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Synthesis of Optically Active N-Benzyl-2,4-Bis(hydroxymethyl) Substituted Azetidines by Lipase Catalyzed Acetylations

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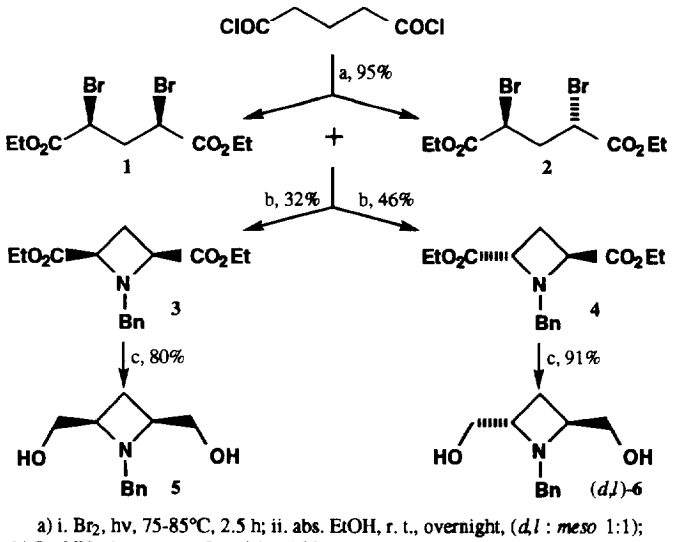
Abstract: Both *cis*- and *trans*-N-benzyl-azetidine-2,4-dimethanols **5** and **6** were prepared and submitted to acetylation in organic solvents catalyzed by lipases. Asymmetrization of diol **5** gave the corresponding monoacetate **7**, while double sequential kinetic resolution of racemic **6** gave optically enriched diol **6b** and its enantiomer as the corresponding diacetate **10a**. Optimized reaction conditions furnished **7**, **6b** and **10a** with e.e. > 99%.

Optically active azetidines substituted with one or two carboxy groups are interesting nonproteinogenic amino acids and have been extensively studied in the last years: actually, they have found application in the synthesis of peptides,[1a] natural products[1a] and rigid glutamate analogues with metabotropic receptor activity.[1b] Moreover, azetidines 2-[2a] or 2,4-substituted[2b] with hydroxymethyl groups have been recently proposed as promising chiral auxiliaries[2b] or catalysts[2a] for asymmetric synthesis. The preparation of these azetidines in optically active form has previously relied mostly on classical resolutions,[1b,2a,b] while the only reported enantiospecific approach involves the intramolecular cyclization of an optically active acyclic intermediate.[2c] Biocatalysis is a very powerful tool in organic synthesis for obtaining optically active compounds and, in the last years, we successfully used lipases for chiral discriminations.[3] As part of our interest in the use of enzymes in organic synthesis, we report here the preparation of *cis*- and *trans*-N-benzyl-azetidine-2,4-dimethanols **5** and **6** and the results of a study of their irreversible acetylation in organic solvents catalyzed by lipases: for compound **5**, which is a *meso* form, monoacetylation would lead to asymmetrization making the two stereogenic centers in positions 2 and 4 not equivalent, while for diol **6**, a C_2 symmetric compound, we planned to separate the enantiomers by selective functionalization of only one of them, through a double sequential kinetic resolution.

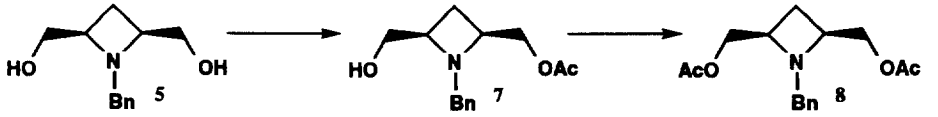
Scheme 1



a) i. Br_2, hv, 75-85°C, 2.5 h; ii. abs. EtOH, r. t., overnight, (*d,l* : *meso* 1:1); b) Bn-NH_2, benzene, reflux, 24 h, (*d,l* : *meso* 6 : 4); c) $LiAlH_4$, Et_2O, 0°C → r. t.

Synthesis of **5** and **6**, was realized following a protocol used

Table 1: Asymmetrization of diol **5** catalyzed by lipases[a]



absolute configuration of **7** is arbitrarily shown

Entry	*Enzyme (mg/mg of 5)*	*Solvent*	*Time (min)*	*Conversion*[b] *(%)*	*5 : 7: 8*[c]	*e.e.*[d] *(%)*
1	Supp. PPL (1.6)	VA[e]	525	56.8	3.8 : 78.8 : 17.4	96.3
2						
3	Supp. PPL (1)	VA : *i*-Pr_2O 1:1	1390	55.7	5.1 : 78.4 : 16.5	98.0
4	Supp. PPL (1.6)	VA : *i*-Pr_2O 1:1	440	49.8	10.6 : 79.2 : 10.2	95.2
5	Supp. PPL (1)	VA : hexane	1400	44.1	26.2 : 59.4 : 14.4	94.6
6	PPL[f] (0.16)	VA	1500	21.7	58.7 : 39.2 : 2.1	68.3
7	Supp. PSL (1.5)[g,h]	VA	1974	20.5	60.7 : 37.7 : 1.6	7.4[i]
8	Supp. PSL (1.5)[g,h]	VA : CH_2Cl_2 1:1	4320	55.2	14.2 : 61.1 : 24.7	8.7
9	PSL[g] (0.16)	VA : CH_2Cl_2 1:1	4320	65.6	11.0 : 46.9 : 42.1	2.7
10	PSL[g] (0.16)	CH_2Cl_2[l]	5760	37.4	40.7 : 43.8 : 15.5	18.4

Note: a) see note 7 for reaction conditions; b) % of acetylated -OH groups *vs* initial -OH groups; c) determined by GLC; isolated yields of **5**, **7**, **8** were in agreement with the gas-chromatographic data; d) determined by GLC using a Cyclodex-B™ (J & W) column ; e) VA = vinyl acetate; f) purchased from Sigma; g) Amano-PS lipase was a gift of Amano company; the conditions were the same as for PPL, but reaction was carried out at reflux; h) prepared as supported PPL; i) the enantiomer was obtained; l) 5 equiv. of vinyl acetate were used.

for the preparation of the analogous pyrrolidine derivatives,[4,5] is summarized in Scheme 1.[3] The two diastereoisomers have been easily separated as the diesters and, finally, both diols were prepared on a multigram scale as nicely crystalline products.

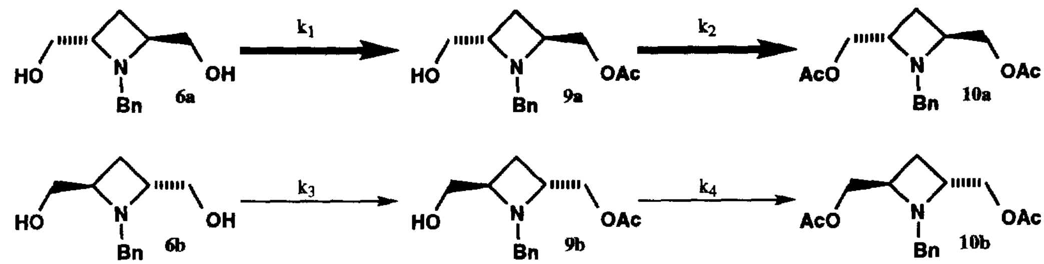
The asymmetrization of **5** was successfully realized using vinyl acetate as irreversible acyl donor and pig pangreatic lipase (PPL), supported on celite as recently described by us,[3] as catalyst. The results are illustrated in Table 1:[7] vinyl acetate was found to be both the acylating agent and the solvent of choice for this kind of reaction; use of solvent mixtures was satisfactory in the case of *i*-Pr_2O (entry 3 & 4), while apolar solvents like hexane slowed down the reaction (entry 5), most likely because of the reduced solubility of **5** in the reaction medium. Substrate selectivity was not excellent in this asymmetrization: anyway, optimized conditions (entry 6, Table 2) permitted monoacetate **7** to be obtained on a gram scale in good isolated yield (around 80%) and high e.e. (up to 98%, depending on conversion). We verified once again that the supported enzyme was superior to the commercial one, most of all in terms of reaction rate, which was dramatically improved. The amount of enzyme used had not an appreciable influence on enantiomeric excess; actually, the only consequence we observed was just on reaction rate, as expected.

Table 2: Influence of conversion on yields and e.e.

Entry	*Time (min)*	*Conversion (%)*	*5 : 7: 8*	*e.e. (%)*
1	60	16.3	67.9 : 31.5 : 0.6	93.7
2	120	26.9	48.0 : 50.2 : 1.8	94.7
3	240	42.0	21.7 : 72.6 : 5.7	95.1
4	360	49.6	11.4 : 77.9 : 10.7	96.2
5	480	54.9	4.3 : 81.6 : 14.1	97.2
6				
7	1440	67.3	0.1 : 65.2 : 34.7	99.5
8	2880	75.1	0 : 49.8 : 50.2	> 99.5

Finally, assuming as the best reaction conditions those reported in entry 2 (Table 1), we studied the influence of the conversion on the chemical yield and on the enantiomeric excess (Table 2). Although the e.e. was quite

Table 3: Double sequential kinetic resolution of diol **6** catalyzed by lipases[a]



$$E_1 = k_1/k_3 ; E_2 = k_2/k_1 ; E_3 = k_4/k_3 ; E_4 = k_2/k_4 ; E_{T(max)} = E_1 x E_4 /2$$

absolute configuration of **6**, **9**, **10** is arbitrarily shown

Entry	*Enzyme (mg/mg of* ***6****)*	*Solvent*	*Time (min)*	*Conversion*[b] *(%)*	***6 : 9 : 10***[c]	*e.e. (%)*[d] ***6, 9, 10***
1	Supp. PPL (1)	VA	1510	39.6	54.3 : 15.3 : 30.4	43.1, *30.2*, 93.0[e]
2	Supp. PPL (1)	VA : THF 1:1	1800	47.5	43.7 : 10.9 : 45.4	99.2 , *8.5* , 97.6[e]
[redacted]						
4	Supp. PPL (2.5)	VA : THF 1:1	178	31.3	53.0 : 26.0 : 21.0	79.7, 82.2, 99.6[f]
5	Supp. PPL (2.5)	VA : Me_2CO 1:1	451	26.7	65.5 : 10.7 : 23.8	43.0, 43.1, 98.7[f]
6	Supp. PPL (2.5)	VA : CH_3CN 1:1	451	26.9	62.0 : 11.8 : 26.2	45.0, 20.5, 97.3[f]
7	Supp. PPL (2.5)	VA : Py 1:1	451	26.5	60.0 : 21.3 : 18.7	61.3, 85.2, 99.4[f]
8	PSL (0.1)[g]	VA : hexane 1:1	1440	17.2	67.1 : 29.0 : 3.9	26.8, 51.9, 75.6[e]

Note: a) For reaction conditions see note 8; b,c) see notes b,c in Table 1; d) major enantiomers were always **6b** and **10a**. In the case of **9**, when **9b** was prevailing, e.e. was written in italic; e) determination of e.e. for **6** and **10**: by transformation into the corresponding Mosher's esters and analyzing them by HPLC using a Herbasil (Carlo Erba) column; for **9**: ^{1}H-n.m.r. analysis of the corresponding monocamphanoate; f) determination of e.e. for **9** and **10**: GLC using a Dmet.terBut.SBeta (persilylated β-cyclodextrin from MEGA) column; diol **6** was previously acetylated, then analyzed like **10**; g) Amano-PS lipase was a gift of Amano company; the conditions were the same as for PPL, but reaction was carried out at reflux.

high from the beginning, by increasing the conversion the influence of the concomitant kinetic resolution became noteworthy and e.e. came up to 99.5%; of course, if the conversion was too high, the chemical yield dropped down; therefore, the conditions reported in entry 6 (Table 2) represent the best compromise between a good chemical yield and a high e.e..

While lipase Amano PS was found to work well on analogous pyrrolidines,[4] unfortunately, on diol **5** we observed sluggish reactions, both with the commercial enzyme and with the celite supported one. As reported in Table 1 (entries 7-10) very long reaction times were necessary to reach an appreciable conversion and, most of all, the e.e.s were absolutely unsatisfactory.

We then turned our attention of **6**. Using vinyl acetate as the only solvent we isolated diacetate **10** with high e.e. (entry 1, Table 3). However, the reaction was too slow, probably because of the scarce solubility of the diol in vinyl acetate at 0°C. For this reason we performed the reaction in the presence of a solubilizing cosolvent. The e.e.s were always high for the diacetate **10** but they were best when conversion was lower than 40% (compare entry 2 and 4). On the other hand, as expected, e.e. of unreacted diol **6** increased with time,

Table 4: Calculation of enantioselectivity factor

Entry	E_1	E_2	E_3	E_4	E_T *(max)*
4 from tab. 3	46.28	0.45	1.14	18.08	418.26
5 from tab. 3	14.88	3.14	1.21	38.65	287.50
6 from tab. 3	10.12	3.16	1.38	23.20	117.40
7 from tab. 3	43.94	0.80	1.30	27.04	594.00

reaching excellent values at high conversions (entry 2). Our resolution was also performed without problems on a gram scale, under the conditions of entry 3; being diol **6** solid, we tried to crystallize it, hoping to enhance its enantiomeric purity (which was 85.6%). We obtained indeed the crystallization of a small quantity of the racemic compound from acetone, leaving the enriched, nearly optically pure main enantiomer (e.e. 94.5%), in the mother liquors.[9] This remarkable solubility difference between the racemic compound and the pure enantiomer adds a further opportunity for the obtainment of this diol in high e.e. even from conditions optimal for the achievement of high diacetate e.e..[10] Finally, we compared the enantioselectivities (E_1 and E_4 values, Table 4) for the two sequential resolutions of some representative reactions, that is the ones performed with different cosolvents (entries 4-7, Table 3), using the method proposed by Sih and co-workers.[11] Our calculations suggest that the best enantioselectivity can be achieved working in a mixture of vinyl acetate and pyridine; anyway, although a little bit less enantioselective, reaction using vinyl acetate and THF is faster and easier to work up: so, we think that conditions reported in entry 3 (Table 3) are definitely the best.[12] We tried lipase Amano PS also in this case: the results were not so discouraging as with diol **5**, but not enough satisfactory for our purposes.

In conclusion, the here reported study allowed the development of practical chemoenzymatic methodologies for the obtainment of optically active azetidines **7**, **6**, and **10**, which are potentially useful chiral building blocks, or chiral auxiliaries. Synthetic applications are currently under investigation in our laboratories.

Finally we would like to thank M.U.R.S.T. and C.N.R. for financial support, Amano company for a generous gift of lipase PS and Dr. Luca Banfi for helpful suggestions.

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5. After completion of our work a similar azetidine synthesis was reported (ref. 2b).
6. All new compounds were fully characterized and gave data consistent with their structure.
7. **5** Was dissolved in dry solvent under nitrogen (1 ml/10 mg **5**), cooled to 0°C and treated with powdered 3Å molecular sieves (0.25 mg/mg **5**). After 15 min enzyme [supported as described in ref. 3 (SPPL-4)] was added and stirring continued for the reported time. Enzyme was filtered off and solvent evaporated *in vacuo*. The crude mixture was purified on silica gel by flash chromatography.
8. The reactions were carried out at 0°C with the procedure described in note 7. **6** was first dissolved at r.t. in the cosolvent before addition of vinyl acetate. Products were separted by flash chromatography.
9. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds* J. Wiley Ed., N.Y., **1994**, p. 162.
10. It is noteworthy that both the racemic diol and the slightly enriched monoacetate can be recycled.
11. Guo, Z.-W.; Wu, S.-H.; Chen, C.-S.; Girdaukas, G., Sih, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 4942-4945.
12. Selected optical rotation values: a) **7**: $[\alpha]_D$ = + 13.5 (c 1.46, $CHCl_3$) [entry 8, Table 2]; b) **6b**: $[\alpha]_D$ = - 34.2 (c 2.58, Me_2CO; e.e. 94.5%); **9a**: $[\alpha]_D$ = + 18.2 (c 2.28, $CHCl_3$); **10a**: $[\alpha]_D$ = + 39.0 (c 2.56, $CHCl_3$) (the optical rotion values reported for **6b**, **9a**, **10a** are referred to products isolated in the reaction described in entry 3, Table 3).

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