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Stereocontrol in the reduction of *meso*-imides using oxazaborolidine, leading to a facile synthesis of (+)-deoxybiotin

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Abstract

Highly enantioselective reduction of *meso*-imides was conducted using oxazaborolidine derived from L-threonine and borane–THF complex to give lactams in high enantiomeric purity. This methodology was successfully applied to the synthesis of (+)-deoxybiotin in an enantio-controlled manner in good overall yield. © 1999 Elsevier Science Ltd. All rights reserved.

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Asymmetrization of *meso*-compounds enables a rapid access to very useful chiral materials possessing multiple asymmetric centers. To this end, a variety of methodologies have been reported.[1] Among them, transformation of *meso*-dicarboxylic acid derivatives offers useful chiral synthons for the synthesis of biologically important compounds.[2] We have already reported that *meso*-dicarboxylic anhydrides are readily converted into chiral monoesters by the action of zinc reagents in the presence of a cinchona alkaloid as a chiral auxiliary,[3] and have also disclosed very recently that the oxazaborolidine-mediated reduction is a useful tool for the preparation of diamines and amino alcohols.[4] In such asymmetric reductions the oxazaborolidine **2** derived from L-threonine and borane complex works in a highly efficient manner to give chiral materials with high enantiomeric purities. In the present study the same oxazaborolidine and borane have been found to work well for the reduction of *meso*-imides **1** to give hydroxy lactam derivatives **3** in good enantiomeric purities (Scheme 1).[5] Further functional group manipulations gave (+)-deoxybiotin **4b**, a precursor of (+)-biotin **4a**, with high enantiomeric excess in a short-step procedure.[6]

The initial examination into the reduction of *meso*-imides **1** was carried out using oxazaborolidine **2**[4] and BH_3·THF (Scheme 2), and the results are summarized in Table 1.

As shown in Table 1, in the reduction of the diacetoxy derivative **1a**[5] the use of a stoichiometric amount of the oxazaborolidine **2** did not always attain a satisfactory enantioselection, whereas in the presence of 0.5 equivalent of the oxazaborolidine the lactam **3a** was obtained with high enantiomeric

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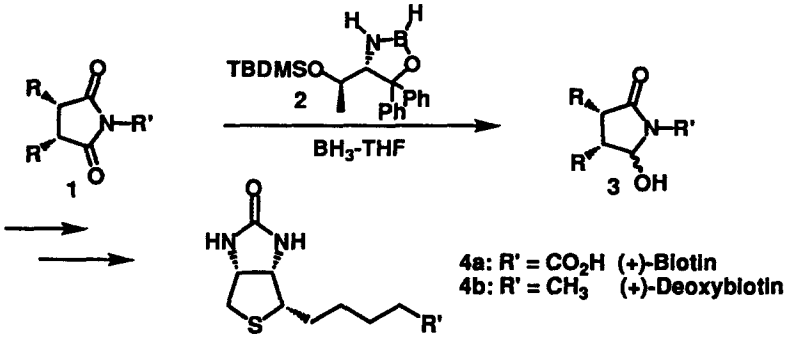
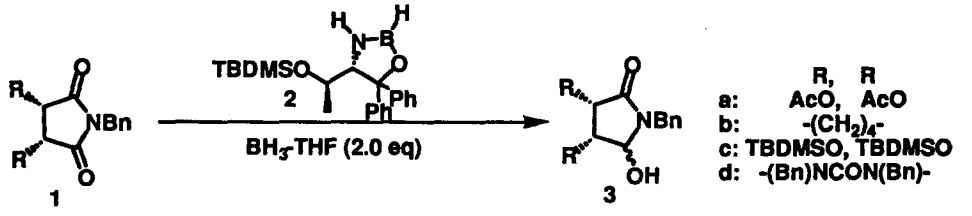


Scheme 1.



Scheme 2.

Table 1
Reduction of *meso*-imide **1** to lactam **3**[a]

Entry	*meso*-Imide **1**	Ligand **2** / eq	Solvent	Temp. / °C	Time / h	Yield / %[b]	% ee[c]
1	**1a**	1.0	THF	rt	21.0	54	89
2	**1a**	0.5	THF	0	16.0	42	98
3	**1a**	0.2	THF	rt	21.0	35	87
4	**1a**	0.2	DME	rt	21.0	19	91
6	**1b**	0.5	THF	0	10.5	50	92
7	**1c**	1.0	THF	rt	13.0	94	98
8	**1c**	0.5	THF	rt	18.0	76	91
9	**1d**	1.0	THF	rt	21.0	73	92
10	**1d**	0.5	THF	rt	20.0	65	98

[a]The reaction was carried out according to the typical procedure.

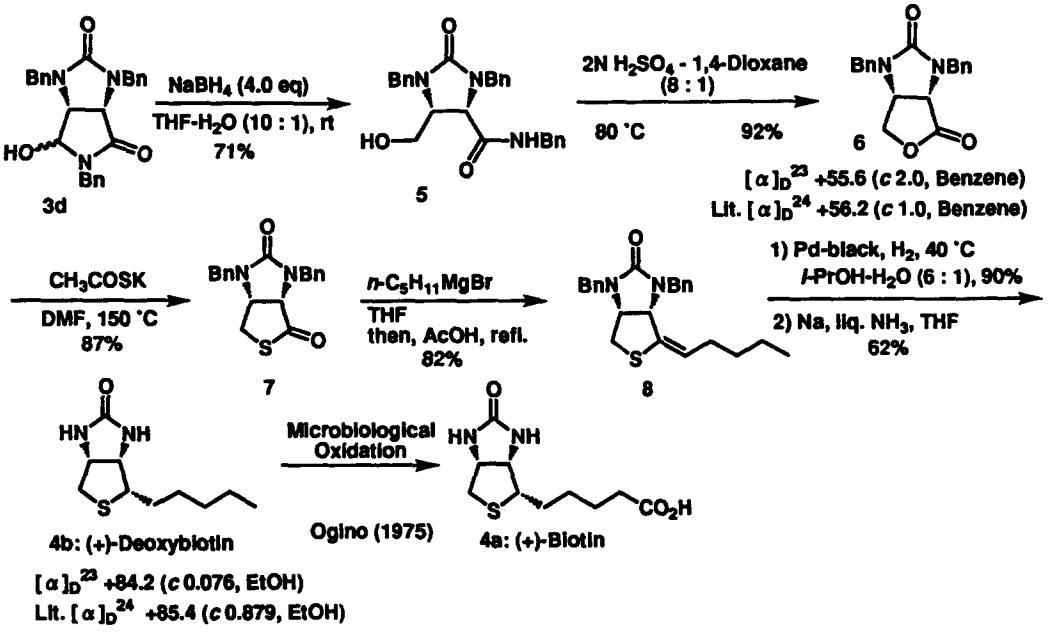
[b]Isolated yields.

[c]Determined by HPLC using a chiral stationary column (Daicel OD) after transformation into ethoxy or acetoxy derivatives according to the reported method (ref 5).

excess (entries 1 and 2). The use of a lesser amount of the oxazaborolidine gave lower yields of the product. When bis-TBDMSO derivative **1c** was used as a substrate in the presence of one equivalent of the oxazaborolidine, the reduction gave the lactam **3c** in 94% yield with 98% ee (entry 7). The higher yield obtained with respect to this particular derivative appears to be due to the solubility of the reduction product **3c** in organic solvents and hence to the readiness for the extraction of the reduction product from the reaction mixture after aqueous work-up. Regarding the reduction of the imidazolidinone derivative **1d**,[7] the reaction in the presence of 0.5 equivalent of the oxazaborolidine gave the desired lactam **3d** in 65% yield with 98% ee (entry 10). The use of one equivalent of the oxazaborolidine did not noticeably improve the enantiomeric purity of the product. One of the reasons for the improved enantioselectivities in the presence of 0.5 equivalent of the oxazaborolidine may involve a facile kinetic resolution of the initially formed mono-reduction products, where product yields of the lactam **3** dropped slightly as

compared with the cases using one equivalent of the oxazaborolidine (entries 1, 2, 9 and 10). In fact, the reduction proceeded slightly faster with the cases using 0.5 equivalent of the oxazaborolidine, resulting in a sort of facile over-reduction. However, the products arising from over-reduction were not always isolable in the present cases, which sometimes resulted in the relatively low material balances. From the standpoint of functional group manipulations, the imide **1d** was chosen as a substrate and the reduction conditions used in the case of entry 10 were employed for the preparation of (+)-deoxybiotin in the present study.[8]

The lactam **3d** thus obtained was used for the preparation of (+)-deoxybiotin via the following transformations (Scheme 3). The hydroxy lactam **3d** was reduced with $NaBH_4$ to give hydroxy amide **4** in 71% yield, and the subsequent treatment with H_2SO_4 gave the lactone **6** in 92% yield. Comparison of the optical rotation value with that of the reported data confirmed that the enantiomeric purity of this particular lactone **6** was not affected during the reduction and cyclization processes. The thiolactone formation was carried out as described in the literature to give **7** in 87% yield.[9] The side-chain was introduced by the addition of a Grignard reagent followed by acid treatment to give **8** in 82% overall yield.[6c,10] Stereospecific hydrogenation was carried out as described earlier in the presence of palladium black to give *N*-benzylated deoxybiotin in 90% yield.[6b] Removal of the *N*-benzyl group was conducted with Na in liquid ammonia to give (+)-deoxybiotin **4b** in 62% yield.[11] The optical rotation value of **4b**[6b,c] indicated that its enantiomeric purity was 98.6% ee which is essentially the same as that of the starting hydroxy lactam **3d**. Thus, no racemization occurred during the functional group manipulations performed. Further transformation into (+)-biotin is a known microbiological process.[12]



Scheme 3.

In conclusion, the present methodology using asymmetrization of *meso*-imides demonstrates the power of the oxazaborolidine-mediated reduction of symmetrical molecules to give a very useful class of compounds with high enantiomeric excess in a single step. Further functional group transformations readily led to a short-step preparation of (+)-deoxybiotin in high enantiomeric excess. Since the starting

material used for the present synthesis was readily available and each step gave the product in good yield, this methodology offers a convenient approach to biologically important materials.

Acknowledgements

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