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Short communication

Enantioselective hydrogenation of 4-(hydroxymethyl) furan-2(5*H*)-one derivatives

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Abstract

Some optically active β-hydroxymethyl-γ-butyrolactone derivatives, useful building blocks for the synthesis of several natural products and biologically active compounds, were obtained in good yields and variable optical purity (2–100% e.e.) from the corresponding 4-(hydroxymethyl)furan-2(5*H*)-one by enantioselective hydrogenation with chiral ruthenium or rhodium BINAP complexes.

Keywords: BINAP; Catalysis; Catalytic hydrogenation; Enantioselective hydrogenation; Unsaturated lactones

1. Introduction

Functionalized γ-butyrolactones (Fig. 1) are important subunits present in a wide variety of natural products and biologically active compounds [1]. Nevertheless, the optically active butyrolactones are not readily accessible [2]. On the other hand, furan-2(5*H*)-ones (butenolides) are more easily available and several of its derivatives are versatile building blocks for natural products syntheses because they serve as a valuable platform for various diastereoselective transformations [3]. The enantioselective hydrogenation of various olefinic substrates catalyzed by chiral BINAP complexes is an efficient method for preparing several chiral, and biologically active molecules [4]. Thus, this asymmetric reduction process can be used as a convenient procedure to prepare chiral non-racemic γ-butyrolactones from the corresponding furanone derivatives [5].

In this paper, we report the enantioselective hydrogenation of 4-(hydroxymethyl)furan-2-one derivatives with chiral BINAP ruthenium or rhodium complexes, in order to obtain optically active γ-butyrolactone derivatives (**1**) with high enantioselectivity. Our main purpose is to demonstrate that lactones bearing an endocyclic C=C double bond and a functionalized substituent group can be hydrogenated with high enantioselectivity.

2. Experimental

2.1. Materials and methods

NMR spectra were recorded on a Bruker DRX-400 (400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR) instrument. IR spectra were recorded on a Perkin-Elmer Spectrum RX IFTIR spectrometer. GC–MS analyses were performed by EI ionization at 70 eV on a Shimadzu model QP-2010 spectrometer. HRMS were recorded on a VG AutoSpec. 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, operating at temperatures in the range 50–200 °C. Chiral GLC was performed in a HP 5890 instrument using an heptakis-(2,6-di-*O*-methyl-3-*O*-phenyl)-β-cyclodextrin column (20% in OV 1701, w/w, 25 m length × 0.25 mm i.d.). HPLC analyses were 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 (206, 215 or 254 nm), and a model CR6-A integrator. The enantiomers were separated

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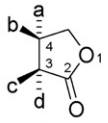


1

1a: (*4S*) a = H, b = CH_2OAc, c = d = H
1b: (*4R*) a = CH_2OAc, b = c = d = H
1c: (*4R*) a = CH_2OH, b = c = d = H
1d: (*4S*) a = H, b = CH_2OH, c = d = H
1e: (*4S*) a = H, b = CH_2OBn, c = d = H
1f: (*4R*) a = CH_2OBn, b = c = d = H
1g: (*4R*) a = CH_2OMOM, b = c = d = H
1h: (*4R*) a = H, b = CH_2O-(+)-menthyl formate, c = d = H
1i: (*3S,4R*) a = CH_2OMOM, b = c = H, d = Ph

Fig. 1. Structures of β-hydroxymethyl-γ-butyrolactone derivatives.

using Chiralpak® AD and Chiralpak® AS columns, and mobile phases consisting of *n*-hexane:ethyl alcohol (90:10, v/v) or *n*-hexane:isopropyl alcohol (85:15, v/v), at a flow rate of 1 mL/min. Optical rotation was measured with a Schmidt + Haensch model Polartronic HH8 polarimeter and a Jasco model DM-370 polarimeter.

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

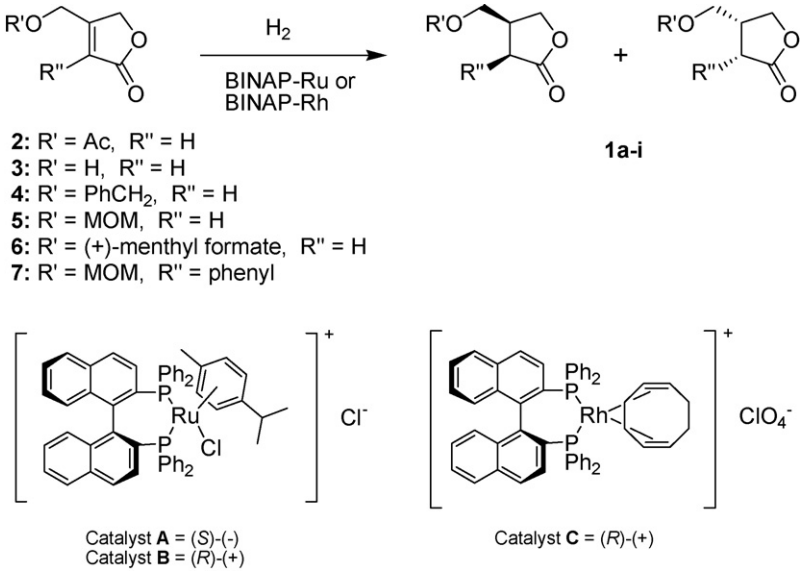
2.2. General procedure for the enantioselective hydrogenation reactions

In a stainless steel 150-mL pressure reactor were placed 30 mg of furanones **2**–**6**, and 1 mol% of the Rh or Ru catalytic complex. The reactor was purged with argon and evacuated to 30 mmHg, and then 4 mL of anhydrous methanol (previously distilled under argon atmosphere) was introduced by suction. The vessel was purged with hydrogen and pressurized with hydrogen at 80 atm. The reaction mixture was stirred at room temperature (or at 50 °C) until hydrogen consumption ceased. After reaction completion, 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 ^{1}H NMR to determine the conversion, and by chiral GLC or chiral HPLC to determine the enantiomeric excess. The IR, ^{1}H and ^{13}C NMR, and mass spectra were consistent with the structure of the desired products.

3. Results and discussion

The 4-[(acetoxy)methyl]furan-2(5*H*)-one (**2**) and 4-(hydroxymethyl)furan-2(5*H*)-one (**3**) were easily prepared from 4-(bromomethyl)furan-2(5*H*)-one according to published procedures [6]. The reaction of **3** with benzyl trichloroacetimidate under acidic conditions (5 mol% trifluoromethanesulfonic acid) produced 4-[(benzyloxy)methyl]-furan-2(5*H*)-one (**4**) in 79% yield [7]. The protection of the hydroxyl group of compound **3** with MOM was performed by reaction with chloromethyl methyl ether and *N*,*N*-diisopropylethylamine (DPEA) [5,8], furnishing compound **5** in 70% yield. The hydroxymethylfuranone **3** was also reacted with (+)-(1*S*,2*R*,5*S*)-menthyl chloroformate in anhydrous pyridine and dichloromethane [9] to give 53% yield of the useful chiral compound **6** (80% d.e.). On the other hand, the di-substituted compound **7** was prepared from the commercial α-bromophenyl acetic acid, as described previously [5].

The enantioselective catalytic hydrogenation of the unsaturated compounds **2**–**7**, to produce the γ-butyrolactone derivatives **1** (Scheme 1), was carried out in the presence of the chiral complexes of BINAP-Rh or BINAP-Ru (molar ratio substrate:catalyst = 100:1) in methanol, by treatment with hydrogen (80 atm) at two different temperatures (25 or 50 °C). Among the several solvents tested, methanol was the best for the hydrogenation of these substrates. The higher reaction temperature



Scheme 1. Enantioselective hydrogenation of 4-(hydroxymethyl)furanone derivatives with BINAP complexes.

Table 1
Enantioselective hydrogenation of 4-(hydroxymethyl)furanone derivatives using ruthenium or rhodium chiral catalysts, via Scheme 1

Entry	Substrate	Catalyst[a]	Reaction time (h)	Reaction temperature (°C)	Conversion of butenolide[b] (%)	γ-Butyrolactone **1**			
						Product	Yield[c] (%)	% e.e.	$[\alpha]_D^{25}$[d]
1	**2**	**A** (*S* − Ru)	168	25	35	**1a**	94	100[e]	+33.1 ($CHCl_3$)
2	**2**	**C** (*R* + Rh)	168	25	35	**1a**	70	100[e]	+33.1 ($CHCl_3$)
3	**2**	**B** (*R* + Ru)	168	50	28	**1b**	40	88[e]	−29.1 ($CHCl_3$)
4	**3**	**A** (*S* − Ru)	96	25	50	**1c**	97	8[f]	−3.7 ($CHCl_3$)
5	**3**	**C** (*R* + Rh)	144	25	100	**1d**	84	2[f]	+1.0 ($CHCl_3$)
6	**4**	**A** (*S* − Ru)	168	25	33	**1e**	74	71[e]	+24.3 ($CHCl_3$)
7	**4**	**A** (*S* − Ru)	168	50	66	**1e**	78	75[e]	+25.7 ($CHCl_3$)
8	**4**	**B** (*R* + Ru)	360	50	90	**1f**	80	57[e]	−19.5 ($CHCl_3$)
9	**5**	**B** (*R* + Ru)	168	25	100	**1g**	97	15[g]	−17.5 ($CHCl_3$)
10	**6**	**B** (*R* + Ru)	168	50	100	**1h**	87	100[e]	+38.3 ($CHCl_3$)
11	**7**	**B** (*R* + Ru)	80	25	46	**1i**	80	87[h]	+5.3 (MeOH)
12	**7**	**C** (*R* + Rh)	72	25	64	**1i**	93	98[h]	+5.8 (MeOH)

[a] Catalysts: **A** = [(*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)ruthenium chloride; **B** = [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]chloro(*p*-cymene)ruthenium chloride; **C** = [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl](1,5-cyclooctadiene)rhodium(I) perchlorate:THF complex (1:1).
[b] Conversion determined by ^{1}H NMR of the crude reaction mixture.
[c] Isolated yield based on the amount of substrate actually transformed.
[d] Optical rotations measured with a Schmidt + Haensch model Polartronic HH8 polarimeter and a Jasco model DM-370 polarimeter.
[e] Enantiomeric excess (% e.e.) evaluated by HPLC analysis using a chiral column Chiralpak® AD with UV detector (206 or 225 nm) and *n*-hexane:ethyl alcohol (90:10) as eluent.
[f] Based on the value for optically pure (−)-1 (R = H), $[\alpha]_D^{22}$ −46.3 (ca. 1.22, $CHCl_3$) [12], due to the poor UV detectability of the product.
[g] Enantiomeric excess (% e.e.) evaluated by HPLC analysis using a chiral column Chiralpak® AS with UV detector (215 nm) and *n*-hexane:isopropyl alcohol (85:15) as eluent.
[h] Diastereomeric excess (% d.e.) evaluated by HPLC analysis using a chiral column Chiralcel® OJ with UV detector (254 nm) and *n*-hexane:propan-2-ol (90:10) as eluent.

does not cause substantial loss of enantioselectivity over the range 25–50 °C. Hydrogen pressure influenced reaction rate, but did not affect the enantiomeric excesses of the products. The obtained results are listed in Table 1.

Some of the reactions were not run to complete conversion. The conversion of acetate **2** did not exceed 35% in the presence of the ruthenium or rhodium catalysts, despite the increase in the reaction temperature to 50 °C (entries 1–3, Table 1). The conversion of hydroxymethyl derivative **3** reached 100% with the rhodium catalyst **C** at 25 °C (entry 5, Table 1), but did not exceed 50% when the ruthenium catalyst **A** was used (entry 4, Table 1). A long reaction time and a higher temperature (50 °C) are essential to obtain a good conversion of benzyloxymethyl derivative **4** in the presence of ruthenium catalysts (entries 6–8, Table 1). The total conversion of both MOM-derivative **5** (at 25 °C) and (+)-menthyl formate-derivative **6** (at 50 °C) were obtained with the ruthenium catalyst **B** (entries 9 and 10, Table 1). On the other hand, the conversion of the di-substituted butenolide **7** with 50 atm of H_2 at room temperature, did not exceed 46% with the ruthenium catalyst **B**, but reached a moderate value (64%) when the rhodium catalyst **C** was used (entries 11 and 12, Table 1), presumably due the steric hindrance of the phenyl group. Since a tetra-substituted olefin is usually reluctant to undergo catalytic hydrogenation [4,5b], the later results can be considered reasonable.

The isolated yields of the butyrolactone **1** derivatives were satisfactory (70–97%) in all cases, except for entry 3 (40%) achieved at 50 °C, probably due to decomposition of acetate **2**. The hydrogenolysis products were detected in small ratio only in the hydrogenation reactions of derivative **3** containing an unprotected allylic hydroxyl group [5a]. The products were obtained with a long range of optical purity (2–100% e.e.), which points to the important influence of the protective assemblage present in the allylic hydroxyl group on the enantioselective hydrogenation reaction of unsaturated derivatives.

The stereoselectivity of asymmetric hydrogenation reactions is highly dependent on the relative positions of the C=C bonds and the oxygen functionalities of the substrates [10,11]. Usually high enantioselectivities for hydrogenation of unsaturated compounds catalyzed by BINAP-Ru complexes are obtained only in the case of substrates displaying another functional group at a neighboring position [10]. It is assumed that such reactions process by double chelation control [11], where substrates having exocyclic C=C bonds can form chelate complexes in which the olefinic part and the oxygen functionality are simultaneously coordinated to the ruthenium atom and leads to high enantioface differentiation. In contrast, endocyclic olefins do not form a chelate complex from the standpoint of steric constraints. Thus, hydrogenation via complexes in which only the C=C bond coordinate to the ruthenium atom might result in low enantioselectivities, as demonstrated in several examples in the literature [10,11].

In our case, the results obtained with BINAP complexes of ruthenium or rhodium indicate that the chelation of substrates to the metal center of the catalyst seems to be greatly affected by the kind of substituents at the lactone skeleton. The asymmetric

hydrogenation products obtained from hydroxymethyl derivative **3** catalyzed by both BINAP-Ru and BINAP-Rh complexes show a very poor enantiomeric excess (2–8% e.e., entries 4 and 5, Table 1), certainly because of the intramolecular transesterification induced by the free hydroxyl group. The hydrogenation of the MOM-protected derivative **5** with the ruthenium catalyst **B** renders a product with a poor enantiomeric excess too (15% e.e., entry 9, Table 1), perhaps because the ethereal oxygen of the substituent does not have a good chelating property [11]. The products obtained from benzyl-protected derivative **4** catalyzed by the ruthenium catalysts **A** and **B** present better optical purities (57–75% e.e., entries 6–8, Table 1). Probably, the π electrons of the aromatic ring interact with the metal center of the catalyst, contributing to the increase in the enantioselectivity of the hydrogenation reaction. Nevertheless, the steric hindrance of the benzyl group renders the reaction temperature more elevated and/or the reaction time relatively long to obtain good conversion (entry 8, Table 1). In addition, the hydrogenation of the di-substituted derivative **7** produces a high proportion of the *cis*-γ-butyrolactone **1i** in good diastereomeric excesses (87–98% d.e.), probably due the attractive interaction of the phenyl group. Moreover, the diastereomeric excess is higher for the rhodium catalyst **C** (98% d.e., entry 12, Table 1) than for the ruthenium catalyst **B** (87% d.e., entry 11, Table 1).

On the other hand, in spite of the low conversions, the product obtained from the acetyl-protected derivative **2** in reactions catalyzed by ruthenium or rhodium complexes at 25 °C exhibit excellent optical purity (100% e.e., entries 1 and 2, Table 1). In a similar approach, the hydrogenation of the chiral (+)-menthyl formate-derivative **6** with the ruthenium catalyst **B** affords a γ-butyrolactone in excellent optical purity and with total conversion of the substrate (100% d.e., entry 10, Table 1). These results confirmed the importance of the simultaneous complexation of the metal atom of the asymmetric catalyst to the olefin and to the carbonyl group of the alkyl moiety of substrate.

4. Conclusion

We have thus demonstrated that the stereoselectivity of the catalytic hydrogenation of 4-(hydroxymethyl)furanone derivatives depends highly on the kind of the protective assemblage, and also on the relative positions of the olefin and the oxygen functional group that will form the chelate complexes with the metal center of catalyst. As suggested by the first results obtained from some computational simulations of the hydrogenation catalytic cycle of compounds **2–7** with BINAP-Ru, which are currently under investigation [13], the occurrence of more than a single point of complexation between the substrate and the metal center of the catalytic complex should lead to a decrease in the activation energy to form the key intermediate, and an increase in the catalytic activity, resulting in higher enantioselectivity.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2006.05.066.

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