

Dynamic kinetic resolution: an efficient route to *anti* α -amino- β -hydroxy esters via Ru-SYNPHOS[®] catalyzed hydrogenation[†]

Céline Mordant, Pascal Dünkelmann, Virginie Ratovelomanana-Vidal* and Jean-Pierre Genet*

Laboratoire de Synthèse Sélective Organique et Produits Naturels, UMR 7573 C.N.R.S., Ecole Nationale Supérieure de Chimie de Paris, 11, rue P. et M. Curie, 75231 Paris Cedex 05, France.

E-mail: genet@ext.jussieu.fr; gvidal@ext.jussieu.fr; Fax: +33 (0)1 4407 1062; Tel: +33 (0)1 4427 6744

Received (in Corvallis, OR, USA) 3rd February 2004, Accepted 31st March 2004

First published as an Advance Article on the web 6th May 2004

The Ru(II)-catalyzed hydrogenation of α -amino- β -keto esters as their hydrochloride salts affords preparation of the corresponding *anti* α -amino- β -hydroxy esters under mild conditions with high diastereoselectivities and enantioselectivities via dynamic kinetic resolution.

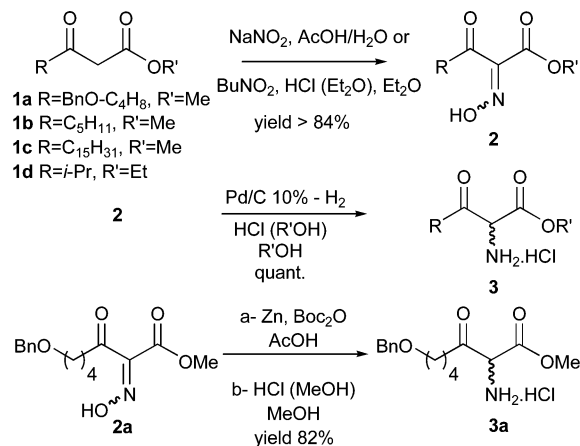
Ruthenium-promoted hydrogenation via Dynamic Kinetic Resolution (DKR) has turned out to be an elegant and powerful method of simultaneously controlling two adjacent stereogenic centers with high levels of selectivity in a single chemical operation.¹ This reaction was first reported independently by Noyori *et al.*² and Genet *et al.*³ in 1989 for the synthesis of threonine. The hydrogenation of α -acetamido- β -keto esters and more generally of non-cyclic α -amido- β -keto esters⁴ with Ru(II)-catalysts affords, under optimized conditions, the corresponding *syn* β -hydroxy esters with excellent diastereoisomeric and enantiomeric excesses. The stereochemical course of the hydrogenation reaction is highly dependent on the nature of the configurationally labile group borne at the α -position of the β -keto ester. α -Chloro-⁵ or cyclic α -alkyl^{1,2,6}- β -keto esters were reduced to the *anti* α -substituted β -hydroxy esters. The first example of an efficient DKR of an α -alkyl- β -keto ester was observed by our group during preliminary studies on Dolastatin 10:⁷ the *anti* β -hydroxy- α -methyl ester was isolated with high stereoselectivity after hydrogenation under mild conditions of the β -keto ester derived from the hydrochloride salt of (*S*)-proline.

Inspired by these encouraging results and as part of our continuing interest in stereoselective hydrogenation, we set out to achieve high *anti* diastereoselectivity by asymmetric Ru(II)-promoted hydrogenation of a β -keto ester α -substituted by a $\text{NH}_2\cdot\text{HCl}$ group displaying non-chelating properties towards the metal.

Moreover, this ' α -amino- β -hydroxy' fragment can be found in numerous natural or synthetic molecules with an *anti* configuration. For example, 3-hydroxyleucine methyl ester is a key unit of many peptide antibiotics such as (+)-lactacystin (Fig. 1), a neurotrophic agent,⁸ while *D*-erythro-dihydrospingosine constitutes the amino portion of symbioramide, a ceramide, which exhibits antileukemic

activity.⁹ Thus, for all organic chemists, it remains a challenge to synthesize one specific isomer of medically important compounds.

In this paper, we wish to report a straightforward and efficient synthesis of *anti* α -amino- β -hydroxy esters based on the DKR of the hydrochloride salts of α -amino- β -keto esters, which, until very recently, has not been reported.¹⁰ In this context, we examined the ruthenium-mediated hydrogenation of a few substrates of synthetic interest. The hydrogenation substrates were easily prepared according to the general scheme depicted below (Scheme 1). The α -amino- β -keto ester hydrochloride salts **3** were obtained from the corresponding α -hydroxyimino- β -keto esters **2**, in turn prepared from β -keto esters **1** according to classic procedures. The reduction of **2** with Pd/C in the presence of a methanolic or ethanolic solution of hydrochloric acid under atmospheric pressure of hydrogen led to the hydrochloride salts **3** (except **3a**) in quantitative yields. Because of the benzyloxy function of the substrate **2a**, the hydrochloride salt **3a** was formed by adding hydrochloric acid to the intermediate α -*tert*-butoxycarbonyl- β -keto ester.



Scheme 1 Synthesis of the hydrogenation substrates **3**.

Following our previous results obtained with the β -keto- α -methyl ester derived from (*S*)-proline hydrochloride,⁷ the preliminary hydrogenation reactions were run in an alcoholic solvent (R'OH) with compounds **3c** and **3d** as representative precursors of 3-hydroxyleucine and dihydrospingosine, respectively. The trials were performed under mild conditions: 12 bar of hydrogen at 50 °C for 24 h (Table 1, entries 1 and 4), in the presence of the *in situ* generated chiral catalyst¹¹ [Ru(MeO-BIPHEP)Br₂]. The *anti* configuration of the resulting α -amino- β -hydroxy ester, isolated with good yield after reprotection of the crude hydrogenated product with benzoic anhydride, was determined by comparison with the well-known *syn* products and authentic samples.¹² The main results are summarized in Table 1.

For substrate **3d**, an excellent diastereoselectivity (98%) and a significant level of enantioselectivity (87%) were observed in ethanol (entry 1). These results remained unchanged regardless of the hydrogen pressure (50 or 100 bar, entries 2 and 3). The hydrogenation proceeded smoothly with high diastereoselectivity (93%) even with the long-chain substrate **3c** though the enantioselectivity was poor (39%, entry 4). Higher hydrogen pressure (50

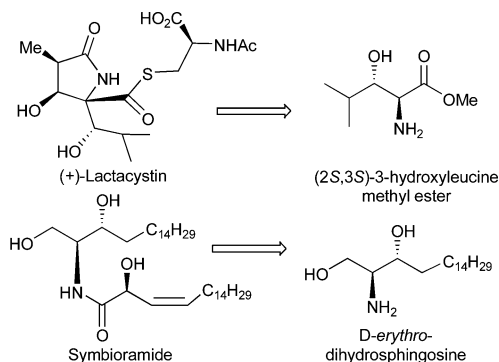


Fig. 1 Examples of molecules with *anti* α -amino- β -hydroxy fragment.

[†] Electronic supplementary information (ESI) available: experimental details for the preparation of compounds **1**–**4**. See <http://www.rsc.org/suppdata/cc/b4/b401631a/>

bar, entry 5) did not improve the e.e. (36%) and only a small increase in enantioselectivity (52%) was observed when the hydrogenation was carried out at 100 °C (entry 6).

Table 1 Hydrogenation reaction^a of compounds **3c** and **3d** in alcoholic solvent

Entry	Substrate	Solvent (R'OH)	P(H ₂)/bar	T/°C	d.e. ^b (%) <i>anti</i>	e.e. ^b (%) (2 <i>S</i> ,3 <i>S</i>)
1	3d R= <i>i</i> Pr	EtOH	12	50	98	87
2	3d R= <i>i</i> Pr	EtOH	50	50	98	87
3	3d R= <i>i</i> Pr	EtOH	100	50	98	87
4	3c R=C ₁₅ H ₃₁	MeOH	12	50	93	39
5	3c R=C ₁₅ H ₃₁	MeOH	50	50	90	36
6	3c R=C ₁₅ H ₃₁	MeOH	12	100	93	52

^a Conversions rates were determined by ¹H NMR (MeOD) spectroscopy before reprotection; all reactions were complete. ^b d.e. and e.e. were determined by HPLC analysis after reprotection.

Based on these first results, the reaction solvent was changed to slow down the reaction rate in order to favor a better discrimination by the catalyst and improve the chiral induction. All hydrogenations of the hydrochloride salts **3** were then conducted in dichloromethane with a small percentage of alcoholic solvent (9%) to maintain homogeneity. 2 mol% of catalyst [Ru(diphosphine)Br₂] were required to ensure complete conversions, the other conditions remaining unchanged (*i.e.* under 12 bar of hydrogen at 50 °C for 24 h). This combination turned out to be the most appropriate to achieve high *anti* diastereoselectivity and enantioselectivity for both linear and branched α -amino- β -keto ester hydrochloride salts **3**, regardless of the length or the hindrance of the side chain and with good to excellent yields (Table 2). In all experiments, the Ru(II)-catalysts were prepared *in situ* from (cod)Ru(2-methylallyl)₂, SYNPHOS[®] ligand recently developed by our group^{13,14} and methanolic HBr according to our convenient procedure.¹¹ As shown in Table 2, the Ru(II)-catalyst containing SYNPHOS[®]

Table 2 Hydrogenation of compounds **3** in optimized conditions^a

Entry	Substrate	Yield ^b (%)	d.e. ^c (%) <i>anti</i>	e.e. ^c (%) (2 <i>S</i> ,3 <i>S</i>)
1	3a R=BnO-C ₄ H ₈	94	92	92
2	3b R=C ₅ H ₁₁	85	93	91
3	3c R=C ₁₅ H ₃₁	83	96	96
4	3d R= <i>i</i> Pr	90	99	97
5 ^d	3d R= <i>i</i> Pr	96	98	96 ^d

^a Reaction conditions: 0.5 mmol of substrate in 2 mL of CH₂Cl₂ and 200 μ L of R'OH. ^b Yield over two steps. ^c d.e. and e.e. were determined by HPLC analysis after reprotection. ^d Reaction conducted with (*R*)-SYNPHOS[®], *e.e.* of (2*R*,3*R*)-isomer.

displayed, under these optimized reaction conditions, an excellent catalytic activity for all the substrates **3** considered, with high levels of *anti* diastereoselectivity (86–99%) and enantioselectivity (91–97%). Both *anti* (2*S*,3*S*)- and (2*R*,3*R*)- α -amino- β -hydroxy esters could be easily synthesized with high diastereoisomeric and enantiomeric excesses by judicious choice of the ligand configuration. It is noteworthy that the diastereoisomeric excesses observed seem linked to the nature of the side chain. The best results were obtained with a long or ramified chain in the β -position (**3c** and **3d**, respectively).

In conclusion, the SYNPHOS[®] catalyzed hydrogenation affords a general and efficient access to *anti* α -amino- β -hydroxy esters by using configurationally labile α -NH₂·HCl- β -keto esters. High levels of enantiomeric and diastereoisomeric excesses are obtained for a variety of alkyl β -keto esters under mild conditions *via* dynamic kinetic resolution. This convenient method complements the well-known hydrogenation of α -amido- β -keto esters which provides the *syn* isomers as major products. This reaction is still under investigation and the application of this strategy to the synthesis of natural products and their analogues is currently underway in our group.

We thank Dr R. Schmid and Dr M. Scalone (Hoffmann-La Roche) for samples of (*S*)-MeO-BIPHEP = (*S*)-(-)-6,6'-dime-thoxy-2,2'-bis(diphenylphosphino)-1,1'-biphenyl. A fellowship from C.N.R.S./D.G.A. (C. M.) is gratefully acknowledged.

Notes and references

- Reviews: R. Noyori, M. Tokunaga and M. Kitamura, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 36; R. S. Ward, *Tetrahedron: Asymmetry*, 1995, **6**, 1475; V. Ratovelomanana-Vidal and J. P. Genet, *Can. J. Chem.*, 2000, **78**, 846; K. Faber, *Chem. Eur. J.*, 2001, **7**, 5005; H. Pellissier, *Tetrahedron*, 2003, **59**, 8291–8327.
- R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, T. Taketomi and H. Kumobayashi, *J. Am. Chem. Soc.*, 1989, **111**, 9134.
- J. P. Genet, S. Mallart and S. Jugé, *Fr. Pat.* 8911159, 1989; J. P. Genet, C. Pinel, S. Mallart, S. Jugé, S. Thorimbert and J. A. Laffitte, *Tetrahedron: Asymmetry*, 1991, **2**, 555.
- K. Mashima, Y. Matsumura, K. Kusano, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa and H. Takaya, *J. Chem. Soc., Chem. Commun.*, 1991, 609; A. Girard, C. Greck, D. Ferroud and J. P. Genet, *Tetrahedron Lett.*, 1996, **37**, 7967; E. Coulon, C. Caño de Andrade, V. Ratovelomanana-Vidal and J. P. Genet, *Tetrahedron Lett.*, 1998, **39**, 6467; P. Phansavath, S. Duprat de Paule, V. Ratovelomanana-Vidal and J. P. Genet, *Eur. J. Org. Chem.*, 2000, 3903.
- C. Caño de Andrade, V. Ratovelomanana-Vidal and J. P. Genet, *Tetrahedron Lett.*, 1995, **36**, 2063; C. Mordant, C. Caño de Andrade, R. Touati, V. Ratovelomanana-Vidal, B. Ben Hassine and J. P. Genet, *Synthesis*, 2003, 2405.
- J. P. Genet, X. Pfister, V. Ratovelomanana-Vidal, C. Pinel and J. A. Laffitte, *Tetrahedron Lett.*, 1994, **35**, 4559.
- D. Lavergne, C. Mordant, V. Ratovelomanana-Vidal and J. P. Genet, *Org. Lett.*, 2001, **3**, 1909.
- J. S. Panek and C. E. Masse, *J. Org. Chem.*, 1998, **63**, 2382.
- H. Azuma, R. Takao, H. Niuro, K. Shikata, S. Tamagaki, T. Tachibana and K. Ogino, *J. Org. Chem.*, 2003, **68**, 2790.
- A. Lei, S. Wu, M. He and X. Zhang, *J. Am. Chem. Soc.*, **126**, 126; After submission of this manuscript, the stereoselective synthesis of *anti* β -hydroxy- α -amino acids *via* DKR was reported: see K. Makino, T. Goto, Y. Hiroli and Y. Hamada, *Angew. Chem., Int. Ed.*, 2004, **43**, 882.
- J. P. Genet, C. Pinel, V. Ratovelomanana-Vidal, S. Mallart, X. Pfister, C. Caño de Andrade and J. A. Laffitte, *Tetrahedron: Asymmetry*, 1994, **5**, 675.
- O. Hara, M. Ito and Y. Hamada, *Tetrahedron Lett.*, 1998, **39**, 5537.
- S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J. P. Genet, N. Champion and P. Dellis, *Eur. J. Org. Chem.*, 2003, 1931 and refs. cited therein.
- J. P. Genet, *Acc. Chem. Res.*, 2003, **36**, 908.