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Asymmetric Hydrogenation of Methyl 3,5-Dioxohexanoate Catalyzed by Ru-binap Complex: A Short Step Asymmetric Synthesis of Dihydro-6-methyl-2*H*-pyran-2-one

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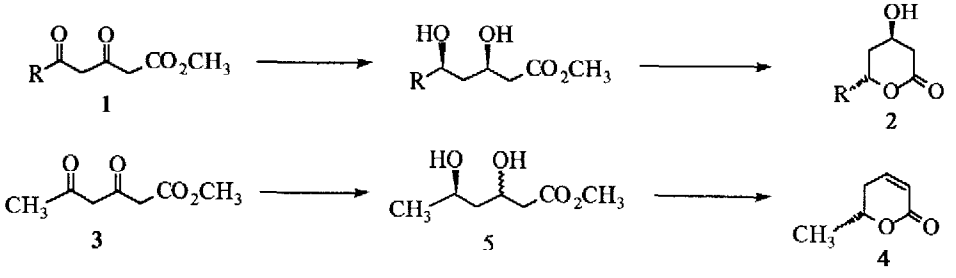
Key words: β,δ-diketoester; Ru-binap catalyst; asymmetric hydrogenation; asymmetric synthesis; lactone.

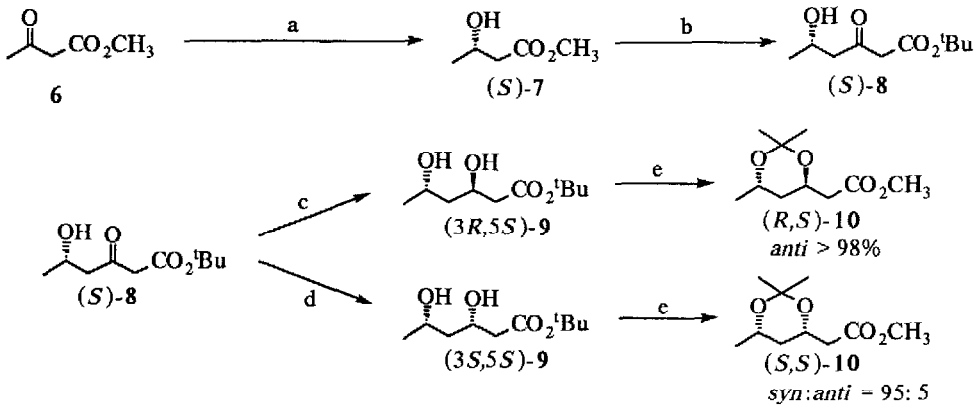
Abstract : *Hydrogenation of methyl 3,5-dioxohexanoate 3 using Ru_2Cl_4((R) or (S)-binap)$_2$(NEt_3) as the catalyst gave dominantly anti 3,5-dihydroxyester 9, which was then converted into unsaturated lactone 4. The pathway of the hydrogenation reaction was also investigated.*

The asymmetric hydrogenation of functionalized carbonyl compounds catalyzed by Ru-binap complexes (binap = (*R*)- or (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) have been studies in detail in recent years.[1,2] Among reported reactions, the hydrogenation of β-diketones[2] provides a typical example of double asymmetric hydrogenation,[3] that can introduce two chiral centers into a molecule in a single procedure. It is of much interest to clarify the stereochemical outcome of the hydrogenation of a β,δ-diketoester to afford a β,δ-dihydroxyester, because the substrate involves partial structures of β-diketone and β-ketoester in a molecule. If a highly enantio- and diastereoselective hydrogenation of β,δ-diketoester **1** was successfully performed to give a *syn*-β,δ-dihydroxyester, it would provide a short and efficient access to a hydroxylactone **2**, the key building block for the synthesis of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, such as compactin[4] and mevinolin.[5] These enzyme inhibitors and even more bioactive analogues have been the targets of intensive studies in organic synthesis.[6] Herein we describe the asymmetric hydrogenation of methyl 3,5-dioxohexanoate **3** catalyzed by Ru-binap complex and a two step procedure of preparing title lactone **4** via the diastereomers of dihydroxyester **5**. Unsaturated lactones analogous to **4** have been employed for precursors of hydroxylactones as **2**.[6,7]



In order to define the stereoselectivity of the hydrogenation, the authentic samples of *syn*- and *anti*-3,5-dihydroxyhexanoates and their acetonide derivatives were prepared by known methods (Scheme 1). Thus, methyl acetoacetate **6** was transformed to hydroxyester (*S*)-**7** with 98% e.e., which was reacted with anion of t-butyl acetate to give (*S*)-**8**.[8,9] Then, (*S*)-**8** was reduced by either $(CH_3)_4NHB(AcO)_3$ or $Et_3B/NaBH_4$.[10,11]

Scheme 1

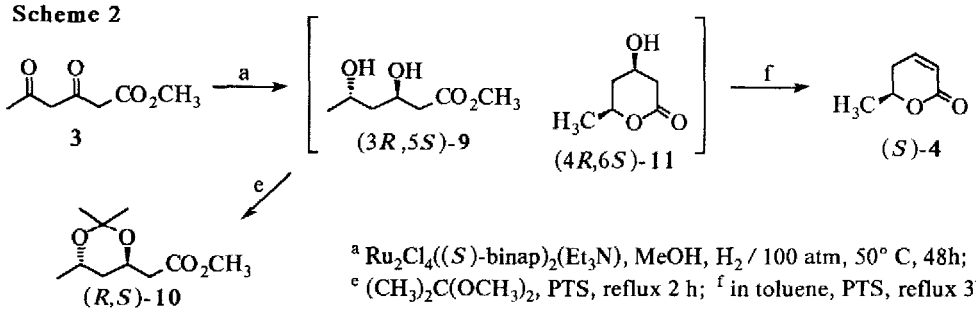


[a] Catalyst, Ru_2Cl_4((S)-binap)(NEt_3); H_2, 100 atm; solvent, MeOH; 50° C; 48 h. [b] AcOtBu / LDA.
[c] $(CH_3)_4NHB(AcO)_3$, CH_3CN, AcOH; [d] $Et_3B/NaBH_4$, THF-MeOH, -78°C, Ar;
[e] $(CH_3)_2C(OCH_3)_2$, PTS, reflux 2h.

The resulting diastereomers of dihydroxyester, (3*R*, 5*S*)-**9** and (3*S*, 5*S*)-**9**, were converted, respectively, into the acetonides (*R* ,*S*)-**10** (*anti*> 98%) and (*S*, *S*)-**10** (*syn* = 95%).[12] It has been demonstrated that the ^{13}C NMR characteristics of methyl groups of such acetonides are diagnostic to the relative stereochemistry of parent 1,3-diols.[13] These standard acetonides served for determining the diastereomer ratio of the hydrogenation products of **3** by means of GC analysis.

Typical procedures of hydrogenation of methyl 3,5-dioxohexanoate **3** and subsequent lactonization of hydrogenation products are as follows. Under a flushing argon atmosphere, a solution of **3** (1.0 g, 6.3 mmol) and Ru_2Cl_4((*S*)-binap)$_2$(NEt_3) (10 mg) in anhydrous methanol was placed in a 50 ml stainless steel autoclave. Hydrogen was pressurized to 100 atm, and the solution was stirred at 50° C for 48 h.[14] The GC analysis showed no substrate remained in the reaction mixture, and methyl 3,5-dihydroxyhexanoate **9** and lactone **11**[15] were obtained as a mixture. **11** should be derived from **9**, because the reaction medium is considerably acidic. A small portion of the mixture was treated with $(CH_3)_2C(OCH_3)_2$ to give a diastereomer mixture of acetonide **10**, the *anti*: *syn* ratio of which was determined to be ca. 4 : 1 by the GC analysis. Further, the whole reaction mixture containing **9** and **11** was evaporated and the residue dissolved in toluene containing PTS, and the solution was heated under reflux for 3 h. After purification by a chromatography (silica gel; hexane/ethyl acetate, 4:1) lactone **4**[16] was obtained in 65 % overall yield. The optical rotation of **4** thus obtained was $[\alpha]_D^{26}$ +160.2° (c = 1.24, ethanol), indicating that the configuration at C-6 is dominantly (*S*) and the optical purity of **4** is 78 %[17] (lit.[18] for (*S*)-**4**, $[\alpha]_D^{24}$ + 206° (c = 1, ethanol)). By similar procedures using Ru_2Cl_4((*R*)-binap)$_2$(NEt_3)

Scheme 2



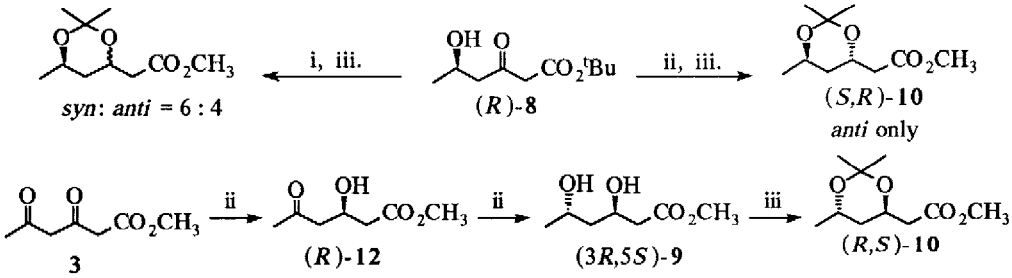
[a] Ru_2Cl_4((*S*)-binap)$_2$(Et_3N), MeOH, H_2 / 100 atm, 50° C, 48h;
[e] $(CH_3)_2C(OCH_3)_2$, PTS, reflux 2 h; [f] in toluene, PTS, reflux 3h.

as a catalyst , **3** was converted in two steps to (*R*)-**4** with an optical purity of ca. 80 %.

The outline of Ru-(*S*)-binap catalyzed hydrogenation of diketoester **3** is given in Scheme 2, where only the preferable isomers of respective products are presented. Since the enantiomeric purity of lactone (*S*)-**4** was 80 %, it is apparent that the configuration at C-5 of dihydroxyester **9** and acetonide **10** is fairly controlled; (*S*) : (*R*) = 9 : 1. The fact that the *anti* isomer is dominant among the diastereomers of **10** suggests that the stereocontrol for the hydrogenation of **3** is, as a whole, similar to that found in the hydrogenation of β-diketones.[2]

With a view to clarify which carbonyl group of C-3 or C-5 in **3** is converted into a hydroxyl group at the first stage of the total reaction, the hydrogenation of t-butyl (*R*)-5-hydroxy-3-oxohexanoate (*R*)-**8** was carried out under the same conditions employed for the hydrogenation of **3** (Scheme 3). It is obvious that the stereochemical outcome in the hydrogenation of **8** is completely different from that observed in the direct hydrogenation of **3**. Thus, contrary to our expectation, the hydrogenation of (*R*)-**8** with Ru-(*R*)-binap complex gave, after usual acetalization, a mixture of (*R,R*)- and (*R,S*)-**10**, the former *syn* -isomer being slightly preferably formed (6 : 4). The hydrogenation of **3** with (*R*)-binap complex should give preferably the *anti* dihydroxy product having (*R*) configuration at C-5. In contrast, practically pure *anti* product (*S,R*)-**10** was obtained by a Ru-(*S*)-binap complex catalyzed hydrogenation of (*R*)-**8**.

Scheme 3



(i). Ru_2Cl_4((*R*)-**binap**)$_2$(Et_3N), H_2/100atm, 50°C, 48 h, MeOH,
(ii) Ru_2Cl_4((*S*)-**binap**)$_2$(Et_3N), H_2/100 atm, 50°C, 48 h, MeOH,
(iii) $(CH_3)C(OCH_3)_2$, PTS, reflux, 2 h.

All of these results suggest that the hydrogenation of **3** proceeds via a reaction sequence shown in Scheme 3. We assume that **3** coordinates to a Ru-binap system predominantly with its 3,5-dicarbonyl moiety, and the C-3 carbonyl group is at first selectively hydrogenated to give methyl 3-(*R*)-hydroxy-5-oxohexanoate (*R*)-**12**.[19] The C-5 carbonyl group is subsequently hydrogenated to afford the dihydroxyester (3*R*,5*S*)-**9** under an *anti* selective stereocontrol similar to the hydrogenation of β-diketones.[2]

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9. **8**: ^{1}H NMR ($CDCl_3$) δ 1.21 (d, 3H, CH_3; J = 6 Hz), 1.47 (s, 9H, CH_3 × 3), 2.64 (dd, 1H, 4-H; J = 18, 9 Hz), 2.74 (dd, 1H, 4-H; J = 18, 3 Hz), 2.92 (br, 1H, OH), 3.38 (s, 2H, CH_2), 4.26 (m, 1H, 5-H)
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12. (*R,S*)-**10**: ^{1}H NMR ($CDCl_3$) δ 1.20 (d, 3H, CH_3; J = 6.4 Hz), 1.26 (m, 1H, 4-H), 1.35 and 1.37 (s × 2, 3H × 2, OCH_3), 1.66 (m, 1H, 4-H), 2.44 (dd, 1H, 2-H; J = 15.6, 5.5 Hz), 2.55 (dd, 1H, 2-H; J = 15.6, 8.2 Hz), 3.69 (s, 3H, CO_2CH_3), 3.97 (m, 1H, 5-H), 4.28 (m, 1H, 3-H). ^{13}C NMR ($CDCl_3$) δ 171.4, 100.4, 63.4, 62.6, 51.6, 40.6, 39.3, 24.8, 21.6.
(*S,S*)-**10**: ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 3H, CH_3, J = 6.1 Hz), 1.17 (overlap, 1H, 4-H), 1.38 and 1.46 (s × 2, 3H × 2, OCH_3), 1.60 (m, 1H, 4-H), 2.39 (dd, 1H, 2-H, J = 15.6, 6.1 Hz), 2.56 (dd, 1H, 2-H; 15.6, 7.0 Hz), 3.69 (s, 3H, CO_2CH_3), 4.01 (m, 1H, 5-H), 4.31 (m, 1H, 3-H). ^{13}C NMR ($CDCl_3$) δ 171.5, 98.8, 65.9, 64.9, 51.6, 41.3, 38.3, 30.2, 22.1, 19.8.
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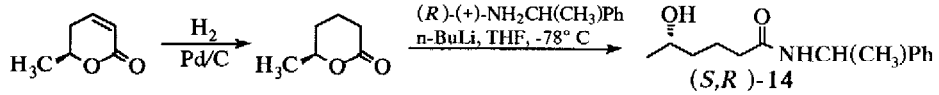
14. A considerable temperature effect was noticed for Ru-binap catalyzed hydrogenation of **4**. No reaction took place at 25° C under the same conditions except temperature, and a less than 5% conversion was obtained at 35°C for 48 h.
15. **11** could be isolated from a reaction mixture by a column chromatography (silica gel; $CHCl_3$:MeOH, 40:1), and characterized by ^{1}H NMR. ($CDCl_3$) δ 1.42 (d, 3H, CH_3; J = 6.1 Hz), 1.60 (m, 1H, 5-H), 2.28 (dddd, 1H, 5-H; J = 13.7, 5.5, 3.1, 1.2 Hz), 2.46 (dd, 1H, 3-H; J = 17.1, 7.6 Hz), 2.89 (ddd, 1H, 3-H; J = 17.1, 5.8, 1.2 Hz), 3.41 (br, 1H, OH), 4.25 (m, 1H, 4-H), 4.37 (m, 1H, 6-H)
16. **4**: ^{1}H NMR ($CDCl_3$) δ 1.45 (d, 3H, CH_3; J = 6.4 Hz), 2.34 (m, 2H, 5-H), 4.58 (m, 1H, 6-H), 6.03 (ddd, 1H, 3-H; J = 9.8, 2.7, 1.0 Hz), 6.80 (ddd, 1H, 4-H; J = 9.8, 5.5, 2.8 Hz).
17. The enantiomeric excess of (*S*)-**4** was determined as follows. (*S*)-**4** was hydrogenated with Pd-C as a catalyst to saturated lactone (*S*)-**13**, and then treated with anion of (*R*)-(+)-α-phenylethylamine to give the amide (*S,R*)-**14**. The diastereomer ratio of **14** ((*S,R*) : (*R,R*)) was determined by HPLC with a silica gel column (hexane-^{i}PrOH = 85:5). The diastereomeric excess, which corresponds to the e.e. of (*S*)-**13**, was almost same (80 %) as the optical purity.



(*S*)-**4** (*S*)-**13** (*S,R*)-**14**

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19. It is possible that the hydrogenation of **3** with Ru-(*S*)-binap catalyst proceeds in small part under the control of C-3 carbonyl and ester carbonyl groups to give dominantly (*S*)-**12**. The contamination of (*S*)-**12** should result in the formation of other diastereomers ((3*S*,5*R*) and (3*S*,5*S*)) of **9** and the lower e.e. of lactone **4**, compared with the e.e. values for the hydrogenation of β-diketones by the same catalyst.

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