Polish J. Chem., **76**, 1707–1711 (2002)

Preparation of Synthetically Useful Chiral Building Blocks – 5-Alkylated γ-Lactones *via* Catalytic Asymmetric Hydrogenation of 4-Oxo Esters

by G. Juszkiewicz[1], M. Asztemborska[2] and J. Jurczak[1,3]

[1]*Department of Chemistry, Warsaw University, Pasteura 1, PL-02-093 Warsaw, Poland*
[2]*Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, PL-01-224 Warsaw, Poland*
[3]*Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, PL-01-224 Warsaw, Poland*

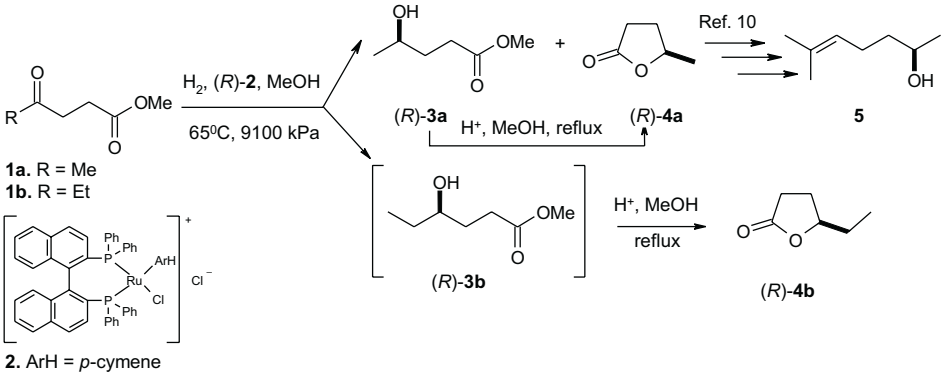
(Received August 2nd, 2002; revised manuscript September 10th, 2002)

Asymmetric hydrogenation of 4-oxo esters, catalyzed by cationic BINAP-Ru(II) complexes, afforded in a good overall yield and with excellent enantioselectivity (> 98% ee), the respective 5-alkylated γ-lactones, useful intermediates for the preparation of pheromones.

Key words: asymmetric hydrogenation, 4-oxo esters, Ru(II)complexes, γ-lactones, pheromones

Steroselective hydrogenation of activated ketones has been extensively studied, due to synthetic significance of homochiral secondary alcohols. Optically active functionalized secondary alcohols are very useful building blocks in the synthesis of biologically important chiral compounds such as inhibitors [1], pheromones [2], antifungal compounds [3], *etc*. In recent years, an enantioselective variant of this process, using chiral phosphine–ruthenium complexes as highly efficient catalysts, has successfully been developed by Noyori and co-workers [4]. Hydrogenation of 2- and 3-oxo esters in this way, using complexes $RuCl_2$(binap) [5], $RuCl_2(binap)_2 \cdot NEt_3$ [6] or [RuCl(arene)(binap)]Cl (arene = benzene, *p*-cymene, ethyl benzoate) [7] gives corresponding secondary alcohols in high yield and with almost complete enantioselectivity [4,8]. For 4-oxo esters, it has been found that owing to their lower activity, hydrogenation failed when cationic catalysts of type **2** were used under mild, efficient for 2- and 3-oxo esters, conditions [9]. In this paper, we would like to present a very convenient procedure for hydrogenation of 4-oxo esters **1a** and **1b**, using BINAP-Ru complex **2** as a catalyst (Scheme 1).

Scheme 1



RESULTS AND DISCUSSION

At the beginning, we performed a series of hydrogenation experiments of methyl 4-oxopentanoate (**1a**) to find optimal conditions of the reaction. The results of optimization procedures are given in Table 1.

Table 1. Optimization of asymmetric hydrogenation of **1a**.

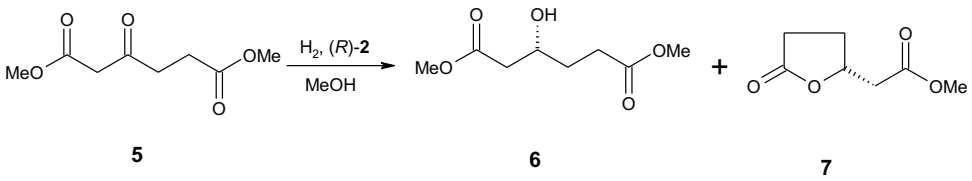
Entry	ΔPH_2 [kPa]	Temp. [°C]	Time [h]	Yield [%]	(*R*)-**3a**:(*R*)-**4a**	(*R*)-**3a** ee [%]	(*R*)-**4a** ee [%]
1	7000	25	24	0	–	–	–
2	9000	30	48	7	–	–	–
3	9000	50	24	20	1:1	98	98
4	9000	65	50	66	1:1.8	98	98
5	9100	65	72	75	1:2	98	98

Asymmetric hydrogenation of methyl 4-oxopentanoate (**1a**), under the best conditions when it was carried out in methanol solution containing 0.5 mol% of (*R*)-**2**, at 65°C under 9100 kPa pressure, led to a mixture of methyl (4*R*)-hydroxypentanoate (**3a**) and (5*R*)-methyltetrahydrofuran-2-one (**4a**) in a 1:2 ratio, which was subjected to column chromatography to afford pure compounds (*R*)-**3a** and (*R*)-**4a**. In an independent experiment, the 1:2 mixture of **3a** and **4a**, dissolved in methanol, was refluxed for a short time with a catalytic amount of an acid, to give exclusively lactone (*R*)-**4a** with excellent (98% ee) enantiomeric purity. Lactone (*R*)-**4a** can be readily, according to the known procedure [10], transformed into (*R*)-sulcatol (**5**), an aggregation pheromone of *Ambrosia Beetle* of North America (Scheme 1). Similar results were obtained for asymmetric hydrogenation of methyl 4-oxohexanoate (**1b**). In this case the intermediate (*R*)-**3b** was not isolated, and the final product (*R*)-**4b** was practi-

cally enantiomerically pure (99% ee). The γ-lactone (*R*)-**4b** is an aggregation pheromone component of *Dermesteed Beetle* [11].

Recently, we have shown [12] that enantiomerically pure 5-substituted γ-lactones can be obtained *via* asymmetric hydrogenation of dimethyl 3-oxohexadienoate (**5**) (Scheme 2).

Scheme 2



5 **6** **7**

Now, we would like to present additional optimization experiments for this valuable asymmetric hydrogenation. In all hydrogenation experiments we obtained of a mixture of alcohol **6** and γ-lactone **7**, but their ratio strongly depended on the reaction conditions. Nonpolar solvents, higher temperature and hydrogen pressure as well as longer reaction time, when the constant amounts of the catalyst were used, caused predomination of the cyclic product **7** in the reaction mixture. So, the content of the catalyst seemed to be crucial point for controlling of the product distribution. Results of such optimization are collected in Table 2.

Table 2. Dependence of the substrate/product ratio (**5**:**6**:**7**) on the catalyst content.

Entry	ΔPH_2 [kPa]	Temp. [°C]	Time [h]	Catalyst [mol%]	Yield (**6**+**7**) [%]	**5:6:7**
1	10000	25	72	1.0	88	0:2:1
2	10000	25	72	0.5	75	0:6:1
3	10000	25	72	0.2	56	1:2:1
4	10000	25	72	0.1	49	1:2:0

The result of such optimization is that shown in entry 2, when 0.5 mol% of the catalyst (**R**)-2 was used; the overall yield of **6** and **7** was acceptable (75%) and the ratio of acyclic product **6** to lactone **7** was the best (6:1).

We believe that the present approach to the preparation of 5-substituted γ-lactones constitutes a general method, which may be used in total syntheses of other natural products.

EXPERIMENTAL

General methods: Optical rotations were measured on a Perkin-Elmer PE-241 polarimeter with a thermally jacketed 10-cm cell, using the sodium D line at 589 nm. IR spectra were obtained with a Magna 550 Nicolet spectrometer in films. ^{1}H NMR spectra were recorded with a Varian 200 Unity Plus (200

MHz) spectrometer in $CDCl_3$ using TMS as an internal standard. ^{13}C NMR spectra were recorded using also a Varian 200 Unity Plus (50 MHz). Mass spectra were recorded on an AMD-604 Intectra instrument using the electron impact (EI) technique. Column chromatography was carried out on silica gel (Merck, Kieselgel 230–400 mesh). Enantiomeric excess was determined using a Hewlett-Packard GC unit with a chiral column β-DEX 225 (30 m × 0.25 mm i.d.) (Supelco, Bellefonte, USA); oven temperature was 170°C isothermal, injector and detector temperatures were 200 and 250°C, respectively; head pressure of argon was 100 kPa.

The (*R*)-ruthenium complex **2** (Fluka) and methyl 4-oxopentanoate (**1a**) were commercial products. Methyl 4-oxohexanoate (**1b**) was prepared according to the literature procedure [13].

General procedure for laboratory scale hydrogenation of methyl 4-oxoalkanoates: To a glass vessel containing a solution of methyl ester **1a** or **1b** (0.5 mmol) in degassed anhydrous methanol (4 mL) was added a [RuCl((*R*)-binap)(*p*-cymene)]Cl (2.2 mg) complex (**2**). The reaction mixture was placed in a 100-mL stainless steel autoclave. Hydrogen was pressurised to 9100 kPa, and the solution was stirred at 65°C for 48 h. After cooling, the excess of hydrogen was removed, the apparatus disassembled, and solvents were evaporated to give an oily residue. The residue was finally purified by column chromatography (hexane-ethyl acetate, 9:1 v/v) to afford a mixture of products **3** and **4**. The mixture was then refluxed with one drop of 50% H_2SO_4 in methanol (4 mL) for 10–15 min, then washed with saturated aqueous $NaHCO_3$, and extracted with ether (3×5 mL). The extracts were combined and dried over anhydrous $MgSO_4$. Evaporation of the solvent and purification by column chromatography afforded the appropriate γ-lactones **4**.

Methyl (*R*)-4-hydroxypentanoate (3a): This hydroxyester was prepared as an oil in 25% yield; $[\alpha]_D^{27}$ + 15.7 (*c* 19.6 in CH_2Cl_2) [Lit. [14] $[\alpha]_D^{25}$ + 15.3 (*c* 19.6 in CH_2Cl_2)]; IR (film): ν = 3530, 2950, 1740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 3.82 (m, 1H), 3.68 (s, 3H), 3.30 (s, 1H), 1.8–1.7 (m, 4H), 1.21 (d, 3H); Enantiomeric excess 98% (enantioseparation factor α = 1.12).

(*R*)-5-Methyl-2-oxotetrahydrofuran (4a): This γ-lactone was prepared as an oil in 72% overall yield; $[\alpha]_D^{22}$ + 29.4 (*c* 0.9 in CH_2Cl_2) [Lit. [10] $[\alpha]_D^{24}$ + 30.1 (*c* 0.85 in CH_2Cl_2)]; IR (film): ν = 2980, 1760 cm^{-1}; ^1H NMR (200 MHz), $CDCl_3$): δ = 4.65 (m, 1H), 2.4–2.6 (m, 4H), 1.42 (d, 3H); ^{13}C NMR (50 MHz, $CDCl_3$); δ = 177.4, 82.3, 29.9, 29.3, 21.2; Enantiomeric excess 98% (enantioseparation factor α = 1.12).

(*R*)-5-Ethyl-2-oxotetrahydrofuran (4b): This γ-lactone was prepared as an oil in 92% yield; $[\alpha]_D^{22}$ + 50.2 (*c* 0.83 in MeOH) [Lit. [15] $[\alpha]_D^{21}$ + 53.0 (*c* 1 in MeOH)]; IR (film): ν = 2920, 1698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 4.41 (m, 1H), 2.54 (t, 2H), 2.4–1.6 (m, 4H), 1.00 (t, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.5, 82.4, 29.1, 28.7, 27.7, 9.6; Enantiomeric excess 99% (enantioseparation factor α = 1.06).

Acknowledgment

This work was supported by the Polish State Committee for Scientific Research (Project PBZ 6.05/T09/1999).

REFERENCES

1. Garcia D.M, Yamada H., Hatakeyama S. and Nishizawa M., *Tetrahedron Lett.,* **35**, 3325 (1994); Ali S.M. and Georg G.I., *Tetrahedron Lett.*, **38**, 1703 (1997); Irako N. and Shioiri T., *Tetrahedron Lett.*, **39**, 5793 (1998); Lebel H. and Jacobsen E.N., *J. Org. Chem.*, **63**, 9624 (1998); Franklin A.S., Ly S.K., Mackin G.H., Overman L.E. and Shaka A.J., *J. Org. Chem.*, **64,** 1512 (1999).
2. Mori K., *Tetrahedron,* **45**, 3233 (1989); Solladié G. and Matloubi-Moghadam F., *J. Org. Chem*., **47**, 91 (1982); Hedenstörm E., Högberg H.-E., Wassgren A.-B., Bergström G., Löfqvist J., Hansson B. and Anderbrant O., *Tetrahedron*, **48**, 3139 (1992); Coutrot Ph., Grison C. and Bomônt C., *Tetrahedron Lett*., **35**, 8381 (1994); Paolucci C., Mazzini C. and Fava A., *J. Org. Chem*., **60**, 169 (1995).
3. Spino C., Mayes N. and Desfosses H., *Tetrahedron Lett*., **36**, 6503 (1996); Keck G.E. and Lundquist G.D., *J. Org. Chem*., **64**, 4482 (1999).

4. Noyori R., Ohkuma T., Kitamura M., Takaya H., Sayo N., Kumobayashi H. and Akutagawa S., *J. Am. Chem. Soc*., **109**, 5856 (1987); Noyori R., *Science*, **248**, 1194 (1990); Noyori R., *Tetrahedron*, **50**, 4259 (1994).
5. Noyori R., Ikeda T., Ohkuma T., Widhalm M., Kitamura M., Takaya H., Akutagawa S., Sayo N., Saito T., Taketomi T. and Kumobayashi H., *J. Am. Chem. Soc*., **111**, 9134 (1989) and references cited therein.
6. Kawano S., Ikariya T., Ishii Y., Saburi M., Yoshikawa S., Uchida Y. and Kumobayashi H., *J. Chem. Soc., Perkin Trans. 1*, 1571 (1989); King S.A., Thompson A.S., King A.O. and Verhoeven T.R., *J. Org. Chem*., **57**, 6689 (1992) and references cited therein.
7. Mashima K., Kusano K., Sato N., Matsumura Y., Nozaki K., Kumobayashi H., Sayo N., Hori Y., Ishizaki T., Akutagawa S. and Takaya H., *J. Org. Chem*., **59**, 3064 (1994).
8. Kitamura M., Tokunaga M., Ohkuma T. and Noyori R., *Tetrahedron Lett*., **32**, 4163 (1991); Genêt J. P., Rotovelomanana-Vidal V., Cańo de Andrade M.C., Pfister X., Guerreiro P. and Lenoir J.Y., *Tetrahedron Lett*., **36**, 4801 (1995); Genêt J.P., *Acros Organics Acta*, **1**, 4 (1995); Doucet H., Ohkuma T., Murata K., Zokozawa T., Kozawa M., Katayama E., England A.F., Ikariya T. and Noyori R., *Angew. Chem., Int. Ed. Engl*., **37**, 1703 (1998).
9. Ohkuma T., Kitamura M. and Noyori R., *Tetrahedron Lett*., **31**, 5509 (1990).
10. Mori K., *Tetrahedron*, **31**, 3011 (1975).
11. Ravid U., Silverstein R.M. and Smith L.R., *Tetrahedron*, **34**, 1449 (1978).
12. Juszkiewicz G., Asztemborska M. and Jurczak J., *Synth. Commun*., **32**, 2605 (2002).
13. Terasawa T. and Okada T., *Tetrahedron*, **33**, 595 (1977).
14. Gutman A.L., Zuobi K. and Boltansky A., *Tetrahedron Lett*., **28**, 3861 (1987).
15. Mori K., Mori H. and Sugai T., *Tetrahedron*, **41**, 919 (1985).