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CHIRAL BUILDING BLOCKS FOR CARBOCYCLIC N- AND C-RIBONUCLEOSIDES THROUGH BIOCATALYTIC ASYMMETRISATION OF *meso*-CYCLOPENTANE-1,3-DIMETHANOLS

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Abstract: Enantiomerically pure chiral building blocks, lactone **1** in either enantiomeric form and cyclopentanecarbonitriles **10** and **15**, were prepared efficiently through lipase catalysed enantioselective hydrolysis of *meso*-diesters **5a-c** or transesterification of their parent diol **2** with vinyl acetate in an organic solvent providing chiral monoesters **6a-c** or *ent*-**6a** of >99% ee in the crucial step. The combined HLADH catalysed and chemical oxidation of **2** resulted in (-)-**1** of 74% enantiomeric purity.

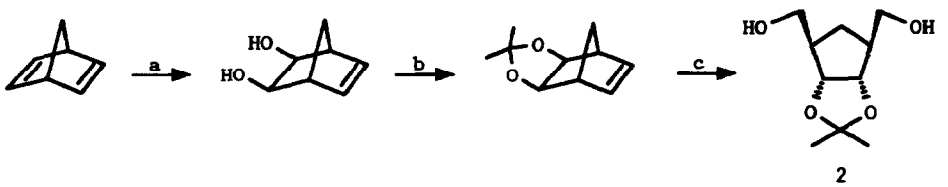
Carbocyclic nucleosides[1,2] are a class of compounds structurally analogous to natural and synthetic nucleosides, with a carba-sugar instead of a glycone of comparable ring size, which have attracted considerable attention due to the antitumor and antiviral properties of certain representatives. As their biological activity usually resides in the enantiomer generally corresponding to the parent D-sugar, it is necessary to prepare enantiomerically pure carbocyclic nucleosides[2] for them to be useful as pharmaceutical agents. Our current interest in the chemistry and biological properties of the base modified analogues of (-)-aristeromycin (carba-adenosine) and carba-guanosine called for a selection of the most suitable starting material for the construction of the β-D-ribo configured carba-sugar moiety. One of these turned out to be Ohno's lactone (+)-**1**,[3-6] a central intermediate in several total asymmetric syntheses of the natural carbocyclic nucleoside (-)-aristeromycin. It is expected to be of value in preparing other carbocyclic N- and especially C-ribonucleosides, since it already possesses the "glycosydic" C-C bond. The enantiopure compound (+)-**1** was first prepared by Ohno *et al*,[3] by enzyme catalysed asymmetric hydrolysis of dimethyl *exo,cis*-5,6-(isopropylidenedioxy)norborn-2-ene-2,3-dicarboxylate to give a chiral half ester in the crucial step, followed by a series of standard chemical procedures. Taking into account the operational simplicity and availability of reagents, this method seemed superior to more recent ones starting from the asymmetric Diels-Alder reaction of cyclopentadiene with a suitable chiral dienophile.[4] In our very recent synthesis of the carbocyclic tetrazole C-ribonucleosides,[6] we prepared the requisite chiral building block (+)-**1** on a synthetic scale through an adaptation of Ohno's small-scale procedure. However, a number of steps, coupled with a moderate enantioselectivity of the enzyme catalysed reaction (~80% ee) requiring enantiomeric enrichment of the final product, resulted in a relatively low overall yield (15-20%) for this nine-step conversion from cyclopentadiene. Consequently, a need existed for a more efficient, but still simple, scalable and inexpensive method for obtaining this compound in enantiopure form. With this in

mind, we considered the readily available *meso*-cyclopentane-1,3-dimethanol derivative **2**[5,7,8] as an alternative precursor to Ohno's lactone, since it had been employed previously in the one-step nonstereoselective oxidation to racemic lactone (±)-**1**.[7] Reported in this study, however, are several attempts at enzyme-catalysed asymmetric conversions of this compound, resulting in either enantiomeric series of lactone **1** as well as some of its closely related cyclopentanecarbonitrile derivatives **10** and **15**. While our work was nearly complete, a similar approach to Ohno's lactone had been published by Sakai *et al*,[5] utilizing the same starting material **2**.

Results and discussion

Large scale preparation of *meso*-diol **2** was easily accomplished from *exo,cis*-5-norbornene-2,3-diol[9] following the method of Just *et al*,[7] with a 72% overall yield (Figure 1).

Figure 1



2

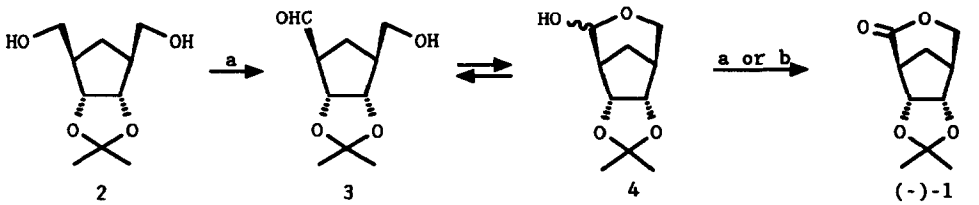
Reagents and conditions: (a) $KMnO_4$; (b) $Me_2C(OMe)_2$/p-TsOH, Me_2CO; (c) O_3, then $NaBH_4$

Next, the enzyme catalysed transformations[10] of this compound were considered as particularly attractive means of effecting its asymmetric conversion. The advantage of using a *meso*-compound in enzymatic reactions is that, in theory, it can all be converted into a single enantiomer.[10,11] Furthermore, regardless of the stereochemical outcome of such a reaction, either enantiomeric series of the final product is usually accessible in a straightforward manner.[12,13] It was decided, therefore, to test the ability of certain oxidoreductive and hydrolytic enzymes to discriminate between the enantiotopic hydroxymethyl groups of *meso*-diol **2** or its diesters **5a-c**.

HLADH catalysed oxidations. We expected the most direct access to enantiomerically enriched Ohno's lactone to be by means of stereoselective enzymatic oxidation of compound **2**. The NAD(H)[14] coenzyme dependent horse liver alcohol dehydrogenase (HLADH),[15] which catalyses oxidoreductions of the type: CH-OH + NAD^+ ⇌ C=O + NADH + H^+, has been the most intensively studied among oxido-reductases for application to organic synthesis. Of special interest in this case is the ability of HLADH to catalyse enantioselective oxidations of a number of cyclic *meso*-1,2-[16] and -1,3-dimethanols,[17] leading directly to chiral lactones with enantiomeric excesses better than 97%. Compound **2** was subjected to HLADH mediated oxidation at pH 9 and ambient temperature using flavin mononucleotide (FMN) to effect recycling[18] of the catalytic quantities of the NAD^+ coenzyme employed (Figure 2). The reaction was relatively fast in the first period, with the highest concentration of lipophilic products being detected by TLC after 1-2 days. Beyond

this time, their concentration gradually decreased and became negligible after 5 days. For this reason, the reaction was terminated at the point of maximum attainable yield of products by acidification and extraction. An inseparable mixture of lactol **4** and lactone **1** was obtained in a 10:3 ratio (Table 1, entry 1) after chromatography of the crude extract, which served to remove the unreacted diol **2**. Inspection of the ^{1}H- and ^{13}C-NMR spectra of this mixture revealed that the initially formed oxidation product, hydroxyaldehyde **3**, exists entirely in its cyclic hemiacetal form **4**, which appeared to be a mixture of two diastereomeric lactols **4α** and **4β**. The ratio of products **1**:**4** indicates that lactol **4** is only a poor substrate for further enzyme mediated oxidation to the corresponding lactone **1**.

Figure 2



Reagents and conditions: (a) HLADH/NAD^{+}/FMN, buffer (pH 9); (b) PDC, CH_2Cl_2, DMF

Table 1. HLADH catalysed oxidation of *meso*-diol **2**[a]

				product ratio(%)[c]		
entry	org.phase	time(d)	yield(%)[b]	**1**	**4α**	**4β**
1	none	1	21	23	54	23
2	ether	7	31	<1	81	19
3	CH_2Cl_2	7	29	4	69	27

[a]Reactions were carried out as described in the Experimental section. [b]Total yield of **1**+**4** after extraction and chromatography. [c]Estimated by ^{1}H-NMR according to ref. 4b.

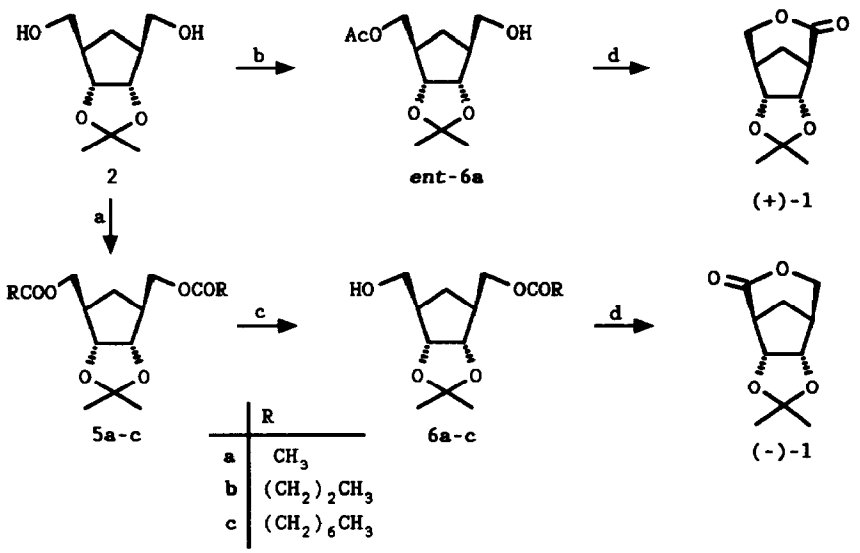
A mixture consisting mainly of **4** and **1**, isolated after a 40 hours period of oxidation on a 1.5 mmol scale, was subjected to chemical oxidation by pyridinium dichromate (PDC) to give lactone (-)-**1** with a 25% overall yield from **2**. The absolute configuration and enantiomeric purity of (-)-**1** was established by comparison of its specific rotation ($[\alpha]_D$ -32.9, c 1.00 $CHCl_3$) with that of authentic material ($[\alpha]_D^{22}$ +44.4, c 1.0 $CHCl_3$; 100% ee), prepared by a different procedure.[6] In contrast to earlier reports[16,17] on the unsubstituted *meso*-cycloalkane-1,2- and -1,3-dimethanols, the HLADH mediated oxidation of **2** is enantiotopically selective for the hydroxymethyl group attached to the R-stereogenic center.

Additional experiments were done in water-organic solvent (ether or CH_2Cl_2) biphasic systems under conditions which would be expected to minimize the negative effects of product inhibition of the enzyme.[19]

Again, a mixture of **4** and **1** was isolated, with the former strongly predominating, but the yields were not improved significantly (Table 1, entries 2,3).

Asymmetrisations catalysed by hydrolytic enzymes. Hydrolytic enzymes[10,20] are known for their ability to catalyse enantiotopically selective monohydrolysis of *meso*-diesters in aqueous media[21] or trans-esterification[22] of *meso*-diols in anhydrous organic solvents.[23] The enzyme esterifies *meso*-diols or hydrolyses its derived *meso*-diesters with the same enantiotopic selectivity and generally results in different enantiomers of the half ester.[12,24] On this basis, we have developed another chemoenzymatic approach to both enantiomeric forms of Ohno's lactone, starting from the *meso*-diol **2** or its diesters **5a-c** (Figure 3).

Figure 3



Reagents and conditions: (a) $(RCO)_2O/Et_3N$/DMAP, MeCN; (b) lipase SAM-2/VA or TFEA, org. solvent, 45°C; (c) lipase, buffer (pH 7); (d) i, PDC/DMF; ii, K_2CO_3/MeOH; iii, Ac_2O/pyridine

We first evaluated a number of enzymes for their abilities to catalyse the enantioselective hydrolysis of *meso*-diesters **5a-c** of varying chain length. From the screening tests, all lipases listed in Table 2, particularly SAM-2, LPS, RD and CV, were found to be highly selective leading to enantiomerically pure half esters **6a-c** (≥96% ee, entries 3-5, 8-14 and 16), except for lipases PP and CC, and CL in the case of **5a**, which displayed only moderate enantioselectivities (entries 1,2,6,7,15). Some other enzymes, like pig liver esterase, α-chymotrypsin and lipases from *Penicillium roqueforti*, *Aspergillus niger*, and Wheat germ, which are even less selective (<50% ee at approx. 50% conversion), are not included in Table 2. Another interesting observation is that the longer chain diesters are better substrates for the particular enzymes used. Dioctanoate **5c** turns out to be the best substrate, but its utility is obscured because both **5c** and its reaction product **6c** have high boiling

points and are difficult to purify by distillation. Diacetate **5a** and dibutyrate **5b** were prepared and purified with ease, but the latter gave faster hydrolysis and is for practical reasons the best substrate to work with.

Table 2. Screening for lipases in hydrolyses of *meso*-diesters **5a-c**[a]

		conditions			yield(%)[d]				
entry	substrate	lipase[b]	enz.ratio[c]	time(h)	**5**	**6**	**2**	ee(%)[e]	$[\alpha]_D$[f]
1	**5a**	CC	149	8	20	80	<1	58	-5.5
2	**5a**	PP	386	1.2	4	92	4	71	-6.6
3	**5a**	SAM-2	17	14	6	94	0	>99	-9.3
4	**5a**	MJ	46	27	7	93	0	98	
5	**5a**	RN	86	48	18	82	<1	99	
6	**5a**	CL	80	32	15	85	0	92	
7	**5b**	PP	114	1.5	7	71	22	64	
8	**5b**	SAM-2	11	4	2	98	0	>99	-9.0
9	**5b**	MJ	46	5	5	92	3	96	-8.7
10	**5b**	RN	86	12	5	93	2	98	
11	**5b**	CL	80	12	7	91	2	98	
12	**5b**	LPS	6	4.2	5	95	0	>99	
13	**5b**	RD	11	11	17	83	0	>99	
14	**5b**	CV	6	3.3	9	91	0	>99	
15	**5c**	PP	149	1	16	59	25	85	-5.9
16	**5c**	SAM-2	4	4	2	98	0	>99	-7.3

[a]All reactions were carried out as described in the Experimental section. [b]Lipase from *Candida cylindracea* (CC), porcine pancreas (PP), *Pseudomonas sp.* (SAM-2), *Mucor javanicus* (MJ), *Rhizopus niveus* (RN), *Candida lipolytica* (CL), *Rhizopus delemar* (RD), *Chromobacterium viscosum* (CV), lipoprotein lipase from *Pseudomonas sp.* (LPS). [c]mg of enzyme/mmol of substrate. [d]Determined by HPLC analysis before purification. [e]Estimated by ^{1}H-NMR in the presence of Eu(hfc)$_3$ for compound **6a** and by ^{19}F-NMR of the corresponding (R)-MTPA esters for compounds **6b** and **6c**. [f]c 4.0 $CHCl_3$.

Enantiomeric purities of monoesters **6b** and **6c** were determined from the relative intensities of the two trifluoromethyl functions from ^{19}F-NMR spectra after conversion into diastereomeric (R)-α-methoxy-α-trifluoromethylphenylacetate (MTPA) esters[25] by treatment with (R)-(-)-MTPA chloride. The enantiomeric purity of the monoacetate **6a** was conveniently estimated from its ^{1}H-NMR spectrum in the presence of a chiral shift reagent tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato]-europium (III) (Eu(hfc)$_3$) for solutions in CD_3CN. The relative position of the diastereotopic peaks in ^{1}H- and ^{19}F-NMR spectra mentioned above and the optical rotation measurements indicate that, with all enzymes employed, the major enantiomers **6a-c** with the same absolute configurations were obtained.

Absolute configurations of monoacetate **6a**, prepared by lipase PP catalysed hydrolysis of **5a**, and of monobutyrate **6b**, prepared by lipase MJ catalysed hydrolysis of **5b**, were established as 1S,2S,3R,4R by their three-step transformation involving oxidation to carboxylic acid by PDC,[26] hydrolysis of the remaining ester group and lactonisation to give (-)-**1**. Since the laevorotatory lactone was obtained, it follows that all enzymes tested have a stereochemical preference for hydrolysis of the ester group attached to the R-stereogenic center

of **5a-c**. The absolute configuration of monooctanoate **6c** was not determined by chemical correlation, but was considered by analogy to be the same as for **6a** and **6b** on the basis of the sign of its optical rotation.

Since enantiomers **6a-c** with undesired absolute configuration were produced by enzymatic hydrolysis, we turned our attention to non-aqueous transesterification of *meso*-diol **2**, which should result, as mentioned before, in antipodal half esters *ent*-**6**. This process has some practical advantages over hydrolysis, since it obviates the derivation step **2** → **5**. From screening tests, we have found that the lipase SAM-2[12] is particularly well suited for this purpose in combination with solvents of low to medium polarity (dichloroethane, ^{t}BuOMe, THF) and trifluoroethyl (TFEA) or vinyl acetate (VA) as acetyl donors[22] (Table 3). Under comparable conditions, other trifluoroethyl and vinyl esters of longer chain acids (butyrates, hexanoates, dodecanoates) are somewhat inferior acyl donors, while butyric and benzoic anhydride and trifluoroethyl and vinyl benzoate gave very slow conversions or were not reactive at all. Treatment of diol **2** on a large scale in dichloroethane at 45°C with vinyl acetate and lipase SAM-2 produced the chiral half ester *ent*-**6a** ($[\alpha]_D$ +9.2, c 4.0 $CHCl_3$) with 87% yield and better than 99% ee along with a 10% yield of diacetate **5a**. The reaction was terminated when the starting material was nearly consumed by simple membrane filtration of the insoluble enzyme, which was then used again in the next run. The lipase displayed excellent stability under the conditions employed, since we noticed only about 15% loss of activity per run.

Table 3. Lipase SAM-2 catalysed transesterification of *meso*-diol **2**[a]

conditions			yield(%)[b]				
acylating agent	solvent	time (h)	**5a**	**6a**	**2**	ee(%)[b]	$[\alpha]_D$
TFEA	$(CH_2Cl)_2$	48	7	93	0	>99	
VA	$(CH_2Cl)_2$	13	6	94	0	>99	+9.2
VA	$CHCl_3$	24	2	94	4	>99	
VA	^{t}BuOMe	5	7	91	2	>99	
VA	THF	24	4	96	0	>99	
VA	MeCN	24	7	89	4	>99	
VA	$(CH_2OMe)_2$	5	5	85	10	>99	

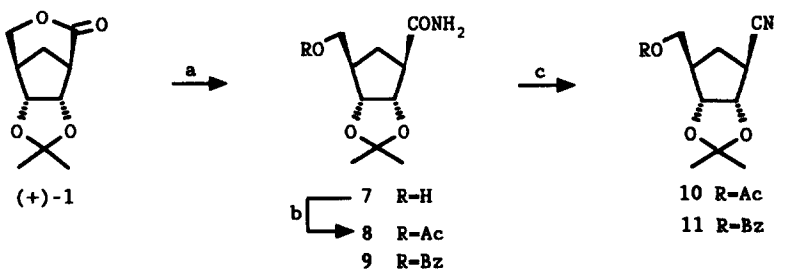
[a]*Conditions*: Lipase SAM-2 (7 mg), solvent (1 mL), diol **2** (0.5 mmol), acylating agent (2 equiv.), temperature 45°C. [b]Determined by HPLC analysis before purification. [c]Estimated by ^{1}H-NMR in the presence of Eu(hfc)$_3$.

The absolute configuration of *ent*-**6a** was established in the same manner as previously described for its enantiomer **6a**, leading to the target Ohno's lactone (+)-**1** ($[\alpha]_D$ +43.5, c 1.0 $CHCl_3$; >99% ee) with 81% yield. Large-scale synthesis of the chiral building block (+)-**1** could be conveniently carried out by starting from a crude 10:1 mixture of *ent*-**6a** and **5a**, removing the latter after the PDC oxidation step by simple extraction from basic medium.

Homochiral cyclopentanecarbonitrile synthons. Lactone (+)-**1**, most efficiently prepared from *ent*-**6a** by lipase catalysed transesterification of the *meso*-diol **2** as described in this work and by others,[5] serves as a well-established chiral bulding block for carbocyclic N- and C-ribonucleosides. We have recently demonstrated[6]

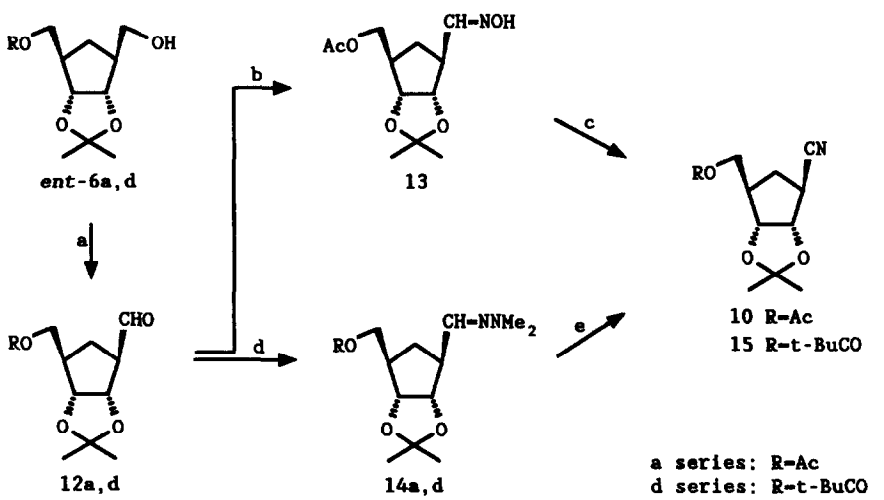
the utility of (+)-**1** in the synthesis of carbocyclic tetrazole C-ribonucleosides through its conversion into the benzoylated cyclopentanecarbonitrile derivative **11** by treatment with methanolic ammonia, protection of the hydroxyl group of **7** as benzoate, and dehydration of the carboxamide function of **9** (Figure 4). Nitrile **10** bearing an acetyl protection could also be synthesized by a similar sequence of reactions (**1**→ **7** → **8** → **10**) with 86% overall yield. Furthermore, the half ester *ent*-**6a**, which does not require enantiomeric upgrading by conversion to lactone (+)-**1** and crystallization, could serve as an even more convenient source of chiral cyclopentanecarbonitriles. We have examined numerous methods for the transformation of the hydroxymethyl group of *ent*-**6a** to the nitrile function, of which two of preparatory significance are given here (Figure 5). In the first, *ent*-**6a** was oxidized by pyridinium chlorochromate (PCC)[27] in methylene chloride to give aldehyde

Figure 4



Reagents and conditions: (a) NH_3, MeOH; (b) Ac_2O/pyridine or Bz_2O/Et_3N/DMAP, MeCN; (c) $(CF_3CO)_2O$/pyridine, THF

Figure 5

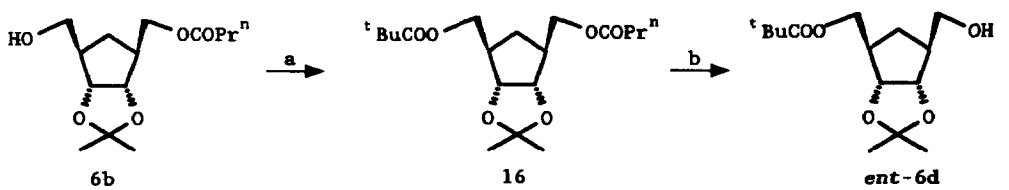


Reagents and conditions: (a) PCC, CH_2Cl_2; (b) NH_2OH·HCl/pyridine; (c) $(CF_3CO)_2O$/ pyridine, THF; (d) NH_2NMe_2, MeOH; (e) MMPP·$6H_2O$, MeOH, 0°C

12a, which was further transformed *in situ* to oxime **13** by treatment with hydroxylammonium chloride in pyridine and final dehydration[28] by trifluoroacetic anhydride, providing nitrile **10** with 35% overall yield. A more efficient procedure[29] is based on the conversion of aldehyde **12a** to dimethylhydrazone **14a** with N,N-dimethylhydrazine and its further oxidation by magnesium monoperoxyphthalate (MMPP) to give the same nitrile **10** with 49% overall yield. The products of all three routes were found to be identical in their spectral data and optical rotation values ($[\alpha]_D$ -51 ± 1, c 4.0 $CHCl_3$).

A disadvantage of using nitrile **10** is that the sensitive acetyl group might not be applicable to every future synthetic purpose. Unfortunately, only this group could be introduced with ease during esterification of *meso*-diol **2** affording *ent*-**6a**. To overcome this problem, we have tried to take advantage of, for example, the half ester **6b**, obtained by enzymatic hydrolysis, as a precursor to differently substituted cyclopentanecarbonitriles. Compound **6b** might be protected by any of the numerous protective groups for alcohols, but in this paper we have worked out one of the more challenging cases, where regioselective discrimination between two different acyl groups was required. In this way, it is possible to prepare the opposite enantiomeric form of the half ester by simple inversion of the pattern of protection. Thus, **6b** was esterified with pivaloyl chloride to give the mixed diester **16**, which was submitted to a second enzymatic hydrolysis,[30] this time using one of the less selective enzymes from Table 2 (Figure 6). Indeed, the lipase CC brought about regioselective deprotection of only the linear n-butyryl group, leading to the half ester *ent*-**6d** with desired absolute configuration bearing the pivaloyl group on the (R)-hydroxymethyl side chain. Apparently, the steric congestion at the bulky pivaloyl ester group prevented enzymatic hydrolysis from occurring at this position, regardless of the enzyme's stereochemical preference.

Figure 6



Reagents and conditions: (a) ^{t}BuCOCl/pyridine; (b) lipase CC, buffer (pH 7.5)

Compound *ent*-**6d** was then converted in a three-step sequence involving PCC oxidation to aldehyde **12d**, formation of dimethylhydrazone **14d**, and MMPP oxidation providing nitrile **15** with 61% overall yield, as outlined in Figure 5.

Conclusion. Comparison has been made between oxidoreductase and hydrolase catalysed transformations of *meso*-cyclopentane-1,3-dimethanol derivatives **2** and **5a-c** in order to develop a synthetically useful procedure for enantiomerically pure carbocyclic ribonucleoside synthons, namely lactone (+)-**1** and cyclopentanecarbonitriles **10** and **15** of proper absolute configuration. In the first case, HLADH catalysed oxidation of **2** resulted mainly in lactol **4**, which was further oxidized chemically rather than enzymatically to give lactone (-)-**1** with undesired absolute configuration, as well as insufficient chemical (25%) and optical

yields (74%). On the other hand, SAM-2 lipase catalysed transesterification of **2** with vinyl acetate in anhydrous organic solvents yields the chiral half ester *ent*-**6a** with excellent chemical (89%) and optical yields (>99% ee) having a proper absolute configuration for further elaboration to the target lactone (+)-**1** or nitrile **10**. In addition, several lipases catalysed hydrolyses of diesters **5a-c**, providing enantiocomplementary half esters **6a-c** of excellent optical purities (>96% ee), whose absolute configuration correlated with lactone (-)-**1**. The absolute configuration of **6b** was inverted by a simple two-step protection-deprotection sequence to give, after introduction of a bulky pivaloyl group and a second regioselective enzymatic hydrolysis, the half ester *ent*-**6d**, which was used in the synthesis of the optically pure nitrile **15**.

Experimental section

Enzymes. Alcohol dehydrogenase from equine liver (HLADH, A-6128), esterase from pig liver (Type I, E-3128), α-chymotrypsin (Type VII, C-3142), and lipases from porcine pancreas (PP, Type II, L-3126), *Candida cylindracea* (CC, Type VII, L-1754), and wheat germ (Type I, L-3001) were obtained from Sigma. Lipases from *Pseudomonas sp.* SAM-2 (cat. no. 62312), *Mucor javanicus* (MJ; cat. no. 62304), *Rhizopus niveus* (RN; cat. no. 62310), *Candida lipolytica* (CL; cat. no. 62303), *Rhizopus delemar* (RD; cat. no. 62311), *Chromobacterium viscosum* (CV; cat. no. 62333), *Penicillium roqueforti* (cat. no. 62308), *Aspergillus niger* (cat. no. 62301) and lipoprotein lipase from *Pseudomonas sp.* (LPS; cat. no. 62335) were obtained from Fluka. Lipase SAM-2 was dried over P_4O_{10} in *vacuo* at 3°C for at least 5 days before being used for transesterification.

Chemicals. NAD^+ (N-7004) and FMN (F-6750) were obtained from Sigma, while the ready-to-use reagent (R)-(-)-MTPACl was obtained from Fluka. Vinyl acetate and solvents, when necessary, were dried according to recommended methods.[31]

General methods. All organic solvent extracts were dried over anhydrous Na_2SO_4. Evaporations were conducted in *vacuo* with a rotary evaporator. For flash chromatography, Silica gel 60 (Merck, 40-63 μm) was used. Thin layer chromatography (TLC) was performed on Silica gel $60F_{254}$ plates (Merck). The spots were visualized by spraying with 3.5% phosphomolybdic acid in ethanol and heating. Analytical high performance liquid chromatography (HPLC) was run on a Knauer instrument fitted with a Nucleosil 10 C8 column, with an eluent acetonitrile at a flow rate of 1 mL/min. Bulb to bulb (Kugelrohr) distillations were performed using a Büchi GKR-50 apparatus at oven temperature. Optical rotations were measured on a Perkin Elmer 241MC polarimeter for solutions in $CHCl_3$ at 25°C. ^1H- (299.94 MHz, internal Me_4Si), ^{13}C- (75.43 MHz, internal $CDCl_3$) and ^{19}F- (282.20 MHz, internal $CFCl_3$) NMR spectra were recorded using a Varian VXR-300 instrument for solutions in $CDCl_3$, except for lantanide induced shift experiments, which were done in CD_3CN. Chemical shifts and coupling constants were obtained from a first order analysis of the spectra. The spectra were assigned by means of the corresponding ^1H-^1H and ^{13}C-^1H chemical shift correlated spectra. Mass spectra were recorded on a VG Autospec Q spectrometer at the Jožef Stefan Institute, Ljubljana. IR spectra were recorded on a Bio-Rad FTS 15/80 spectrophotometer.

General procedure for HLADH catalysed oxidation of *meso*-diol 2 (Table 1). The diol **2** (0.10 g, 0.50 mmol), FMN (1.20 g, 2.50 mmol), and NAD^+ (0.10 g, 0.15 mmol) were dissolved in 0.1 M glycine-NaOH buffer (pH 9, 30 mL) and the pH was readjusted to 9 with 2 M NaOH. After addition of HLADH (40 mg, 84

units), organic solvent (20 mL) was carefully poured into the reaction mixture so as not to disturb the water layer. The reaction mixture was gently stirred at r.t. for the time indicated in Table 1. The organic phase was separated, the aq. phase was acidified to pH 4 with 2 N HCl, saturated with NaCl and extracted with ether (3 × 30 mL). Collected organic phases were chromatographed using ethylacetate/n-hexane (1:2) to give a mixture of **1** and **4**.

(1S,5S,6S,7R)-6,7-(Isopropylidenedioxy)-3-oxabicyclo[3.2.1]octan-2-one ((-)-1). A mixture of **1**, **4α** and **4β**, and **2** in a 20:20:15:2 ratio, obtained by HLADH catalysed oxidaton of diol **2** (0.30 g, 1.48 mmol) after 40 hours in the absence of organic solvent, and after extraction, was dissolved in a mixture of methylene chloride (3.5 mL) and N,N-dimethylformamide (1 mL) and treated overnight with PDC (1.80 g, 4.78 mmol) at r.t.. The reaction mixture was diluted with ether (15 mL) and then filtered. After concentration, the residue was chromatographed using ethylacetate/n-hexane (1:2) to give a colorless solid **1** (73 mg, 25%); mp 128-141°C; $[\alpha]_D$ -32.8, c 1.0 $CHCl_3$ {ref.[3] mp 140-141.5°C, $[\alpha]_D$ +44.4 (c 1.0 $CHCl_3$, 100% ee); ref.[7] mp (of racemate) 128-129°C}.

Preparation of diesters 5a-c. A solution of diol **2** in acetonitrile (2 mL/mmol **2**) was treated with triethylamine (2.6 equiv.), 4-(dimethylamino)pyridine (0.016 equiv.), and the appropriate anhydride (2.6 equiv.) (for **5a** and **5b**) or acid chloride (for **5c**). The last of these was added to precooled solution at 0°C, and further stirred at r.t.. When the reaction was complete (TLC, mobile phase CH_2Cl_2/i-PrOH 40:1), the solution was concentrated. The residue was suspended in ether (4.5 mL/mmol **2**) and washed with saturated aqueous $NaHCO_3$, water, and brine. The ethereal solution was concentrated and the residue distilled to give products **5a-c**.

***anti,syn,anti*-2,3-(Isopropylidenedioxy)cyclopentane-1,4-dimethanol diacetate (5a).** 86% yield; bp 120-121°C (0.03 Torr); IR (film) ν 2985, 2941, 2900, 1742, 1458, 1373, 1244, 1161, 1070, 1035; ^{1}H-NMR δ 1.31 and 1.50 (2s, 6H, $C(CH_3)_2$), 1.27 (td, 1H, H-5a; J_{gem} 13.2 Hz, $J_{1,5a}$ and $J_{4,5a}$ 10.8 Hz), 2.09 (s, 6H, $COCH_3$), 2.12 (td, 1H, H-5b; $J_{1,5b}$ and $J_{4,5b}$ 7.1 Hz), 2.38 (m, 2H, H-1,4), 4.08 and 4.12 (2dd, 2H, CH_2OCO; J_{gem} 11.2 Hz, $J_{4,Ha}$ 6.3 Hz, $J_{4,Hb}$ 6.4 Hz), 4.34 (m, 2H, H-2,3); ^{13}C-NMR δ 20.86 ($CO\underline{C}H_3$), 25.12 and 27.53 ($C(\underline{C}H_3)_2$), 31.23 (C-5), 44.19 (C-1,4), 65.36 ($\underline{C}H_2OCO$), 82.86 (C-2,3), 112.75 ($\underline{C}(CH_3)_2$), 171.01 (CO).

***anti,syn,anti*-2,3-(Isopropylidenedioxy)cyclopentane-1,4-dimethanol dibutyrate (5b).** 95% yield; bp 165-168°C (0.02 Torr); IR (film) ν 2965, 2940, 2879, 1737, 1460, 1377, 1302, 1255, 1180, 1071; ^{1}H-NMR δ 0.96 (t, 6H, $CH_2C\underline{H}_3$; *J* 7.4 Hz), 1.28 (m, 1H, H-5a), 1.30 and 1.49 (2s, 6H, $C(CH_3)_2$), 1.66 (sextet, 4H, $CH_2C\underline{H}_2CH_3$; *J* 7.4 Hz), 2.09 (m, 1H, H-5b), 2.31 (t, 4H, $C\underline{H}_2CH_2CH_3$; *J* 7.4 Hz), 2.38 (m, 2H, H-1,4), 4.09 and 4.14 (2dd, 4H, CH_2OCO; J_{gem} 11.1 Hz, $J_{1,Ha}$ 6.1 Hz, $J_{1,Hb}$ 6.4 Hz), 4.34 (m, 2H, H-2,3); ^{13}C-NMR δ 13.63 ($CH_2\underline{C}H_3$), 18.39 ($\underline{C}H_2CH_3$), 25.14 and 27.56 ($C(\underline{C}H_3)_2$), 31.23 (C-5), 36.08 ($CO\underline{C}H_2$), 44.28 (C-1,4), 65.06 ($\underline{C}H_2OCO$), 82.84 (C-2,3), 112.75 ($\underline{C}(CH_3)_2$), 173.57 (CO). HRMS: m/z $(M-15)^+$ calcd for $C_{17}H_{27}O_6$ 327.181, found 327.180. *Anal.* Calcd for $C_{18}H_{30}O_6$ (342.43): C, 63.14; H, 8.83. Found: C, 63.36; H, 8.55.

***anti,syn,anti*-2,3-(Isopropylidenedioxy)cyclopentane-1,4-dimethanol dioctanoate (5c).** 96% yield; bp (Kugelrohr) 220°C (0.02 Torr); IR (film) ν 2953, 2929, 2858, 1739, 1462, 1376, 1253, 1211, 1165, 1107, 1070; ^{1}H-NMR δ 0.88 (t, 6H, $CH_2C\underline{H}_3$; *J* 6.0 Hz), 1.2-1.4 (m, 20H, CCH_3, $(C\underline{H}_2)_4CH_3$, H-5a), 1.49 (s, 3H, CCH_3), 1.62 (m, 4H, $COCH_2C\underline{H}_2$), 2.10 (td, 1H, H-5b; J_{gem} 13.4 Hz, $J_{1,5b}$ and $J_{4,5b}$ 7.0 Hz), 2.32 (t, 4H, $COCH_2$; *J* 7.6 Hz), 2.38 (m, 2H, H-1,4), 4.08 and 4.13 (2dd, 4H, $C\underline{H}_2OCO$; J_{gem} 11.2 Hz, $J_{1,Ha}$ 6.1 Hz, $J_{1,Hb}$

6.4 Hz), 4.34 (m, 2H, H-2,3); ^{13}C-NMR δ 13.99 ($CH_2\underline{C}H_3$), 22.54 ($\underline{C}H_2CH_3$), 24.91 ($\underline{C}H_2CH_2CH_3$), 25.12 and 27.54 ($C(\underline{C}H_3)_2$), 28.88 ($\underline{C}H_2(CH_2)_2CH_3$), 29.04 ($\underline{C}H_2(CH_2)_3CH_3$), 31.24 (C-5), 31.61 ($\underline{C}H_2(CH_2)_4CH_3$), 34.91 ($CO\underline{C}H_2$), 44.29 (C-1,4), 65.08 ($\underline{C}H_2OCO$), 82.87 (C-2,3), 112.72 ($\underline{C}(CH_3)_2$), 173.72 (CO). HRMS: m/z (M-15)$^+$ calcd for $C_{25}H_{43}O_6$ 439.306, found 439.306. *Anal.* Calcd for $C_{26}H_{46}O_6$ (454.65): C, 68.69; H, 10.20. Found: C, 68.86; H, 10.27.

General procedure for enzymatic hydrolyses of diesters 5a-c (Table 2). Diester **5** (0.88 mmol) was treated with an enzyme in 15 mL of water (for acetates and butyrates) or t-BuOH/water 1:1 mixture (for octanoates) at r.t.. The mixture was stirred for the time indicated in Table 2. During this interval, the pH was maintained in the range 6.8-7.2 by periodic addition of 0.1 M NaOH. The hydrolysis was terminated by extraction with methylene chloride (3 × 25 mL). The extract was concentrated and chromatographed using a gradient of ethylacetate (25-100%) in n-hexane. Monoesters **6a-c** were obtained after Kugelrohr distillation as colorless oils.

(1S,2S,3R,4R)-(4-Hydroxymethyl-2,3-isopropylidenedioxy-1-cyclopentyl)methyl acetate (6a), (Table 2, entry 3): bp (Kugelrohr) 125°C (0.03 Torr); $[\alpha]_D$ -9.3, c 4.0 $CHCl_3$; >99% ee; IR (film) ν 3471, 2985, 2936, 1741, 1457, 1375, 1247, 1215, 1161, 1068, 1042. ^{1}H-NMR δ 1.28 (td, 1H, H-5a; J_{gem} 13.0 Hz, $J_{1,5a}$ and $J_{4,5a}$ 10.8 Hz), 1.31 and 1.51 (2s, 6H, $C(CH_3)_2$), 2.08 (s, 3H, $COCH_3$), 2.09 (td, 1H, H-5b; $J_{1,5b}$ and $J_{4,5b}$ 7.1 Hz), 2.18 (s, 1H, OH), 2.26 (m, 1H, H-4), 2.38 (m, 1H, H-1), 3.63 and 3.70 (2dd, 2H, $C\underline{H}_2OH$; J_{gem} 10.6 Hz, $J_{4,Ha}$ 6.7 Hz, $J_{4,Hb}$ 5.9 Hz), 4.11 (d, 2H, CH_2OCO; *J* 6.4 Hz), 4.35 (dd, 1H, H-2; $J_{1,2}$ 5.3 Hz, $J_{2,3}$ 7.0 Hz), 4.41 (dd, 1H, H-3; $J_{3,4}$ 5.0 Hz); ^{13}C-NMR δ 20.86 ($\underline{C}H_3CO$), 25.05 and 27.47 ($C(\underline{C}H_3)_2$), 30.82 (C-5), 44.32 (C-1), 47.32 (C-4), 64.18 (CH_2OH), 65.52 ($\underline{C}H_2OCO$), 82.96 (C-2), 83.21 (C-3), 112.68 ($\underline{C}(CH_3)_2$), 171.15 (CO).

(1S,2S,3R,4R)-(4-Hydroxymethyl-2,3-isopropylidenedioxy-1-cyclopentyl)methyl butyrate (6b), (Table 2, entry 8): bp (Kugelrohr) 145°C (0.03 Torr); $[\alpha]_D$ -9.0, c 4.0 $CHCl_3$; >99% ee; IR (film) ν 3477, 2963, 2936, 2872, 1736, 1459, 1377, 1303, 1256, 1208, 1183, 1068, 1019; ^{1}H-NMR δ 0.95 (t, 3H, $CH_2\underline{C}H_3$; *J* 7.3 Hz), 1.27 (td, 1H, H-5a; J_{gem} 13.2 Hz, $J_{1,5a}$ and $J_{4,5a}$ 10.9 Hz), 1.31 and 1.50 (2s, 6H, $C(CH_3)_2$), 1.66 (sextet, 2H, $C\underline{H}_2CH_3$; *J* 7.3 Hz), 2.08 (td, 1H, H-5b; $J_{1,5b}$ and $J_{4,5b}$ 7.1 Hz), 2.19 (br s, 1H, OH), 2.25 (m, 1H, H-4), 2.31 (t, 2H, $C\underline{H}_2CH_2CH_3$; *J* 7.3 Hz); 2.38 (m, 1H, H-1), 3.63 and 3.69 (2dd, 2H, $C\underline{H}_2OH$; J_{gem} 10.7 Hz, $J_{4,Ha}$ 6.7 Hz, $J_{4,Hb}$ 5.9 Hz), 4.10 and 4.14 (2dd, 2H, CH_2OCO; J_{gem} 11.1 Hz, $J_{1,Ha}$ and $J_{1,Hb}$ 6.5 Hz), 4.34 (dd, 1H, H-2; $J_{1,2}$ 5.3 Hz, $J_{2,3}$ 7.0 Hz), 4.40 (dd, 1H, H-3; $J_{3,4}$ 5.0 Hz); ^{13}C-NMR δ 13.59 ($CH_2\underline{C}H_3$), 18.35 ($\underline{C}H_2CH_3$), 25.05 and 27.48 ($C(\underline{C}H_3)_2$), 30.85 (C-5), 36.06 ($CO\underline{C}H_2$), 44.40 (C-1), 47.36 (C-4), 64.21 (CH_2OH), 65.24 ($\underline{C}H_2OCO$), 82.89 (C-2), 83.22 (C-3), 112.66 ($\underline{C}(CH_3)_2$), 173.70 (CO). HRMS: m/z (M-15)$^+$ calcd for $C_{13}H_{21}O_5$ 257.139, found 257.139. *Anal.* Calcd for $C_{14}H_{24}O_5$ (272.34): C, 61.74; H, 8.88. Found: C, 61.82; H 8.66.

(1S,2S,3R,4R)-(-4-Hydroxymethyl-2,3-isopropylidenedioxy-1-cyclopentyl)methyl octanoate (6c), (Table 2, entry 16): bp (Kugelrohr) 160°C (0.01 Torr); $[\alpha]_D$ -7.3, c 4.0 $CHCl_3$; >99% ee; IR (film) ν 3483, 2952, 2930, 2859, 1734, 1460, 1376, 1255, 1211, 1164, 1104, 1068, 1021; ^{1}H-NMR δ 0.90 (t, 3H, $CH_2C\underline{H}_3$; *J* 6.7 Hz), 1.30 (m, 9H, $(C\underline{H}_2)_4CH_3$ and H-5a), 1.33 and 1.52 (2s, 6H, $C(CH_3)_2$), 1.64 (m, 2H, $COCH_2C\underline{H}_2$), 2.09 (td, 1H, H-5b; J_{gem} 13.6 Hz, $J_{1,5b}$ and $J_{4,5b}$ 7.1 Hz), 2.28 (m, 1H, H-4), 2.34 (t, 2H, $COCH_2$; *J* 7.6 Hz), 2.41 (m, 1H, H-1), 3.64 and 3.71 (2dd, 2H, $C\underline{H}_2OH$; J_{gem} 10.7 Hz, $J_{4,Ha}$ 6.8 Hz, $J_{4,Hb}$ 5.7 Hz), 4.13 (m, 2H, CH_2OCO), 4.36 (dd, 1H, H-2; $J_{1,2}$ 5.3 Hz, $J_{2,3}$ 7.0 Hz), 4.42 (dd, 1H, H-3; $J_{3,4}$ 5.0 Hz); ^{13}C-NMR δ 14.02

($CH_2\underline{C}H_3$), 22.55 ($\underline{C}H_2CH_3$), 24.92 ($\underline{C}H_2CH_2CH_3$), 25.06 and 27.50 ($C(\underline{C}H_3)_2$), 28.88 ($\underline{C}H_2(CH_2)_2CH_3$), 29.04 ($\underline{C}H_2(CH_2)_3CH_3$), 30.86 (C-5), 31.61 ($\underline{C}H_2(CH_2)_4CH_3$), 34.22 ($CO\underline{C}H_2$), 44.39 (C-1), 47.40 (C-4), 64.31 ($\underline{C}H_2OH$), 65.26 ($\underline{C}H_2OCO$), 82.99 (C-2), 83.27 (C-3), 112.73 ($\underline{C}(CH_3)_2$), 173.94 (CO). HRMS: m/z $(M-15)^+$ calcd for $C_{17}H_{29}O_5$ 313.201, found 313.200. *Anal.* Calcd for $C_{18}H_{32}O_5$ (328.45): C, 65.82; H, 9.82. Found: C, 65.87; H, 9.92.

Preparative-scale production of (-)-6b. Lipase MJ (3.0 g, 15 units) was added to a stirred suspension of dibutyrate **5b** (30.82 g, 0.09 mol) in 0.1 M phosphate buffer (pH 7, 1L) at 31°C. The pH was maintained in the range 6.8-7.2 by periodic addition of 1 M NaOH. The reaction was stopped after 1 equiv. of base had been added (8.5 hours). The reaction mixture was filtered through Celite and extracted with methylene chloride (3 × 700 mL). The extract was concentrated yielding monobutyrate **6b** along with a small amount of dibutyrate **5b** (0.5%). Distillation (bp 153-157°C at 0.02 Torr) afforded **6b** (22.63 g, 92%) as a colorless oil; $[\alpha]_D$ -8.7, c 4.0 $CHCl_3$; 96% ee. The sample was spectroscopically identical with the lipase SAM-2 derived **6b** (Table 2, entry 8).

Formal inversion of configuration of compound (-)-6b. (1S,2S,3R,4R)-(4-Pivaloyloxymethyl-2,3-isopropylidenedioxy-1-cyclopentyl)methyl butyrate (16). Freshly distilled pivaloyl chloride (9.2 mL, 0.075 mol) was added dropwise to a stirred solution of **6b** (16.34 g, 0.069 mol; 96% ee) in pyridine (100 mL) at 0°C, and stirring continued overnight at 4°C. The mixture was treated with water (4 mL) for 15 min and then concentrated. The residue was suspended in ether (400 mL) and washed with saturated aqueous $NaHCO_3$ (250 mL), water (250 mL), and brine (100 mL). Evaporation gave an oily residue, which was distilled to give **16** (20.23 g, 95%) as a colorless oil; bp 150-154°C (0.01 Torr); $[\alpha]_D$ +1.5, c 4.0 $CHCl_3$; IR (film) ν 2968, 2940, 2879, 1734, 1479, 1459, 1374, 1282, 1255, 1209, 1160, 1071; ^{1}H-NMR δ 0.95 (t, 3H, $CH_2C\underline{H}_3$; *J* 7.3 Hz), 1.21 (s, 9H, $C(CH_3)_3$), 1.30 and 1.49 (2s, 6H, $C(CH_3)_2$), 1.31 (td, 1H, H-5a; J_{gem} 12.9 Hz, $J_{1,5a}$ and $J_{4,5a}$ 11.2 Hz), 1.66 (sextet, 2H, $C\underline{H}_2CH_3$; *J* 7.4 Hz), 2.07 (td, 1H, H-5b; $J_{1,5b}$ and $J_{4,5b}$ 7.1Hz), 2.31 (t, 2H, $C\underline{H}_2CH_2CH_3$; *J* 7.4 Hz), 2.38 (m, 2H, H-1,4), 4.12 (m, 4H, 2 × CH_2OCO), 4.34 (m, 2H, H-2,3); ^{13}C-NMR δ 13.58 ($CH_2\underline{C}H_3$), 18.34 ($\underline{C}H_2CH_3$), 25.11 and 27.55 ($C(\underline{C}H_3)_2$), 27.09 ($C(\underline{C}H_3)_3$), 31.06 (C-5), 36.02 ($CO\underline{C}H_2$), 38.74 ($\underline{C}(CH_3)_3$), 44.20 and 44.31 (C-1,4), 64.88 and 64.95 (2 × $\underline{C}H_2OCO$), 82.62 and 82.68 (C-2,3), 112.71 ($\underline{C}(CH_3)_2$), 173.48 ($\underline{C}OCH_2$), 178.21 ($\underline{C}OC(CH_3)_3$). *Anal.* Calcd for $C_{19}H_{32}O_6$ (356.46): C, 64.02; H, 9.05. Found: C, 64.18; H, 8.97.

(1R,2R,3S,4S)-(4-Hydroxymethyl-2,3-isopropylidenedioxy-1-cyclopentyl)methyl pivaloate (*ent*-6d). Lipase CC (3.6 g, 2500 units) was added to a stirred suspension of diester **16** (17.82 g, 0.05 mol) in 0.1 M phosphate buffer (pH 7.5, 400 mL) at 31°C. The pH was maintained at 7.5 by periodic addition of 1 M NaOH. The reaction was complete after 1 equiv. of base had been added (13 hours). The mixture was filtered through Celite and extracted with methylene chloride (2 × 400 mL). The extract was concentrated and the residue distilled to give *ent*-**6d** (13.19 g, 92%) as a colorless oil; bp 148-152°C (0.01 Torr); $[\alpha]_D$ +9.2, c 4.0 $CHCl_3$; 98% ee; IR (film) ν 3482, 2978, 2936, 2876, 1728, 1480, 1459, 1375, 1285, 1255, 1211, 1160, 1068; ^{1}H-NMR δ 1.21, (s, 9H, $C(CH_3)_3$), 1.30 (m, 1H, H-5a), 1.31 and 1.50 (2s, 6H, $C(CH_3)_2$), 1.93 (br s, 1H, OH), 2.06 (td, 1H, H-5b; J_{gem} 12.9 Hz, $J_{1,5b}$ and $J_{4,5b}$ 7.1 Hz), 2.27 (m, 1H, H-4), 2.39 (m, 1H, H-1), 3.64 and 3.70 (2dd, 2H, $C\underline{H}_2OH$; J_{gem} 10.7 Hz, $J_{4,Ha}$ 6.7 Hz, $J_{4,Hb}$ 5.9 Hz), 4.08 and 4.15 (2dd, 2H, CH_2OCO; J_{gem} 11.0 Hz, $J_{1,Ha}$ 6.5 Hz, $J_{1,Hb}$ 6.1 Hz), 4.33 (dd, 1H, H-2; $J_{1,2}$ 5.4 Hz, $J_{2,3}$ 6.8 Hz), 4.39 (dd, 1H, H-3; $J_{3,4}$ 5.2 Hz); ^{13}C-NMR δ 25.10 and 27.55 ($C(\underline{C}H_3)_2$), 27.13 ($C(\underline{C}H_3)_3$), 30.83 (C-5), 38.90 ($\underline{C}(CH_3)_3$), 44.50 (C-1), 47.39

(C-4), 64.33 (CH_2OH), 65.22 ($\underline{C}H_2OCO$), 82.87 (C-2), 83.22 (C-3), 112.73 ($\underline{C}(CH_3)_2$), 178.50 (CO). *Anal.* Calcd for $C_{15}H_{26}O_5$ (286.37): C, 62.91; H, 9.15. Found: C, 63.25; H, 9.20.

Lipase SAM-2 catalysed transesterification of *meso*-diol 2. (1R,2R,3S,4S)-(4-Hydroxymethyl-2,3-isopropylidenedioxy-1-cyclopentyl)methyl acetate (*ent*-6a). A solution of diol **2** (10.00 g, 49.4 mmol) in 1,2-dichloroethane (100 mL) containing vinyl acetate (9.2 mL, 2 equiv.) was shaken with a lipase SAM-2 (700 mg, 22 kunits) at 45°C. Reaction progress was monitored by HPLC. When the starting material was consumed (32 hours in the first run), the reaction was terminated by filtering off the enzyme. Evaporation gave a mixture of diacetate **5a** and monoacetate *ent*-**6a** in a 1:10 ratio, which was separated by flash chromatography using ethylacetate/n-hexane (1:2) giving **5a** (1.40 g, 10%) and *ent*-**6a** (10.52 g, 87%) as a colorless oil; $[\alpha]_D$ +9.2, c 4.0 $CHCl_3$; >99% ee. The enzyme was dried and used again in subsequent experiments. We noticed only about 15% loss of activity per every run; repeated use, however, did not affect either the **5a**/*ent*-**6a** ratio or the ee value of *ent*-**6a**.

(1R,5R,6R,7S)-6,7-(Isopropylidenedioxy)-3-oxabicyclo[3.2.1]octan-2-one ((+)-1). A crude 1:10 mixture of **5a** and *ent*-**6a** (9.92 g, containing 40.6 mmol *ent*-**6a**) was treated with PDC (53.42 g, 0.142 mol) in N,N-dimethylformamide (105 mL) overnight. The reaction mixture was poured into saturated aq. $NaHCO_3$ (700 mL). Diacetate **5a** was removed by extraction into ether (700 mL); the aqueous layer was then acidified to pH 4.5 with 2 M HCl, and continously extracted with ether for 1 day. The concentrated extract was stirred with K_2CO_3 (5.30 g) in methanol (150 mL) overnight. After removal of the solvent, the residue was stirred overnight with acetic anhydride (50 mL) in pyridine (80 mL). The mixture was concentrated and treated with 5% aq. $NaHCO_3$ (100 mL). Extraction with methylene chloride (2 × 100 mL) followed by flash chromatography using ethylacetate/methylene chloride (1:2) gave **1** (6.48 g, 81%) as a colorless solid: mp 141-143°C; $[\alpha]_D$ +43.5, c 1.0 $CHCl_3$. This material was identical with an authentic sample, prepared[6] by another route: mp 142-143°C; $[\alpha]_D^{22}$ +44.4, c 1.0 $CHCl_3$.

(1S,2S,3R,4R)-4-Acetoxymethyl-2,3-(isopropylidenedioxy)cyclopentane-1-carbonitrile (10).[32]

Method A: To a mixture of PCC (9.70 g, 0.045 mol) in dry methylene chloride (60 mL) was added a solution of *ent*-**6a** (7.33 g, 0.030 mol) in the same solvent (20 mL). The reaction mixture was stirred for 4 hours at r.t., diluted with ether (300 mL) and filtered through Florisil. The concentrated residue was dissolved in methanol (100 mL) and stirred with N,N-dimethylhydrazine (3.20 mL, 0.042 mol) for 2 hours. The solution of hydrazone was then added dropwise to magnesium monoperoxyphtalate hexahydrate (56 g, approx. 0.096 mol) suspended in methanol (100 mL) at 0°C; stirring was continued at this temperature for 10 min. Ether (750 mL) and water (750 mL) were added, and the organic layer was separated and washed with water (400 mL) and brine (250 mL). The dried organic layer was evaporated and purified by flash chromatography using ethylacetate/petrolether (1:15) and Kugelrohr distilled yielding **10** (3.50 g, 49%) as a colorless oil; bp 140°C (0.02 Torr); $[\alpha]_D$ -51.3, c 4.0 $CHCl_3$; >99% ee; IR (film) ν 2987, 2941, 2243 (CN), 1742, 1457, 1377, 1241, 1161, 1073, 1044; ^{1}H-NMR δ 1.31 and 1.47 (2s, 6H, $C(CH_3)_2$), 1.89 (m, 1H, H-5a), 2.11 (s, 3H, $COCH_3$), 2.48 (m, 1H, H-5b), 2.51 (m, 1H, H-4), 2.95 (m, 1H, H-1), 4.14 (d, 2H, CH_2OCO; $J_{4,H}$ 5.9 Hz), 4.54 (dd, 1H, H-3; $J_{2,3}$ 6.1 Hz, $J_{3,4}$ 2.4 Hz), 4.82 (dd, 1H, H-2; $J_{1,2}$ 3.9 Hz); ^{13}C-NMR δ 20.73 ($CO\underline{C}H_3$), 24.44 and 26.78 ($C(\underline{C}H_3)_2$), 31.42 (C-5), 35.04 (C-1), 44.18 (C-4), 64.10 ($\underline{C}H_2OCO$), 82.82 (C-3), 83.66 (C-2), 112.47 ($\underline{C}(CH_3)_2$), 120.55 (CN), 170.61 (CO). HRMS: m/z $(M-15)^+$ calcd for $C_{11}H_{14}NO_4$ 224.093, found 224.093. *Anal.* Calcd for $C_{12}H_{17}NO_4$ (239.27): C, 60.24; H, 7.16; N, 5.85. Found: C, 60.09; H, 7.16; N, 5.83.

Method B: To a mixture of PCC (14.89 g, 0.069 mol) in dry methylene chloride (92 mL) was added a solution of *ent*-**6a** (10.29 g, 0.042 mol) in the same solvent (45 mL). After 5 hours, the reaction mixture was diluted with ether (400 mL) and filtered through Florisil. The concentrated residue was dissolved in pyridine (15 mL) and treated with hydroxylammonium chloride (3.07 g, 0.044 mol) for 15 min. The mixture was diluted with dry tetrahydrofuran (50 mL) and trifluoroacetic anhydride (7.3 mL, 0.052 mol) was added dropwise with stirring at a temperature below 5°C. The mixture was kept at r.t. overnight, and partitioned between methylene chloride (300 mL) and saturated aq. $NaHCO_3$ (150 mL). The organic phase was concentrated and chromatographed using ethylacetate/n-hexane (1:8) to give **10** (3.53 g, 35%) as an oil; $[\alpha]_D$ -50.9, c 4.0 $CHCl_3$, after Kugelrohr distillation.

Method C: Lactone (+)-**1** (1.00 g, 5.1 mmol) was treated with methanolic ammonia (27%, 10 mL) at r.t. overnight and the solution was then concentrated. The residue was treated overnight with acetic anhydride (7 mL) in pyridine (10.5 mL) at r.t.. Concentration gave an oily residue[33] which was dissolved in tetrahydrofuran (8 mL) containing pyridine (0.82 mL, 10.1 mmol), treated with trifluoroacetic anhydride (0.79 mL, 5.6 mmol) below 5°C, and then stirred at r.t. for 5 hours. Solvents were evaporated, the residue suspended in methylene chloride (25 mL) and washed with saturated aq. $NaHCO_3$ (2 × 15 mL) and water (15 mL). The organic phase was concentrated and chromatographed with ethylacetate/n-hexane (1:2) to give **10** (1.04 g, 86%) as an oil; $[\alpha]_D$ -50.3, c 4.0 $CHCl_3$, after Kugelrohr distillation.

(1S,2S,3R,4R)-4-Pivaloyloxymethyl-2,3-(isopropylidenedioxy)cyclopentane-1-carbonitrile (15). Nitrile **15** was prepared from *ent*-**6d** in the same manner as described above for nitrile **10** (*Method A*) with 61% yield; bp 150°C (0.01 Torr); $[\alpha]_D$ -30.9°, c 4.0; 98% ee; IR (film) ν 2978, 2934, 2876, 2243 (CN), 1730, 1480, 1459, 1377, 1283, 1213, 1158, 1073; ^{1}H-NMR δ 1.22 (s, 9H, $C(CH_3)_3$), 1.31 and 1.48 (2s, 6H, $C(CH_3)_2$), 1.87 (td, 1H, H-5a; J_{gem} 13.2 Hz, $J_{1,5a}$ and $J_{4,5a}$ 7.5 Hz), 2.41 (td, 1H, H-5b; $J_{1,5b}$ and $J_{4,5b}$ 7.5 Hz), 2.49 (quasi d of quartets, 1H, H-4; $J_{3,4}$ 3.3 Hz), 2.93 (td, 1H, H-1; $J_{1,2}$ 4.2 Hz), 4.11 and 4.17 (2dd, 2H, CH_2OCO; J_{gem} 11.7 Hz, $J_{4,Ha}$ 6.5 Hz, $J_{4,Hb}$ 6.8 Hz), 4.50 (dd, 1H, H-3; $J_{2,3}$ 6.3 Hz), 4.80 (dd, 1H, H-2); ^{13}C-NMR δ 24.61 and 26.96 ($C(\underline{C}H_3)_2$), 27.10 ($C(\underline{C}H_3)_3$), 31.52 (C-5), 34.88 (C-1), 38.78 ($\underline{C}(CH_3)_3$), 44.46 (C-4), 63.66 ($\underline{C}H_2OCO$), 82.47 (C-3), 83.48 (C-2), 112.97 ($\underline{C}(CH_3)_2$), 120.43 (CN), 178.07 (CO). *Anal.* Calcd for $C_{15}H_{23}NO_4$ (281.36): C, 64.03; H, 8.24; N 4.98. Found: C, 63.98; H, 8.43; N, 5.17.

Enantiomeric excess determinations. a) Of **6a** and *ent*-**6a**. ^{1}H-NMR spectrum was recorded in CD_3CN solution in the presence of Eu(hfc)$_3$ (2 mg/mg of **6**). The signals due to the $COCH_3$ protons of the two diasteromeric complexes were used as markers: δ 2.20 (*ent*-**6a**), 2.21 (**6a**).

b) Of **6b**, **6c** and *ent*-**6d**. Each compound was converted[25] to its (R)-(-)-MTPA ester, and the ^{19}F-NMR spectrum was recorded. The signals due to the CF_3 fluorine atoms of the two diastereomers were used as markers: δ -71.98 ± 0.01 (for MTPA ester of **6**), -72.05 ± 0.01 (for MTPA esters of *ent*-**6**).

Absolute configuration determinations. The absolute configurations of compounds **6a** and **6b** were determined in the same manner as described above for the conversion of *ent*-**6a** → (+)-**1**. The lactones (-)-**1** prepared through lipase PP catalysed hydrolysis of **6a** (Table 2, entry 2) had $[\alpha]_D$ -31.0 (c 1.0 $CHCl_3$); these prepared through lipase MJ catalysed hydrolysis of **6b** (Table 2, entry 9) had $[\alpha]_D$ -42.4 (c 1.0 $CHCl_3$). The absolute configuration of lactone (+)-**1** was taken from the literature assignment ($[\alpha]_D$ +44.4, c 1.0 $CHCl_3$).[3]

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