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Remote Stereocenter Discrimination in the Enzymatic Resolution of Piperidine-2-ethanol. Short Enantioselective Synthesis of Sedamine and Allosedamine

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Abstract: Kinetic resolution of *N*-Boc-piperidine-2-ethanol (2), a case of remote stereocenter discrimination, was accomplished by sequential transesterification mediated by two enzymes, Lipase PS and porcine pancreatic lipase, showing opposite enantioselectivity. The gram-scale availability of the two enantiomeric *N*-Boc alcohols **2a** (*R*) and **2c** (*S*) enlarges their synthetic exploitation for the enantioselective preparation of piperidine alkaloids. As an example, the convenient three-step synthesis of both the enantiomers of sedamine and allosedamine is described.

Several multistep synthetic procedures describe the use of racemic[1] or enantiopure[2,3] piperidine-2-ethanol **1** for the total synthesis of natural products[2] and for the preparation of pharmacologically active compounds.[1,3]

Continuing our efforts in the total synthesis of piperidine alkaloids, we have recently reported on the elaboration of racemic **1** for the total synthesis of the C_{15} lupinine alkaloid aloperine.[4] As a logical further step in the exploitation of this synthon, we became interested in a convenient method for the production of enantiopure piperidine-2-ethanol in gram scale. Different synthetic approaches to the single stereoisomers of **1** are described in the literature. Initially, the careful diastereoselective crystallization of the corresponding *d*-10-camphorsulfonate salt has been reported.[5] More recently, (*S*)-**1** has been prepared from the expensive *N*-Boc-protected (*S*)-pipecolic acid by a two-step reaction sequence.[6] In turn, Kibayashi prepared (*R*)-**1** using 2-(1-aminoethyl)phenol as a chiral auxiliary[7] in a seven-step procedure.[3a] The corresponding *N*-Cbz aldehydes were obtained by intermolecular 1,3-dipolar cycloaddition of 2,3,4,5-tetrahydropyridine 1-oxide with a chiral allyl ether followed by a three-step synthetic elaboration.[8]

On the contrary, despite the fact that enzymatic kinetic resolutions of racemates have been widely exploited in the past years for the preparation of enantiopure synthons,[9] to our knowledge a biocatalyzed approach to (*R*)- and (*S*)-**1** has never been described.

The amino alcohol **1** is a bifunctional compound and therefore, desiring to apply an enzymatic methodology for its resolution, the amine moiety was blocked with a protective group in order to avoid possible effects related to enzyme chemoselectivity. Thus, the enantioselective acylation of the residual primary alcohol by a set of hydrolases could be investigated in various organic solvents.[10] This was not an easy task even for enzymes, as we were dealing with a conformationally flexible primary alcohol located two carbons away from the molecule stereocenter. Nevertheless, literature reports on the ability of proteases[11] and lipases[12] to discriminate remote stereocenters. More specifically, a paper on the lipase-catalyzed kinetic resolution of a chromanethanol (en route to the synthesis of an α-tocopherol analogue)[13] prompted us to start a systematic study on the performances of a set of commercially available lipases.

The amino group of **1** was protected to give the related *N*-Boc (**2**), *N*-Cbz (**3**), and *N*-Fmoc (**4**) derivatives (Scheme 1). Methyl *tert*-butyl ether and vinyl acetate were chosen as solvent and acylating agent, respectively. Over 20 different lipase preparations were tested by shaking the reaction mixture at 45 °C, and Table 1 shows the best results obtained. This preliminary screening pointed out that enantioselectivity (*E*) values[14] were quite low, as it might be expected, but also that the crude porcine pancreatic preparation possessed an opposite enantioselectivity compared to all the other lipases. The *N*-Boc derivative **2** was a slightly better substrate, and Lipase PS was the more selective enzyme among the "(*R*)-lipases".

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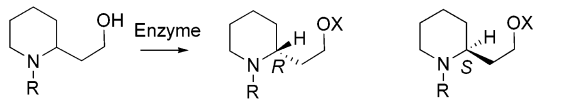
SCHEME 1



1 R = H **a** X = H, **b** X = Ac **c** X = H **d** X = Ac
2 R = Boc
3 R = Cbz
4 R = Fmoc

TABLE 1. Evaluation of Lipase Enantioselectivity in the Acetylation of Substrates 2, 3, and 4[a]

lipase	preferred enantiomer	*E* values[e] 2	3	4
pancreatic lipase[b]	*S*	6.0	3.6	4.4
Lipase PS[c]	*R*	5.3	2.6	6.4
Lipase R[c]	*R*	2.6	2.2	2.5
Lipozyme[d]	*R*	2.1	1.3	4.2
Lipase G[c]	*R*	1.5	1.5	2.6
Candida rugosa lipase[b]	*R*	1.4	1.6	1.6
Novozyme 435[d]	*R*	1.2	1.8	2.9
Lipase F-AP 15[c]	*R*	1.1	1.6	1.1
Lipase CE-5[c]	*R*	1.1	1.0	1.4

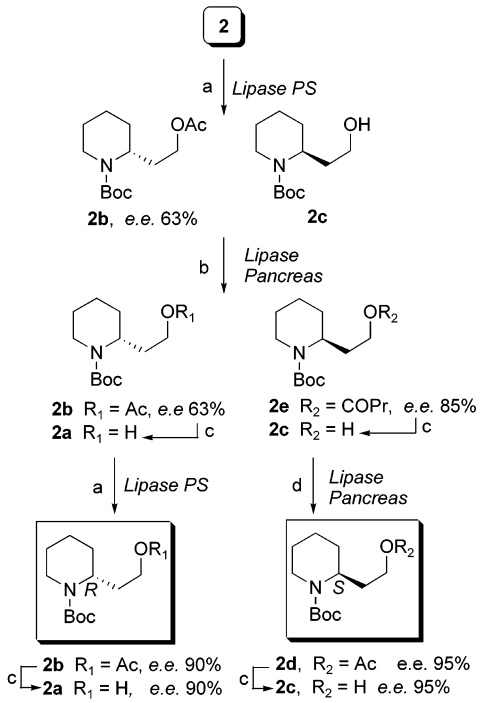
[a] $E = \ln[1 - c(1 + ee_P)]/\ln[1 - c(1 - ee_P)]$. [b] Sigma. [c] Amano. [d] Novozymes. [e] The enantiomeric excesses (ee_P) and the ratios of conversion (*c*) were evaluated by HPLC analysis (Chiralcel OD).

It is well-known that the reaction medium can significantly effect the enzymatic performances (activity and selectivity).[15] Accordingly, the *E* values of the acetylation reactions catalyzed by Lipase PS and porcine pancreatic lipase were evaluted in different solvents. It was found that hexane was a slightly better solvent for Lipase PS ($E = 8.1$) (see the Supporting Information), while methyl *tert*-butyl ether remained the solvent of choice for the pancreatic enzyme. In fact, by changing the reaction medium, small improvements in terms of selectivity were accompanied by significant decreases of the activity of this lipase.

In spite of the low *E* values of the two enzymes, the observed complementary enantioselectivity was the basis of an optimized protocol for the preparation of the enantiomers **2a** (*R*) and **2c** (*S*) (Scheme 2). Racemic **2** was dissolved in hexane and acetylated by Lipase PS to give **2b** with 63% ee at 45% conversion. The enzyme was filtered, the solvent and the unreacted vinyl acetate were evaporated, and the crude mixture was dissolved in methyl *tert*-butyl ether. The residual alcohol, enriched in the (*S*)-enantiomer, was butanoylated by the pancreatic lipases to give the corresponding ester with 85% ee. The crude reaction mixture—containing the acetate **2b**, the butanoate **2e**, and the unreacted almost racemic **2** (**2a** + **2c**)— was easily purified by flash chromatography.

Compounds **2b** and **2e** were chemically hydrolyzed to the corresponding enriched alcohols (**2a** and **2c**, respectively) and submitted to a second round of acetylation with the respective enzymes. In this way, the low selectivity of the two lipases was enhanced, and the two enantiomers **2a** and **2c** could be isolated in 90 and 95% ee, respectively.[16]

SCHEME 2[a]



[a] Reagents and conditions: (a) $AcOCH{=}CH_2$, hexane, 20 °C, 190 min (45%); (b) $PrCOOCH{=}CH_2$, MTBE, 20 °C, 11.5 h (30%), flash chromatography (AcOEt−hexane 1:9); (c) CH_3OH, Na_2CO_3; (d) $AcOCH{=}CH_2$, MTBE, 20 °C, 46 h (48%).

Having the enantiomeric enriched compounds **2a** and **2c** in hand, we started to explore new approaches to optically active piperidine alkaloids bearing a stereogenic carbon at the C-2 position.[17] As a first example, we faced the stereoselective preparation of sedamine (**8** and **13**) and allosedamine (**9** and **14**).[18] Both levorotatory sedamine (**8**) and its dextrorotatory enantiomer (**13**) were found in a number of *Sedum* species.[19] (−)-Allosedamine (**9**) has been isolated from *Lobelia inflata*,[20] which furnished a crude extract useful for the treatment of respiratory illnesses such as asthma, bronchitis, and pneumonia.[21] Numerous syntheses of sedamine, either in racemic form[22] or as a single enantiomer,[23] have been reported,

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(16) This protocol was highly reproducible and easily scaled-up: approximately 2.5 g of **2a** and 1.8 g of **2c** were produced from 10 g of racemic **2**.

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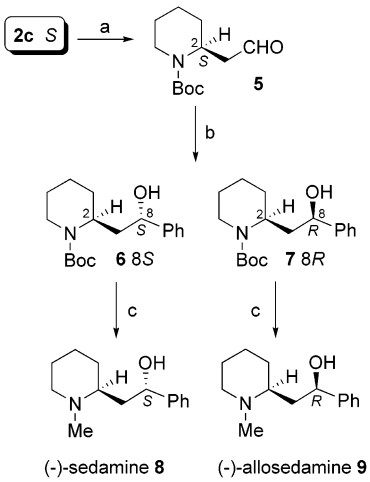
SCHEME 3[a]

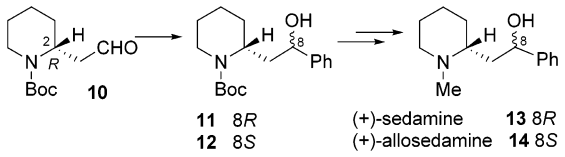


[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N; (b) PhMgBr, THF, −20 °C; (c) $LiAlH_4$, THF, reflux.

while the synthesis of allosedamine received minor attention.[24] To the best of our knowledge, allosedamine has been prepared only as the (−)-enantiomer **9**.[25] The reported stereoselective syntheses of sedamine, allosedamine and related alkaloids were based on elaborated construction of the piperidine ring or on the introduction of the chain at the C-2 piperidine carbon, obtaining interesting results by applying noteworthy chemical procedures.

In our plan, compounds **2a** and **2c** represented an attractive and convenient starting material offering the opportunity to introduce diverse appendages at C-8 while retaining the configuration at the stereogenic C-2. Specifically, we envisaged the corresponding aldehyde **5**[26] (Scheme 3) and its enantiomer **10** as the appropriate synthons for the target- and diversity-oriented synthesis.[27] The preparation of **5** was secured by Swern oxidation of **2c** to give a stable compound in 80% yield ($[\alpha]^{20}_D = -50.6$, $c = 0.85$, $CHCl_3$). The subsequent step—the introduction of the phenyl group with the generation of the hydroxyl function—was made possible by reaction with phenylmagnesium bromide in THF at −20 °C. A quantitative conversion to a 2:3 mixture of compounds **6** and **7** was obtained after 3 h. The structural assignments of the absolute configuration of the alcohols could not be assessed a priori and ultimately rested with their conversion into sedamine and allosedamine. The enantiomeric excess of compounds **6** and **7** (95%), evaluated by HPLC analysis (Chiralcel OD), was in accord with that of the corresponding starting material.

SCHEME 4



After separation of **6** and **7** by column chromatography, reduction of the Boc group with $LiAlH_4$ in refluxing THF for 6 h gave (−)-sedamine (**8**, 70% yield, ee 95%) and (−)-allosedamine (**9**, 71% yield, ee 95%), respectively. Analogously (Scheme 4), the aldehyde **10** ($[\alpha]^{20}_D = 48$, $c = 1$, $CHCl_3$) was obtained by Swern oxidation of **2a**. In turn, the reaction with phenylmagnesium bromide gave the quantitative conversion to a 2:3 mixture of compounds **11** and **12**. Reduction of the Boc group gave (+)-sedamine (**13**) from (+)-**11** and (+)-allosedamine (**13**) from (+)-**12**, both showing 90% ee.

In conclusion, we have demonstrated that the enzymatic resolution of *N*-Boc-piperidine-2-ethanol could be accomplished by the sequential use of Lipase PS and porcine pancreatic lipase exploiting their opposite enantioselectivity. The gram scale availability of the two enantiomers **2a** and **2c** enlarges their synthetic application, as these chiral building blocks are expected to provide general access to enantiopure piperidine alkaloids. The corresponding aldehydes **5** and **10** are also suitable synthons for diversity-oriented synthesis, and their requisite configurational stability has been demonstrated in the enantioselective synthesis of both the enantiomers of sedamine and allosedamine. Incidentally, the present report describes the first enantioselective synthesis of (+)-allosedamine (**14**).

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Supporting Information Available: Experimental procedures and characterization for all new compounds. ^1H and ^{13}C NMR spectra for compounds. Tables regarding the medium engineering for the pancreatic lipase- and Lipase PS-mediated acylation of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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