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# Diastereoselective Alkylation of Homochiral 1,2,3,4-Tetrahydroisoquinolin-3-one. A Potential Route to Enantiomerically Pure 4-Substituted Tetrahydroisoquinolines

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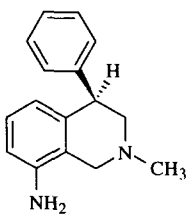
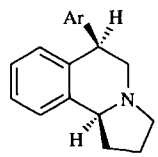
**Abstract:** Enantiomerically pure 1,4-dihydroisoquinolin-3-one **1** was prepared in four steps with an overall yield of 60%. Alkylation of the corresponding lactam enolate has been studied and has proven to be highly diastereoselective. Thus, 4-substituted-1,4-dihydroisoquinolin-3-ones **7a-d** were obtained in high chemical yields with up to 97% diastereoisomeric excesses.

During the past few years much attention has been paid to the development of highly stereoselective syntheses of 1-substituted tetrahydroisoquinolines[1] which are useful as key intermediates for the preparation of enantiopure tetrahydroisoquinolines alkaloids[2]. Enantiomerically pure tetrahydroisoquinoline derivatives substituted at C-3 and/or at C-4 are of considerable interest due to their biological activity and as naturally occuring alkaloids[3] (Figure **1**). Although such a substitution pattern is found in nature quite often, there is only a few efficient and general stereoselective methods available to control the stereochemistry at these positions[4].

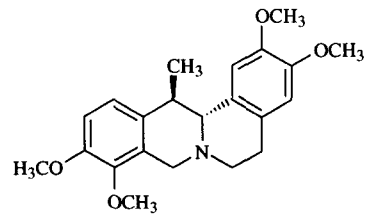
Figure **1**




(S)-Nomifensine




4-aryl hexahydropyrrolo[2,1-a] isoquinolines

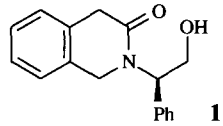



Corydaline

As part of a project aimed at developing asymmetric syntheses of tetrahydroisoquinolines, it occurred to us that it would be interesting to investigate the diastereoselective alkylation of homochiral 1,4-dihydroquinolin-3-ones bearing a chiral auxiliary at the nitrogen of the lactam. A survey of the literature revealed that diastereoselective alkylation of chiral amide enolates in which the chiral auxiliary is derived from aminoalcohols have been reported with success[5] as well as diastereoselective alkylation of lactam enolates[6]. For instance, Husson *et al* have recently described the highy diastereoselective alkylation of chiral lactams in the piperidine series[7] in which the chiral auxiliary is derived from (R)-phenylglycinol.

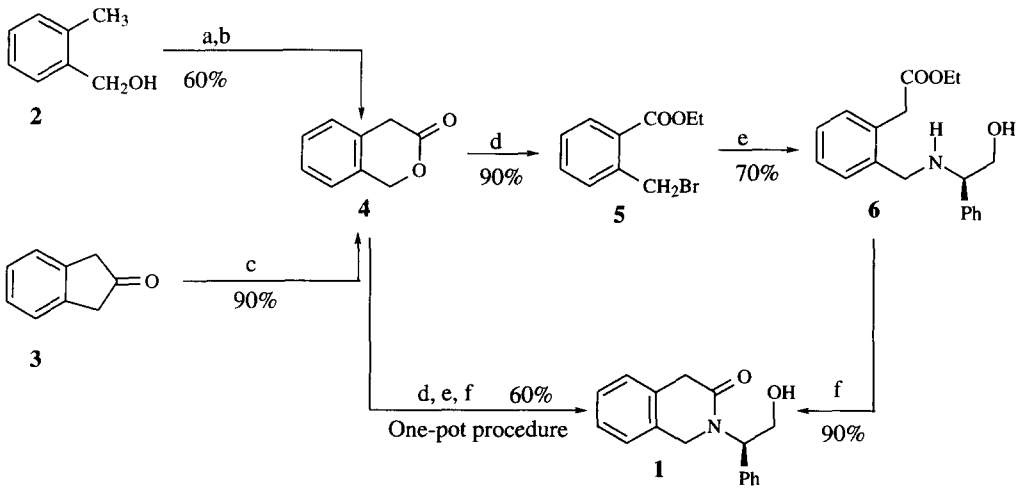
Consequently, we were interested in using this attractive methodology in the isoquinoline series with a view to accessing enantiomerically pure 4-substituted tetrahydroisoquinoline derivatives. We wish to report in this paper our preliminary results about diastereoselective alkylation of the chiral tetrahydroisoquinolin-3-one **1** (Scheme **1**).

Scheme **1**



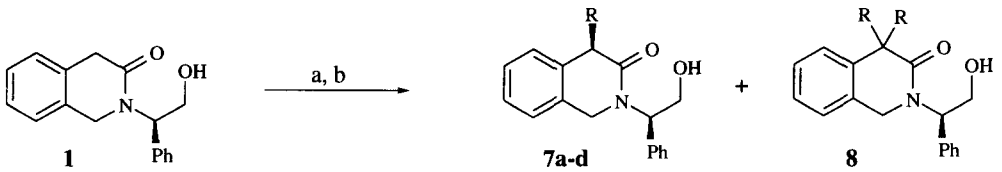

**1**

The homochiral tetrahydroisoquinolin-3-one **1** was prepared in a four step sequence either by lateral metallation[8] of 2-methylbenzyl alcohol **2** or by Baeyer-Villiger oxidation[9] of 2-indanone **3** to afford 3-isochromanone **4** in 60% and 90% yields respectively. The lactone **4** was then treated with an ethanolic solution of hydrobromic acid[10] to give the bromo ester **5** (80%) which in turn was condensed with (R)-phenylglycinol to afford the amine ester **6** (70%). Compound **6** was then cyclized in refluxing ethanol furnishing the desired 1,4-tetrahydroisoquinolin-3-one **1**[11] (80%). A one-pot procedure was alternatively used on a multigram preparative scale from 3-isochromanone **4** to yield the desired tetrahydroisoquinolin-3-one **1** in a 60% yield (Scheme **2**).




Scheme **2**: a, n-Buli / rt / $Et_2O$; b, $CO_2$; c, m-CPBA / $CH_2Cl_2$; d, HBr / EtOH; e, (R)-$NH_2CH(CH_2OH)Ph$ /EtOH; f, $K_2CO_3$ / EtOH / reflux.

Diastereoselective alkylation of the homochiral tetrahydroisoquinolin-3-one **1**, thus obtained, was studied (Scheme **3**) under various conditions (Table **1**). In first attempts, the enolate formation with alkyllithium bases or LDA followed by addition of methyl iodide, afforded the Cα–methylated lactam **7a** in good chemical yield with modest to good diastereoisomeric excesses ($65 < d.e. < 85$)[12] (Entries 1-4). The major enantiomer of compound **7a** was thought to have the S-configuration at C-4 , since this is the expected absolute configuration considering the mechanism of the reaction in the piperidine series[7]. The use of HMPA (3 eq) as co-solvent or addition of methyl iodide at lower temperature (-90°C) resulted in a somewhat higher diastereoselectivity (Entries 5-8). Finally, we found out that LiHMDS reacted efficiently and greatly improved the stereoselectivity of the reaction (d.e.> 97%) (Entry 9).




**1** **7a-d** **8**

Scheme **3**: a, Base (2.4 eq) / THF; b, RX

**7a** R = $CH_3$ **7b** R = $CH_3CH_2$ **7c** R = $CH_3(CH_2)_2$ **7d** R = $PhCH_2$

R = $CH_3$

Whatever the conditions used, it should be specified that 5 to 10% of the dimethylated dihydroisoquinolinone **8** could be identified by $^1H$ NMR and HPLC analysis of the crude product (Scheme **3**). In contrast, NaHMDS was much less satisfactory, leading mainly to the dimethylated compound **8** (80%) along with the desired monomethylated compound **7a** (15%) in a poor diastereoisomeric excess (d.e. = 8%) (Entry 10). Various alkylating agents were reacted with lactam **1** under the best conditions selected (LiHMDS/THF/-78°C)[13] to afford 4-alkylated tetrahydroisoquinolin-3-ones **7b-d** in good yields and excellent diastereoselectivities (Entries 11-13).

**Table 1**: Diastereoselective alkylation of tetrahydroisoquinolin-3-one **1**

| Entry | Base | t°C | RX | Chem. yield (%) | d.e. (%)[12] |
|---|---|---|---|---|---|
| 1 | n-BuLi | -78 | $CH_3I$ | 80 | 65 |
| 2 | s-BuLi | -78 | $CH_3I$ | 85 | 70 |
| 3 | t-BuLi | -78 | $CH_3I$ | 85 | 70 |
| 4 | LDA | -78 | $CH_3I$ | 80 | 85 |
| 5 | t-BuLi / HMPA | -78 | $CH_3I$ | 87 | 85 |
| 6 | s-BuLi / HMPA | -78 | $CH_3I$ | 83 | 75 |
| 7 | LDA / HMPA | -78 | $CH_3I$ | 81 | 90 |
| 8 | t-BuLi / HMPA | -90 | $CH_3I$ | 80 | 85 |
| 9 | LiHMDS | -78 | $CH_3I$ | 88 | >97 |
| 10 | NaHMDS | -78 | $CH_3I$ | 15 | 8 |
| 11 | LiHMDS | -78 | EtI | 85 | >97 |
| 12 | LiHMDS | -78 | n-PrI | 87 | >97 |
| 13 | LiHMDS | -78 | $PhCH_2Br$ | 80 | >97 |

In conclusion, the highly diastereoselective alkylation of the readily available tetrahydrodroisoquinolin-3-one **1** has been achieved in good chemical yield. Optimization of the reaction conditions as well as the use of other electrophiles are currently being investigated to extend this potentially important method for introducing C-4 substituents and to develop access to enantiomerically pure tetrahydroisoquinolines derivatives of biological interest.

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11. Compound **1**: $^1$H NMR data (δ, ppm; *J*, Hz): ($CDCl_3$ at 200 MHz) δ 3.73 (s, 2H), 4.12 (d, 1H, *J* = 15.5), 4.18 (dd, 1H, *J* = 11.7 and 8.6), 4.22 (dd, 1H, *J* = 11.7 and 5), 4.36 (d, 1H, *J* = 15.5), 5.81 (dd, 1H, *J* = 8.6 and 5), 7.00 (d, 1H, *J* = 7.5), 7.17-7.33 (m, 8H). *Anal.* Calcd. for $C_{17}H_{17}N0_2$: C, 75.27; H, 6.71; N, 5.21. Found: C, 75.42; H, 6.89; N, 5.07.
12. Diastereoisomeric excesses were measured by $^1$H NMR spectroscopy of the crude product [major diastereoisomer: δ=1.54 (d, *J*=7.2 Hz, $CH_3$); minor diastereoisomer: δ=1.53 (d, *J*=7.2 Hz, $CH_3$)] and by HPLC analysis [Chromatographic conditions: column: Sepralyte C18 (4.6 X 250 mm; 5μm) purchased from Analytichem International; UV detection (λ=210nm); Mobile phase: $CH_3CN$/ $H_20$ (70/30); Flow rate: 1 ml / min; Injection: 20 μl (1 mg of sample in 20 ml of eluent)].
13. Alkylation of compound **1** (typical procedure): To a solution of **1** (0.75 mmol) in dry THF (8 mL) cooled to -78°C was added under nitrogen a solution of LiHMDS in THF (380 μL, 2.6 M, 0.290 mmol). The resulting yellow solution was stirred for 30 min at -78°C after which time methyl iodide (140 μL, 0.319 mmol) was added at this temperature. The solution was stirred at -78°C for 3 hours. After treatment with sat aq $NH_4Cl$ ( 10 mL), THF was evaporated and the aqueous solution was extracted with ethyl acetate (3 X 20 mL). After drying ($MgSO_4$) and evaporation of the solvent the crude product was chromatographed on silica gel (eluent: $CH_2Cl_2$/EtOH 9.8/0.2) affording 185 mg (88%) of compound **7a**. Diastereoisomeric excess >97% $^1$H NMR data of the major diastereoisomer (δ, ppm; *J*, Hz): ($CDCl_3$ at 200 MHz) δ 1.54 (d, 3H, *J* = 6), 3.59 (q, 1H, *J* = 7.3), 4.10 (d, 1H, *J* = 15.5), 4.13 (dd, 1H, *J* = 11.7 and 8.6), 4.20 (dd, 1H, *J* = 11.7 and 5.1), 4.29 (d, 1H, *J* = 15.5), 5.82 (dd, 1H, *J* = 8.6 and 5.1), 6.88 (d, 1H, *J* = 7.5), 7.11-7.35 (m, 8H). *Anal.* Calcd. for $C_{18}H_{19}N0_2$: C, 76.84; H, 6.93; N, 5.07. Found: C, 76.71; H, 6.83; N, 4.98.

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