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Highly enantioselective hydrogenation of 3,5-diketo esters: a formal synthesis of tetrahydrolipstatin

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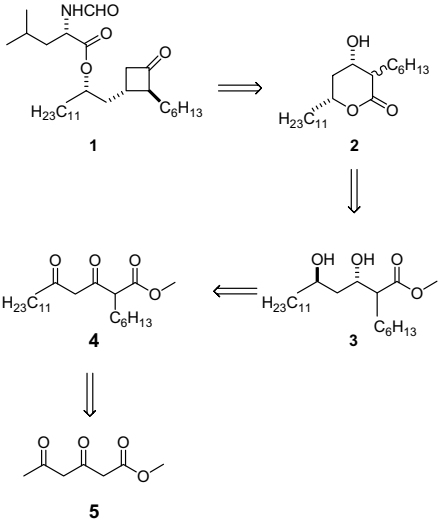
Abstract—Compound **4**, obtained via a sequence of two consecutive alkylations of methyl 3,5-dioxohexanoate (**5**), was transformed into the enantiomerically pure lactone (3*S*,4*S*,6*R*)-**2** being the precursor of tetrahydrolipstatin (**1**). The reaction sequence involves asymmetric catalytic hydrogenation of **4** as a crucial step.

Asymmetric catalytic hydrogenation of keto esters is an ideal method for preparation of the corresponding synthetically significant alcohols. In the last decade, high catalytic activity and excellent enantioselectivity have been obtained by means of chiral phosphine-Ru complexes.[1]

Recently, we have demonstrated that 3-keto esters[2] and 4-keto esters[3] as well as 3,5-diketo esters[4] were efficiently hydrogenated in the presence of cationic BINAP-Ru(II) complexes, affording almost enantiomerically pure (95–99% ee) hydroxy esters, useful intermediates for the preparation of pheromones.

Now we report a new application of this methodology to the highly stereoselective synthesis of tetrahydrolipstatin (**1**),[5] a saturated derivative of lipstatin[6,7] isolated from *Streptomyces toxytricini*, an inhibitor of pancreatic lipases.

Based on the retrosynthetic analysis of tetrahydrolipstatin (**1**) as shown in Scheme 1, we concluded that the hydroxy lactone **2**,[8,9] readily accessible via asymmetric hydrogenation of the suitably substituted 3,5-diketo ester **4**,[10] would be a suitable intermediate for the target compound **1**.



Scheme 1.

In the first step of the synthesis, we converted 3,5-dioxohexanoic acid methyl ester (**5**) into its racemic 2,6-dialkyl derivative **4** (Scheme 2). The reaction of ester **5** with copper(II) diacetate resulted in formation of complex **6**, which was then subjected to alkylation with *n*-hexyl bromide.[11] The racemic compound **7** obtained was then alkylated with *n*-decyl bromide, to give the desired derivative **4** in 40% overall yield. The intermediate **4** can be prepared in similar yield by changing the reaction sequence to **5** → **8** → **9** → **4** (Scheme 2).

Keywords: Tetrahydrolipstatin; Asymmetric synthesis; 3,5-Diketo esters; Enantioselective catalysis.
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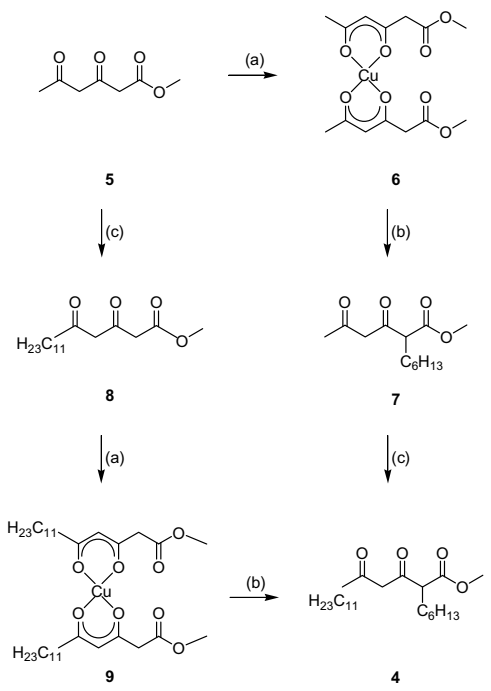


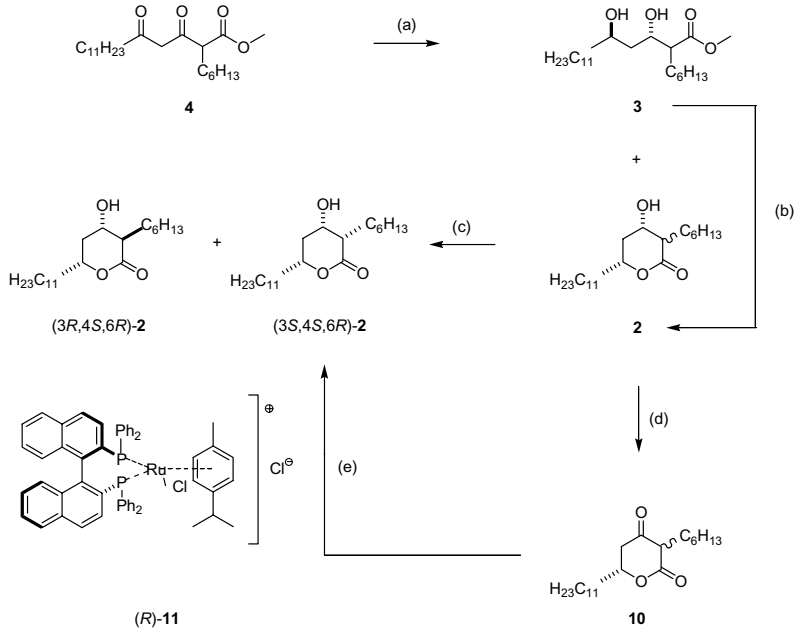
Scheme 2. (a) $Cu(OAc)_2$, $MeOH/H_2O$; (b) NaH, $C_6H_{13}Br$, KI, Bu_4NBr, THF, reflux; (c) (i) NaH, BuLi, THF, 0 °C; (ii) $C_{10}H_{21}Br$, reflux.

The key step of the synthesis was the asymmetric hydrogenation of ester **4** in the presence of (*R*)-**11** as catalyst[1] in methanolic solution at 60 °C under a hydrogen pressure of 100 atm for 18 h. This resulted in a mixture of the ester **3** and the hydroxy lactone **2** in a 3:1 ratio in 80% overall yield (Scheme 3). The product mixture containing the compounds **2** and **3** was in turn treated with PPTS in toluene to afford a 3:1 mixture of *cis*,*cis*-**2** and *trans*,*cis*-**2** diastereoisomers. Chromatographical separation allowed us to obtain analytical samples of both pure diastereoisomers, however, it was preparatively ineffective. Therefore, we decided to subject the resulting mixture of hydroxy lactones **2** to oxidation with Jones reagent, expecting equilibration of the product **10** to the more thermodynamically stable diastereoisomer. The latter, hydrogenated again in the presence of Adam's catalyst, should afford the stereochemically pure product. Indeed, this transformation gave the required product (3*S*,4*S*,6*R*)-**2** in greater than 98% ee. Its analytical data[12] were in agreement with the literature values.[8]

The sequence of consecutive oxidations and reductions presented herein allowed us to use both diastereoisomers of the hydroxy lactone **2** for the synthesis of tetrahydrolipstatin (**1**). The formal synthesis of tetrahydrolipstatin has been achieved in this manner, since the intermediate (3*S*,4*S*,6*R*)-**2** has been successfully used by Barbier and Schneider[8] in their highly stereoselective synthesis of **1** published earlier.

References and notes

1. Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamomoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 199–246.
2. Juszkiewicz, G.; Asztemborska, M.; Jurczak, J. *Synth. Commun.* **2002**, *32*, 2605.
3. Juszkiewicz, G.; Asztemborska, M.; Jurczak, J. *Polish J. Chem.* **2002**, *76*, 1707.
4. Juszkiewicz, G.; Jurczak, J. *Org. Prep. Proced. Int.* **2002**, *34*, 187.
5. Hogan, S.; Fleury, A.; Hadvary, P.; Lengsfeld, H.; Meier, M. K.; Triscari, J.; Sullivan, A. C. *Int. J. Obes.* **1987**, *11*(Suppl. 3), 35.



Scheme 3. (a) H_2, (*R*)-**11** (cat), MeOH, 100 atm, 60 °C, 18 h, 80%; (b) PPTS, toluene, 50 °C, 2 h, 92%; (c) chromatographic separation; (d) CrO_3, H_2SO_4, acetone, 0 °C, 1 h, 0%; (e) H_2, Pt (cat), EtOAc, 45 atm, 20 °C, 48 h, 85%.

6. Weibel, E. K.; Hadvary, P.; Hochuli, E.; Kupfer, E.; Lengsfeld, H. *J. Antibiot.* **1987**, *40*, 1081.
7. Hochuli, E.; Kupfer, E.; Maurer, R.; Meister, W.; Mercadal, Y.; Schmidt, K. *J. Antibiot.* **1987**, *40*, 1086.
8. Barbier, P.; Schneider, F. *J. Org. Chem.* **1988**, *53*, 1218.
9. Chadha, N. K.; Batcho, A. D.; Tang, P. C.; Courtney, L. F.; Cook, C. M.; Wovkulich, P. M.; Uskokovic, M. R. *J. Org. Chem.* **1991**, *56*, 4714.
10. Batelaan, J. G. *Synth. Commun.* **1976**, *6*, 81.
11. Carvello, J.; Marquet, J.; Moreno-Manas, M. *Tetrahedron* **1990**, *46*, 2035.
12. Selected analytical data for (3*S*,4*S*,6*R*)-**2**: mp 95–96 °C (from ether/hexane); $[\alpha]_D^{27}$ 43.0 (*c* 0.32, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 4.4–4.3 (dt, 1H, $J_{aa} = 8.5$, $J_{ae} = 3.5$ Hz), 4.3–4.1 (m, 1H), 2.5–2.1 (m, 2H), 2.0–1.9 (m, 1H), 1.8–1.2 (m, 31H), 0.88 (t, 6H, $J = 7$ Hz).