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Daucus carota Mediated-Reduction of Cyclic 3-Oxo-amines

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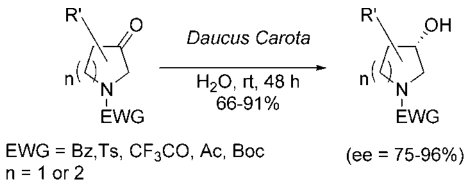
ABSTRACT



Carrots (*Daucus carota*) were used to reduce cyclic amino-ketones in high yields and enantiomeric excesses. This cheap, eco-compatible, and efficient reducing reagent allows the easy access to precursors of biologically active products.

Numerous natural and non-natural products with interesting biological activities contain in their structure a piperidine core of type **A**, possessing a quaternary stereogenic center at C3 with the (*R*)- or (*S*)-configuration. These piperidines of type **A** are present in non-natural products such as capromorelin,[1] or in natural products such as isonitramine[2] and sibirine[2a,3] (Figure 1). Piperidines of type **B** can be the precursors of piperidines of type **A** and can be obtained from 4-hydroxypiperidino esters **C**, using a diastereoselective alkylation developed by Frater[4] where the control of the quaternary stereogenic center is directed by the hydroxy group at C4 (Scheme 1).

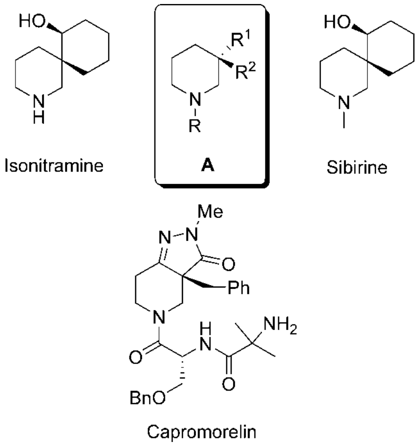


Figure 1. Piperidine derivatives containing a quaternary center.

Numerous chemical and biochemical methods have been developed for reducing β-keto-esters of type **D** to the corresponding optically pure β-hydroxyesters.[5] However, difficulties still remain such as the use of expensive chiral

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[1] Carpino, P. A.; Lefker, B. A.; Toler, S. M.; Pan, L. C.; Hadcock, J. R.; Cook, E. R.; DiBrino, J. N.; Campeta, A. M.; DeNinno, S. L.; Chidsey-Fink, K. L.; Hada, W. A.; Inthavongsay, J.; Mangano, M. F.; Mullins, M. A.; Nickerson, D. F.; Ng, O.; Pirie, C. M.; Ragan, J. A.; Rose, C. R.; Tess, D. A.; Wright, A. S.; Yu, L.; Zawistoski, M. P.; DaSilva-Jardine, P. A.; Wilson, T. C.; Thompson, D. D. *Bio. Med. Chem.* **2003**, *11*, 581–590.

[2] (a) Wanner, M. J.; Koomen, G. J. *Tetrahedron Lett.* **1989**, *30*, 2301–2304. (b) Carruthers, W.; Moses, R. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1625–1628. (c) Fujii, M.; Kawaguchi, K.; Nakamura, K.; Ohno, A. *Chem. Lett.* **1992**, *8*, 1493–1496. (d) Kozikowski, A. P.; Yuen, P.-W. *J. Chem. Soc., Chem. Commun.* **1985**, *13*, 847–848. (e) Mieczkowski, J. B. *Bull. Pol. Acad. Sci. Chem.* **1985**, *33*, 13–18. (f) Deyine, A.; Poirier, J.-M.; Duhamel, L.; Duhamel, P. *Tetrahedron Lett.* **2005**, *46*, 2491–2494. (g) Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367–370.

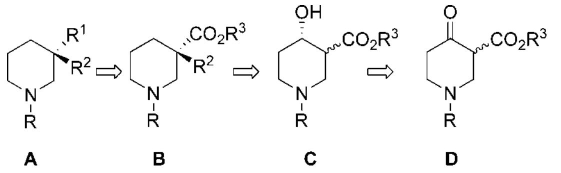
[3] (a) Snider, B. B.; Cartaya-Marin, C. P. *J. Org. Chem.* **1984**, *49*, 1688–1691. (b) Hellberg, L. H.; Beeson, C.; Somanathan, R. *Tetrahedron Lett.* **1986**, *27*, 3955–3956.

[4] Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825–2828.

[5] (a) Knight, D. W.; Lewis, N.; Share, A. C.; Haigh, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, *22*, 3673–3684. (b) Willert, M.; Bols, M. *Acta Chem. Scand.* **1998**, *52*, 461–468.

10.1021/ol8029214 CCC: $40.75

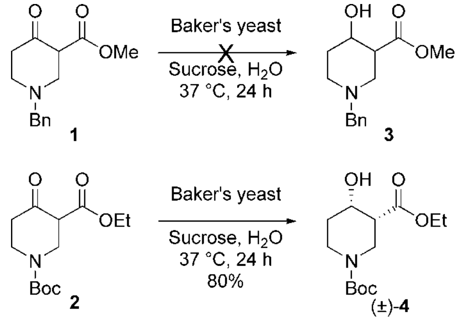
Scheme 1. Retrosynthesis Analysis of Optically Active Piperidines of Type **A**



agents as well as the isolation of pure β-hydroxyesters in high yields from the reaction or fermentation media.[6]

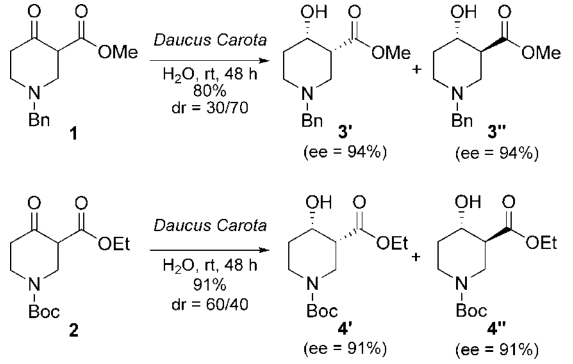
Recently, plant cell culture and plant roots have been used in reductions. These biocatalysts are active in aqueous media under mild, economically viable conditions, and they are more eco-compatible than organometallics.[7] The most common biocatalyst used to selectively reduce the ketone in ketoesters is baker's yeast.[8] Appropriately, the reduction of *N*-benzyl-β-piperidinone ester **1** using baker's yeast was initially examined. When compound **1** (2 mmol) was treated with baker's yeast (4 g) in the presence of sucrose (5 g) in water (60 mL) at 37 °C for 24 h, the corresponding β-hydroxyester **3** was not detected. On the contrary, when *N*-Boc-β-ketoester **2** was treated under the same conditions used for **1**, the expected *cis*-4-hydroxypiperidine ester **4** was isolated in 80% yield but, very disappointgly, in its racemic form (Scheme 2). We have to point out that the reduction of *N*-Boc-β-ketoester **2** by baker's yeast was already described in the literature to provide *cis*-4-hydroxyester **4** with a good enantiomeric excess,[5a] but these results have been contradicted by Bols and Willert[5b] who have reported the formation of **4** as a racemate which confirmed our results.

Scheme 2. Reduction of β-Keto-ester by Baker's Yeast



On the basis of these results, and as reductases are present in a great variety of plants and vegetables,[9] carrots (*Daucus carota*) were selected to reduce piperidinones **1** and **2** because this plant usually gives good results[10] (Scheme 3).

Scheme 3. Reduction of β-Keto-ester by *Daucus carota*



Compound **1** (2 mmol) was treated with carrots (140 g) in water (600 mL) at rt, and after 48 h, K_2CO_3 was added (pH = 10) before extraction [the reaction media was acidic (pH = 5)] and two hydroxyesters **3′** (*cis*-isomer) and **3″** (*trans*-isomer) were isolated in 80% yield in a ratio of 70/30 in favor of the *trans*-isomer. Both isomers **3′** and **3″** were obtained with an identical enantiomeric excess (ee = 94%). *N*-Boc-piperidone ester **2** was also reduced by carrots and **4′** (*cis*-isomer) as well as **4″** (*trans*-isomer) were isolated in 91% yield in a diastereomeric ratio of 60/40 in favor of the *cis*-isomer. Compounds **4′** and **4″** were obtained with a similar enantiomeric excess of 91%. The absolute configuration of the stereogenic centers were determined by comparison of the $[\alpha]^D$ of compounds **4′** and **4″** descibed in the literature.[11]

We have to point out that the ratio **4′**/**4″** depends on the pH of the solution. When the reduction was achieved in the presence

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(6) (a) Kitamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron Asymmetry* **1990**, *1*, 1–4. (b) Ratovelomanana-Vidal, V.; Genêt, J. P. *J. Organomet. Chem.* **1998**, 163–172. (c) Servi, S. *Synthesis* **1990**, 1. (d) Kaouwka, W. S.; Sabucky, M. J.; Vinayand, D. *J. Chem. Soc., Chem Commun.* **1972**, 10–12. (e) Hajos, A. In *Complex Hydrides and Related Reducing Agents In Organic Synthesis*; Elsevier: New York, 1979. (f) Bosnich, B.; Fryzuk, M. D.; Geoffray, G. L. In *Topics in Inorganic and Organomettalic Stereochemistry*; Wiley: New York, 1981; pp 119−125. (g) Baiker, A. *J. Mol. Catal. A: Chem.* **2000**, *163*, 205–220. (h) Kroutil, W.; Mang, H.; Edegger, K.; Faber, K. *Curr. Opin. Chem. Biol.* **2004**, *8*, 120–126. (i) Engelking, H.; Pfaller, R.; Wich, G.; Weuster-Botz, D. *Enzyme Microb. Technol.* **2006**, *38*, 536–544.

(7) (a) Wong, C. H.; Whitesides, G. M. In *Enzymes in Synthetic Organic Chemistry*; Pergamon Press: Oxford, 1994. (b) Drauz, K.; Waldmann, H. In *Enzymes Catalysis in Organic Synthesis*; VCH: New York, 1995; Vols. *I*, *II*, and *III*. (c) Faber, K. In *Biotransformations in Organic Chemistry*, 5th ed.; Springer: Berlin, Heidenberg, Germany, 2004. (d) Gavrilescu, M.; Chisti, Y. *Biotechnol. Adv.* **2005**, *23*, 471–499. (e) Nakamura, K.; Matsuda, T. *Curr. Org. Chem.* **2006**, *10*, 12217–1246.

(8) (a) Padhi, S. K.; Kaluzna, I. A.; Buisson, D.; Azerad, R.; Stewart, J. D. *Tetrahedron: Asymmetry* **2007**, *18*, 2133–2138. (b) Alonso, E. R.; Tehrani, K. A.; Boelens, M.; De Kimpe, N. *Syn. Lett.* **2005**, *11*, 1726–1730. (c) Yadav, J. S.; Nanda, S.; Reddy, P. T.; Rao, A. B. *J. Org. Chem.* **2002**, *67*, 3900–3903. (d) Bertau, M.; Buerli, M.; Hungerbuehler, E.; Wagner, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2103–2108. (e) Miya, H.; Kawada, M.; Sugiyama, Y. B. *Biotechnol. Biochem.* **1996**, *60*, 760–764. (f) Seebach, D.; Roggo, S.; Maetzke, T.; Braunschweiger, H.; Cercus, J.; Krieger, M. *Helv. Chim. Acta* **1987**, *70*, 1605–1615. (g) Herradon, B.; Seebach, D. *Helv. Chim. Acta* **1989**, *72*, 690–714. (h) Kometani, T.; Kitatsuji, E.; Matsuno, R. *Chem. Lett.* **1989**, 1465–1466. (i) Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1986**, *27*, 2631–2634. (j) Spiliotis, V.; Papahatjis, D.; Ragoussis, N. *Tetrahedron Lett.* **1990**, *31*, 1615–1616. (k) Deol, B. S.; Ridley, D. D.; Simpson, G. W. *Aust. J. Chem.* **1976**, *29*, 2459–2467.

(9) Nishida, T.; Miyafuji, A.; Ito, Y. N.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 7053–7058.

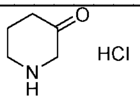
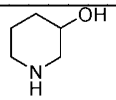
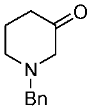
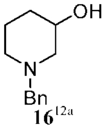
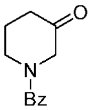
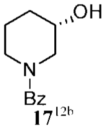
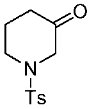
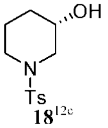
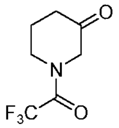
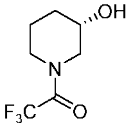
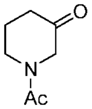
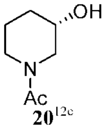
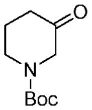
(10) Review: Blanchard, N.; Van de Weghe, P. *Org. Biomol. Chem.* **2006**, *4*, 2348–2353.

(11) Knight, D. W.; Lewis, N.; Share, A. C.; Haigh, D. *Tetrahedron Asymmetry* **1993**, 625–628.

of a phosphate buffer (pH = 7), the ratio **4′**/**4″** was determined to be 85/15. Furthermore, when **4′** was treated with carrots for 48 h at rt, the pH of the solution was determined to be five and epimerization of **4′** to **4″** was observed. However, this epimerization was not observed when compound **4′** was treated in acidic conditions (pH = 5) without carrot plants. These results suggested that the epimerization is due to the enzymatic machinery present in carrots.

As D*aucus carota* seems suitable for the enantioselective reduction of piperidones, piperidin-3-ones **5**−**11** were examined (Table 1). When piperidin-3-one ammonium chloride **5** and *N*-benzyl-piperidin-3-one **6** were treated with carrots, the recovery of the corresponding piperidin-3-ols was very low (0% to 11%) due probably to the high solubility of the hydroxylamines in water. To avoid extraction problems, the amino group of the piperidin-3-one was protected with electron-withdrawing groups such benzoyl (compound **7**), tosyl (compound **8**), trifluoroacetyl (compound **9**), acetyl (compound **10)** and *tert*-butoxycarbonyl (compound **11**) groups.

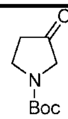
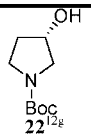
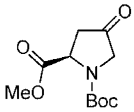
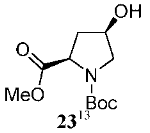
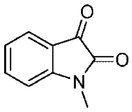
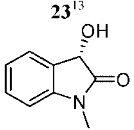
Table 1. Reduction of Six-Membered Ring Amino-Ketones by *Daucus carota*

entry	starting materials	products	yield / ee (%)
1	 **5**	 **15**	0 / -
2	 **6**	 **16**[12a]	11 / -
3	 **7**	 **17**[12b]	66 / 88
4	 **8**	 **18**[12c]	78 / 92
5	 **9**	 **19**[12d]	75 / 75
6	 **10**	 **20**[12e]	76 / 89
7	 **11**	 **21**[12f]	73 / 95

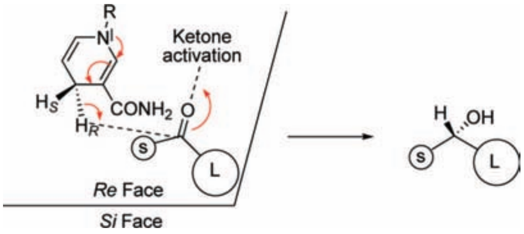
When submitted to reduction with carrots, **7**−**11** were transformed to the corresponding piperidin-3-ols in good yield (66−78%) and good enantiomeric excess (75−95%). The best enantiomeric excesses were obtained for the *N*-tosyl- and *N*-Boc-piperidin-3-ones **8** and **11**. The (*S*)-configuration of the newly created stereogenic center in **18** and **21** was established by comparison with the $[\alpha]_D$ reported in the literature.[12]

In order to determine the scope and limitation of the reduction of cyclic amino ketones by carrots, pyrrolidinones **12**−**14** were examined (Table 2). When **12**−**14** were treated with carrots, the corresponding 3-hydroxypyrrolidines were isolated in good yield (67−83%) and good enantiomeric excess (82−96%). In the case of compound **13**, the *cis*-hydroxyproline ester **23** was isolated with a diastereoselectivity of 98%. It is worth noting that for all the obtained 3-hydroxypiperidines and 3-hydroxypyrrolidines, the configuration of the stereogenic center at C3 was (*S*) except for compound **23**, in which the configuration of the stereogenic center bearing the hydroxy group is (*R*).[13] These results are in perfect agreement with the Prelog's rules as the Pro-*R* "hydride" of the NADH is transferred to the *Re* face of the ketone.[14] A model can be proposed in order to rationalize the hydride transfer (Scheme 4).

Table 2. Reduction of Five-Membered Ring Amino-Ketones by *Daucus carota*

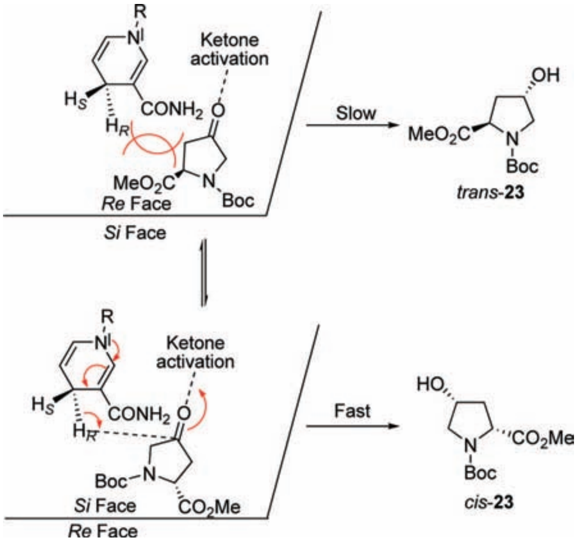
entry	starting materials	products	yield / ee (%)
1	 **12**	 **22**[12g]	76 / 96
2	 **13**	 **23**[13]	67 / - de = 98 %
3	 **14**	 **24**[12h]	83 / 82

Scheme 4. Prelog Model



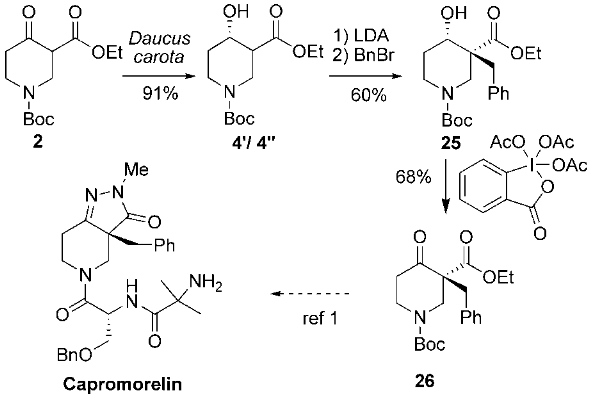
In the case of the reduction of L-proline derivative **13**, it can be suggested that the configuration of the methyl ester plays a role in the control of the (*R*)-configuration of the corresponding hydroxy group in **23**. We suppose that the conventional Pro-*R* "hydride" transfer on the *Re* face of the ketone is related to a steric effect due to the configuration of the methyl ester. The "hydride" transfer should certainly be faster on the *Si* face of the ketone thus generating the formation of *cis*-diastereomer **23** (Scheme 5).

Scheme 5. Reduction of **13**



The enantioselective reduction of cyclic *β*-amino ketones by *Daucus carota* can be applied to the synthesis of an advanced precursor of capromorelin, an antiaging drug (Scheme 6). After transformation of **2** to **4′**/**4″** by *Daucus carota* (yield = 91%, ee = 91%), the mixture of **4′** and **4″** were diastereoselectively alkylated by benzylbromide [LDA (2.5 equiv), BnBr (1.3 equiv), THF, −78 to 0 °C] to produce **25** in 60% yield. After the oxidation of **25**, using Dess-Martin periodinane, **26** was isolated in 68% yied. This later compound constitutes a formal synthesis of capromorelin.[1]

Scheme 6. Formal Synthesis of Capromorelin



In summary, we have developed an alternative, cheap, convenient, and eco-compatible procedure for the preparation of optically active cyclic 3-hydroxyamines and we have applied this methodology for the enantioselective synthesis of an advanced precursor of capromorelin.

Acknowledgment. Sanofi-aventis is thanked for financial support and for a grant to R.L.

Supporting Information Available: Experimental procedures and spectroscopic characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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