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Asymmetric synthesis of γ-butyrolactones by enantioselective hydrogenation of butenolides

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Abstract—Some optically active γ-butyrolactones derivatives, useful building blocks for the synthesis of several natural products, have been obtained by a convenient procedure using catalytic asymmetric hydrogenation. 3,4-Disubstituted γ-butyrolactones were obtained in good yields and in high enantiomeric excess through the enantioselective hydrogenation of the corresponding butenolides catalyzed by BINAP-Rh or Ru complexes.

1. Introduction

Functionalized chiral γ-butyrolactones are important subunits present in a large variety of natural products and biologically active compounds, such as alkaloids, lignan lactones and sex attractant insect pheromones.[1] The very attractive biological properties of these compounds prompted us to develop a program for the synthesis of several versatile compounds containing the γ-butyrolactone unit and for their utilization as therapeutic agents. Recently, we described a new synthetic method which could be generally applicable to the preparation of racemic hydroxy-lactones, as well as α,α-disubstituted β-methylene-γ-butyrolactones and butenolides.[2] Enantioselective hydrogenation of various olefinic substrates catalyzed by BINAP-Rh or Ru complexes has been shown to be one of the most efficient methods for preparing several kinds of chiral biologically active molecules.[3] We decided to extend this asymmetric reduction process to the preparation of the optically active γ-butyrolactones derivatives and herein we describe a convenient procedure to prepare chiral non-racemic γ-butyrolactones, from the corresponding butenolides, using catalytic enantioselective hydrogenation as a key reaction.

2. Results and discussion

Racemic 4-(hydroxymethyl)-3-phenyldihydrofuran-2(3*H*)-one **2**, an important intermediate for the antibacterial penicillanic acid derivatives,[4] can be easily prepared from commercial α-bromophenyl acetic acid **1** in three steps with 70% overall yield.[2] Protection of the hydroxyl group of **2** with chloromethyl methyl ether[5] afforded compound **3** in 91% yield, which on treatment with LDA, phenylselenenyl chloride[6] and H_2O_2 produced butenolide **4**, in 82% yield (Scheme 1).

The asymmetric catalytic hydrogenation of the butenolide **4** to form γ-butyrolactone **5**, was carried out in the presence of the chiral complexes BINAP-Rh or Ru (molar ratio substrate:catalyst = 100:1) in methanol by treatment with H_2 (50 atm) at room temperature. The substrate conversion reached a fairly good value (64–75%) with the BINAP-Rh complexes but did not exceed 46% when the Ru catalyst was used (see Table 1). Since a tetra-substituted olefin is usually reluctant to undergo catalytic hydrogenation,[7] these results can be considered satisfactory. The yield (see note on Table 1) of the desired γ-butyrolactone **5** was very high (96–98%) in all cases. Hydrogenolysis products in varying ratio have been observed in the hydrogenation reactions of butenolides containing an unprotected allylic hydroxyl group.[8] No hydrogenolysis product, however, was detected in the hydrogenation of **4**. The hydrogenation

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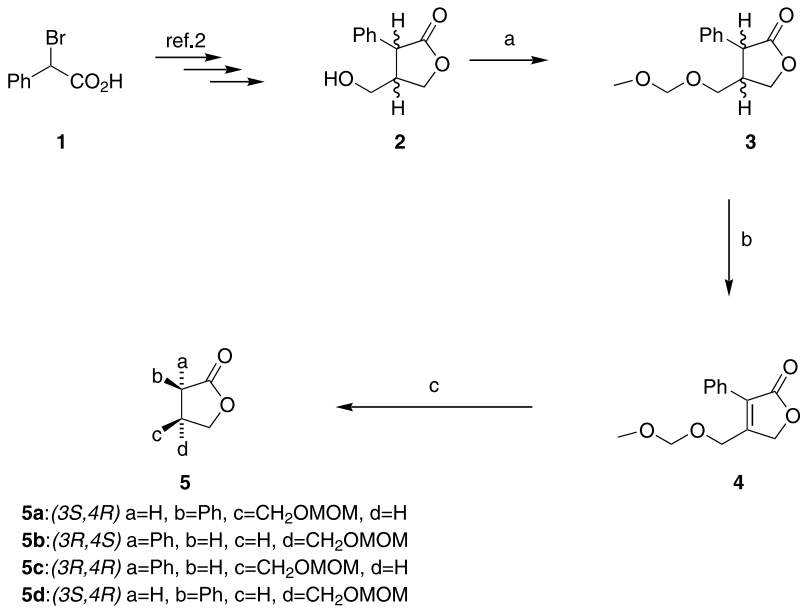


Scheme 1. Enantioselective synthesis of γ-butyrolactone **5**. *Reagents and reaction conditions*: (a) MOMCl, DPEA, CH_2Cl_2, rt, 12 h, 91%; (b) LDA, PhSeCl, THF, −78°C, 4 h, then H_2O_2, rt, 82%; (c) H_2 (50 atm), chiral catalyst, MeOH, rt, 72–80 h (see Table 1).

Table 1. Enantioselective hydrogenation of butenolide **4** to γ-butyrolactone **5** using ruthenium and rhodium chiral catalyst

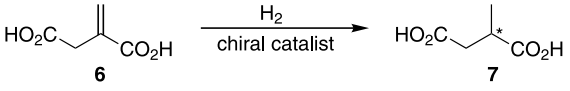
Entry	Catalyst[a]	Reaction time (h)	Conversion[b] of butenolide **4** (%)	Yield[c] of **5** (%)	γ-Butyrolactone **5**					
					5a (%)	**5b** (%)	**5** (**c** or **d**) (%)	**5** (**d** or **c**) (%)	% Ee[d]	$[\alpha]_D^{25}$ (MeOH)
1	A	80	46	97	5.4	75.0	1.6	18.0	87	+5.3 (*c* 0.5)
2	B	72	64	96	0.9	92.0	1.4	5.7	98	+5.8 (*c* 0.5)
3	C	72	75	98	90.8	0.7	6.3	2.2	98.5	−7.3 (*c* 0.5)

[a] A = [(*R*)-(+)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)ruthenium chloride. B = [(*R*)-(+)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl](1,5-cyclooctadiene)rhodium(I) perchlorate:THF complex (1:1). C = [(*S*)-(−)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl](1,5-cyclooctadiene)rhodium(I) perchlorate: THF complex (1:1).

[b] Conversion determined by gas chromatography (GLC) of the crude reaction mixture.

[c] Isolated yield calculated based on the amount of butenolide actually transformed.

[d] Enantiomeric excess (% ee) were evaluated by HPLC analysis using a Chiralcel OJ® column.



Scheme 2. Enantioselective hydrogenation of itaconic acid **6**.

of butenolide **4** produces a higher proportion of the *cis*-γ-butyrolactones **5** (**5a**+**5b**). In fact, a (91.5–92.9):(7.1–8.5) ratio of *cis* (**5a**+**5b**) to *trans* (**5c**+**5d**) isomers was produced with Rh catalysts, while a 80.4:19.6 ratio of *cis* to *trans* isomers was obtained with the Ru catalyst. Moreover, the enantiomeric excess is higher (∼98% ee) for the Rh catalysts than for Ru (87% ee).

For comparative purposes the itaconic acid **6** was submitted to the asymmetric hydrogenation (Scheme 2) with the same types of catalysts, under the conditions shown in Table 2. Comparison of the specific rotation of the products with data reported in the literature,[9] demonstrated that the asymmetric Rh catalysts show higher enantioselectivity than the Ru catalyst, even when a di-substituted olefin such as the itaconic acid was used as a substrate.

3. Experimental

Melting points were determined on a Reichert Kofler block melting point apparatus and are uncorrected. NMR spectra were measured using a Bruker DPX-300

Table 2. Enantioselective hydrogenation[a] of itaconic acid **6** using ruthenium and rhodium chiral catalyst

Entry	Catalyst[b]	Reaction time (h)	Conversion[c] of **6** (%)	Yield[d] of **7** (%)	% Ee[e]	$[\alpha]_D^{25}$ (EtOH)	Config.
1	B	2	100	95	97	+16.4 (*c* 15.2)	*R*
2	C	2	100	95	94	−15.9 (*c* 14.5)	*S*
3	D	2	98	92	85	−14.4 (*c* 15.7)	*S*
4	E	2	95	88	96	+16.2 (*c* 12.8)	*R*

[a] All these hydrogenations were carried out under 18 atm of H_2.

[b] Catalysts: B = [(*R*)-(+)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl](1,5-cyclooctadiene)rhodium(I) perchlorate: THF complex (1:1). C = [(*S*)-(−)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl](1,5-cyclooctadiene)rhodium(I) perchlorate: THF complex (1:1). D = [(*S*)-(−)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)ruthenium chloride. E = (+)-1,2-Bis[(*2S*, *5S*)-2,5-diethylphospholano]benzene (cyclooctadiene)rhodium (I) trifluoromethanesulfonate.

[c] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture.

[d] Isolated yield calculated based on the amount of substrate actually transformed.

[e] Based on the values for enantiomerically pure (*R*)-(+)-7, $[\alpha]_D^{20} = +16.9$ (*c* 2.2, EtOH).[9]

(300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR) instrument. GC-MS spectra were obtained by EI ionization at 70 eV on a HP-5988-A spectrometer. IR spectra were measured with a Perkin–Elmer 1600 FT spectrometer. Analytical gas chromatography (GLC) separations were performed on a Varian GC 3400 instrument with a fused silica capillary column (30 m length×0.25 mm i.d.) coated with DB-1701 (phase thickness 0.25 μm) operating at temperatures in the range 50–200°C. HPLC analysis was performed with a Shimadzu instrument consisting of a model LC-10AS solvent pump, a model 7125 Rheodyne injector with a 20 μL loop, a model SPD-10A UV detector (254 nm), and a model CR6-A integrator. The enantiomers were separated using a 10 μm Chiralcel OJ® column (4.6×250 mm) and a mobile phase consisting of *n*-hexane:isopropyl alcohol (9:1, v/v), at a flow rate of 1 mL/min. Optical rotation was measured with a Schmidt+Haensch model Polartronic HH8 polarimeter. TLC was performed on precoated silica gel 60 F254 (0.25 mm thick, Merck), and for column chromatography silica gel 60 70–230 mesh (Merck) was used. Given yields correspond to materials with the same purity as the samples used in the subsequent steps.

(*R*)-(+)- and [(*S*)-(−)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl](1,5-cyclooctadiene)rhodium(I) perchlorate: tetrahydrofuran complex (1:1), and [(*R*)-(+)-2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)-ruthenium chloride were purchased from Aldrich. (+)-1,2-Bis[(*2S*,*5S*)-2,5-diethylphospholano]benzene (cyclooctadiene)rhodium(I) trifluoromethanesulfonate was purchased from Strem Chemicals.

3.1. 4-[(Methoxymethoxy)methyl]-3-phenyldihydrofuran-2(3*H*)-one 3

To a solution of compound **2** (1.00 g, 5.20 mmol) in anhydrous dichloromethane (10 mL), maintained under a nitrogen atmosphere and cooled to 0°C, was added chloromethylmethylether (0.44 mL, 5.40 mmol) and *N*,*N*,*N*-diisopropylethylamine (0.73 g, 5.70 mmol). The reaction mixture was stirred at 0°C for 1 h and at room temperature for 12 h. The organic solution was washed with saturated sodium bicarbonate solution, saturated brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography through silica gel, eluting with ethyl acetate/hexane (1:1) to give compound **3**. Yield 1.10 g (4.73 mmol, 91%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 4.65 (s, 2H), 4.55 (dd, $J_1 = 9.04$ Hz, $J_2 = 7.91$ Hz, 1H), 4.20 (t, $J = 9.0$ Hz, 1H), 3.70 (d, $J = 10.2$ Hz, 1H), 3.64 (dd, $J_1 = 10.18$ Hz, $J_2 = 4.14$ Hz, 1H), 3.58 (dd, $J_1 = 10.17$ Hz, $J_2 = 6.03$ Hz, 1H), 3.35 (s, 3H), 2.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.95 (C=O), 135.86–127.84 (aromatics C), 96.68 (OCH_2O), 68.96 (CH_2 ring), 65.81 (CH_2), 55.54 (benzyl C), 48.26 (CH_3), 45.06 (CH); MS *m*/*z* (rel. intensity) 191 (12) (M^+–45), 161 (20), 117 (98), 91 (59), 77 (22), 32 (100).

3.2. 4-[(Methoxymethoxy)methyl]-3-phenylfuran-2(5*H*)-one 4

To a solution of *N*,*N*-diisopropylamine (0.68 mL, 4.86 mmol) in anhydrous THF (5 mL), maintained at 0°C under a nitrogen atmosphere, was added a solution of *n*-butyllithium in *n*-hexane (4.65 mmol). After stirring for 20 min at 0°C, the solution was cooled to −78°C and a solution of compound **3** (1.00 g, 4.23 mmol) in anhydrous THF (2 mL) was added. Stirring was continued for 30 min, and then a solution of phenylselenenyl chloride (0.81 g, 4.23 mmol) in THF (2 mL) was added. After stirring for 4 h at −78°C, the reaction mixture was quenched by addition of water and extracted with ether. The ethereal solution was washed with water, dried over $MgSO_4$ and evaporated.

The crude residue obtained (1.48 g) was diluted with dichloromethane (10 mL), and stirred at 0°C with 30% aqueous H_2O_2 (2 mL) for 2 h. After separation, the aqueous solution was extracted with dichloromethane. The organic solution was washed with saturated brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography through silica gel, eluting with ethyl acetate/hexane (1:1) to give compound **4** as a white crystalline solid: mp 45–48°C. Yield 0.81 g (3.47 mmol, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 5.00 (s, 2H), 4.70 (s, 4H), 3.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.83 (C=O), 157.59 (benzyl C), 126.81 (C olefinic), 129.34–129.01 (aromatics C), 96.05 (OCH_2O), 70.34 (CH_2

ring), 62.88 (CH_2), 55.68 (CH_3); MS m/z (rel. intensity) 172 (54) (M^+–62), 144 (7), 117 (10), 77 (6), 45 (100). Anal. calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.84; H, 6.13.

3.3. General procedure for the enantioselective hydrogenation reaction

In a stainless steel 150 mL pressure reactor were placed 100 mg ($\sim$0.4 mmol) of solid butenolide **4** (or $\sim$2.0 mmol of the itaconic acid) and 1 mol% of the catalytic complex. The reactor was purged with argon, evacuated to 30 mmHg and 5 mL of anhydrous methanol (previously distilled under argon atmosphere) was introduced by suction.

The vessel was purged with hydrogen, pressurized with hydrogen (at 50 atm for butenolide **4** and at 18 atm for itaconic acid) and stirred at room temperature. After the reaction was completed, the reaction mixture was filtered through a short-path column (8 cm) containing silica gel (230–400 mesh) to remove the catalyst. The solvent was evaporated and the residue was analyzed by gas chromatography or ^{1}H NMR to determine the conversion, and by HPLC to determine the enantiomeric excess. The ^{1}H and ^{13}C NMR spectra and mass spectra were consistent with the structure of desired products. For analytical purposes a small sample compound **5** was purified by column chromatography through silica gel, eluting with hexane/ethyl ether (7:3). Analytical data for the major (3*R*,4*S*) stereoisomer **5b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (m, 5H), 4.60 (s, 2H), 4.49 (dd, $J_1=9.04$ Hz, $J_2=6.50$ Hz, 1H), 4.45 (dd, $J_1=6.78$ Hz, $J_2=6.03$ Hz, 1H), 4.43 (dd, $J_1=6.78$ Hz, $J_2=6.03$ Hz, 1H), 4.32 (dd, $J_1=9.05$ Hz, $J_2=6.50$ Hz, 1H), 4.05 (d, $J=8.67$ Hz, 1H), 3.3 (s, 3H), 3.0 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.95 (C=O), 135.86–127.84 (aromatics C), 96.68 (OCH_2O), 68.96 (CH_2 ring), 65.81 (OCH_3), 55.54 (CH_2OR), 48.26 (benzyl C), 45.06 (CH ring); MS m/z (rel. intensity) 236 (11) (M^+), 205 (7), 175 (17), 117 (21), 91 (20), 75 (5), 45 (100). Anal. calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.96; H, 6.74.

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