Pergamon

Tetrahedron Letters 40 (1999) 1069–1072

TETRAHEDRON LETTERS

Enantioselective Synthesis of 3-Hydroxypiperidin-2-ones

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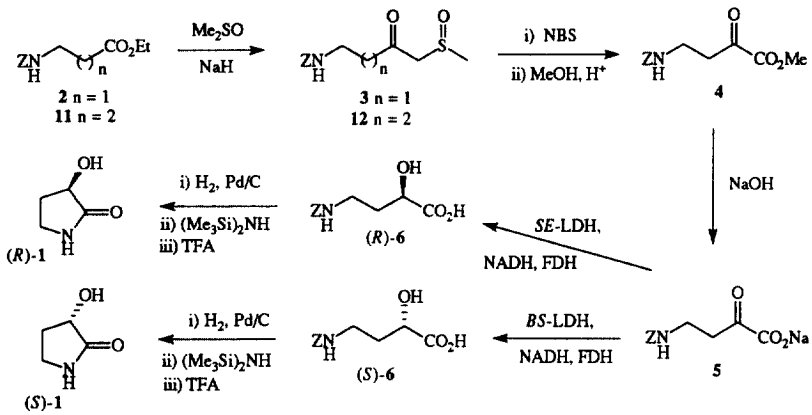
Received 11 November 1998; accepted 23 November 1998

Abstract: An efficient synthesis of (*S*)- and (*R*)-3-hydroxypiperidin-2-ones from methyl 5-nitro-2-oxopentanoate is described. A one-pot enzyme catalysed hydrolysis of the ester and reduction of the ketone gave enantiopure 2-hydroxy-5-nitropentanoic acids which on esterification, catalytic hydrogenation over a platinum(IV) oxide catalyst and intramolecular cyclisation gave the target compounds in 93% overall yield and >99% ee. © 1999 Elsevier Science Ltd. All rights reserved.

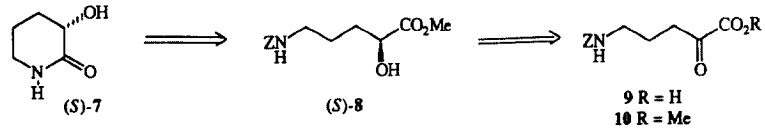
Hydroxylated five and six-membered ring nitrogen containing heterocycles are widespread in nature and are components of many biologically active compounds.[1] Recently we described the synthesis of (*S*)- and (*R*)-3-hydroxypyrrolidin-2-ones (*S*)-**1** and (*R*)-**1**, valuable building blocks for the preparation of nitrogen containing heterocycles.[2]



Scheme 1

Our approach involved the lactate dehydrogenase (LDH) catalysed reduction of the sodium salt of 4-benzyloxycarbonyl(Z)-amino-2-oxobutanoic acid **5** (prepared from ethyl 3-Z-aminopropanoate **2** *via* a β-ketosulfoxide **3** according to a literature procedure[3]) followed by deprotection of the amine and cyclisation (Scheme 1). This was the first report of an LDH catalysed reduction of an α-keto acid containing a nitrogen functionality in the side chain. Use of commercially available LDH from *Bacillus stearothermophilus* (*BS*-LDH)[4] for the reduction of **5** gave (*S*)-2-hydroxy acid (*S*)-**6** in 91% yield while LDH from *Staphylococcus epidermidis* (*SE*-LDH)[5] gave the enantiomer (*R*)-**6** in 95% yield. In each case the cofactor NADH was recycled using the formate/formate dehydrogenase (FDH) method described by Shaked and Whitesides.[6] We anticipated that we could extend the utility of this

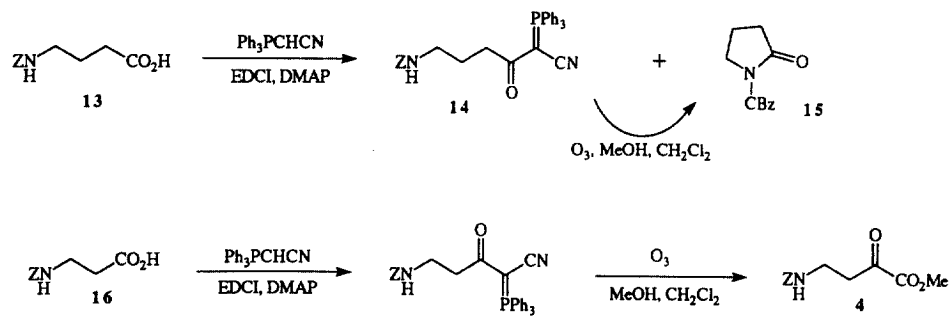
PII: S0040-4039(98)02529-5



Scheme 2

approach to the synthesis of enantiomerically pure six membered ring homologues of γ-lactam **1**, namely 3-hydroxypiperidin-2-one **7** *via* LDH catalysed reduction of Z-protected 5-amino-2-oxopentanoic acid **9** (Scheme 2).

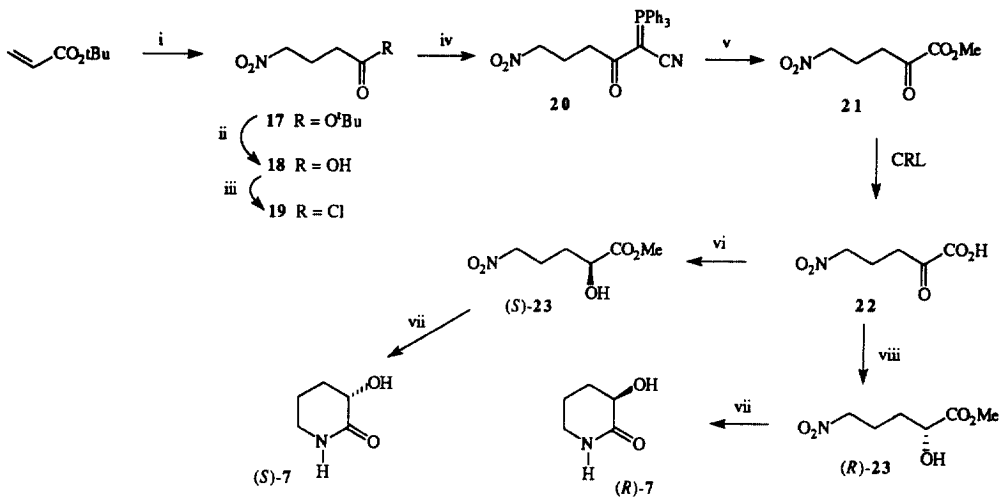
First we examined the synthesis of the required α-keto ester **10** by an analogous procedure to that used for the preparation of **4** (Scheme 1). Although treatment of ethyl 4-Z-aminobutanoate **11** with dimsyl sodium gave β-keto sulfoxide **12**, further attempted elaboration of **12** to α-keto ester **10** by reaction with *N*-bromosuccinimide produced only a complex mixture of products. Clearly an alternative approach for the synthesis of **10** was required. Wasserman and coworkers have described a valuable method for the homologation of a carboxylic acid to an α-keto ester *via* ozonolysis of a β-ketocyanophosphorane.[7] Coupling 4-Z-aminobutanoic acid **13** with cyanomethylenetriphenylphosphorane in the presence of EDCI/DMAP gave **14** in a disappointing 35% yield along with pyrrolidinone **15** (Scheme 3). Ozonolysis of **14** in methanol-dichloromethane returned only the cyclised product **15**, none of the required α-keto ester **10** was obtained. In contrast, methyl 4-Z-amino-2-oxobutanoate **4** was readily prepared from 3-Z-aminopropanoic acid **16** using this approach. Thus it was evident that the problems inherent to the synthesis of the required α-keto ester **10** originate from the nucleophilic nitrogen leading to cyclisation to the 5-membered ring lactam, whereas in the synthesis of methyl 4-Z-amino-2-oxobutanoate **4** cyclisation to the more strained β-lactam was not observed.



Scheme 3

One way to circumvent these problems was to design an α-keto acid with a non-nucleophilic nitrogen containing functionality in the side-chain which, following the enzyme catalysed reduction of the ketone, may be converted to an amine to effect the required cyclisation to 3-hydroxypiperidin-2-one. A nitro group can be considered as a masked amine and so our new target α-keto ester was methyl 5-nitropentanoic acid **21**. Use of a nitro group has two potential advantages over a Z-protected amine, first it is non-nucleophilic so cyclisations will not occur and secondly its compact size may allow an improved rate of turnover in the enzyme compared with a more bulky Z-protected amine (cf.

SE-LDH catalysed reduction of the sodium salt of Z-protected α-keto acid **5** took 7 days to reach completion on a 1 mmol scale giving a 95% yield of (*R*)-**6**[2]).



Reagents: i) $MeNO_2$, DBU; ii) TFA; iii) $SOCl_2$; iv) Ph_3PCHCN, BSA; v) O_3, MeOH, CH_2Cl_2; vi) *BS*-LDH, FDH, NADH; vii) H_2, PtO_2; viii) *SE*-LDH, FDH, NADH.

Scheme 4

Methyl 5-nitro-2-oxopentanoate **21** was prepared in five steps from commercially available starting materials (Scheme 4). Conjugate addition of nitromethane to *tert*-butyl acrylate in the presence of DBU[8] gave a quantitative yield of methyl 4-nitrobutanoate **17**. Removal of the *tert*-butyl group, conversion of the resulting carboxylic acid **18** to an acid chloride **19**, and coupling with cyanomethylenetriphenylphosphorane using bis(trimethylsilyl)acetamide (BSA) as a proton scavenger furnished **20** in good yield. Ozonolysis of **20** in methanol-dichloromethane gave α-keto ester **21** in 51% yield over the five steps. It was then necessary to convert ester **21** into the corresponding α-keto acid. This may be achieved by saponification but a more convenient approach is to use a dual enzyme procedure to hydrolyse the ester and reduce the ketone in a one-pot process.[9] Thus **21** was incubated with a lipase from *Candida rugosa* (CRL)[10] prior to the addition of *BS*-LDH, FDH and the cofactor NADH. After work up, (*S*)-2-hydroxy-5-nitropentanoic acid was isolated and then methylated with diazomethane to give 2-hydroxy ester (*S*)-**23** in 93% yield over the 3 steps. The (*R*)-enantiomer was obtained in an analogous manner but using *SE*-LDH to catalyse the reduction of keto acid **22**. Interestingly on a 1 mmol scale the *SE*-LDH catalysed reduction of **22** was complete within 2 days which compared favourably with the 7 days required for the reduction of the more bulky 4-Z-amino-2-oxobutanoic acid **5**. ^1H- and ^{19}F-NMR analysis of the (*R*)-(+)-MTPA (Mosher[11]) derivatives of the hydroxy esters **23** were used to determine the enantiomeric purity of each product from the enzyme

catalysed reductions, and was found to be >99%ee in both cases. The chemical shift differences between the diastereomers were entirely consistent with the expected absolute configuration at C-2 according to correlation models of Mosher[11] and Yamaguchi. [12]

Reduction of the nitro group in (*S*)-**23** to the amine was accomplished by hydrogenation over a platinum(IV) oxide catalyst[13] at atmospheric pressure, and spontaneous cyclisation gave (*S*)-3-hydroxypiperidin-2-one (*S*)-**7** in quantitative yield. Spectroscopic data, melting point and optical rotation of this product were in complete agreement with those reported in the literature.[14] (*R*)-3-Hydroxypiperidin-2-one (*R*)-**7** was obtained in an analogous manner from (*R*)-**23**.

In conclusion, an efficient chemoenzymatic method has been developed for the enantioselective synthesis of (*S*)- and (*R*)-3-hydroxypiperidin-2-ones in 93% yield and >99%ee from 5-nitro-2-oxopentanoic acid **22**.

Acknowledgements.

We are very grateful to the following for financial support: BBSRC (LM), EPSRC (GG and MJH) and Genzyme (MJH) and to Dr. Howard Marriage for valuable discussions.

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