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Asymmetric hydrogenations of glycoside derived β-ketoesters

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Abstract—The catalytic hydrogenation of β-ketoesters bearing a sugar moiety at C-3 is reported. Hydrogenations in the presence of chiral ruthenium(II) complexes are highly diastereoselective. The hydrogenation stereoselectivity of the ribose derived β-ketoester was controlled by the catalyst. The C-5 substituent of the xylose derived β-ketoester influenced the stereochemical course of the catalytic hydrogenation: the diastereoselectivity was controlled by the substrate if the C-5 substituent is a bulky group.

1. Introduction

Optically active β-hydroxyesters belong to a very important class of compounds, as they are widely used for natural product synthesis. The biological activities of these products are often directly associated with their stereochemistry, thus presenting a challenge for their preparation by stereoselective synthesis. One way to prepare enantiomerically pure β-hydroxyesters consists of the asymmetric hydrogenation of the corresponding β-ketoesters, especially using chiral diphosphine ruthenium(II) complexes.[1–6]

Sugar derived β-ketoesters have been described in the literature as key intermediates for the synthesis of compounds such as polyhydroxylated piperidines,[7] coumarin *C*-glycosyl derivatives,[8] α-diazo-β-ketoesters.[9] Our aim was to develop the synthesis of diastereomerically pure sugar derived β-hydroxyesters from the corresponding β-ketoesters. In the literature, glycoside derived β-hydroxyesters are generally synthesized via an aldol reaction giving mixtures of diastereomers.[10] To our knowledge, the hydrogenation of glycoside derived β-ketoesters in the presence of chiral ruthenium catalysts has never been investigated. Recently we proposed the synthesis of the ribose derived α-amino-β-hydroxyester constituent of the diazepanone core of the liposidomycins.[11] Herein we report the hydrogenation of β-ketoesters bearing a glycosyl moiety at C-3, namely ribo- and xylofuranose.

2. Results and discussion

The β-ketoester derived from the protected ribose **1** was hydrogenated for 24 h at atmospheric pressure in the presence of a freshly prepared ruthenium complex (2% mol),[12] leading to a diastereoisomeric mixture of (*S*)-**2** and (*R*)-**2** (Scheme 1). The use of the (*R*)-Binap-$RuBr_2$ catalyst gave the major (*S*)-**2** in a quantitative yield and with a diastereoisomeric excess of 80% (Table 1, entry 1).

The hydrogenation in the presence of the antipode (*S*)-$BinapRuBr_2$ led to its epimer (*R*)-**2** with a de of 90% (entry 2). The absolute configuration of the two diastereoisomers was confirmed by its transformation into an α-amino-β-hydroxyester derivative and X-ray crystallographic analyses.[11] The catalytic hydrogenation of **1** was run in the presence of *rac*-$BinapRuBr_2$ complex and afforded the β-hydroxyester in a diastereomeric ratio (*S*)-**2**/(*R*)-**2**: 58/42 (entry 3). These results are in favor of a control of diastereoselectivity by chirality of the diphosphane ligand in the ruthenium catalyst.

On the other hand, the reduction was conducted using sodium borohydride, leading to the alcohols (*S*)-**2**/(*R*)-**2** in a ratio of 3/1 (entry 4). This result can be explained according to the Felkin–Ahn model. In the transition state (Fig. 1) the attack of the hydride from the opposite face of the furanose ring oxygen is favored, leading to

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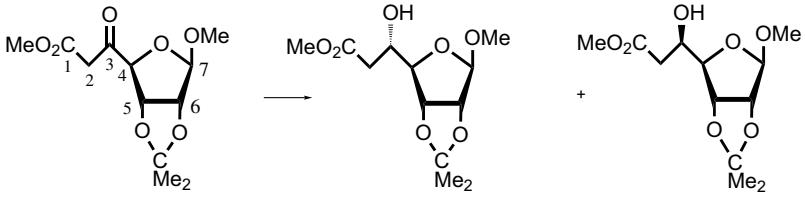


1 (*S*)-2 (*R*)-2

Scheme 1. Catalytic hydrogenation of protected ribose **1**. Reagents and conditions: see Table 1.

Table 1. Transformation of the β-ketoesters **1**, **3**, and **5** into their corresponding β-hydroxyesters

Entry	Substrate	Reagent	% Recovered	Yield (%)	Dr (*S*)/(*R*)[d]	De (%)
1	**1**	H_2, (*R*)-BinapRuBr$_2$[a]	—	>99	90/10	80
2	**1**	H_2, (*S*)-BinapRuBr$_2$[a]	—	>99	5/95	90
3	**1**	H_2, *rac*-BinapRuBr$_2$[a]	—	>99	58/42	16
4	**1**	$NaBH_4$[c]	—	84	75/25	50
5	**3**	H_2, (*R*)-BinapRuBr$_2$[b]	—	>99	>99/1	>98
6	**3**	H_2, (*S*)-BinapRuBr$_2$[b]	16	74	82/18	64
7	**3**	H_2, *rac*-BinapRuBr$_2$[b]	29	71	90/10	80
8	**3**	H_2, DPPERuBr$_2$[b]	76	24	95/5	90
9	**3**	$NaBH_4$[c]	—	>99	74/26	48
10	**5**	H_2, (*R*)-BinapRuBr$_2$[b]	—	>99	85/15	70
11	**5**	H_2, (*S*)-BinapRuBr$_2$[b]	50	50	10/90	80
12	**5**	$NaBH_4$[c]	49	51	50/50	0

[a] 40 °C, 24 h, 1 atm, MeOH.
[b] 45 °C, 24 h, 1 atm, MeOH.
[c] RT, 4 h, MeOH.
[d] Diastereoisomeric ratios have been measured by ^{1}H NMR spectroscopy on the crude products.

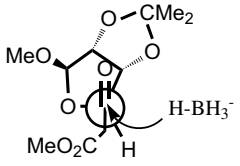
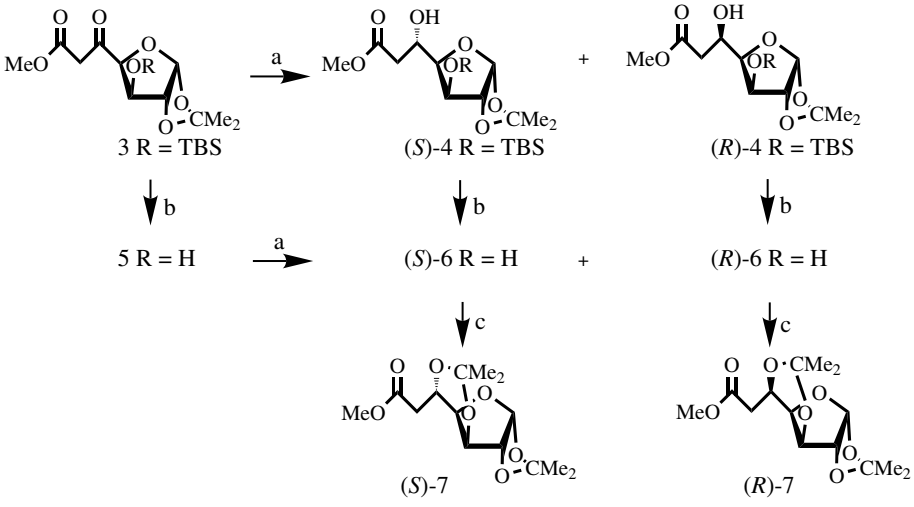


Figure 1. Felkin–Ahn model for the transition state during the reduction of **1** with $NaBH_4$.

the major (*S*)-**2** epimer. Reductions in the presence of zinc bromide did not enhance or alter the stereoselectivity of the reduction. The β-hydroxyester was obtained as a mixture of diastereomers in a ratio of (*S*)-**2**/(*R*)-**2**: 66/34 probably due to competitive chelations of the metal with the alkoxy substituents.

The catalytic hydrogenation applied to the xylose derived β-ketoester **3** led to the hydroxy derivatives **4** (Scheme 2).



3 R = TBS (*S*)-4 R = TBS (*R*)-4 R = TBS
5 R = H (*S*)-6 R = H (*R*)-6 R = H
(*S*)-7 (*R*)-7

Scheme 2. Catalytic hydrogenation of xylofuranose derivatives **3** and **5**. Reagents and conditions: (a) See Table 1; (b) TBAF, THF, RT, 1.5 h, 70% for **5**; (c) Me_2CO, H_2SO_4, 87% from (*S*)-**4**, 75% from (*R*)-**4**.

In the presence of (*R*)-BinapRuBr$_2$ complex, the hydrogenation yielded exclusively one diastereoisomer, as evidenced by ^{1}H NMR spectrum of the crude product (entry 5). We then showed that this derivative was the (*S*)-**4** epimer (see below). Using (*S*)-BinapRuBr$_2$ as the catalyst, the same compound was obtained as the major diastereomer with a (*S*)-**4**/(*R*)-**4** ratio of 82/18 (entry 6). This result was confirmed using racemic Binap or symmetric DPPE (diphenylphosphanylethane) as ligands (entries 7 and 8). In the presence of these catalysts, ^{1}H NMR spectroscopy of the crude products showed complete formation of the (*S*)-**4** isomer. A diastereomeric ratio of (*S*)-**4**/(*R*)-**4**: 90/10 was observed with the *rac*-BinapRuBr$_2$ catalyst while a ratio of 95/5 was seen with the DPPERuBr$_2$ catalyst; however in this case the chemical yield was lower (24%). These results are in favor with the fact that the substrate controls the diastereoselectivity of the catalytic hydrogenation.

With the aim of proving the influence of the bulky *O*-*tert*-butyldimethylsilyl ether at C-5 of the xylose moiety on the substrate control, we deprotected **3** with the resulting β-ketoester **5** being hydrogenated under the same experimental conditions to give the corresponding β-hydroxyester **6** (R = H). The catalytic hydrogenation of **5** in presence of (*R*)-BinapRuBr$_2$, led to (*S*)-**6** with a de of 70% (entry 10). (*R*)-**6** was obtained as the major diastereomer with a de of 80% using (*S*)-BinapRuBr$_2$ as catalyst (entry 11). The reduction of **3** or **5** with sodium borohydride gave, respectively, the alcohols **4** or **6** in the ratios (*S*)/(*R*): 3/1 or 1/1 (entries 9 and 12).

Finally, we determined the configurations of the newly formed stereocenters of the xylofuranose derivatives **4**. Both compounds (*S*)-**4** and (*R*)-**4**, easily separable by silica gel chromatography, were treated with tetrabutylammonium fluoride leading, respectively, to the compounds (*S*)-**6** and (*R*)-**6**, previously obtained by hydrogenation of **5**. A classical acetalation of these diols afforded the compounds (*S*)-**7** and (*R*)-**7**. NOE experiments of the first product showed the vicinal nature of the protons H-3, H-4, and H-5 (Fig. 2). For the second product, we noticed effects showing the spatial proximity of H-3 and H-7 and of the two H-2, H-4, and H-5 (Fig. 2). All the experimental are in concordance with the proposed structures of (*S*)-**7** and (*R*)-**7**, and confirm the stereochemistry of **4** and **6** after the hydrogenation steps.

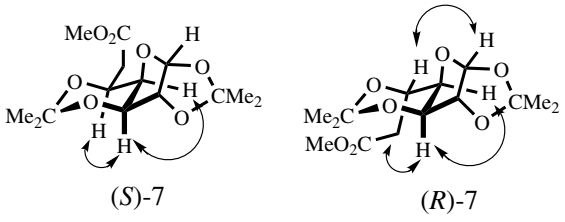


Figure 2. NOE experiments for **7**.

3. Conclusion

In conclusion we have prepared stereoselectively sugar derived β-hydroxyesters **2**, **4**, and **6**, namely ribo- and xylofuranose, by asymmetric catalytic hydrogenation of the corresponding β-ketoesters **1**, **3**, and **5**. Using the (*R*) or (*S*) chiral ligand in the Ru-complexes, each diastereomer of the β-hydroxyesters has been obtained with a good or excellent de. We have shown the importance of the C-5 substituent on the diastereoselectivity of the catalytic hydrogenation. When this one was protected with a bulky group such as a *O*-*tert*-butyldimethylsilyl ether, the stereoselectivity was controlled by the substrate. The configurations of the new asymmetric centers have been confirmed by NOE experiments on the acetals **7**.

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