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New Members of the Chiral Pool: β-Hydroxypiperidine Carboxylates from Baker's Yeast Reductions of the Corresponding Keto-esters

David W. Knight,* Neil Lewis and Andrew C. Share
Chemistry Department, University Park, Nottingham, NG7 2RD, UK.
David Haigh
SmithKline Beecham Pharmaceuticals, Yew Tree Bottom Road, Great Burgh, Epsom, Surrey, KT18 5XQ.

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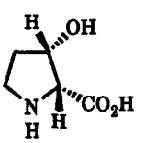
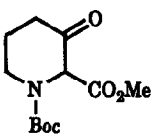
Summary:- Baker's yeast reduction of the keto-piperidinecarboxylates **2** and **6** leads to the corresponding hydroxy-esters **3** and **7a** in good chemical yields and with >99% d.e. and >93% e.e. in both cases.

Amongst the many applications of baker's yeast in asymmetric synthesis, the reduction of (racemic) β-keto-esters to the corresponding β-hydroxy-esters is one of the most useful transformations which can be achieved using this organism.[1] Thus, when we recently required access to 3-hydroxyproline **1**, yeast reductions of 3-ketoprolines, protected at nitrogen, proved to be a viable option.[2,3] The success of this conversion encouraged us to examine similar reactions of related ketopiperidine carboxylates, in the hope of gaining access to some useful new chiral pool members in an area which is somewhat depleted in terms of the availability of homochiral starting materials.



1



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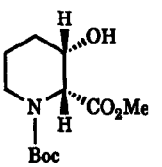

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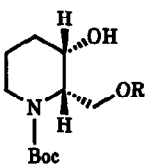
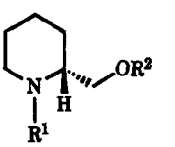


4

a) R = H
b) R = TBDPS



5

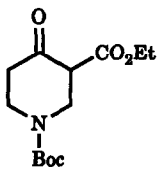
a) R^1 = Boc; R^2 = TBDPS
b) R^1 = Ts; R^2 = TBDPS
c) R^1 = Ts; R^2 = H
d) R^1 = R^2 = Ts

Exposure of the keto-piperidine carboxylate **2**[4] to fermenting baker's yeast in aqueous sucrose[5] (48h, 30°C) followed by filtration through kieselguhr, saturation of the filtrate with sodium chloride and ethyl acetate extraction (5x) gave a hydroxypiperidine carboxylate in 75-80% yield (5-10 g scale) as an oil, which was a single diastereoisomer according to ^{13}C NMR

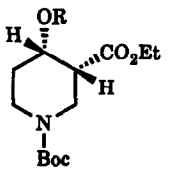
data,[6] and which showed $[\alpha]_D$ + 47.9, (c, 3.8, CH_2Cl_2). It has been established that the 2-substituent in such 1,2-disubstituted piperidines adopts an axial position in order to avoid steric interactions between the two functions.[7] As the 3-proton (CHOH) was evidently axial,[8] the product was the *cis* isomer **3**, or its (2**S**, 3**R**)-enantiomer.

The optical purity and absolute configuration were determined by deoxygenation to the corresponding 2-piperidinemethanol derivative **5d**. Reduction ($LiAlH_4$, THF, 20°C, 3h; 72%) of the initial product **3** led to the diol **4a** which was protected at the primary position (TBDPSCl, DMAP, Et_3N, 20°C, 12h; 79%). Deoxygenation[9] ($Bu^n{}_3SnH$, AIBN, toluene, reflux) of the resulting monosilyl ether **4b** *via* the corresponding thionourethane (Im_2CS) then gave the piperidine methanol derivative **5a** (50%). Following protecting group exchange at nitrogen (TFA, CH_2Cl_2, 20°C, 1h then TsCl, Et_3N, cat. DMAP, CH_2Cl_2, 20°C, 2h; 70%), the resulting sulfonamide **5b** was desilylated (TBAF, THF, 20°C, 16h) to give the alcohol **5c** which was finally converted (TsCl, 1 equiv. DMAP, Et_3N, CH_2Cl_2, 20°C, 16h) into the *bis*-tosylate **5d**, an oil, (Lit.[10] oil), which showed $[\alpha]_D$ + 55, (c, 0.8, EtOH) [(Lit.[10] $[\alpha]_D$ + 56.6 (c, 1.03, EtOH) for the (**R**)-enantiomer]. Hence, the absolute stereochemistries of the initial yeast reduction product **3** as well as the subsequent intermediates **4** and **5** are as depicted. The optical rotation values indicate an enantiomeric excess of 97%; chiral shift experiments (Tris [3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium (III), $CDCl_3$), using *rac*-**5d** as standard, failed to show the presence of (-)-**5d**, indicating that this is a minimum value.

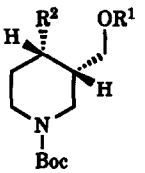
A similar reduction of the 4-ketopiperidine-3-carboxylate **6**[11] also led, in 78% isolated yield, to a single diastereoisomer of a hydroxypiperidine carboxylate **7a**, m.p. 58 - 60°C,[12] $[\alpha]_D$ +25.6, (c, 2.4, CH_2Cl_2), the identity of which was proven in a similar manner and in similar yields to the foregoing example.



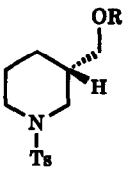
6



7
a) R = H
b) R = Ac



8
a) R^1 = TBDPS; R^2 = OH
b) R^1 = TBDPS; R^2 = H

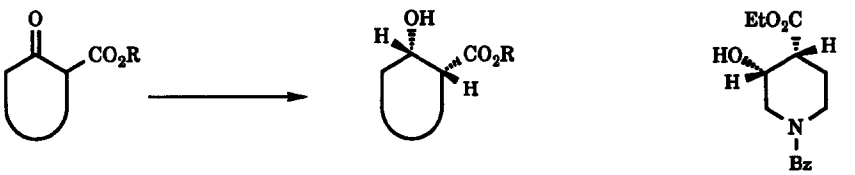


9
a) R = TBDPS
b) R = H
c) R = Ts

Firstly, the corresponding acetate **7b** showed $J_{3a,4e}$ = 3.2Hz, and hence has a *cis* relative stereochemistry.[13] Secondly, reduction ($LiAlH_4$) and monosilylation provided the alcohol **8a** (70%) which was deoxygenated *via* the pentafluorophenyl thionocarbonate[14] to give the 3-piperidinemethanol derivative **8b**. Subsequent protecting group exchange (*vide supra*) at nitrogen led to the *N*-tosyl derivative **9a** and thence to the *bis*-tosylate **9c**, following fluoride-

induced desilylation to give the alcohol **9b** and tosylation. The *bis*- tosylate **9c**, m.p. 88-89°C, (Lit.[15] m.p. 87-89°C for the (R)-enantiomer) showed $[\alpha]_D$ - 50.2, (c, 1.1, $CHCl_3$) [Lit.[15] $[\alpha]_D$ + 54.0, (c, 1.4, $CHCl_3$) for the (R)-enantiomer]. Thus, our sample is clearly the (S)-enantiomer as shown and has an enantiomeric enrichment of 93%, according to the optical rotation data. However, chiral shift reagent experiments (Tris [3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium (III), $CDCl_3$) using *rac*-**9c** as a standard, did not show the presence of any of the (R)-enantiomer in the *bis*-tosylate **9c** indicating that this is also a minimum value for the e.e. of the initial yeast reduction product **7a**. Appropriate checks on other column fractions and mother liquors showed that no significant enantiomeric enrichment was occurring during the foregoing transformations and therefore that the initial reduction product **7a** has at least 93% e.e.

Finally, we note that similar reductions of the carbon and sulfur analogues of these piperidines (*ie.* **6** with CH_2 or S in place of NBoc, respectively) also produce very high optical yields of the corresponding hydroxy-esters .[1,16] In addition, the sense of the reduction is the same, as indicated by the general transformation **10** ->**11**. The same absolute configuration has also been found in a reduction of ethyl *N*-benzyl-3-ketopiperidine-4-carboxylate to the hydroxy-ester **12**, using non-fermenting baker's yeast.[17] However, this method requires a very large excess of yeast and special isolation techniques and, although the chemical and optical yields are excellent (65% and 95% respectively), the d.e. (73%) is relatively poor. The excellent levels of chiral induction achieved in these present reductions suggests that the two products (**3** and **7a**) will find a number of applications in the synthesis of chiral piperidine derivatives; efforts in this direction are in progress.



10 **11** **12**

Acknowledgments

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6. δ_C ($CDCl_3$, 20°C) 23.3 and 23.6 (5-CH_2), 28.1 (Bu^t), 29.9 (4-CH_2), 40.1 and 41.2 (6-CH_2), 52.1 (OMe), 57.2 and 58.4 (2-CH), 68.7 (3-CH, sl. br), 80.5 ($OCMe_3$), 154.5 (NCO, br) and 172.3 (CO_2Me). The rotameric resonances coalesced at ~ 55°C. No other isomers were detected, indicating a diastereomeric purity of > 99%.
7. Y. L. Chow, C. J. Colon and J. N. S. Tam, *Can. J. Chem.*, 1968, **46**, 2821.
8. δ_H ($CDCl_3$, 20°C) ~ 4.9 (1H, br., $\omega_{1/2}$ = 24 Hz).
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11. Prepared from the commercially available hydrochloride (Boc_2O, Et_3N, CH_2Cl_2, 20°C, 16h, 89%).
12. δ_C ($CDCl_3$, 20°C) 13.9 (CH_3), 28.1 (Bu^t), 31.3 (5-CH_2), 38.1 (6-CH_2, br), 40.3, (2-CH_2, br), 45.6 (3-CH), 60.7 (CH_2), 64.8 (4-CH, sl. br), 79.5 ($OCMe_3$), 154.5 (NCO) and 172.5 (CO_2Me). No other isomers were detected, indicating a diasteroisomeric purity of >99%.
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