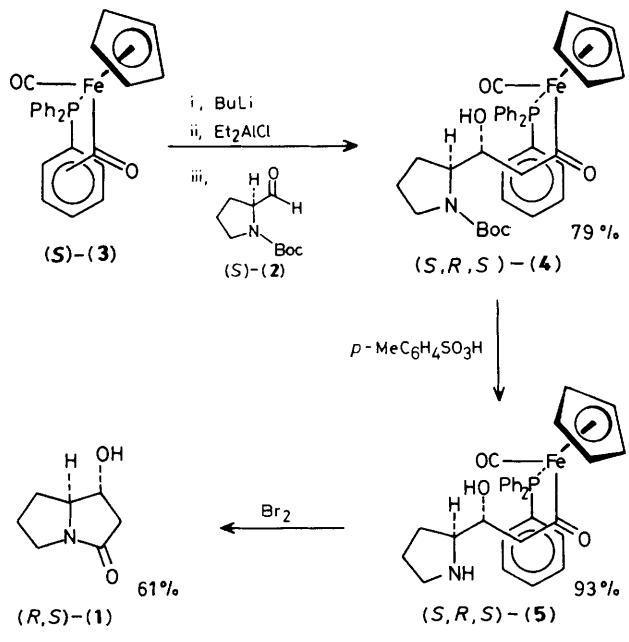
The aldol reaction between the aluminium enolate derived from (*S*)-[(η^5-C_5H_5)Fe(CO)(PPh_3)(Ac)] (*S*)-(**3**) and Boc-L-prolinal (*S*)-(**2**) gives, after deprotection and decomplexation, (1*R*,8*S*)-1-hydroxypyrrolizidin-3-one, (**1**), while its epimer (1*S*,8*S*)-(**1**) is obtained in a similar way from (*R*)-(**3**), the inherent stereocontrol of (**2**) being overpowered by the iron chiral auxiliary.

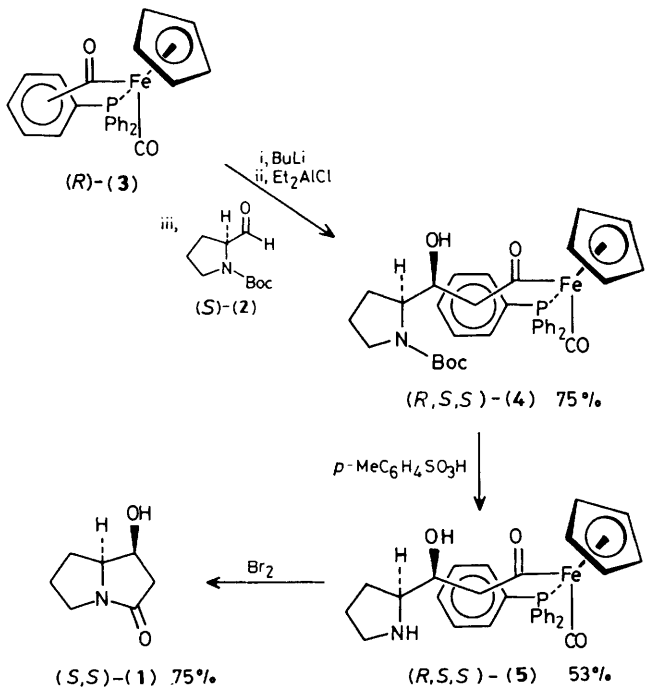
The pyrrolizidine alkaloids represent an important class of plant-derived natural products, many of which contain substituents in the 1-position.[1] Recently Hanson and co-workers[2] demonstrated the synthesis of (1*R*,8*S*)-1-hydroxypyrrolizidin-3-one (**1**) by the addition of ethyl acetate enolate to Boc-L-prolinal (*S*)-(**2**) followed by deprotection and lactamisation. Unfortunately, the aldol condensation showed little stereoselectivity and yielded a 4:1 mixture of aldol products from which the major (*RS*)-diastereoisomer could be separated and converted into (1*R*,8*S*)-(**1**). We have previously shown that the aluminium enolate derived from the chiral iron acetyl [(η^5-C_5H_5)Fe(CO)(PPh_3)(Ac)] (**3**)† undergoes highly stereoselective (>100:1) aldol reactions with aldehydes.[3] We report here that in the aldol reaction between the aluminium enolate derived from (**3**) and Boc-L-prolinal (S)-(**2**), the iron chirality overpowers the latent stereoselectivity inherent in Boc-L-prolinal to allow, after deprotection and decomplexation, the synthesis of (1*R*,8*S*)-(**1**) and (1*S*,8*S*)-(**1**) from (*S*)-(**3**) and (*R*)-(**3**), respectively.

Deprotonation of (*S*)-(**3**) gave the corresponding lithium enolate. Transmetallation with diethylaluminium chloride and addition of (*S*)-(**2**) gave (*S*,*R*,*S*)-(**4**) as a single diastereoisomer (>300:1). Deprotection with toluene-*p*-sulphonic acid gave the corresponding (*S*,*R*,*S*)-β-hydroxy-γ-amino complex (**5**), which on oxidative decomplexation yielded the known (1*R*,8*S*)-1-hydroxypyrrolizidin-3-one (**1**) directly,‡ m.p. 81—82 °C, $[\alpha]_D^{20}$ −97.0° (*c* 0.3, $CHCl_3$): lit.[2] m.p. 84—86 °C, $[\alpha]_D^{20}$ −91.5° (*c* 1, $CHCl_3$).

Addition of Boc-L-prolinal (**2**) to the aluminium enolate derived from (*R*)-(**3**) gave (*R*,*S*,*S*)-(**4**) together with a small amount of the (*R*,*R*,*S*)-diastereoisomer (ratio 35:1). Deprotection and oxidative cyclisation gave (1*S*,8*S*)-(**1**) contaminated with a small amount of the (1*R*,8*S*)-epimer (ratio 35:1). A single recrystallisation gave the novel compound (1*S*,8*S*)-1-hydroxypyrrolizidin-3-one diastereoisomerically pure,‡ m.p. 118—119 °C, $[\alpha]_D^{20}$ −48.8° (*c* 0.3, $CHCl_3$).

The differing stereoselectivities observed in the reactions of (*S*)- and (*R*)-(**3**) with Boc-L-prolinal is compatible with the





† (*R*)-(**3**) and (*S*)-(**3**) were obtained from New Specialities Business, B.P. Chemicals Limited, Belgrave House, 76 Buckingham Palace Road, London SW1W 0SU, U.K.

‡ Satisfactory spectroscopic data were obtained for all compounds. Compounds (*S*,*R*,*S*)-(**4**), (*R*,*S*,*S*)-(**4**), (*R*,*S*)-(**1**), and (*S*,*S*)-(**1**) gave satisfactory elemental analytical data. ^{1}H n.m.r. (300 MHz) (*R*,*S*)-(**1**) δ ($CDCl_3$) 4.22 (1H, m, H-1), 3.74 (1H, m, H-8), 3.54 (1H, m, H-5β), 3.22 (1H, d, *J* 5.1 Hz, OH), 3.03 (1H, m, H-5α), 2.73 (2H, d, *J* 8.3 Hz, H-2α,2β), 2.14 (1H, m, H-7β), 2.08—1.95 (2H, m, H-6α,6β), and 1.45 (1H, m, H-7α); (*S*,*S*)-(**1**) δ ($CDCl_3$) 4.41 (1H, m, H-1), 4.00 (1H, m, H-8), 3.86 (1H, d, *J* 6.2 Hz, OH), 3.56 (1H, m, H-5β), 3.06 (1H, m, H-5α), 2.98 (1H, dd, *J* 16.7 and 4.9 Hz, H-2α), 2.44 (1H, d, *J* 16.7 Hz, H-2β), 2.17—2.05 (3H, m, H-6α,6β and H-7β), and 1.79 (1H, m, H-7α). Assignments were supported by COSY data.

concept of double asymmetric induction.[4] In the former reaction the two original chiral centres are acting in concert whereas in the latter they are opposed. The iron chiral auxiliary however overpowers the latent stereoselectivity inherent in Boc-L-prolinal to make both (1*R*,8*S*)- and (1*S*,8*S*)-(**1**) readily accessible.

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