

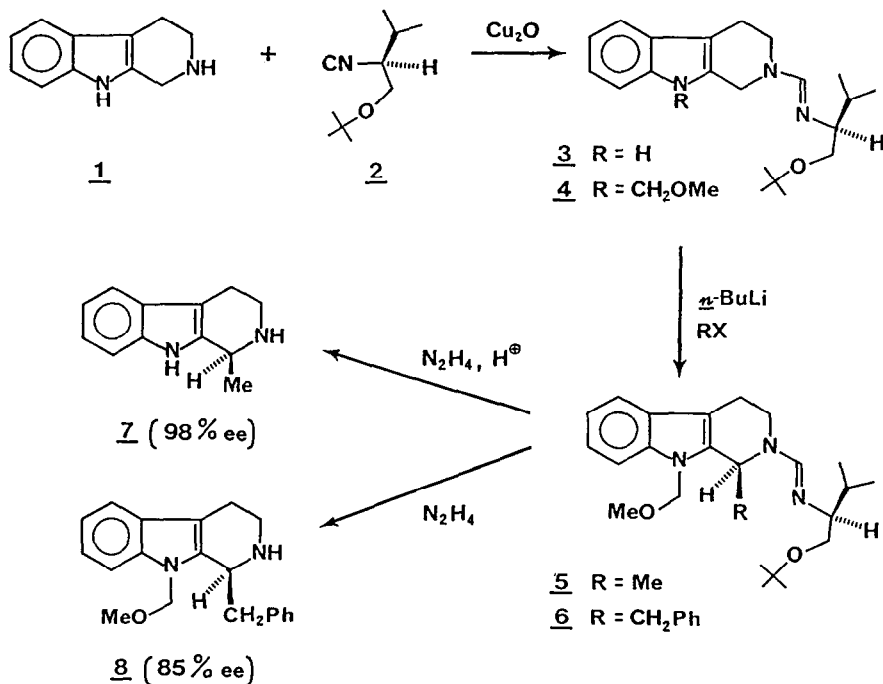
AN ASYMMETRIC SYNTHESIS OF INDOLE ALKALOIDS

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Summary: Chiral formamidines derived from β -carboline are metallated and alkylated stereoselectively opening a route to indole alkaloids and analogous compounds.

In our continuing studies on asymmetric alkylation of chiral formamidines which have thus far led to enantioselective syntheses of isoquinoline alkaloids,¹ we have probed other heterocyclic amines in an effort to expand the scope of this useful process. We now can report that, in addition to isoquinoline alkylations, the β -carboline system 1 can also be utilized as the starting point for enantioselective indole alkaloid syntheses. We have already described, in racemic systems, the construction of a variety of indole alkaloids,²

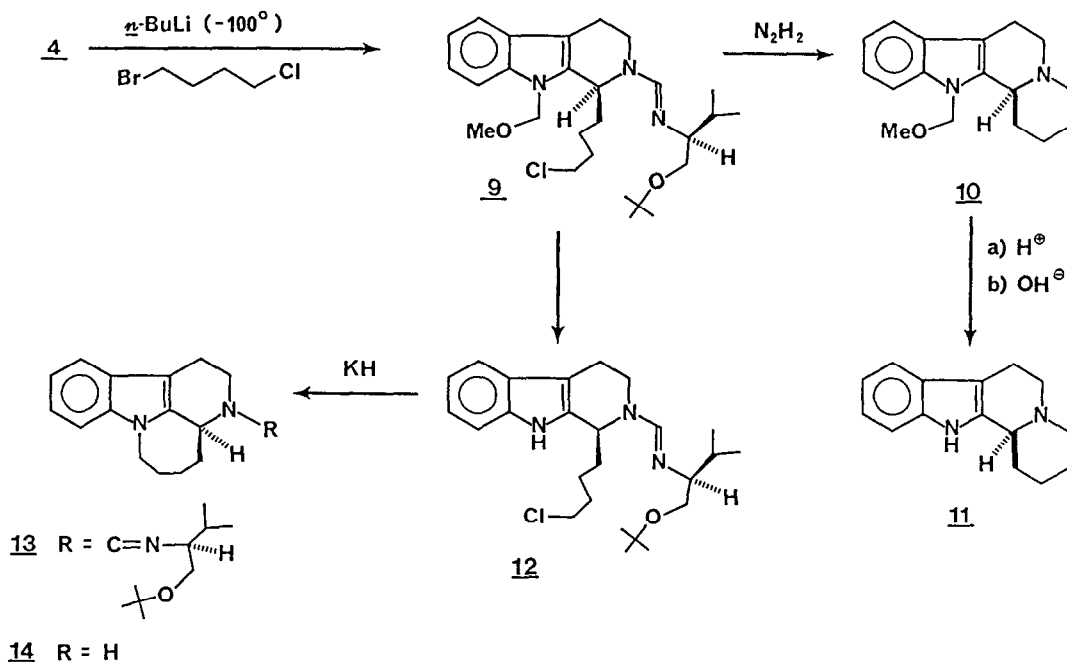


piperidines,³ and related heterocycles⁴ which can be prepared in good yields via the formamidine-activated dipole stabilized carbanions and this report will outline our preliminary studies using chiral formamidines.

Transformation of 1 into the chiral formamidine 3 was accomplished using the isocyanide 2⁵ (0.5 eq Cu₂O, PhMe, reflux) in 70% yield. The indole nitrogen required protection as the MOM ether 4 (KH, ClCH₂OMe, TMEDA, 85%) since the N-Li or N-K salts were unsuitable for the subsequent reactions.⁶ Treatment of 4 with n-BuLi (-78°, THF, 1 h) followed by addition of methyl iodide at -78° (30 min) gave after aqueous quench, the C-methyl product 5, isolated in crude form after ether extraction. To remove the formamidine, the latter was dissolved in a solution of ethanol-water-acetic acid-hydrazine (8:1:1:2) and stirred for 2 h. Evaporation left a residue which was taken up in ether, washed with 10% KOH, dried, and concentrated. The methoxymethyl group was removed as follows: addition of ether to the residue followed by 10% HCl (2 h), separation of the layers, basification of the aqueous layer, ether extraction, drying (K₂CO₃), and concentration gave (S)-7 (silica gel, EtOAc-MeOH-Et₃N; 100/10/5; mp 142-144°, [α]_D²⁵ -66.08°; c 2, EtOH). The alkaloid, tetrahydroharman, obtained in 52% overall yield, was subjected to chiral HPLC analysis⁷ and found to possess 98% ee.⁸

In a similar fashion 4 was transformed into 6 upon metallation and treatment with benzyl chloride. Removal of the formamidine moiety with hydrazine solution, as above, gave 8 in 67% overall yield (mp 71-72°, [α]_D²⁵ -20.4°; c 1, CHCl₃). The methoxymethyl group in 8 was removed (10% HCl, then 10% KOH), however, the free indole NH product was very sensitive to air and heat and, therefore, was not further characterized. The enantiomeric purity of 8 was determined using chiral HPLC analysis and gave a 92.5% S - 7.5% R ratio (85% ee).

The versatility of this indole alkaloid synthesis has also been exemplified by the efficient approach to natural (-)-indoloquinolizine 11 which utilized 4-bromo-1-chlorobutane in the alkylation step affording 9 in 85% yield. Hydrazinolysis gave the tetracyclic product 10 which, after hydrolysis, furnished the natural alkaloid 11 (mp 144-146°, [α]_D²⁵ -81.0°)⁹ in 96% ee. In addition to transforming 9 into 11, it was also possible to cyclize



the chlorobutyl group toward the indole nitrogen. Thus, the methoxymethyl group in 9 was removed (95.6% yield, 3N HCl-ether, 25° followed by 5% KOH) to give 12 which was smoothly cyclized (KH, THF-TMEDA, 2 h) to 13 in 94.8% yield. After removal of the formamidine group using the hydrazine solution (2 h, 25°) the tetracyclic indole 14 was obtained in 80% yield. Chiral HPLC analyses indicated that 14 contained 99% S and 1% R enantiomers; 98% ee (mp 105-107°, $[\alpha]_D^{25}$ -66.8°, 1.07, CHCl₃).¹⁰ Thus, we have demonstrated a highly versatile approach to indole alkaloids even at this early stage of our studies. Additionally, we have probed the underlying factors responsible for this highly selective alkylation, both in the carboline and isoquinoline series, and found some pertinent facts which are crucial to its success. These are reported in the accompanying paper.¹¹

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5. Isocyanide 2 prepared from the N-formylvalinol t-butyl ether (ref. 1a) by treatment of a DMF solution with SOCl_2 -DMF at -45° . After warming to -25° , Na_2CO_3 solution was added and stirred overnight. Extraction with ether and water wash gave 2 in 75% yield, bp 72° (3 torr), $\alpha_D +1.76^\circ$ (c 1.2, CHCl_3).
6. The N-Li derivative of 3 (R=Li) did not give the dilithio salt on metalation, whereas the N-K salt gave only a 70:30 ratio of enantiomers of 7. The N-Me derivative (3 R=Me) also gave high (> 97% ee) alkylation indicating that the indole N must be covalently substituted.
7. The "Pirkle Column," J. T. Baker and Co. was employed, see ref. 12 of the accompanying paper. The chiral HPLC analysis gave poor peak separation on 7, however when the indole N was methylated (KH-MeI), the peaks were baseline separated. Similarly, 8 gave good peak separation.
8. The literature report of mp 177° and $\alpha_D -52^\circ$ (S. Yamada, et al., Chem. Pharm. Bull. (Japan), **22**, 2614 (1974)) was based on an indirect correlation with the degradation product of (S)-(-)-salsolidine and "presumed to be optically pure." It should be noted that racemic tetrahydroharman (+)-7 was reported to have mp 178-180; G. M. Badger and A. F. Beecham, Nature, **168**, 517 (1951).
9. H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa, and S. Yamada, Bull. Soc. Chim. (Japan), **22**, 2614 (1974) report mp 149-151 $^\circ$, $\alpha -84^\circ$ (c 1 MeOH).
10. All new compounds gave satisfactory mass, elemental and spectral (270 MHz) analyses.
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