Pergamon

Tetrahedron Letters, Vol. 36, No. 26, pp. 4551-4554, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00819-X

Asymmetric Organic Synthesis. Preparation and Birch Reduction-Alkylation of 2-Methyl-3,4-dihydroisoquinolin-1-ones

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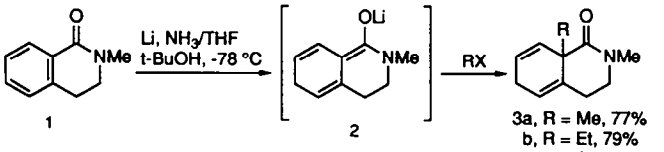
Abstract: Birch reductions of 2-methyl-3,4-dihydroisoquinolin-1-ones **1** and **6** generate enolates **2a** and **2b** and alkylations provide 1,4-cyclohexadienes **3a-3e** and **7a-7c**. The synthesis of a racemic structural analogue, **9**, of the potent analgetic levorphanol is described.

The Birch reduction-alkylation of substituted benzamides derived from L-prolinol has provided a wide range of enantiomerically pure cyclohexane derivatives for utilization in organic synthesis.[1] We now report Birch reduction-alkylations of 2-methyl-3,4-dihydroisoquinolin-1-one (**1**) and the chiral 2,3-dimethyl analogue **6**, the latter readily available from (1*R*,2*S*)-ephedrine. To our knowledge, the Birch reductions of simple aromatic lactams have not been previously reported,[2] although Birch reductions and reductive alkylations of achiral tetralones and related aromatic ketones have received some attention from synthetic chemists.[3] It is expected that the methodology outlined in this note will offer unique opportunities for the enantioselective synthesis of alkaloids and other nitrogen-containing heterocyclic systems. An application to the synthesis of a racemic analogue of levorphanol, a potent analgetic, is described.



1 2

3a, R = Me, 77%
b, R = Et, 79%
c, R = CH_2=$CHCH_2$, 78%
d, R = $C_6H_5CH_2$, 75%
e, R = p-$MeOC_6H_4CH_2$, 77-87%

Dihydroisoquinolinone **1** is easily prepared from 2-phenylethylamine by literature procedures.[4] Conversion of **1** to enolate **2** is accomplished by reduction with lithium in ammonia at -78°C. Alkylation with methyl iodide gave **3a** in 77% yield; alkylations with ethyl iodide, allyl bromide, benzyl bromide and *p*-methoxybenzyl bromide provided **3b-3e**. An experimental procedure describing the conversion of **1** to **3e** is representative.

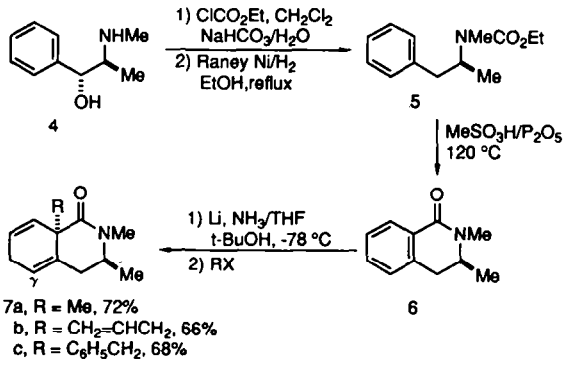
A solution of lactam **1** (3.90 g, 0.0242 mol) and tert-butyl alcohol (2.3 mL, 1 equiv) in THF (50 mL) was cooled to -78°C and ammonia (~800 mL) was added. Lithium (0.38 g, 2.3 equiv) was added in small pieces and after 15 min excess metal was consumed by the addition of piperylene (1 mL). *p*-Methoxybenzyl bromide (7.3 g, 1.5 equiv) in THF (10 mL) was added and the reaction mixture was stirred at -78°C for 1 h.

Ammonia was allowed to evaporate, water was added, and the mixture was extracted with methylene chloride (3 x 200 mL). The combined organic layers were washed with 10% sodium thiosulfate, dried over $MgSO_4$, filtered, evaporated and flash chromatographed (hexane/ethyl acetate, 1:1) to afford diene **3e** (5.26 g, 77%) as a pale-yellow solid. Recrystallization from hexane/ethyl acetate provided colorless crystals (m.p. 118-122°C) of analytical purity. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.11; H, 7.41; N, 4.87.

The conversion of (1*R*,2*S*)-ephedrine (**4**) to 2,3-dimethyl-3,4-dihydroisoquinolin-1-one **6** is shown in Scheme 1. Acylation of **4** with ethyl chloroformate, followed by hydrogenolysis with Raney Ni in refluxing ethanol provided the urethane **5** in 73% yield. Cyclization of **5** to **6** (60% isolated by distillation; 102°C at 0.35 mm Hg) was carried out in methanesulfonic acid/P_2O_5 (10:1 by weight) at 120°C.

It was necessary to demonstrate that racemization had not occurred during hydrogenolysis with Raney Ni by a competing process that involved dehydration followed by olefin hydrogenation to give *rac*-**5**. The racemate of **6** was prepared by reductive amination ($NaBH_3CN/NH_4OAc$) of phenylacetone, followed by acylation ($ClCO_2Et$), cyclization ($MeSO_3H/P_2O_5$) and *N*-methylation (NaH/THF, MeI). HPLC analyses (Daicel Industries Chiralcel OD; hexane/2-propanol, 95:5) showed that **6** had been prepared from **4** without racemization.

Scheme 1



The Birch reduction-alkylations of **6** occurred with >20:1 diastereoselectivity to give **7a-7c**, isolated by flash chromatography on silica gel. In all cases, ^1H NMR data were obtained for chromatographically purified major and minor isomers. Stereochemical assignments were made with a high degree of confidence by comparison of experimentally determined coupling constants for protons at C(3) and C(4) with those determined by utilization of MacroModel, Version 3.0 (MM2). Product diastereomer ratios were determined by HPLC analysis (μ Porasil; hexane/2-propanol, 9:1) before chromatographic separation. Only in the conversion **6** → **7b** was a small amount of the product of γ-alkylation detected.

The high degree of 1,4-intraannular chirality transfer exhibited by alkylations of enolate **2b** (Figure 1) is remarkable in light of the modest stereoselectivities observed for enolates derived from 4-substituted cyclohexanecarboxylic acid derivatives.[5] Stereocontrol with **2b** is comparable to that found with alkylations

of anions generated from bislactim ethers.[6] The C(3) methyl substituent in **2b** provides unusually effective shielding of the β-face of the enolate as a result of the avoidance of eclipsing interactions with the neighboring *N*-methyl substituent (Figure 1).[7]

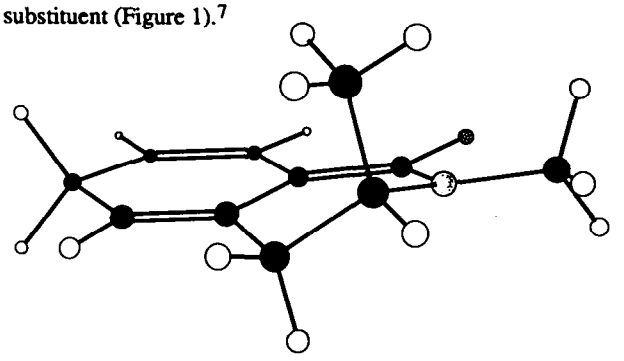
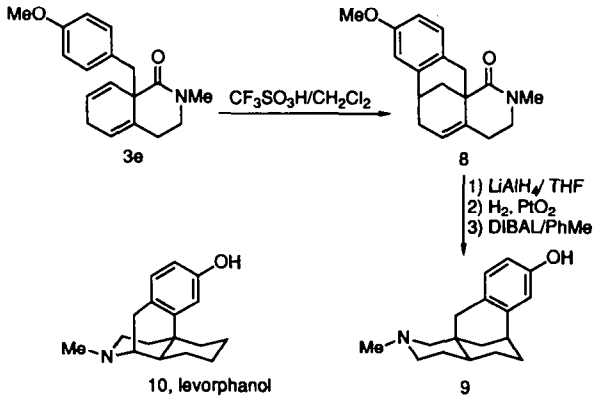


Figure 1. Most stable conformation of enolate 2b (MM2, MacroModel).

N-Methylmorphinan was first synthesized in 1946 by Grewe;[8] the levo isomer called levorphanol (**10**) is four times as potent as morphine.[8c] We have been involved in the preparation of novel structural analogues of morphine and other opiate alkaloids[1b,9] and expected that **9** would be available from the *p*-methoxybenzyl substituted bicyclic lactam **3e**. The distance from the phenolic hydroxy group in **9** is greater than that in **10**; i.e., levorphanol can be considered to be an arylethyl amine while **9** is an arylpropyl amine.[10] Furthermore, the orientation of the electron pair on nitrogen in **10** is anti to the phenolic ring, whereas in **9** the orientation is syn.[11]

The conversion of **3e** to *rac*-**9** is shown in Scheme 2. Grewe cyclization of **3e** with trifluoromethanesulfonic acid in CH_2Cl_2 at room temperature gave the bridged olefin **8** in 66% isolated yield (m.p. 146-148°C). Reduction of the lactam in **8** with $LiAlH_4$ afforded the corresponding amine (m.p. 79-81°C). Olefin hydrogenation followed by cleavage of the methyl ether with diisobutylaluminum hydride[12] gave the phenolic amine **9**. Preliminary opiate receptor binding studies[1b] with **9** showed modest affinity for the μ-receptor,[13] suggesting that more extensive structure-receptor affinity studies may be worthwhile.[14,15]

Scheme 2



Finally, it is anticipated that the aromatic amino acids (*R*)- and (*S*)-phenylalanine, (*R*)- and (*S*)-tyrosine, and (*R*)- and (*S*)-phenylglycine will provide strategically functionalized analogues of the bicyclic lactam **7** by modification of the chemistry reported in Scheme 1.

Acknowledgment. This work was supported by the National Institutes of Health (GM 33061). We thank Fonds der Chemischen Industrie for a postdoctoral fellowship to R.R. and BASF AG-Ludwigshafen for additional financial assistance.

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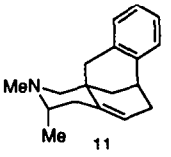
11. For a discussion of the uncertainty associated with the importance of nitrogen lone pair orientation with respect to analgetic activity, see (a) Belleau, B.; Conway, T.; Ahmed, F. R.; Hardy, A. D. *J. Med. Chem.* **1974**, *17*, 907. (b) Belleau, B.; Morgan, P. *J. Med. Chem.* **1974**, *17*, 908. (c) Shiotani, S.; Kometani, T.; Iitaka, Y.; Itai, A. *J. Med. Chem.* **1978**, *21*, 153.
12. *German Patent (DBP)* **1974**, 2409990, 2409991 Schering AG.
13. We thank Dr. Alice Sebastian, RPI laboratories, for μ, κ and δ-receptor binding studies with **9**; details of the receptor pharmacology of **9** and analogues will be published elsewhere.
14. Satisfactory combustion analyses (C,H,N) or high resolution mass spectra were obtained for all new compounds reported in this paper.
15. The assignment of *trans*- rather than *cis*-perhydroisoquinoline stereochemistry in **9** is based on an expected shielding of the double bond in **8** by the bridging arylmethylene unit and an inability to hydrogenate **11**, obtained from **7c**; the axial methyl substituent at C(3) in **11** very effectively blocks the other face of the double bond.



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(*Received in USA* 28 *March* 1995; *revised* 3 *May* 1995; *accepted* 5 *May* 1995)