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Diastereocontrolled reduction of cyclic β-enaminones. A new diastereoselective route to 2,6-disubstituted piperidines

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Abstract—A new diastereoselective synthesis of 2,6-disubstituted piperidinic alkaloids is presented. Three natural compounds, the (−)-pinidinone **1a**, the (+)-dihydropinidine **1b** and the (−)-pinidinol **1c** were prepared from optically pure (6*R*)-6-methylpiperidin-2-one **2**. This method is based on the chemo- and diastereocontrolled reductions of an exocyclic β-enamino ketone.

Substituted piperidine systems are present in many natural compounds and some of them exhibit an extensive range of biological activities.[1] During our continuing studies on natural products, we have recently reported a new enantioselective synthesis of 2-substituted piperidines from chiral 6-alkylpiperidin-2-ones.[2]

In this paper, we describe a diastereoselective and versatile approach to three *cis*-2,6-disubstituted piperidine alkaloids: the (−)-pinidinone **1a**, the (+)-dihydropinidine **1b** and the (−)-pinidinol **1c** starting from a common chiral synthon, the (6*R*)-6-methylpiperidin-2-one **2** (Scheme 1).

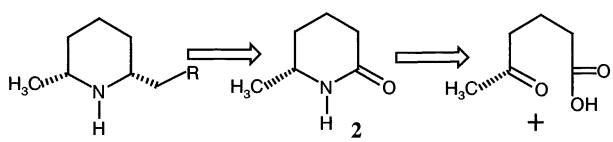
This optically pure piperidinic lactam is easily prepared in a few steps from (−)-phenylglycinol and a δ-keto acid.[2] If numerous asymmetric syntheses of dihydropinidine **1b** were described in the literature,[3] only one hemisynthesis starting from natural (−)-pinidinol **1c** was published,[4] followed by one enantioselective synthesis of the pinidinone **1a**, which was presented by Meyers et al. from a chiral bicyclic lactam.[5] The (−)-pinidinol **1c** was non-stereoselectively synthesized firstly by Leete et al.,[6] and then a long but enantioselective approach was proposed by Momose et al.[7]

Our strategy to a general access to these alkaloids was based upon the easy availability of cyclic β-enamino ketone **4**.

Two approaches were described for the preparation of such compounds.

A 'one-pot' condensation of acetylacetone with a lactim ether in the presence of triethylamine led directly to a β-enamino ketone but this method was only used with unsubstituted lactams.[8] The second way consisted in the condensation of a β-keto ester with lactim ether followed by a decarboxylation with boric acid.[9]

We have developed a general and versatile methodology for preparing chiral 6-substituted-β-enamino ketones. Direct condensation of chiral lactim ether **3** with acetylacetone in the presence of catalytic nickel acetylacetonate gave the (*Z*) isomer of the β-enamino ketone **4**[10] stereoselectively in 60% yield (Scheme 2).



1a R = $COCH_3$: (-)-Pinidinone
1b R = CH_2-CH_3 : (+)-Dihydropinidine
1c R = CHOH-CH_3 : (-)-Pinidinol

Scheme 1.

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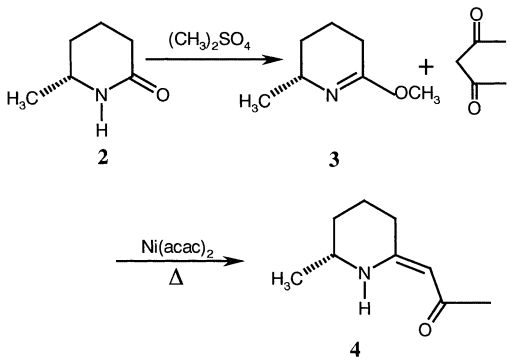


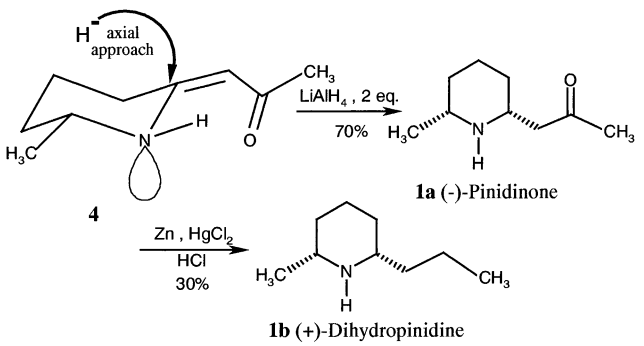
Scheme 2.

The reduction of the C=C of compound **4** was the next step of the synthesis. Catalytic hydrogenation conditions were not chemoselective irrespective of the catalyst employed. Thus, we carried out a chemical reduction with lithium aluminium hydride. Under these conditions, (−)-pinidinone **1a** was regio- and diastereoselectively obtained in 70% yield (d.e. >98%).

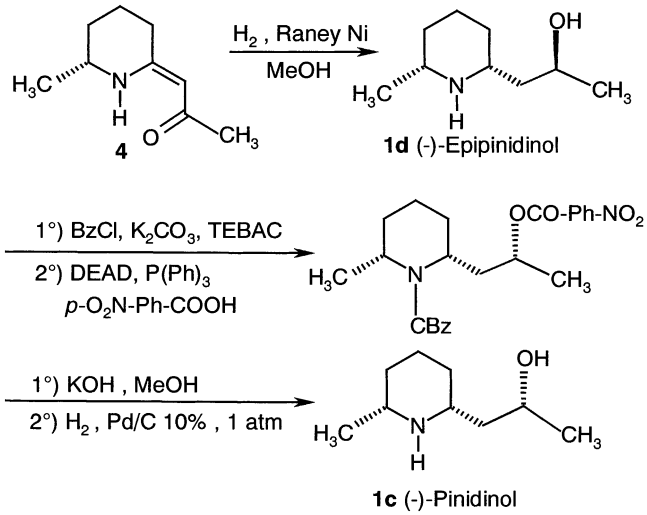
The chemoselectivity of this reduction of an amide vinylogous was described earlier.[11] It is a 1,4-reduction and the keto group is transformed into its enolate salt and released during the hydrolytic work-up.

The very high diastereoselectivity observed during the reduction can be easily rationalized by the characteristic structure of the β-enamino ketone **4**. In fact the (*Z*) geometry of **4**, due to an intramolecular H-bond which planarizes the molecule, permits an axial approach of the hydride to furnish the *syn* 1,3-relationship for the two substituents of the pinidinone **1a** (Scheme 3).

Starting from optically pure (6*R*)-6-methylpiperidin-2-one **2**, (−)-pinidinone **1a** was obtained in three steps and in 26% overall yield ($[\alpha]_D^{20}$ −41 (*c* 0.9, EtOH).[12] This specific rotation is higher than the value proposed by Meyers for the same enantiomer ($[\alpha]_D^{20}$ +25 (*c* 0.4, EtOH).[5] It can be noted that no trace of any diastereomer was detected during our synthesis. Only one value was proposed for the natural product ($[\alpha]_D^{20}$ −4 (*c* 3.5, MeOH)[4] but this rotation was determined after extraction and then chemical transformation of the mixture.



Scheme 3.



Scheme 4.

In order to confirm the optical purity of our product, we finally decided to transform compound **1a** into a well-known alkaloid, namely the (+)-dihydropinidine **1b**. Direct total reduction of the carbonyl function was effected by using Clemensen conditions and then **1b** was isolated as its hydrochloride in 30% yield and in a good optical purity: ($[\alpha]_D^{20}$ +12 (*c* 1.2, EtOH);[13] lit. ($[\alpha]_D^{20}$ +12.7 (*c* 1.0, EtOH).[14] The poor yield of this step was due to the difficulties encountered during the extraction from the Zn–Hg amalgam. The non-epimerizing conditions of this reduction confirmed the structure of (−)-pinidinone **1a**.

The last part of our work lay in the synthesis of the (−)-pinidinol **1c**, isolated from *Picea engelmannii*[15] and whose absolute configuration was determined by X-ray crystal determination.[16]

Catalytic hydrogenation conditions of **4** using Ni Raney or Pd/C as catalysts diastereoselectively led to only one diastereomer of **1c** (Scheme 4). The asymmetric secondary alcohol was then inverted, after carbamation, with a Mitsunobu's reaction[17] using *p*-nitrobenzoic acid to lead to the inverted ester. After hydrolysis and then hydrogenolysis, the (−)-pinidinol **1c** was isolated with a very good optical purity: ($[\alpha]_D^{20}$ −17.5 (*c* 0.63, $CHCl_3$);[18] lit. ($[\alpha]_D^{20}$ −17 (*c* 0.99, $CHCl_3$).[15] This synthesis is a highly enantioselective route to (−)-pinidinol starting from non-natural material.

In conclusion, we have reported a new, versatile and diastereoselective synthesis of 2,6-disubstituted piperidinic alkaloids starting from an easily available chiral lactam.

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References

1. (a) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633–640 and references cited therein; (b) Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699–6703.
2. Fréville, S.; Célérier, J. P.; Thuy, V. M.; Lhommet, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2651–2654.
3. (a) Hill, R. K.; Yuri, T. *Tetrahedron* **1997**, *33*, 1569–1571; (b) Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H. P. *J. Org. Chem.* **1986**, *51*, 4475–4477; (c) Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H. P. *Heterocycles* **1992**, *33*, 17–20; (d) Takahata, H.; Bandoh, H.; Hanayama, M.; Momose, T. *Tetrahedron: Asymmetry* **1992**, *3*, 607–608.
4. Tawara, J. N.; Blokhin, A.; Foderaro, T. A.; Stermitz, F. R.; Hope, H. *J. Org. Chem.* **1993**, *58*, 4813–4818.
5. Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399–5400.
6. Leete, E.; Carver, R. A. *J. Org. Chem.* **1975**, *40*, 2151–2153.
7. Takahata, H.; Yotsui, Y.; Momose, T. *Tetrahedron* **1998**, *54*, 13505–13516.
8. Oishi, T.; Nagai, M.; Onuma, T.; Moriyama, H.; Tsutae, K.; Ochiai, M.; Ban, Y. *Chem. Pharm. Bull. Jpn.* **1969**, *17*, 2306–2313.
9. Delbecq, P.; Bacos, D.; Célérier, J. P.; Lhommet, G. *Can. J. Chem.* **1991**, *69*, 1201–1206.
10. Spectral data for **4**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.10 (d, 3H, $J=6.4$ Hz), 1.25–1.87 (m, 4H), 1.92 (s, 3H), 2.20 (m, 2H), 3.41 (m, 1H), 4.85 (s, 1H), 11.0 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 18.5, 22.4, 27.8, 28.2, 30.2, 46.9, 92.7, 163.3, 193.6; Eb (0.1 mmHg) 105°C; $[\alpha]_D^{20}$ −92 (*c* 1.0, EtOH).
11. (a) Walker, G. N. *J. Org. Chem.* **1962**, *27*, 4227–4231; (b) Martin, J. C.; Barton, K. R.; Gott, P. G.; Meen, R. H. *J. Org. Chem.* **1966**, *31*, 943–945; (c) Schuda, P. F.; Ebner, C. B.; Moargan, T. N. *Tetrahedron Lett.* **1986**, *27*, 2567–2570; (d) Michael, J. P.; Parsons, A. S. *Tetrahedron* **1996**, *52*, 2199–2216.
12. Spectral data for **1a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.10 (d, 3H, $J=6.4$ Hz), 1.20–1.80 (m, 6H), 2.14 (s, 3H), 2.60 (d, 2H, $J=6.3$ Hz), 2.72 (m, 1H), 3.05 (m, 1H), 10.51 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 22.8, 24.5, 30.6, 31.6, 33.6, 50.2, 52.1, 52.4, 208.5; $[\alpha]_D^{20}$ −41 (*c* 0.9, EtOH).
13. Spectral data for **1b**·HCl: ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.85 (t, 3H, $J=7.4$ Hz), 1.10–1.24 (m, 10H), 1.53 (d, 3H, $J=6.5$ Hz), 2.85 (m, 1H), 3.00 (m, 1H), 9.01 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 13.7, 18.8, 19.5, 22.9, 27.5, 30.7, 35.2, 54.5, 58.4; F (acetonitrile) 210°C; $[\alpha]_D^{20}$ +12 (*c* 1.2, EtOH).
14. Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H. P. *J. Am. Chem. Soc.* **1983**, *105*, 7754–7755.
15. Schneider, M.; Stermitz, F. R. *Phytochemistry* **1990**, *29*, 1811–1814.
16. Stermitz, F. R.; Miller, M. M.; Schneider, M. J. *J. Nat. Prod.* **1990**, *53*, 1019–1020.
17. Hughes, D. H. *Org. React.* **1992**, *42*, 335–656.
18. Spectral data for **1c**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.00 (d, 3H, $J=6.2$ Hz), 1.10 (d, 3H, $J=6.2$ Hz), 1.20–1.80 (m, 8H), 2.60 (m, 1H), 2.90 (m, 1H), 4.10 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 22.3, 23.6, 24.2, 29.9, 32.9, 43.2, 52.9, 54.9, 64.4; $[\alpha]_D^{20}$ −18 (*c* 0.63, $CHCl_3$).