



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

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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.

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INTRODUCTION

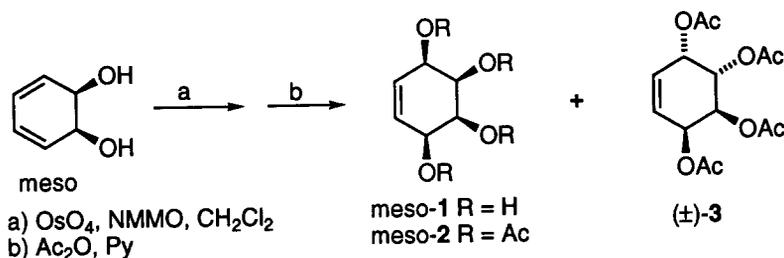
Conduritols (5-cyclohexen-1,2,3,4-tetrols) constitute a prominent class of compounds useful for the preparation of inositol derivatives,¹ some of which are important mediators in many cellular processes^{2,3} or key intermediates in the synthesis of aminocyclitols with glycosidase-inhibitory activity.⁴ 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, conduritol exists 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 our⁶ 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

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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	<i>R</i>	–
2		60	27	73			–
3	Lipozyme [®] IM	3	70	30	>95	<i>R</i>	–
4		6	19	61			20
5		48	–	11			89
6	CCL	12	65	35	>95	<i>R</i>	–
7		60	28	38			34

^aExperimental conditions: solvent *t*-BME, substrate 10 mg/mL, enzyme 20 mg/mL, *n*-BuOH 1 eqv., 40 °C, 300 rpm. ^bPPL = lipase from porcine pancreas; Lipozyme IM = immobilised lipase from *Mucor miehei*; CCL = lipase from *Candida cylindracea*. ^cDetermined by ¹H NMR analysis. ^dDetermined by ¹H NMR in the presence of Eu(hfc)₃. ^eStereochemistry assigned by chemical correlation with (+)-conduritol C (see text).

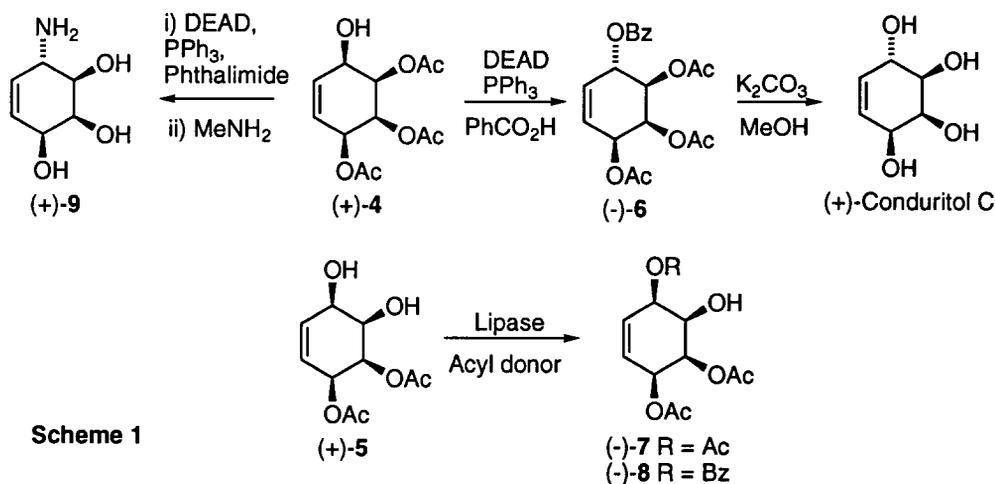
The PPL-catalysed reaction after 24 h gave a single, optically active product, whose ¹H NMR contained three signals for acetoxy groups (entry 1). The allylic nature of the hydroxymethine proton was evidenced by extensive homonuclear decoupling, thus allowing the assignment of structure (+)-**4** to the transesterification product. ¹H 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 ¹H NMR spectra run in methanol before and after addition of CF₃COOH 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).



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 ¹³C NMR spectra were registered in CDCl₃, unless otherwise stated, at 250.13 and 62.9 MHz respectively. Chemical shifts are in ppm) downfield from Me₄Si. 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 OsO₄ (12 mg, 0.04 mmol) were added to a solution of 1,2-dihydroxycyclohexa-3,5-diene (700 mg, 6.25 mmol) in CH₂Cl₂ (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 CH₂Cl₂. 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%), [α]_D +17.5 (c 1.5, CHCl₃), 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); ¹³C 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), [α]_D –2.3 (c 2.2, CHCl₃), 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); ¹³C 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 (+)-(1R,2R,3S,4S)-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, $CHCl_3$); ¹H 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); ¹³C NMR 20.76, 20.83, 66.65, 67.00, 67.57, 70.34, 125.43, 131.39, 169.82, 169.86.

Enzymatic preparation of (-)-(1R,2R,3S,4S)-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); ¹H 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); ¹³C 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 (-)-(1R,2R,3S,4S)-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); ¹H 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); ¹³C 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 (+)-(1S,2R,3S,4S)-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); ¹H NMR (CD_3OD) 3.48 (m, 1H), 3.62 (m, 1H), 4.02 (m, 1H), 4.24 (m, 1H), 5.60 (m, 2H); ¹³C NMR 51.97, 69.67, 73.70, 75.29, 128.01, 131.85. ¹H 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); ¹³C 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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