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Enzyme-Catalysed Hydrolysis of N-Benzyloxycarbonyl-cis-2,6-(acetoxymethyl)piperidine. A Facile Route to Optically Active Piperidines

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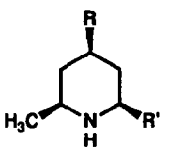
Abstract: We report the first enzymatic asymmetrization of a piperidine system. Hydrolysis of N-benzyloxycarbonyl-cis-2,6-(acetoxymethyl)piperidine in the presence of *Aspergillus niger* lipase gave the corresponding 2R, 6S mono-acetate in good chemical yield and very high optical purity (ee ≥ 98%).

A number of alkaloids contain a cis-2,6-disubstituted piperidine (or dihydropyridine) ring and some of them exhibit significant biological activity.[1] For instance, pinidine 1 and dihydropinidine 2 have been isolated from various species of *Pinus* plants.[2] Several cis-2,6-dialkylpiperidines such as 3 produced by venomous myrmicine ants have fungicidal, insecticidal, and repellent properties.[3] Alkaloid 4 has been isolated from the poison frog *Dendrobates speciosus*.[4,5] Betalains (general structure 5) constitute a class of chromoalkaloids isolated from plants of the caryophyllale order.[6]

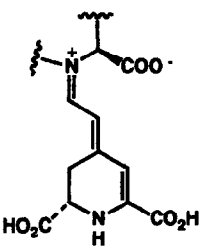


1 R = H R' = $-CH_2CH{=}CH_2$

2 R = H R' = $-C_3H_7$

3 R = H R' = $-C_{13}H_{27}$

4 R = OH R' = $-C_9H_{13}$



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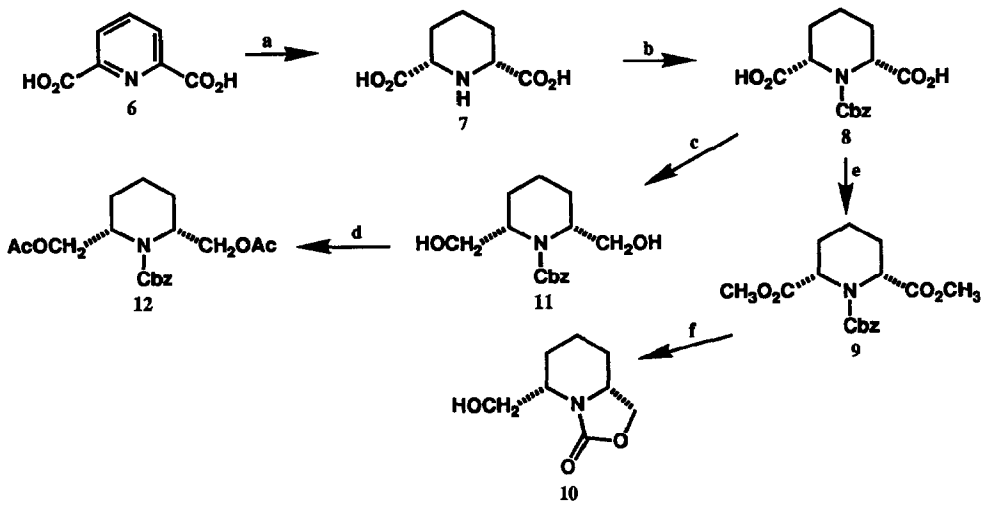
A simple and general approach to the asymmetric synthesis of these piperidine or dihydropyridine alkaloids may be envisaged by enzymatic asymmetrization of meso 2,6- or meso 2,4,6-substituted piperidine compounds. There are a few reports on the enzymatic asymmetrization of cis-2,5-pyrrolidines[7,8,9] but as far as we know there is no report on the asymmetrization of the six membered ring analogs. As part of a program directed to the asymmetric synthesis of natural piperidine or dihydropyridine alkaloids, we investigated the enzymatic asymmetrization of meso-2,6-disubstituted piperidines.

Scheme 1



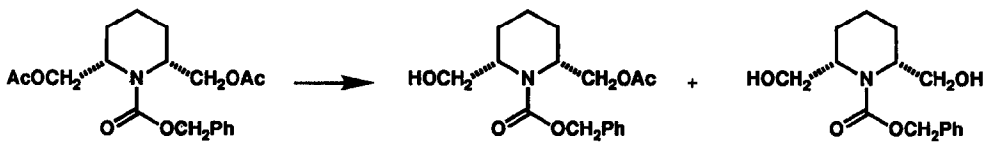
Reagents and conditions: a) H_2 (2 atm.), 10% Pd/C, H_2O, 50°C, 95%; b) Ph-CH_2-O-COCl, H_2O, NaOH, 0°-50°C, 72%; c) THF-BH_3, THF, 70%; d) Ac_2O, DMAP, pyridine, 96%; e) MeOH, H^+ resin, reflux, 75%; f) $NaBH_4$, t-BuOH, MeOH, reflux, 65%.

The substrates were prepared as outlined in Scheme 1. Catalytic hydrogenation of pyridine-2,6-dicarboxylic acid **6** over palladium gave piperidine-cis-2,6-dicarboxylic acid **7**. Protection of the amino group in **7** with benzyl chloroformate followed by esterification of **8** gave the diester **9**. Unexpectedly, the reduction of **9** with sodium borohydride produced the bicyclic compound **10**. On the other hand, reduction of diacid **8** with borane-THF complex afforded diol **11** which was acetylated with acetic anhydride to give diacetate **12**. Initial attempts to asymmetrize the 2,6-disubstituted piperidine system involved enzymatic hydrolysis of diester **9**. Almost all enzymes in various reaction conditions showed no hydrolytic activity. The sole exception was pig liver esterase (PLE). However, this reaction was very slow (less than 10% hydrolysis after 4 days) and there appeared to be an inhibitory effect at work as hydrolysis would stop after 10% of the diester had been hydrolysed. On the basis that steric crowding was preventing enzyme access to the ester carbonyl, the diol **11** and the diacetate **12** were used as substrates instead of diester **9**.

Enzyme activity was found with both the diol **11** and the diacetate **12**. Acetylation of diol **11** in organic solvent with acetic anhydride as acetylating agent and in the presence of enzymes adsorbed on celite[10] gave poor yields of mono-acetate, competitive conversion to diacetate and long reaction times. Three enzymes hydrolysed the diacetate **12** (Table 1). Hydrolysis in the presence of PLE was fast but the product was the diol **11** (Scheme 2) indicating that the monoacetate **13** is a better substrate than the starting material **12**. Wheat germ lipase (WGL)-catalysed hydrolysis provided **13** of good enantiomeric purity (ee = 81%) but the chemical yield was low (43%). Lipase from *Aspergillus niger* (ANL) gave very high enantiomeric excess values (ee ≥ 98%) and good chemical yields under various conditions. The initial experiments were run in

phosphate buffer (pH 7) with a drop of Triton-X as surfactant. These conditions produced some autolysis of the enzyme which made monitoring the reaction more difficult and necessitated the addition of more enzyme to finish the reaction. This problem was solved by addition of 5% acetonitrile. Although the reaction rate was slower, no degradation of the enzyme was observed and both chemical (83%) and optical yield (ee ≥ 98%) were high. The optical purity of the alcohol was established by formation of Mosher's ester and analysis of diastereoisomeric composition by ^{19}F NMR and HPLC.

Scheme 2



12 13 11

Table 1: Enzyme-catalysed hydrolysis of meso-diacetate 12

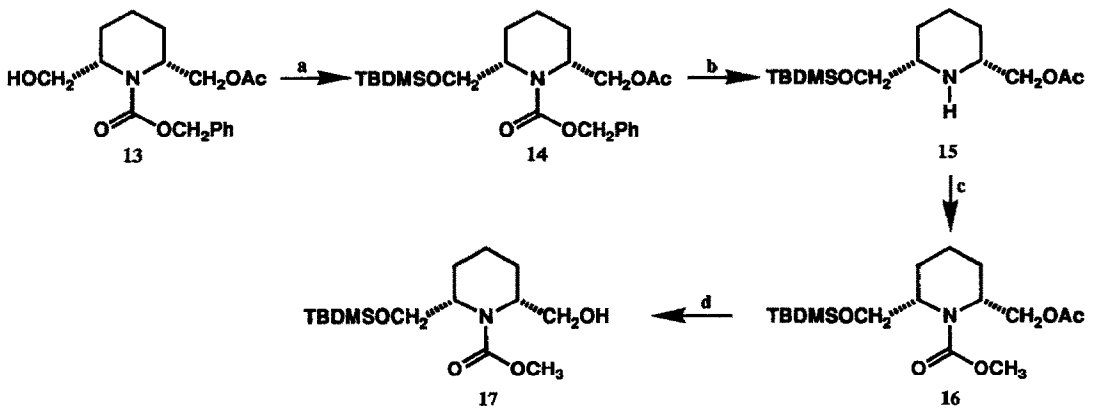
Enzyme	Conditions	Time (h)	Yield[1](%)			ee of 13[2] (%)
			12	13	11	
PLE	Phosphate buffer pH 7	1.5	50	–	50	–
WGL	Phosphate buffer pH 7	40	15	43	25	81
ANL	Phosphate buffer pH 7, Triton-X	50	4	73	12	≥95
	Phosphate buffer pH 7, CH_3CN 5%	108	9	83	–	≥98

[1] Yields after purification by column chromatography.
[2] HPLC analysis of Mosher's ester.

The absolute configuration of **13** as 2R, 6S was determined by conversion to **17**, the (+)-2R, 6S enantiomer of which has been described.[11] The 2R, 6S configuration of **13** was then assigned from the sign of its optical rotation. Thus, protection of the hydroxyl in **13** with t-butyldimethylsilyl chloride (TBDMS) in the presence of tetramethylguanidine (TMG) followed by catalytic hydrogenation of **14** gave **15** (Scheme 3). Reaction of **15** with methyl chloroformate and subsequent enzymatic hydrolysis of **16** gave (+)-(2R, 6S) **17**.

As far as we know, this is the first enzymatic asymmetrization of a piperidine system. The asymmetrization of other piperidine derivatives, namely 2,4,6-substituted compounds, and asymmetric synthesis of naturally occurring alkaloids from **13** are now in progress.

Scheme 3



Reagents and conditions: a) TBDMSCl, CH_3CN, Et_3N, TMG; b) MeOH, H_2, 10% Pd/C; c) MeOCOCl, THF, Et_3N; d) PLE, pH 7.

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