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# Enzymatic Desymmetrisation of Conduritol D. Preparation of Homochiral Intermediates for the Synthesis of Cyclitols and Aminocyclitols

**Angela Patti, Claudia Sanfilippo, Mario Piattelli and Giovanni Nicolosi***

Istituto C.N.R. per lo Studio delle Sostanze Naturali di Interesse Alimentare e Chimico-Farmaceutico#

Via del Santuario 110, 95028 Valverde CT, Italy

**Abstract:** From *meso*-conduritol D tetraacetate four homochiral partial derivatives, namely (+)-(1*R*,2*R*,3*S*,4*S*)-1-hydroxy-2,3,4-triacetoxy-5-cyclohexene, (−)-(1*R*,2*R*,3*S*,4*S*)-2-hydroxy-1,3,4-triacetoxy-5-cyclohexene, (−)-(1*R*,2*R*,3*S*,4*S*)-1-benzoyloxy-3,4-diacetoxy-2-hydroxy-5-cyclohexene and (+)-(1*R*,2*R*,3*S*,4*S*)-3,4-diacetoxy-1,2-dihydroxy-5-cyclohexene, have been prepared through enzymatic reactions catalysed by one of the following lipases: from porcine pancreas, from *Mucor miehei* and from *Candida cylindracea*. These compounds are of potential utility in the synthesis of cyclitols and aminocyclitols. As an example, the preparation of the previously unreported (+)-conduramine C-4 is also reported.


## INTRODUCTION

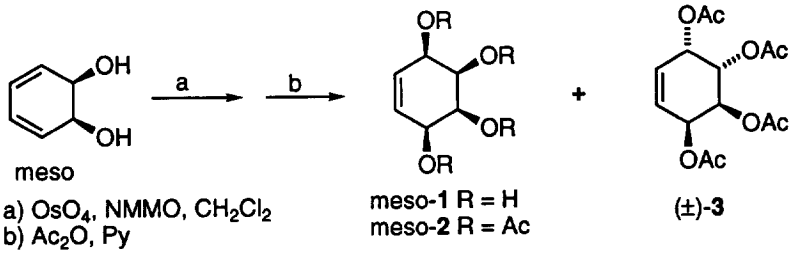
Conduritols (5-cyclohexen-1,2,3,4-tetrols) constitute a prominent class of compounds useful for the preparation of inositol derivatives,[1] some of which are important mediators in many cellular processes[2,3] or key intermediates in the synthesis of aminocyclitols with glycosidase-inhibitory activity.[4] Moreover, they are building blocks in the synthesis of biologically important compounds, as for instance pancratistatine, licoricidine and aminoglycosidic antibiotics.[5] Due to the presence of four stereogenic centres, conduritols exist as six stereoisomers, two of them *meso*-forms. Desymmetrisation of the latter is a goal of great interest for the synthesis of optically active molecules possessing more than two stereogenic centres. For this purpose, lipase-mediated enantiotoposelective hydrolysis and transesterification appear particularly attractive and their use is in fact consistently increasing. Cyclic diols have been thus desymmetrised in both our[6] and other laboratories,[7] as well as polyols partially derivatized to reduce the number of groups recognizable by the enzyme.[8] This strategy has been used, for instance, in the desymmetrisation of one of the *meso*-forms of conduritol, namely conduritol A.[9] In the present work we wish to report the results obtained in the lipase-assisted asymmetrisation of the other *meso*-conduritol, conduritol D, using as substrate its tetraacetate (the free tetrol owing to its sparing solubility in most organic solvents was considered unsuitable for biotransformations in non-aqueous media). This led to the preparation of four homochiral partial esters, that may find utilisation in the synthesis of cyclitols and aminocyclitols. As an example of their synthetic potential, conversion of triester (+)-4 into homochiral (+)-conduramine C-4 is also reported.

## RESULTS AND DISCUSSION

Conduritol D, *meso*-(1*R*,2*R*,3*S*,4*S*)-1,2,3,4-tetrahydroxy-5-cyclohexene, **1**, has been prepared from the commercially available *cis*-1,2-dihydroxycyclohexa-3,5-diene following essentially the procedure described

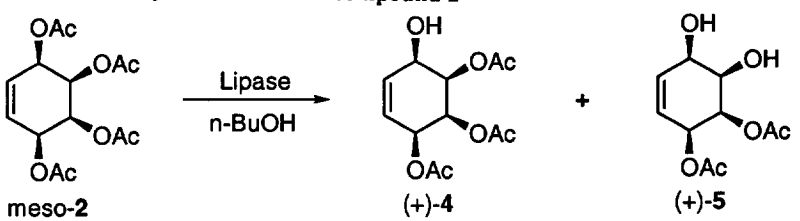
#Associated to the National Institute for the Chemistry of Biological Systems, C.N.R. (Rome)

by Carless,[10] but modifying the experimental conditions in order to enhance the percentage of the product with all-*cis* configuration. The crude **1** was converted into tetraacetate **2** by conventional acetylation.




Compound **2** in *tert*-butyl methyl ether (*t*-BME) was subjected to transesterification with *n*-butanol in the presence of one of the following lipases: from *Candida antarctica* (Novozym® 435), *Candida cylindracea* (CCL), *Chromobacterium viscosum, Mucor miehei* (Lipozyme® IM), *Pseudomonas cepacia* and porcine pancreas (PPL). PPL, Lipozyme® IM and CCL proved sufficiently active and gave the results summarised in Table 1.

**Table 1. Enzymatic Desymmetrisation of compound 2**[a]




| Entry | Enzyme[b] | time, h | 2, %[c] | (+)-4,%[c] | ee,%[d] | Ster.[e] | (+)-5,%[c] |
|---|---|---|---|---|---|---|---|
| 1 | PPL | 24 | 44 | 56 | >95 | *R* | – |
| 2 | | 60 | 27 | 73 | | | – |
| 3 | Lipozyme® IM | 3 | 70 | 30 | >95 | *R* | – |
| 4 | | 6 | 19 | 61 | | | 20 |
| 5 | | 48 | – | 11 | | | 89 |
| 6 | CCL | 12 | 65 | 35 | >95 | *R* | – |
| 7 | | 60 | 28 | 38 | | | 34 |

[a]Experimental conditions: solvent *t*-BME, substrate 10 mg/mL, enzyme 20 mg/mL, *n*-BuOH 1 eqv., 40 °C, 300 rpm. [b]PPL = lipase from porcine pancreas; Lipozyme IM = immobilised lipase from *Mucor miehei*; CCL = lipase from *Candida cylindracea*. [c]Determined by $^1$H NMR analysis. [d]Determined by $^1$H NMR in the presence of Eu(hfc)$_3$. [e]Stereochemistry assigned by chemical correlation with (+)-conduritol C (see text).

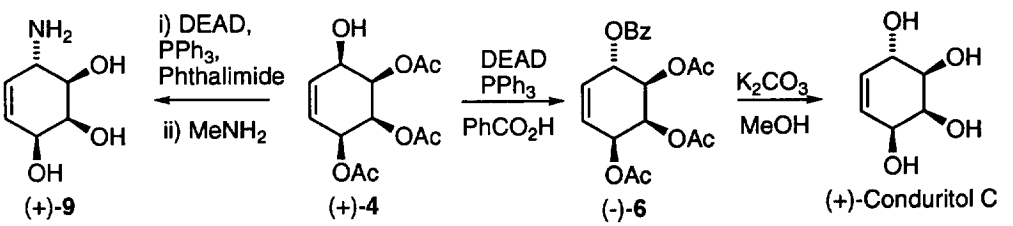
The PPL-catalysed reaction after 24 h gave a single, optically active product, whose $^1$H NMR contained three signals for acetoxy groups (entry 1). The allylic nature of the hydroxymethine proton was evidenced by extensive homonuclear decoupling, thus allowing the assignment of structure (+)-**4** to the transesterification product. $^1$H NMR analysis in the presence of the chiral shift reagent Eu(hfc)$_3$, in comparison with a sample of racemic **4** prepared chemically, indicated the presence of a single enantiomer.[11] When the incubation time was prolonged, conversion increased without loss of enantiomeric purity or formation of additional products of alcoholysis (entry 2). The absolute configuration of (+)-**4**, (1*R*,2*R*,3*S*,4*S*)-1-hydroxy-2,3,4-triacetoxy-5-

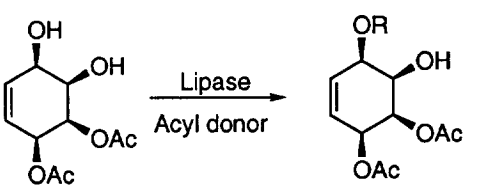
cyclohexene, was determined *via* inversion of the stereogenic centre at C-1 according to Mitsunobu,[12] followed by conversion into (+)-conduritol C (ee >95%).

Lipozyme® IM (entries 3-5) was more active than PPL and gave the same product, (+)-**4**, but in this instance prolonging the reaction time resulted in the alcoholysis of the ester group at C-2 to afford enantiomerically pure (+)-**5**. After 48 h incubation the substrate disappeared and the main product was diester (+)-**5**. CCL behaved similarly to Lipozyme IM and gave the same products, (+)-**4** and (+)-**5**, the main difference being the longer reaction times required (entries 6 and 7).

Diester (+)-**5** can undergo esterification with vinyl acetate in the presence of PPL, which possesses 1*R*-stereopreference, to give (–)-**7**, whose structure has been determined on the basis of NMR data. The product of complete acylation was not detected, even after prolonged incubation. The same reaction in the presence of Lipozyme® IM afforded the same product with greater reaction rate. However, when conversion reached ca. 90% moderate amounts of tetraester were also obtained. The use of a more bulky acyl donor, vinyl benzoate, did not change the situation and formation of benzoate (–)-**8** was followed, at high levels of conversion, by the appearance of the corresponding dibenzoate-diacetate.

The homochiral triester (+)-**4** was used as starting material for the synthesis of a previously unreported aminoconduritol. According to Scheme 1, (+)-**4** was subjected to the Mitsunobu reaction with triphenylphosphine, diethyl azodicarboxylate and phthalimide to give (+)-conduramine C-4 (**9**) in fair yield. A comparison of the $^1$H NMR spectra run in methanol before and after addition of $CF_3COOH$ allowed to assign the resonance of the aminomethine proton on the basis of the downfield shift following acidification. Subsequent homonuclear decouplings on the acidified sample allowed to prove the inversion at C-1, supported by the H-1–H-2 *J* value (9 Hz).




**Scheme 1**

## CONCLUSIONS

Lipases from *Mucor miehei* (Lipozyme® IM), *Candida cylindracea* (CCL) and porcine pancreas (PPL) have been used successfully for the asymmetrisation of **2**. These enzymes all cause the preferential alcoholysis of the ester group at C-1 to give triester (+)-**4**. Moreover, when Lipozyme is used, prolonging the incubation time diester (+)-**5** is obtained with high chemical and optical yields. Diester (+)-**5** can be in turn converted by enzyme-assisted esterification into triesters (-)-**7** and (-)-**8**. The partial esters thus obtained are promising intermediates in the preparation of cyclitols and aminocyclitols, and their synthetic potential is exemplified by the preparation of enantiomerically pure (+)-conduramine C-4 (**9**).

## EXPERIMENTAL

Lipases from *Candida cylindracea* and porcine pancreas were obtained from Sigma; Lipozyme® IM (immobilised lipase from *Mucor miehei*) and Novozym® 435 (immobilised lipase from *Candida antarctica*) are registered marks from Novo Nordisk. Lipase from *Pseudomonas cepacia* was obtained from Amano International Enzyme Co. Preparative chromatography was performed on Si gel, Si Diol or Dowex 50. Melting points are uncorrected. $^1H$ and $^{13}C$ NMR spectra were registred in $CDCl_3$, unless otherwise stated, at 250.13 and 62.9 MHz respectively. Chemical shifts are in ppm) downfield from $Me_4Si$. Optical rotations were measured on a DIP 135 JASCO instrument.

**Preparation of 1,2,3,4-tetra-*O*-acetylconduritol D 2.** *N*-Methylmorpholine-*N*-oxide (806 mg, 6.88 mmol) and $OsO_4$ (12 mg, 0.04 mmol) were added to a solution of 1,2-dihydroxycyclohexa-3,5-diene (700 mg, 6.25 mmol) in $CH_2Cl_2$ (60 mL) and the mixture was stirred at 30 °C for 24 h (85% conversion). After removal of the solvent, the residue was dissolved in pyridine and acetylated according to the standard procedure. The reaction mixture was partitioned between dil. HCl and $CH_2Cl_2$. The organic layer was taken to dryness to leave a residue containing 1,2,3,4-tetra-*O*-acetylconduritols D and E in a 2.6:1 ratio ($^1H$ NMR analysis). Column chromatography (ethyl acetate/hexane 4:6) afforded **2** (recrystallised from ethyl acetate/hexane, 1.076 g, 55% yield), whose $^1H$ NMR features fully agreed with literature data,[13] and (±)-**3** (recrystallised from ethyl acetate/hexane, 395 mg, 20% yield), $^1H$ NMR δ 2.03 (s, 6H), 2.07 (s, 6H), 5.43 (m, 2H), 5.68 (m, 2H), 5.90 (m, 2H).

**General procedure for the enzymatic alcoholysis of 2.** *n*-BuOH (0.055 mL, 0.60 mmol) and enzyme (100 mg) were added to a solution of **2** (50 mg, 0.15 mmol) in *t*-BME (5 mL). The suspension was shaken at 40 °C and 300 rpm. Substrate conversion was determined by $^1H$ NMR analysis of an aliquot of the reaction mixture. After purification on Si Diol, the enantiomeric excess (ee) of (+)-**4** was determined by $^1H$ NMR analysis in the presence of $Eu(hfc)_3$.

**Enzymatic preparation of (+)-(1*R*,2*R*,3*S*,4*S*)-1-hydroxy-2,3,4-triacetoxy-5-cyclohexene, (+)-4.** Compound **2** (410 mg, 1.3 mmol), *n*-BuOH (0.48 mL, 5.24 mmol), PPL (1.64 g) in *t*-BME (40 mL) were stirred at 40 °C and 300 rpm for 24 h. The mixture was filtered and the filtrate taken to dryness. The residue was chromatographed on Si Diol eluting with hexane/ethyl acetate 1:1 vol/vol to give (+)-**4** (215 mg, yield 61%), $[\alpha]_D$ +17.5 (*c* 1.5, $CHCl_3$), ee >95%; $^1H$ NMR 2.04 (s, 3H), 2.11 (s, 3H), 2.14 (s, 3H), 2.24 (d, $J$ =10.6 Hz, 1H), 4.35 (1H, m), 5.10 (dd, $J$ = 4.8 and 1.8 Hz, 1H), 5.51 (m, 2H), 5.71 (m, 1H), 6.06 (ddd, $J$ = 10.2, 4.0 and 1.9 Hz, 1H); $^{13}C$ NMR 20.71, 20.83, 64.82, 66.97, 67.33, 68.53, 68.88, 125.53, 130.77, 169.60, 169.87, 170.14.

**(+)-Conduritol C from (+)-4.** A toluene solution (10 mL) containing triphenylphosphine (184 mg, 0.70 mmol), diethyl azodicarboxylate (0.11 mL, 0.70 mmol) and benzoic acid (85 mg, 0.70 mmol) was added to a solution of (+)-**4** (120 mg, 0.44 mmol) in toluene (6 mL). The reaction mixture was stirred at rt for 2 h until complete conversion of the substrate and then chromatographed on Si gel with hexane/acetone 4:1 vol/vol as the solvent to give (1*S*,2*R*,3*S*,4*S*)-1-benzoyloxy-2,3,4-triacetoxy-5-cyclohexene, (–)-**6** (125 mg, 75% yield), $[\alpha]_D$ –2.3 (*c* 2.2, $CHCl_3$), $^1H$ NMR 2.00 (s, 3H), 2.05 (s, 3H), 2.16 (s, 3H), 5.43 (dd, $J$ = 8.5 and 1.7 Hz, 1H), 5.71 (m, 3H), 5.92 (m, 2H), 7.45 (m, 2H), 7.58 (m, 1H), 8.00 (dd, $J$ = 8.5 and 1.4); $^{13}C$ NMR 20.72, 67.78, 69.97, 70.26, 70.39, 127.19, 127.61, 128.52, 129.43, 129.78, 133.43, 166.04, 169.77, 169.94, 170.35.

Hydrolysis of (–)-**6** with $K_2CO_3/CH_3OH$ gave (+)-conduritol C, $[\alpha]_D$ +205 (*c* 1.2, $H_2O$) [lit.[13] $[\alpha]_D$ –209 (*c* 2, $H_2O$) for the enantiomer].

**Enzymatic preparation of (+)-(1*R*,2*R*,3*S*,4*S*)-3,4-diacetoxy-1,2-dihydroxy-5-cyclohexene, (+)-5.** Lipozyme® IM (880 mg) was added to a solution of compound **2** (440 mg, 1.4 mmol) and *n*-BuOH (0.52 mL, 5.68 mmol) in *t*-BME (44 mL). The mixture was stirred for 48 h at 40 °C and 300 rpm. The enzyme was filtered off and the filtrate evaporated to dryness to give a residue that was recrystallised from hexane/ethyl acetate to yield (+)-**5** (225 mg, 0.98 mmol, 70% yield), mp 141-143 °C, $[\alpha]_D$ +45.1 (*c* 1, $CHCl_3$); $^1$H NMR 2.04 (s, 3H), 2.08 (s, 3H), 2.47 (d, *J* = 10.6 Hz, 1H), 3.11(d, *J* = 8.3 Hz, 1H), 3.92 (ddd, *J* = 8.3, 4.8 and 2.1 Hz, 1H), 4.18 (dddd, *J* = 10.6, 4.8, 3.4 and 1.1 Hz, 1H), 5.34 ( m, 1H), 5.50 (m, 1H), 5.72 (ddd, *J* = 9.8, 3.0 and 1.1 Hz, 1H), 6.03 (ddd, *J* = 9.8, 3.4 and 1.5 Hz, 1H); $^{13}$C NMR 20.76, 20.83, 66.65, 67.00, 67.57, 70.34, 125.43, 131.39, 169.82, 169.86.

**Enzymatic preparation of (–)-(1*R*,2*R*,3*S*,4*S*)-2-hydroxy-1,3,4-triacetoxy-5-cyclohexene, (–)-7.** Lipozyme® IM (400 mg) was added to a solution of (+)-**5** (200 mg, 0.87 mmol) in *t*-BME/vinyl acetate (7:3 vol/vol, 20 mL). The reaction mixture was stirred 6 h at 40 °C and 300 rpm and then quenched filtering off the enzyme. The filtrate was taken to dryness and the residue chromatographed on Si Diol (hexane/ethyl acetate 1:1 vol/vol as the solvent) to give (–)-**7** (166 mg, 70% yield) $[\alpha]_D$ –29.1 (*c* 1.8, $C_6H_6$); $^1$H NMR 2.05 (s, 3H), 2.07 (s, 3H), 2.09 (s, 3H), 2.74 (d, *J* = 7.3 Hz, 1H), 4.15 (m, 1H), 5.23 (dd, *J* = 4.5 and 2.0 Hz, 1H), 5.38 (m, 1H), 5.52 (m, 1H), 5.85 (m, 2H); $^{13}$C NMR 20.81, 20.93, 66.35, 67.21, 68.67, 69.21, 126.93, 127.92, 169.91, 170.33, 170.58.

**Enzymatic preparation of (–)-(1*R*,2*R*,3*S*,4*S*)-1-benzoyloxy-3,4-diacetoxy-2-hydroxy-5-cyclohexene, (–)-8.** Lipozyme® IM (200 mg) was added to a solution of (+)-**5** (100 mg, 0.43 mmol) in *t*-BME/$CH_2Cl_2$ (85:15 vol/vol, 10 mL) containing vinyl benzoate (0.15 mL, 1.1 mmol). The reaction mixture was stirred 24 h at 40 °C and 300 rpm and then quenched filtering off the enzyme. The filtrate was taken to dryness and the residue chromatographed on Si Diol with hexane/ethyl acetate 3:1 vol/vol as the solvent to give (–)-**8** (100 mg, 70% yield) $[\alpha]_D$ –72.6 (*c* 0.5, $C_6H_6$); $^1$H NMR 2.11 (s, 3H), 2.15 (s, 3H), 4.30 (dd, *J* = 4.6 and 2.0 Hz, 1H), 5.40 (dd, *J* = 4.5 and 2.0 Hz, 1H), 5.62 (m, 1H), 5.68 (m, 1H), 5.92 (ddd, *J* = 10.2, 3.2 and 1.4 Hz, 1H), 6.07 (ddd, *J* = 10.2, 3.2 and 1.5 Hz, 1H), 7.46 (m, 2H), 7.59 (m, 1H), 8.10 (m, 2H); $^{13}$C NMR 20.90, 66.61, 67.36, 68.84, 69.32, 127.45, 127.76, 128.47, 129.76, 129.99, 130.19, 133.43, 133.71, 166.00, 169.97, 170.59.

**Preparation of (+)-(1*S*,2*R*,3*S*,4*S*)-1-amino-2,3,4-trihydroxy-5-cyclohexene (conduramine C-4), (+)-9.** A toluene (15 mL) suspension of triphenylphosphine (175 mg, 0.82 mmol), diethyl azodicarboxylate (0.130 mL, 0.82 mmol) and phthalimide (120 mg, 0.82 mmol) was added to a toluene (10 mL) solution of (+)-**4** (185 mg, 0.68 mmol). The reaction mixture was stirred at rt and after 2 hr filtered. A 40% aqueous solution of methylamine was added to the filtrate and the mixture shaken at rt. The aqueous phase was applied to a Dowex-50 ($H^+$ form) column which was eluted 2N $NH_4OH$. The alkaline eluate was taken to dryness to give (+)-**9** (95 mg , 80% yield) $[\alpha]_D$ +155 (*c* 0.7, $CH_3OH$); $^1$H NMR ($CD_3OD$) 3.48 (m, 1H), 3.62 (m, 1H), 4.02 (m, 1H), 4.24 (m, 1H), 5.60 (m, 2H); $^{13}$C NMR 51.97, 69.67, 73.70, 75.29, 128.01, 131.85. $^1$H NMR ($CD_3OD$ in the presence of $CF_3COOH$) 3.67 (dd, *J* = 9.1 and 1.8 Hz, 1H), 3.88 (m, 1H), 4.06 (dd, *J* = 3.5 and 1.8 Hz, 1H), 4.27 (m, 1H), 5.60 (ddd, *J* = 10.3, 2.2 and 1.7 Hz, 1H), 5.78 (m, 1H); $^{13}$C NMR ($CD_3OD$ in the presence of $CF_3COOH$) 52.57, 69.40, 72.30, 73.58, 122.87, 135.10.

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11. As a consequence of the addition of $Eu(hfc)_3$ part of **4** undergoes intramolecular acyl migration. However, this does not interfere with the determination of the enantiomeric excess, since the new signals are well separated from those of the original compound.
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