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A novel building block for the synthesis of isofagomin analogues

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Abstract

The *de novo* synthesis of the novel potent building blocks phenyl (*R*)-3-acetoxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylate (−)-**7** and phenyl (*S*)-3-butyryl-oxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylate (+)-**8** starting from commercially available methyl-1-benzyl-4-oxo-3-piperidinecarboxylate is described. The key steps are the enantioselective esterification of the racemic alcohol **6** and the enantioselective hydrolysis of the racemic acetate **5**, respectively, using lipase P from *Pseudomonas caepacia*. *© 1998 Elsevier Science Ltd. All rights reserved.*

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1. Introduction

Sugar analogues, in which the ring oxygen of a pyranose has been replaced by nitrogen[1] — commonly known as azasugars — have often been found to be specific and effective inhibitors of enzymes which are involved in the building up or cleavage of glycosides of the related sugar,[2] thereby having the potential to produce beneficial therapeutic effects such as cancerostatic[3] or antiviral activities.[4] Recently it has been shown that piperidine systems where the nitrogen is at the position of the anomeric carbon of the corresponding sugar are also very potent glycosidase inhibitors.[5] All of the known routes to these compounds (isofagomin and some derivatives) start from the chiral pool[6] and are not very flexible.

A potent building block is 3-hydroxymethyl-1,2,3,6-tetrahydropyridine **1** or a protected form of the alcohol, which has potential not only for the synthesis of isofagomin, but also for the synthesis of stereoisomeric isofagomin analogues (Scheme 1).

We want to present an easy synthesis of the enantiomerically pure building block **1** by using enzymatic resolution. To our knowledge neither such an approach for the synthesis of isofagomin analogues nor the preparation of the enantiomerically pure alcohol **1** has been reported in the literature, only the synthesis of a racemic derivative of **1** ($R=H$, $R'=CH_3$) has been described in a patent.[7]

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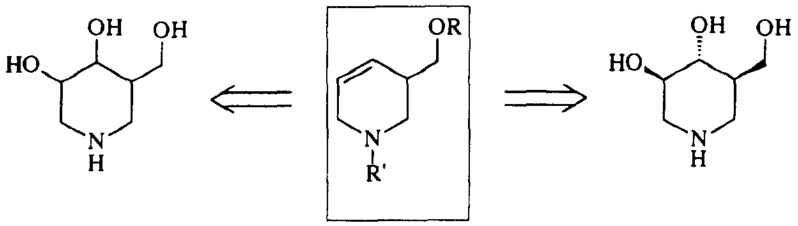


Isofagomin analogues

1: R' = R = H

Isofagomin

Scheme 1.

2. Results and discussion

Methyl 1-benzyl-1,2,3,6-tetrahydropyridine-3-carboxylate[8] **3** was synthesised starting from the commercially available β-keto ester **2** using the Shapiro reaction for the introduction of the double bond.[9] In accordance with the results of P. L. Fuchs and C. A. Bunnell,[9] who have investigated the Shapiro reaction of carbocyclic β-keto esters, only one regioisomer was formed in 73% yield. Reduction of the ester **3** with $LiAlH_4$, followed by protection with Ac_2O in pyridine gave the acetate **4** in nearly quantitative yield. As the carbamate protecting group proved to be superior to the benzyl group with respect to the determination of the enantiomeric purity, the benzyl protected compound **4** was transformed to the carbamate **5** by treatment with phenoxycarbonyl chloride.[10] On hydrolysis with sodium hydroxide in ethanol the alcohol **6** could be prepared from **5** (Scheme 2).

Although the successful enzymatic resolution of racemic primary alcohols is rather rare,[11] we were encouraged by some recent work in this area[12,13] to try lipase catalysed esterfication or hydrolysis for this purpose, especially as B. Wirtz and W. Walther had reported that a saturated derivative of **1**, *t*-butyl-3-(hydroxymethyl)-piperidinecarboxylate, could be resolved efficiently using lipase from *Pseudomonas fluorescens*.[12]

In screening experiments with the unsaturated system **5** and **6** lipase P from *Pseudomonas caepacia* (PCL) showed the best enantiomeric excess of all the tested enzymes.[14]

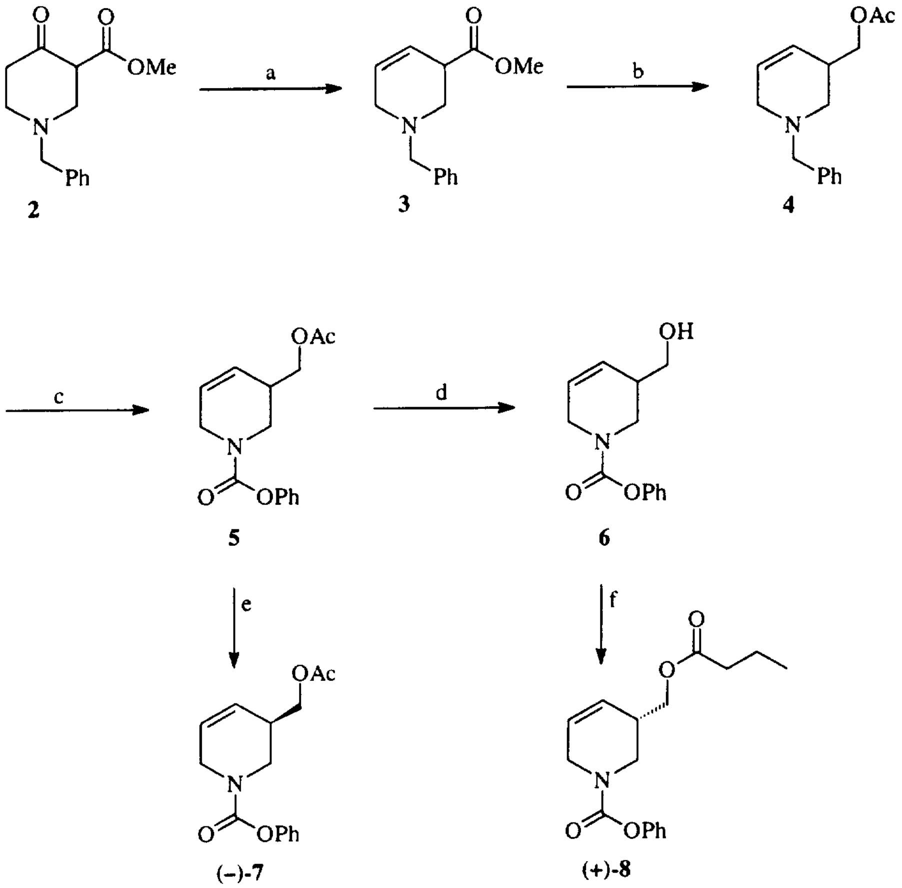
The enantioselective esterification of the racemic alcohol **6** using PCL in hexane/CH_2Cl_2 in the presence of vinyl butyrate delivered the butyryl ester (+)-**8** in 33% yield with an enantiomeric excess of 93% ee (determined by HPLC).[15] The enantiomeric ratio[16] E of the reaction was 42.

The inverse reaction, the enantioselective hydrolysis, using the same enzyme in a phosphate buffer, led to the enantiomeric acetate (−)-**7** in 94% ee[17] (determined by HPLC) after 58% conversion with an E value of 19.

The absolute configurations of the ester **7** and **8** were determined by chemical correlation to the known (*R*)-3-(hydroxymethyl)piperidine,[18] which was obtained from (+)-**8** by reduction of the double bond with H_2/Pd–C, followed by a hydrolysis with aq. sodium hydroxide.

3. Conclusion

As a result of our studies an easy preparation of the formerly unknown building blocks (*R*)-3-acetoxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylate (−)-**7** and phenyl (*S*)-3-butyryl-oxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylate (+)-**8** has been realised, which can permit the synthesis of isofagomin derivatives and analogues in both enantiomeric forms by manipulation of the double bond.



Reagents and conditions:a) i. H_2NNHTs/CH_2Cl_2, ii. 3 eq. LDA/THF, 73 % overall;
b) i. $LiAlH_4/Et_2O$; 95 %, ii. Ac_2O/pyridine, 98 %; c) $ClCO_2Ph$/toluene, 72 %;
d) 0.2 N NaOH/EtOH; e) *Pseudomonas caepacia* lipase/phosphate buffer/1 M NaOH;
f) *Pseudomonas caepacia* lipase/CH_2Cl_2/hexane/vinyl butyrate.

Scheme 2.

4. Experimental

4.1. General

The β-keto ester **2** was purchased from ACROS. Organic solvents were distilled before use or, if otherwise noted, dried according to the typical procedures. All reactions were monitored by TLC prior to work-up. TLC was run on silica plates 60 F_{254} (Merck) and visualised with UV fluorescence (254 and 366 nm) and/or molybdatophosphoric acid. ^1H and ^{13}C NMR were recorded on a Bruker ARX 400, specific rotation values on a Perkin–Elmer Polarimeter 241, mass spectra on a Varian MAT 311 and IR spectra on a Perkin–Elmer IR-Spectrometer 1420. High-performance liquid chromatography analyses were performed using liquid chromatograph model Shimadzu 6a equipped with a Shimadzu SPD-6a detector and DAICEL CHIRACEL OD column. Flash chromatography was performed on Merck Kieselgel 60 (40–63 μm).

*4.2. Methyl-1-benzyl-1,2,3,6-tetrahydropyridine-3-carboxylate **3***

To a solution of the β-keto ester **2** (11.0 g, 44.5 mmol) in dry CH_2Cl_2 (200 mL) *p*-toluenesulfonylhydrazine (9.9 g, 53 mmol) was added under argon at room temperature. After stirring for 2 days the reaction mixture was evaporated and the residue was dissolved in THF (160 mL). At −78°C 155.8 mmol of LDA, prepared from diisopropylamine and *n*-butyllithium in THF at −20°C, was added. The yellow solution became deep red, when warmed to room temperature. After 18 h stirring at room temperature the mixture was poured into cold saturated NH_4Cl (150 mL) and the layers were separated. The aqueous phase was extracted with ether (2×120 mL) and the combined organic portions were washed with H_2O (150 mL) and brine (150 mL) and then dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography on silica gel (cyclohexane:ethyl acetate=60:40) to yield the title compound **3** (7.5 g, 73%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ=2.95 (*A*BX, 1H, ^{3}J=5.10 Hz, NCH_2CH=CH), 3.04 (A*B*X, 1H, ^{3}J=2.54 Hz, N*CH*$_2$CH=CH), 3.36 (s, broad (br), 1H, *CH*CO_2Me), 3.72 (s (br), 5H, *CH*$_2$Ph, *CH*$_3$), 5.87 (*A*BX, 1H, ^{2}J=9.9 Hz, ^{3}J=5.1 Hz, ^{3}J=2.54 Hz, *CH*=CHCH), (A*B*X, 1H, ^{2}J=9.9 Hz, ^{2}J=4.6 Hz, CH=*CH*CH), 7.35 (m, 5H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.9 (t), 42.0 (d), 51.3 (t), 51.8 (q), 52.3 (t), 62.3 (t), 123.0 (d), 127.0 (d), 128.2 (d), 128.3 (d), 129.0 (d), 137.9 (s), 173.0 (s). IR [film]: ν=1740 cm^{-1}; ms (70 eV): 233 [M$^+$]; $C_{14}H_{17}NO_2$ (233.29). Calcd C 72.63, H 7.35, N 6.05, found C: 72.32, H 7.25, N 5.75.

*4.3. 1-Benzyl-3-acetoxymethyl-1,2,3,6-tetrahydropyridine **4***

A solution of methyl-1-benzyl-1,2,3,6-tetrahydropyridine-3-carboxylate **3** (2.7 g, 11.7 mmol) in dry ether (70 mL) was added dropwise to a suspension of $LiAlH_4$ (0.4 g, 11.7 mmol) in dry ether (30 mL) at 0°C under an argon atmosphere. After 10 h, water (0.4 mL), 15% NaOH (0.4 mL) followed by more water (1.3 mL) were successively added to the reaction mixture. The suspension was stirred for 30 min and the precipitate was filtered off over Celite. The organic layer was dried ($MgSO_4$) and evaporated. The light yellow liquid was treated with pyridine (15 mL) and acetic anhydride (10 mL) at 0°C. After 5 h the volatiles were removed on a rotary evaporator at 2×10^{-2} mbar and the residue was purified by flash chromatography on silica gel (cyclohexane:ethyl acetate=80:20) to yield the acetate **4** (2.7 g, 93%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.02 (s, 3H, *CH*$_3$), 2.20 (m, 1H, *CH*CH_2O), 2.65, (m, 2H, N*CH*$_2$CHCH_2O), 3.02, (m, 2H, N*CH*$_2$CHCH), 3.64 (AB, 2H, ^{2}J=13.23 Hz), 4.09 (ABX, 2H, J_{ab}=10.68 Hz, *CH*$_2$O), 5.68 (m, 1H, CH*CH*CH), 5.82 (ddd, 1H, ^{3}J=1.52 Hz, ^{3}J=3.05 Hz, ^{2}J=11.71 Hz, CH_2*CH*CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.8 (q), 35.9 (d), 51.7 (t), 52.8 (t), 62.4 (t), 65.9 (t), 125.0 (d), 127.1 (d), 127.6 (d), 128.2 (d), 129.0 (d), 138.1 (s), 170.9 (s). IR [film]: ν=1750 cm^{-1}, 1250 cm^{-1}, 1040 cm^{-1}; ms (70 eV): 245 [M$^+$]; $C_{15}H_{19}NO_2$ (245.32).

*4.4. Phenyl-3-acetoxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylate **5***

To a solution of the 1-benzyl-3-acetoxymethyl-1,2,3,6-tetrahydropyridine **4** (2.0 g, 8.1 mmol) in dry toluene was added phenoxycarbonyl chloride (1.4 g, 8.94 mmol). The reaction mixture was heated under reflux for 18 h and then the volatiles were evaporated on a rotary evaporator at 2×10^{-2} mbar. The residue was purified by flash chromatography on silica gel (cyclohexane:ethyl acetate=70:30) to yield the carbamate **5** (1.6 g, 72%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.09 (s, 3H, CH_3), 2.71 (s (br), 1H, *CH*CH_2O), 3.77 (m (br), 2H, N*CH*$_2$), 3.80 (m (br), 2H, N*CH*$_2$), 4.09 (m, 2H, CH*CH*$_2$O), 5.84 (m (br), 2H, CH2*CH*=*CH*CH), 7.23 (m, 5H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) two amide isomers:

δ=21.0 (q), 34.9 (d), 35.2 (d), 42.9 (t), 43.5 (t), 44.0 (t), 64.7 (t), 64.9 (t), 121.9 (d), 125.1 (d), 125.7 (d), 126.1 (d), 126.9 (d), 129.4 (d), 151.1 (s). IR [film]: ν=1720–1750 cm^{-1}; ms (70 eV): 275 [M$^+$]; $C_{15}H_{17}NO_4$ (275.30). Calcd C 65.38, H 6.18, N 5.09, found C 64.85, H 5.95, N 4.95.

4.5. *Phenyl-3-hydroxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylate* **6**

An alcoholic NaOH solution (0.2 N, 4 mL) was added over a period of 30 min to a stirred solution of acetate **5** (1.1 g, 4 mmol) in dry EtOH (50 mL) under ice cooling. The resulting mixture was neutralised with AcOH and extracted with CH_2Cl_2. The solvent was evaporated on a rotary evaporator at 2×10^{-2} mbar and purified by flash chromatography on silica gel (cyclohexane:ethyl acetate=60:40). The alcohol **6** was obtained as a yellow oil (0.8 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.53 (s (br), 2H, *CH*CH$_2$O*H*), 3.59 (m, 2H, N*CH*$_2$), 4.01 (m, 2H, N*CH*$_2$), 4.27 (m, 2H, *CH*$_2$OH), 5.81 (m, 2H, *CH*=*CH*), 7.30 (m, 5H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) two amide isomers: δ=38.0 (d), 41.3 (t), 43.44 (t), 57.2 (t), 61.3 (t), 115.4 (d), 117.43 (d), 125.2 (d), 126.1 (d), 129.2 (d), 156.2 (s). IR [film]: ν=3400–3450 cm^{-1}, 1690 cm^{-1}; ms (70 eV): 232 [M$^+$−H]; $C_{13}H_{15}NO_3$ (233.30).

4.6. *Phenyl (*R*)-3-acetoxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylate (−)-7*

A rapidly stirred suspension of (±)-phenyl-3-acetoxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylate (**5**) (0.5 g, 1.8 mmol) in phosphate buffer (7 mL, pH 7) containing lipase from *Pseudomonas caepacia* (30 mg) was maintained at pH 7 by automatic titration with NaOH (1 N). The reaction mixture was filtered after 58% conversion over Celite and extracted with ethyl acetate (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel (cyclohexane:ethyl acetate=70:30) to yield the acetate (−)-**7** (0.2 g, 40%) as a yellow oil. The enantiomeric excess was determined by HPLC (heptane:isopropanol=90:10) to be 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.09 (s, 3H, CH$_3$), 2.71 (s (br), 1H, *CH*CH$_2$O), 3.77 (m (br), 2H, N*CH*$_2$), 3.80 (m (br), 2H, N*CH*$_2$), 4.09 (m, 2H, CH*CH*$_2$O), 5.84 (m (br), 2H, CH2*CH*=*CH*CH), 7.23 (m, 5H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) two amide isomers: δ=21.0 (q), 34.9 (d), 35.2 (d), 42.9 (t), 43.5 (t), 44.0 (t), 64.7 (t), 64.9 (t), 121.9 (d), 125.1 (d), 125.7 (d), 126.1 (d), 126.9 (d), 129.4 (d), 151.1 (s); ms (70 eV): 275 [M$^+$]; $C_{15}H_{17}NO_4$ (275.30). IR [film]: ν=1720–1750 cm^{-1}. Calcd C 65.38, H 6.18, N 5.09, found C 64.85, H 5.95, N 4.95.

4.7. *Phenyl (*S*)-3-butyryloxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylate (+)-8*

To a rapidly stirred mixture of (±)-phenyl-3-hydroxymethyl-3,6-dihydro-2*H*-pyridine-1-carboxylate (**5**) (0.5 g, 2.1 mmol) in a small amount of CH_2Cl_2 and hexane (8 mL) lipase from *Pseudomonas caepacia* (30 mg), vinyl butyrate (1.20 g, 10.5 mmol) was added. After 33% conversion (detected by HPLC) the reaction mixture was filtered off over Celite and the solvent was evaporated. The crude product was purified on silica gel using cyclohexane:ethyl acetate (80:20) to give the title compound as a light yellow oil (0.2 g, 30%). The enantiomeric excess was determined by HPLC (heptane:isopropanol=90:10) to be 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.00 (t, 3H, CH$_3$), 1.70 (s, 2H, *CH*$_2$CH$_3$), 2.38 (q, 2H, *CH*$_2$CH$_2$CH$_3$), 3.75 (s (br), 1H, *CH*CH$_2$O), 3.76 (m (br), 2H, N*CH*$_2$), 4.31 (m, 4H, N*CH*$_2$ and CH*CH*$_2$O), 5.83 (m (br), 2H, CH2*CH*=*CH*CH), 7.27 (m, 5H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.6 (q), 18.4 (t), 34.8 (d), 35.1 (d), 36.1 (t), 42.4 (t), 42.7 (t), 43.4 (t), 43.8 (t), 64.2 (t), 64.5 (t), 121.6 (d), 125.0 (d), 125.3 (d), 125.8 (d), 126.6 (d), 129.2 (d), 151.3 (s), 173.4 (s). $[\alpha]_D^{20}$=+44; (c 2.66, CH_2Cl_2). IR [film]:

ν=1720 cm^{-1}; ms (70 eV): 303 [M$^+$]; $C_{17}H_{21}NO_4$ (303.35). Calcd C: 67.25, H 6.92, N 4.62, found C 66.73, H 6.90, N 4.03.

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References

1. (a) Le Merrer, Y.; Poitout, L.; Depezay, J.-C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M.-J. *Bioorg. Med. Chem.* **1997**, *5*, 519. (b) Huwe, C. M.; Blechert, S. *Synthesis* **1997**, 61. (c) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856. (d) Carretero, J. C.; Arrayas, R. G.; Storch de Gracia, I. *Tetrahedron Lett.* **1997**, *38*, 8537. (e) Brandstetter, T. W.; Davis, B.; Hyett, D.; Smith, C.; Hackett, L.; Winchester, B. W.; Fleet, G. W. J. *Tetrahedron Lett.* **1995**, *36*, 7511. (f) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182.
2. (a) Winchester, B.; Fleet, G. W. *Glycobiology* **1992**, *2*, 199, and references cited therein. (b) Kausal, G. P.; Elbein, A. D. *Trends Gycosci. Glycotechnol.* **1993**, *5*, 209. (c) Sinnott, M. L *Chem. Rev.* **1990**, *90*, 1171.
3. Tsuruoka, T.; Fukuyasu, H.; Ishii, M.; Usui, T.; Shibahara, S.; Inouye, S. *J. Antibiotics* **1996**, *9*, 155.
4. Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petrrsson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Chan Son, J.; Wilson, F.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W.; *FEBS Lett.* **1988**, *237*, 128.
5. (a) Jerpersen, T. M.; Dong, W.; Sierks, M. R.; Skrydstrup, T.; Lundt, I.; Bols, M. *Angew. Chem.* **1994**, *106*, 1858. (b) Ichikawa, M.; Ichikawa, Y. *Tetrahedron Lett.* **1995**, *36*, 4585.
6. (a) Ref. 5. (b) Jerspersen, T. M.; Bols, M.; Sierks, M. R.; Skrydstrup, M. R. *Tetrahedron* **1994**, *50*, 13449. (c) Bols, M. *Tetrahedron Lett.* **1996**, *37*, 2097. (d) Hansen, A.; Tagmose, T. M.; Bols, M. *Chem. Commun.* **1996**, 2649. (e) Jerpersen, T.; Dong, W.; Sierks, M. R.; Skrydstrup, T.; Bols, M. *Biochemistry* **1996**, *35*, 2788. (f) Hansen, A.; Tagmose, T. M.; Bols, M. *Tetrahedron* **1997**, *53*, 697. (g) Ichikawa, M.; Ichikawa, Y. *Bioorg. Med. Chem.* **1995**, *3*, 161.
7. Treves, G.; Baum, B.; Burton, M. (FMC Corp.), U.S. patent 4467095 A, **1984** [*Chem. Abstr.* **1984**, *101*, 211000s].
8. (a) Allan, R. D.; Fong, J. *Aust. J. Chem.* **1983**, *36*, 601. (b) Müller-Uri, C.; Singer, E. A.; Fleischhacker, W. *J. Med. Chem.* **1986**, *29* , 125. (c) Clinch, K.; Marquez, C. J.; Parrott, M. J.; Ramage, R. *Tetrahedron* **1989**, *45*, 239.
9. Bunnell, C. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1977**, *99*, 5184.
10. (a) Wright, W. B.; Brabander, H. J. *J. Org. Chem.* **1961**, *26*, 4057. (b) Oediger, H.; Joop, N. *Liebigs Ann. Chem.* **1972**, *764*, 21.
11. However, there are many examples of enzyme catalysed enantiotopos-differentiating acylation of prochiral primary diols or of enzyme catalysed enantiotopos-differentiating hydrolysis of prochiral primary diol diacetates. See: (a) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis*, VCH, Weinheim; 1995. (b) Weissfloch, A. N. E.; Kazlauskas, R. J. *J. Org. Chem.* **1995**, *60*, 6959.
12. Wirtz, B.; Walther, W. *Tetrahedron: Asymmetry* **1992**, *3*, 1049.
13. For successful enzymatic resolutions in related 5-membered systems see: (a) Altenbach, H.-J.; Merhof, G. F.; Brauer, D. J. *Tetrahedron: Asymmetry* **1996**, *7*, 2493. (b) Schieweck, F.; Altenbach, H.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 403.
14. Screening with enzymes from *Candida antartica* (Novozym 435), *Candida cylindracae* (Sigma), *Candida cylindracae* (Meito MY), *Pseudomonas caepacia* Amano PS), *Pseudomonas fluorescens* (Fluka), *Aspergillus oryzae* (Lipozym IM), *Pseudomonas* species (Amano AK), *Alcaligens* species (Meito PL), *Acromobacter* species (Meito AL), pig pancreas lipase (Type II, Aldrich) and pig liver esterase.
15. $[\alpha]_D^{20}$=+44; (c 2.66, CH_2Cl_2). HPLC: Chiracel OD-column (DAICEL Chemical Industry); heptane:ispropanol=90:10.
16. Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Shih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
17. $[\alpha]_D^{20}$=−60 (c 1.23; CH_2Cl_2). HPLC: Chiracel OD-column (DAICEL Chemical Industry); heptane:ispropanol=90:10.
18. Bettoni, G.; Duranti, E.; Tortorella, V. *Gazz. Chim. Ital.* **1972**, *102*, 189.