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TETRAHEDRON: *ASYMMETRY*

A chemoenzymatic synthesis of both enantiomers of a *cis*-lignan lactone

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Abstract

The stereoselective acetylation of *meso*-2,3-bis(3,4-dimethoxybenzyl)butanediol by vinyl acetate in the presence of *Candida antarctica* lipase in benzene gave the corresponding (+)-(2*S*,3*R*) monoester (ee ≥98%). Transesterification of *meso*-2,3-bis(3,4-dimethoxybenzyl)butyl diacetate, in the presence of the same enzyme, by ethanol in benzene/isopropyl ether gave the corresponding (−)-(2*R*,3*S*) monoester (ee ≥98%). Both enantiomers of the known *cis*-2,3-bis(3,4-dimethoxybenzyl)butyrolactone were synthesized from these monoesters.

1. Introduction

Lignans are natural products of widespread occurrence in plants, their structures containing two characteristic phenylpropanoid units.[1–3] Lignans are known to exhibit a wide range of biological activity[1–5] (anti-tumor, antiviral, diuretic, platelet-activating factor antagonism, antioxidant, etc.) and have attracted great interest on account of their cancer-protective properties.[6,7] Also, the biological significance of these secondary metabolites remains to be established. Considerable interest has been focussed on the synthesis of lignans and analogues because of their intriguing biological activities. Several methods for the asymmetric synthesis of *trans*-dibenzylbutyrolactones have been developed[8–18] but very few methods for the asymmetric synthesis of the corresponding *cis*-lactones[8] have been previously reported. Recently, Ward et al.[19,20] reported the enantioselective synthesis of *cis*-2,3-bis(3,4-dimethoxybenzyl)butyrolactone **6** via desymmetrization of *meso*-2,3-dibenzylbutanedioic acid anhydride by reaction with (+)-α-methylbenzylamine (d.e. 86%). We report here the synthesis of both enantiomers of *cis*-2,3-bis(3,4-dimethoxybenzyl)butyrolactone **6** via enzymatic desymmetrization (transesterifications) of *meso*-2,3-bis(3,4-dimethoxybenzyl)butanediol **2** and the corresponding diacetate **4**.

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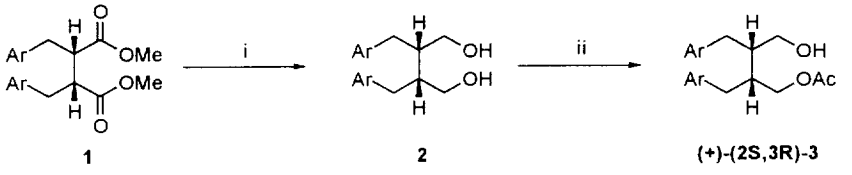
2. Results and discussion

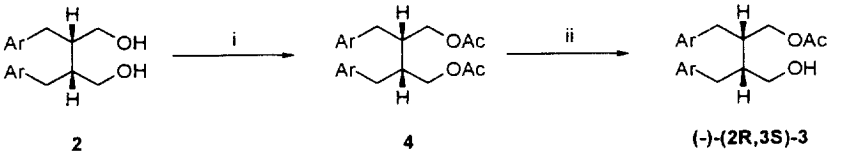
Diester **1** was prepared according to the method of Ward et al.[19] Reduction of diester **1** with lithium aluminum hydride gave the *meso*-diol **2** in 98% yield (Scheme 1). Diol **2** was subjected to the enzyme catalyzed esterification by treatment with *Candida antarctica* lipase (CAL) in benzene using vinyl acetate as acyl donor to give the optically active monoester (+)-(2*S*,3*R*)-**3** in 74% yield. The enantiomeric composition of **3** was measured by ^{19}F NMR (282 MHz) analysis of the corresponding (+)-α-methoxy-α-trifluoromethyl-α-phenyl acetate (MTPA, Mosher's ester). The enantiomeric excess was determined to be higher than 98%. The absolute configuration of monoester **3** (2*S*,3*R*; $[\alpha]_D^{23}$=+2.88 (c 2.3, $CHCl_3$)) was determined by correlation with lactone **6** of known absolute configuration.



(Ar = 3,4-dimethoxyphenyl in this and subsequent schemes)

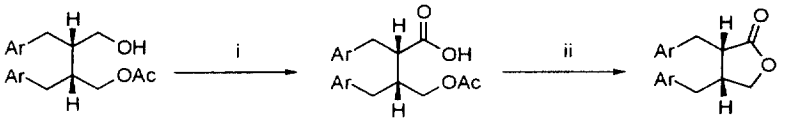
Scheme 1. Reagents: (i) $LiAlH_4$, CH_2Cl_2:ether (3:2), r.t., 98%; (ii) *Candida antartica* lipase, vinyl acetate, benzene, r.t., 74%, ee>98%

The synthesis of the opposite enantiomer, (−)-(2*R*,3*S*)-**3**, is reported in Scheme 2. Diol **2** was acetylated by acetic anhydride in pyridine in the presence of DMAP to give *meso*-diacetate **4** in 96% yield. Transesterification of diacetate **4** by treatment with ethanol in the presence of CAL in diisopropyl ether/benzene provided (−)-(2*R*,3*S*)-**3** in 80% yield ($[\alpha]_D^{25}$=−2.95 (c 2.7, $CHCl_3$)). The enantiomeric excess was determined to be higher than 98% (Mosher's ester as above).



Scheme 2. Reagents: (i) Acetic anhydride, 4-DMAP, pyridine, r.t., 96%; (ii) *Candida antartica* lipase, EtOH, isopropyl ether:benzene (5:2), 80%, ee>98%

Both enantiomers of *cis*-2,3-bis(3,4-dimethoxybenzyl)butyrolactone **6** were synthesized from monoesters (−)-(**3**) and (+)-(**3**). Alcohol (+)-(2*S*,3*R*)-**3** was oxidized with pyridinium dichromate in DMF to yield acid (+)-(2*R*,3*S*)-**5** in 60% yield which upon treatment with 5 N HCl and *p*-toluenesulfonic acid in benzene gave lactone (+)-(2*R*,3*S*)-**6** of known absolute configuration in 80% yield ($[\alpha]_D^{25}$=+75.33 (c 1.16, CH_2Cl_2); lit.[19] $[\alpha]_D^{21}$=+32.3 (c 1.434, CH_2Cl_2). The same reaction sequence applied to alcohol (−)-(2*R*,3*S*)-**3** provided lactone (−)-(2*S*,3*R*)-**6** ($[\alpha]_D^{21}$=−75.22 (c 1.01, CH_2Cl_2)) (Scheme 3). The enantiomeric composition of acid **5** was measured by reaction with (*S*)-(+)-1-(1-naphthyl)ethyl amine in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) followed by ^1H NMR (300 MHz) analysis of the resulting diastereoisomeric amides (ee ≥98%).



Scheme 3. Reagents: (i) PDC, DMF, r.t., 60%; (ii) *p*-TsOH, 5 N HCl, toluene, reflux, 80%

3. Experimental section

NMR spectra were recorded in $CDCl_3$ solutions at 300 MHz (^1H), 282 MHz (^{19}F), 75 MHz (^{13}C) on a Bruker AC-300 instrument. Optical rotation values were obtained from a JASCO DIP-300 polarimeter. Infrared spectra were recorded on Perkin–Elmer 781 spectrometer. Melting points were recorded on a Thomas Hoover 6427-H10 melting point apparatus, and are uncorrected. *Candida antarctica* lipase was a gift from Novo Nordisk. Column purifications were conducted by flash chromatography in silica gel 60 (230–400 mesh, adsorbant to compound ratio ~50).

3.1. *Preparation of* meso-*2,3-bis(3,4-dimethoxybenzyl) butanediol (2)*

The diester **1** (2.16 g, 4.84 mmol) was dissolved in CH_2Cl_2 (30 mL) and diethyl ether (20 mL). The solution was cooled to 0°C and $LiAlH_4$ (809 mg, 2.32 mmol) was added slowly. The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with a 3 N HCl solution, diluted with water and extracted with CH_2Cl_2 (3×100 mL). The combined extracts were dried (Na_2CO_3) and the solvent was evaporated to give a crude product purified by flash chromatography (EtOAc) to give a white solid (1.854 mg, 98%) (m.p.: 90–92°C). IR (neat): 3250 (OH), 1590 and 1520 (C=C), 1260 (Ar–O), 1030 (C–OH), 860 (=C–H); ^1H NMR ($CDCl_3$): 2.02 (m, 2H, H-2 and H-3), 2.53 (dd, J=6.27, J=13.75, 2H, H-5 and H-6), 2.67 (dd, J=9.23, J=13.75, 2H, H-5 and H-6), 3.50 (dd, J=2.77, J=11.00, 2H, H-1 and H-4), 3.59 (dd, J=6.83, J=11.00, 2H, H-1 and H-4), 3.82 and 3.83 (s, 12H, OCH_3), 6.67 (s, 2H, H-2N and H-2O), 6.71 (dd, J=1.71, J=9.00, 2H, H-6N and H-6O), 6.77 (d, J=9.00, 2H, H-5N and H-5O); ^{13}C NMR ($CDCl_3$): 33.2 (C-2, C-3), 44.9 (C-5, C-6), 55.7 and 55.8 (OCH_3), 63.1 (C-1, C-4), 111.1 (C-5N, C-5O), 12.1 (C-2N, C-2O), 120.9 (C-6N, C-6O), 132.9 (C-1N, C-1O), 147.3 (C-3N, C-3O), 148.8 (C-4N, C-4O). HRMS (EI) calcd for $C_{22}H_{30}O_6$ (M^+) 390.2042, found 390.2048.

3.2. *Preparation of* meso-*2,3-bis(3,4-dimethoxybenzyl)butyl diacetate (4)*

The diol **2** (244 mg, 625 μmol) was dissolved in pyridine (20 mL) under nitrogen. Acetic anhydride (1.00 mL, 10.6 mmol) and 4-dimethylaminopyridine (9 mg) were added and the mixture was stirred overnight. The mixture was diluted with AcOEt (100 mL) and successively washed with 3 N HCl (3×40 mL), aq. $NaHCO_3$ (3×40 mL) and brine (3×4 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt:hexanes, 11:9) to give a white solid (284 mg, 96%) (m.p.: 95–96°C). IR (neat): 1740 (C=O), 1590 and 1520 (C=C), 1250 (Ar–O), 1150 (C–O–C), 850 (=C–H); ^1H NMR: 2.02 (s, 3H, CH_3COO), 2.21 (m, 2H, H-2 and H-3), 2.56 (dd, J=8.65, J=13.90, 2H, H-5 and H-6), 2.72 (dd, J=6.10, J=13.90, 2H, H-5 and H-6), 3.82 and 3.83 (s, 12H, OCH_3), 4.06 (m, 4H, H-1 and H-4), 6.59 (s, 2H, H-2N and H-2O), 6.66 (d, J=8.14, 2H, H-6N and H-6O), 6.76 (d, J=8.14, 2H, H-5N and H-5O); ^{13}C NMR: 20.8 (CH_3COO), 33.8 (C-2 and C-3), 39.5 (C-5 and C-6), 55.7 and 55.8 (OCH_3), 64.8 (C-1 and C-4), 111.1

(C-5N and C-5O), 111.8 (C-2N and C-2O), 120.8 (C-6N and C-6O), 132.1 (C-1N and C-1O), 147.4 (C-3N and C-3O), 148.8 (C-4N and C-4O), 170.8 (CH_3COO). HRMS (EI) calcd for $C_{26}H_{34}O_8$ (M^+) 474.2253, found 474.2259.

3.3. Preparation of (+)-(2S,3R)-2,3-bis(3,4-dimethoxybenzyl)-4-hydroxybutyl acetate (3)

A solution of diol **2** (197.1 mg, 505.1 μmol) in benzene (50 mL) containing *Candida antarctica* lipase (30.3 mg) and vinyl acetate (240 μL, 2.53 mmol) was stirred for 23 h at room temperature. The mixture was filtered and the solvent was evaporated. The residue was purified by flash chromatography (EtOAc:hexanes, 7:3) to yield the monoacetate (+)-**3** (162 mg, 74%) as a viscous colorless oil. $[\alpha]_D^{23}$=+2.88 (2.3, $CHCl_3$); IR (film): 3500 (OH), 1740 (C=O), 1590–1510 (C=C), 1260 (Ar–O), 1240 (C(=O)–O–C), 1160–1140 (C–O–C), 1030 (C–OH); ^{1}H NMR ($CDCl_3$): 1.83 (s, 1H, OH), 1.99 (s, 3H, CH_3COO), 2.01 (m, 1H, H-3), 2.27 (m, 1H, H-2), 2.47–2.74 (m, 4H, H-5 and H-6), 3.57 (m, 2H, H-4), 3.78, 3.79, 3.81 (s, 12H, OCH_3), 3.98 (dd, J=11.19, J=5.82, 1H, H-1), 4.19 (dd, J=11.19, J=6.25, 1H, H-1), 6.60–6.76 (m, 6H, aromatics); ^{13}C NMR ($CDCl_3$): 20.9 (CH_3COO), 33.4 (C-3), 34.3 (C-2), 39.6 (C-5), 42.8 (C-6), 55.7, 55.8 (O–CH_3), 63.2 (C-4), 65.1 (C-1), 111.1 (C-5N, C-5O), 111.9 (C-2N, C-2O), 120.7, 120.8 (C-6N, C-6O), 132.5, 132.9 (C-1N, C-1O), 147.3 (C-3N, C-3O), 148.8 (C-4N, C-4O), 171.1 (CH_3COO). HRMS (EI) calcd for $C_{24}H_{32}O_7$ (M^+) 432.2148, found 432.2141.

3.4. Preparation of (−)-(2R,3S)-2,3-bis(3,4-dimethoxybenzyl)-4-hydroxybutyl acetate (3)

A solution of diacetate **4** (56 mg, 129 μmol) in isopropylether (5 mL) and benzene (2 mL) containing *Candida antarctica* lipase (50 mg) and ethanol 95% (30 μL, 511 μmol) was stirred for 23 h at room temperature. The mixture was filtered and the solvent was evaporated. The residue was purified by flash chromatography (EtOAc:hexanes, 7:3) to yield the hydroxyacetate (−)-**3** (46.9 mg, 80%) as a viscous colorless oil. $[\alpha]_D^{25}$=−2.95 (2.7, $CHCl_3$).

3.5. Preparation of (−)-(2S,3R)- and (+)-(2R,3S)-4-acetyloxy-2,3-bis(3,4-dimethoxybenzyl)butanoic acid (5)

A solution of monoacetate (−)-**3** (143 mg, 331 μmol in N,N-dimethylformamide (1.2 mL) and pyridinium dichromate (435 mg, 1.16 mmol) was stirred for 18 h under dry nitrogen. Then one equivalent of PDC was added 3 times at 18 h intervals. The reaction mixture was diluted with water (pH=3) (12 mL) and extracted with EtOAc (3×50 mL). The combined extracts were dried (Na_2CO_3) and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc:hexanes:AcOH, 50:49:1) to give an oil (85.5 mg, 58%). (−)-**5** $[\alpha]_D^{23}$=−8.99 (1.1, CH_2Cl_2); (+)-**5** $[\alpha]_D^{23}$=+8.22 (3.16, CH_2Cl_2); IR (neat): 3100 (OH), 1740 (C=O), 1590–1510 (C=C), 1260 (Ar–O), 1240 (C(=O)–O–C), 1160–1140 (C–O–C), 1030 (C–OH); ^{1}H NMR ($CDCl_3$): 1.99 (s, 3H, CH_3COO), 2.40 (m, 1H, H-3), 2.61 (dd, J=14.15, J=9.09, 1H, H-6), 2.76 (dd, J=14.15, J=6.06, 1H, H-6), 2.84–2.98 (m, 3H, H-2 and H-5), 3.81, 3.82, 3.83, 3.84 (s, 12H, OCH_3), 4.08 (d, J=5.64, 2H, H-4), 6.64–6.79 (m, 6H, aromatics); ^{13}C NMR ($CDCl_3$): 20.6 (CH_3COO), 33.4 (C-3), 34.2 (C-2), 41.0 (C-6), 47.6 (C-5), 55.6, 55.7, 55.8 (O–CH_3), 63.6 (C-4), 111.1 (C-5N, C-5O), 111.9 (C-2N, C-2O), 120.7, 120.9 (C-6N, C-6O), 131.3 (C-1N, C-1O), 147.5 (C-3N, C-3O), 148.8 (C-4N, C-4O), 170.7 (CH_3COO), 179.9 (C-1). HRMS (EI) calcd for $C_{24}H_{26}O_6$ (M^+) 446.1941, found 446.1951.

3.6. Preparation of (−)-(2S,3R)- and (+)-(2R,3S)-2,3-bis(3,4-dimethoxybenzyl)butyrolactone (6)

The acid (−)-**5** (80 mg, 179 μmol) was dissolved in toluene (10 mL) containing *p*-toluenesulfonic acid (20 mg) in the presence of 5 N HCl (2.5 mL). The mixture was heated under reflux for 6 h. The reaction mixture was diluted in EtOAc, washed successively with aq. $NaHCO_3$ (3×50 mL) and brine (3×50 mL). The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (CH_2Cl_2:acetone, 49:1) and recrystallization in diethyl ether gave a white solid (55.8 mg, 80%). (−)-**6** $[\alpha]_D^{23}=-75.22$ (1.01, CH_2Cl_2), m.p.: 108–109°C; (+)-**6** $[\alpha]_D^{25}=+75.33$ (1.16, CH_2Cl_2), m.p.=111–112°C; lit.[19] $[\alpha]_D^{21}=+32.3$ (c 1.434, CH_2Cl_2), oil. IR (neat): 1770 (C=O), 1590–1510 (C=C), 1260 (Ar–O), 1230 (C(=O)–O–C), 1160–1140 (C–O–C); ^{1}H NMR ($CDCl_3$): 2.26 (dd, J=13.07, J=12.80, 1H, H-6), 2.56–2.63 (m, 1H, H-3), 2.71 (dd, J=14.74, J=10.43, 1H, H-5), 2.89 (dd, J=12.80, J=4.05, 1H, H-6), 3.01 (ddd, J=10.43, J=6.99, J=4.72, 1H, H-2), 3.19 (dd, J=14.79, J=4.72, 1H, H-5), 3.74, 3.77, 3.81, 3.82 (s, 12H, OCH_3), 3.97 (dd, J=13.12, J=8.92, 2H, H-4), 6.41–6.78 (m, 6H aromatics); ^{13}C NMR ($CDCl_3$): 30.4 (C-6), 32.5 (C-5), 40.0 (C-3), 45.3 (C-2), 55.8 (O–CH_3), 69.4 (C-4), 111.3, 111.4 (C-5N, C-5O), 111.7, 111.9 (C-2N, C-2O), 120.3, 120.7 (C-6N, C-6O), 130.7, 131.0 (C-1N, C-1O), 147.7 (C-3N, C-3O), 149.0 (C-4N, C-4O), 177.8 (C-1). HRMS (CI, NH_3) calcd for $C_{22}H_{26}O_6$ (M^+) 386.1729, found 386.1722.

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