ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 4247–4249

www.rsc.org/chemcomm

COMMUNICATION

Acid-labile δ-ketal-β-hydroxy esters by asymmetric hydrogenation of corresponding δ-ketal-β-keto esters in the presence of $CaCO_3$†

Weizheng Fan,[a] Wanfang Li,[a] Xin Ma,[a] Xiaoming Tao,[a] Xiaoming Li,[a] Ying Yao,[a] Xiaomin Xie[a] and Zhaoguo Zhang*[ab]

Received 11th February 2012, Accepted 28th February 2012
DOI: 10.1039/c2cc31002c

A series of acid-labile, optically pure ε-substituted δ-ketal-β-hydroxy esters were obtained by a Ru-SunPhos catalyzed asymmetric hydrogenation of the corresponding ε-substituted δ-ketal-β-keto esters. $CaCO_3$ played a dual role in the hydrogenation reaction—removing the acid generated during the formation of the catalyst and maintaining the activity of the catalyst.

Statins are among the most commonly applied lipid regulation drugs world-wide.[1] The annual market value has been approximately 23 billion US$ during the past 10 years (Fig. 1). Statins, in particular those containing a C=C double bond, can be efficiently synthesized by olefination of a heteroaryl aldehyde with a phosphorous or phosphorane side chain (Scheme 1).[2]

Over the last three decades, diverse strategies to construct this phosphorous or phosphorane side chain possessing one chiral center have been developed.[3] However, almost all approaches were focused on the construction of the key chiral intermediates, 3-hydroxyglutaric acid derivatives **B** (Scheme 1). Interestingly, the chiral alkyl 6-chloro-3-hydroxy-5-oxohexanoate **A** can be readily converted to a side chain through the Arbuzov reaction[4] (Scheme 1), however, no efficient method for preparing compound **A** has been reported. Therefore, it's of great value to devise an efficient method for its synthesis.

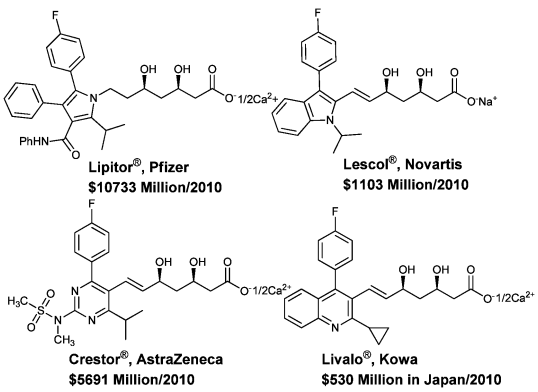
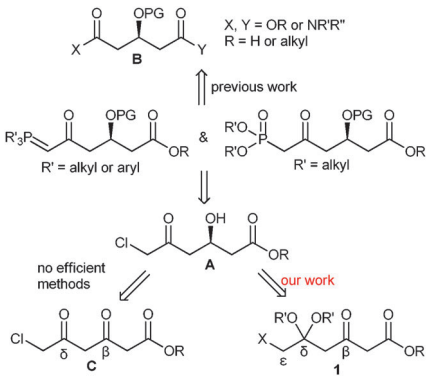


Fig. 1 Structures of some important artificial statins.



Scheme 1 The asymmetric hydrogenation protocol for side chains of superstatins.

Reduction of β,δ-diketo esters, **C**, to β-hydroxy-δ-oxo esters with both high regio- and enantioselectivity is the most straightforward way, but it is difficult to realize. The ruthenium-catalyzed asymmetric hydrogenation of substrate **C** always gave a β,δ-dihydroxy ester with moderate diastereoselectivity, as it involves moieties of both β-diketones and β-keto esters in the molecule.[5] It is noteworthy that Saburi *et al.* reported that a ruthenium-catalyzed asymmetric hydrogenation of β,δ-diketo esters proceeded sequentially at positions C-3 (β) and C-5 (δ) with moderate *anti*-selectivity and enantioselectivity, but the monohydrogenation product was neither isolated nor identified from the reaction mixture.[6] Under optimized reaction conditions, Carpentier *et al.* first reported a regioselective hydrogenation of the C-3 (β) carbonyl group of methyl 3,5-dioxohexanoate with high yields, but fair enantiomeric excess (78% *ee*).[7]

Several investigations have involved β-keto esters bearing adjacent heteroatoms, such as a benzyloxyl group,[8] alkoxyl group,[3g,9] halogen atoms[10] or carbonylamino groups,[11] in the vicinity of the keto group. Recently, Börner *et al.* reported a new approach to synthesise chiral 3-hydroxyglutaric acid derivative **B** based on the asymmetric hydrogenation of 5,5-dimethoxy-3-oxopentanoate as a key step.[3g] We envisioned

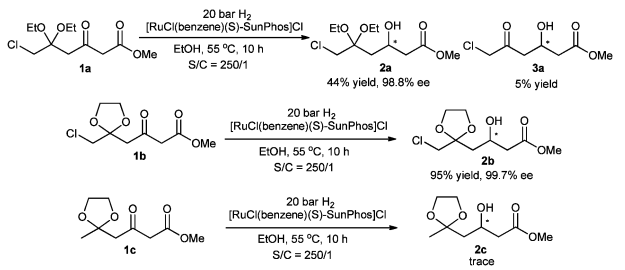
[a] *School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China*
[b] *Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai 200032, China. E-mail: zhaoguo@sjtu.edu.cn*

† Electronic supplementary information (ESI) available: Experimental procedures and full characterization data for all compounds are provided. See DOI: 10.1039/c2cc31002c

that if the hydrogenation of ε-chloro substituted δ-ketal-β-keto esters **1** could be successfully performed to yield enantiomerically pure ε-chloro substituted δ-ketal-β-hydroxy esters, it would provide a short and efficient access to the chiral ε-chloro substituted β-hydroxy-δ-oxo esters **A** by deprotecting the hydrogenated products. Herein we present an unprecedented work in the highly enantioselective hydrogenation of ε-substituted δ-ketal-β-keto esters.

Initially, the evaluation of the hydrogenation of **1a** was carried out at 55 °C with 0.4 mol% of [RuCl(benzene)(*S*)-SunPhos]Cl (ref. 12) in EtOH under 20 bar of H_2. Although complete conversion and up to 98.8% *ee* were observed, the combined yield of **2a** and **3a** was only 49%. To our delight, when the carbonyl protective group was changed to a glycol ketal, the hydrogenated product **2b** was obtained in excellent enantioselectivity (99.7% *ee*) and high yield (95%). However, when **1c** was hydrogenated, no expected product was observed and the ^{1}H NMR spectra of the crude hydrogenation products showed that the ketal was completely deprotected and a complicated mixture of byproducts was obtained (Scheme 2). *Because the hydrogenation substrates* **1a** *and* **1c** *are relatively stable under acidic conditions, we may conclude that the degradation occurred after the hydrogenation*. Comparing these results, we may infer that it was the strong electron-withdrawing ability of the chloro atom that restrained the formation of carbocations, which was crucial during the deprotection of δ-ketal.[14] Because diethoxy ketal is not as stable as glycol ketal,[14] the deprotection of the hydrogenated product occurred in the acidic system,[5c,13] and the deprotected product was further converted to a complex of unidentified byproducts. Without an electron-withdrawing group at the ε position, deprotection of the product would readily occur, and other byproducts would thereby come up. Unfortunately, no conversion of **2b** was observed when deprotection of the glycol ketal was conducted under commonly-used conditions, and only a 33% yield of the expected product was obtained when **2b** was treated with 2 M H_2SO_4 and refluxed in acetone for 14 h.[14] Because of the harsh reaction conditions, a complicated mixture of byproducts was obtained.

The low yields after the hydrogenation of **1a** and the deprotection of **2b** posed a dilemma for us when developing a practical asymmetric hydrogenation for a wide scope of ε-substituted δ-ketal-β-keto esters and obtaining the key intermediate **A** for statins. However, when we treated **2a** with a catalytic amount of *p*-toluenesulfonic acid in a mixed solvent of acetone and water, the diethoxy ketal was readily deprotected and a quantitative yield was obtained. Therefore, *it is desirable to establish the hydrogenation conditions under which degradation of the hydrogenated products can be avoided.*



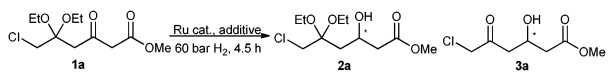
Scheme 2 Asymmetric hydrogenations of ε-substituted δ-ketal-β-keto esters.

To restrain the deprotection of the hydrogenated product **2a**, we increased the hydrogen pressure to 60 bar, based on initial hydrogenation conditions, and **1a** was completely converted after 4.5 h. The ratio of **2a** to deprotected product **3a** was 79/21, and they had the same *ee* of 99.2% (entry 1, Table 1), supporting our previous hypothesis that deprotection occurs after the hydrogenation, and the substrate is more stable than the product. After careful analysis of the hydrogenation products, unidentified complex products were found and the combined yields of **2a** and **3a** were generally less than 70%. Therefore, it is not efficient to suppress the degradation of the hydrogenated product by increasing the hydrogen pressure to shorten the reaction time, keeping the reaction conditions neutral during the hydrogenation process is an alternative that possibly works.

To remove the acidity, different alkali additives were tested. When organic nitrogen bases were used, only imidazole could give full conversion of **1a**, but the deprotection of the hydrogenated product was not effectively inhibited. The addition of Et_3N and iPr_2NEt impaired the activity of the catalyst, which may be due to the catalyst being poisoned by nitrogen (entries 2–4, Table 1). Consequently, when other alkali additives that did not contain nitrogen were tested, such as AcONa, inorganic carbonates or basic Al_2O_3, only $CaCO_3$ could not only completely restrain the deprotection of ketal during the hydrogenation, but also had no adverse affects on the activity of the catalyst (entries 5–8, Table 1). Furthermore, on adding more $CaCO_3$ to the system, the activity of the catalyst was not impaired and the same results were obtained (entry 7 *vs.* entry 9, Table 1).

To our surprise, the additive was also effective for substrates with 1,3-dioxolane ketals **1c** and **1d**, affording the corresponding hydrogenated products in high yields and with excellent *ee*s, **2c** (99.3%) and **2d** (99.5%) (entries 2 and 3, Table 2, respectively), while no expected product was observed when **1c** was hydrogenated under the initial hydrogenation

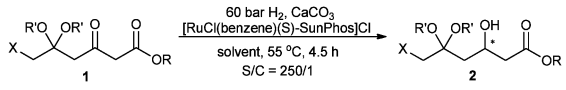
Table 1 Effects of additives on catalytic hydrogenation of **1a**[a]



Entry	Additives	Conv. (%)[b]	**2a**/**3a**[c]	*ee* of **2a** (%)[d]
1	none	100	79/21	99.2/99.2[d]
2	Et_3N	86	54/46	99.0
3	iPr_2NEt	90	**2a**	98.9
4	Imidazole	100	28/72	99.3
5	AcONa	92	**2a**	99.0
6[e]	K_2CO_3	0	NA	NA
7[f]	$CaCO_3$	100	**2a**	99.2
8[f]	Al_2O_3	100	79/21	99.0
9[g]	$CaCO_3$	100	**2a**	99.2

[a] Reaction conditions: **1a** (1.25 mmol), 0.4 mol% of [RuCl(benzene)(*S*)-SunPhos]Cl, and 0.4 mol% of additive in EtOH (3 mL). [b] Determined by ^{1}H NMR. [c] The molar ratio of **2a**/**3a** was calculated by the direct integration of appropriate signals. [d] The *ee* of **2a** and **3a** was determined *via* their corresponding 4-chlorobenzenethiol substituted derivatives by HPLC (see ESI). [e] 1.2 mol% of K_2CO_3. [f] 3.2 mol% of additives. [g] 9.6 mol% of $CaCO_3$, 97% isolated yield.

Table 2 The asymmetric hydrogenation of **1** by [RuCl(benzene)(*S*)-SunPhos]Cl in the presence of $CaCO_3$[a]



Entry	X	R'	R	2	Yield (%)[b]	*ee* (%)[c]
1	Cl	Et	Me	**2a**	97	99.2[d]
2	H	–$(CH_2)_2$–	Me	**2c**	79	99.3(*S*)[e]
3	Me	–$(CH_2)_2$–	Me	**2d**	81	99.5[e]
4	Cl	Et	Et	**2e**	95	99.4[d]
5[f]	Cl	Me	Me	**2f**	91	99.2[d]
6[g]	BnO	–$(CH_2)_2$–	Me	**2g**	93	99.2[h]
7[i]	BnO	–$(CH_2)_2$–	Et	**2h**	91	99.2[h]
8	BnO	–$(CH_2)_2$–	*t*Bu	**2i**	95	99.6[h]

[a] Reaction conditions: **1** (1.25 mmol), $CaCO_3$ (12 mg) and 0.4% mol [RuCl(benzene)(*S*)-SunPhos]Cl in EtOH (3 mL). [b] Yield of isolated product. [c] Absolute configuration of **2c** was determined by the comparison of the optical rotation of **3c** with literature values, the configuration of other products can be assigned as *S* according to the well-established general trend (see ref. 7*a* and 15). [d] Values of the *ee* of the corresponding 4-chlorobenzenethiol substituted derivatives. [e] Values of the *ee* of their *p*-nitrobenzoates. [f] MeOH as solvent. [g] 65 °C. [h] The *ee* values were determined directly by HPLC. [i] 75 °C, 10 h.

conditions. Additionally, the asymmetric hydrogenation of substrates possessing acyclic ketals, **1e** and **1f**, gave excellent *ee*s of **2e** (99.4%) and **2f** (99.2%) (entries 4 and 5, Table 2, respectively). However, a higher temperature was needed for the full conversion of ε-benzyloxy substituted substrates with glycol ketals. Asymmetric hydrogenations of **1g** and **1h** were conducted at 65 °C and 75 °C, respectively, and the same excellent *ee*s of **2g** (99.2%) and **2h** (99.2%) were obtained. Substrate **1i** (R = *tert*-butyl) was hydrogenated successfully to yield **2i** with 99.6% *ee* and 95% yield (entries 6–8, Table 2).

To illustrate the utility of hydrogenated products, **2a**, **2c** and **2d** can be readily deprotected using a catalytic amount of tosylic acid in high yields, giving β-hydroxy-δ-oxo esters, which could be used to synthesize key intermediates of chiral drugs.[16,17]

In conclusion, we have described an effective method for Ru-catalyzed asymmetric hydrogenation of ε-substituted δ-ketal-β-hydroxy esters in the presence of catalytic amounts of $CaCO_3$, giving the hydrogenated products with remarkably high enantioselectivities and high yields. Calcium carbonate played a key role in removing the acidity and maintaining the high enantioselectivity during the hydrogenation reaction. These hydrogenated products can be readily converted into β-hydroxy-δ-oxo esters, which are important chiral building blocks for many pharmaceutical products.

This work was financially supported by National Natural Science Foundation of China.

Notes and references

1 (*a*) M. H. Davidson and J. G. Robinson, *Expert Opin. Pharmacother.*, 2006, **7**, 1701; (*b*) J. Kidd, *Nat. Rev. Drug Discovery*, 2006, **5**, 813.
2 Z. Časar, *Curr. Org. Chem.*, 2010, **14**, 816.
3 (*a*) T. Rosen and C. H. Heathcock, *J. Am. Chem. Soc.*, 1985, **107**, 3731; (*b*) C. H. Heathcock, C. R. Hadley, T. Rosen, P. D. Theisen and S. J. Hecker, *J. Med. Chem.*, 1987, **30**, 1858; (*c*) D. S. Karanewsky, M. F. Malley and J. Z. Gougoutas, *J. Org. Chem.*, 1991, **56**, 3744; (*d*) T. Konoike and Y. Araki, *J. Org. Chem.*, 1994, **59**, 7849; (*e*) M. Acemoglu, A. Brodbeck, A. Garcia, D. Grimier, M. Hassel, B. Riss and R. Schreiber, *Helv. Chim. Acta*, 2007, **90**, 1069; (*f*) K.-M. Lim, *PCT Int. Appl. WO2003087112*, 2003; (*g*) A. Korostylev, V. Andrushko, N. Andrushko, V. I. Tararov, G. König and A. Börner, *Eur. J. Org. Chem.*, 2008, 840; (*h*) V. Andrushko, N. Andrushko, G. König and A. Börner, *Tetrahedron Lett.*, 2008, **49**, 4836; (*i*) N. Andrushko, V. Andrushko, V. Tararov, A. Korostylev, G. König and A. Börner, *Chirality*, 2010, **22**, 534.
4 (*a*) A. Michaelis and R. Kaehne, *Ber.*, 1898, **31**, 1048; (*b*) A. E. Arbuzov, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 687; (*c*) M. Kitamura, M. Tokunaga and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 2931.
5 (*a*) I. Ojima, *Catalytic Asymmetric Synthesis*, Wiley, Hoboken, 3rd edn, 2010; (*b*) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029; (*c*) R. Noyori, *Angew. Chem., Int. Ed.*, 2002, **41**, 2008.
6 (*a*) L. Shao, T. Seki, H. Kawano and M. Saburi, *Tetrahedron Lett.*, 1991, **32**, 7699; (*b*) L. Shao, H. Kawano, M. Saburi and Y. Uchida, *Tetrahedron*, 1993, **49**, 1997.
7 (*a*) V. Blandin, J. F. Carpentier and A. Mortreux, *Eur. J. Org. Chem.*, 1999, 3421; (*b*) V. Blandin, J. F. Carpentier and A. Mortreux, *Eur. J. Org. Chem.*, 1999, 1787; (*c*) V. Blandin, J. F. Carpentier and A. Mortreux, *New J. Chem.*, 2000, **24**, 309; (*d*) K. Everaere, N. Franceschini, A. Mortreux and J. F. Carpentier, *Tetrahedron Lett.*, 2002, **43**, 2569; (*e*) G. Juszkiewicz and J. Jurczak, *Org. Prep. Proced. Int.*, 2002, **34**, 187.
8 (*a*) O. Labeeuw, D. Blanc, P. Phansavath, V. Ratovelomanana-Vidal and J.-P. Genêt, *Eur. J. Org. Chem.*, 2004, **11**, 2352; (*b*) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya and R. Noyori, *J. Am. Chem. Soc.*, 1988, **110**, 629; (*c*) W. Fan, W. Li, X. Ma, X. Tao, X. Li, Y. Yao, X. Xie and Z. Zhang, *J. Org. Chem.*, 2011, **76**, 9444.
9 (*a*) O. Poupardin, C. Greck and J.-P. Genêt, *Synlett*, 1998, **11**, 1279; (*b*) V. I. Tararov, N. Andrushko, V. Andrushko, G. König, A. Spannenberg and A. Börner, *Eur. J. Org. Chem.*, 2006, **24**, 5543.
10 (*a*) K. Junge, B. Hagemann, S. Enthaler, G. Oehme, M. Michalik, A. Monsees, T. Riermeier, U. Dingerdissen and M. Beller, *Angew. Chem., Int. Ed.*, 2004, **43**, 5066; (*b*) C.-C. Pai, C.-W. Lin, C.-C. Lin, C.-C. Chen, A. S. C. Chan and W. T. Wong, *J. Am. Chem. Soc.*, 2000, **122**, 11513; (*c*) Y.-G. Zhou, W. Tang, W. B. Wang, W. Li and X. Zhang, *J. Am. Chem. Soc.*, 2002, **124**, 4952.
11 T. Nishi, M. Kitamura, T. Ohkuma and R. Noyori, *Tetrahedron Lett.*, 1988, **29**, 6327.
12 (*a*) W. Li, X. Ma, W. Fan, X. Tao, X. Li, X. Xie and Z. Zhang, *Org. Lett.*, 2011, **13**, 3876; (*b*) Y. Yao, W. Fan, W. Li, X. Ma, L. Zhu, X. Xie and Z. Zhang, *J. Org. Chem.*, 2011, **76**, 2807.
13 V. I. Tararov, G. König and A. Börner, *Adv. Synth. Catal.*, 2006, **348**, 2633.
14 (*a*) P. G. M. Wuts and T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, Wiley, Hoboken, 4th edn, 2007, p. 431; (*b*) S. W. Smith and M. S. Newman, *J. Am. Chem. Soc.*, 1968, **90**, 1249.
15 J.-P. Genêt, C. Pinel, V. Ratovelomanana-Vidal, S. Mallart, X. Pfister, L. Bischoff, M. C. Caño De Andrade, S. Darses, C. Galopin and J. A. Laffitte, *Tetrahedron: Asymmetry*, 1994, **5**, 675.
16 (*a*) C. L. Sann, T. J. Simpson, D. I. Smith, P. Watts and C. L. Willis, *Tetrahedron Lett.*, 1999, **40**, 4093; (*b*) K.–M. Cheung, S. J. Coles, M. B. Hursthouse, N. I. Johnson and P. M. Shoolingin-Jordan, *Angew. Chem., Int. Ed.*, 2002, **41**, 1198.
17 D.-D. Donatienne, F. Andreas, K. Ernst, O. Lukas and S. Gottfried, *PCT Int. Appl. WO 2004056832*, 2004.