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A stereoselective synthesis of (—)-tetrahydrolipstatin

Arun K. Ghosh and **Chunfeng Liu**

Department of Chemistry, University of Illinois at Chicago, 845 W. Taylor Street, Chicago, Illinois 60607, USA

A stereoselective synthesis of (2)-tetrahydrolipstatin has been accomplished utilizing olefin metathesis of an acrylate ester as the key step.

Tetrahydrolipstatin **1**, a member of the lipstatin class of blactone microbial agents, is a potent and irreversible inhibitor of pancreatic lipase.[1] The lipase enzyme is responsible for the digestion of fat in the diet of humans.[2] The strained b-lactone functionality of **1** is critical to its lipase inhibitory properties. The inactivation mechanism involves an irreversible acylation of the active site serine residue of pancreatic lipase by the blactone moiety.[3] Recent clinical studies have revealed that treatment with **1** along with diet modifications have led to sustained weight loss in humans.[4] Indeed, Hoffman-La Roche Laboratories have now introduced (2)-tetrahydrolipstatin under the trade name Xenical® as an anti-obesity agent. The important biological properties along with its unique structural features have stimulated interest in the synthesis of **1** and its structural variants.[5] Herein we report an asymmetric synthesis of (2)-tetrahydrolipstatin. The key synthetic strategy involves a stereoselective construction of a *syn*-1,3-diol synthon by olefin metathesis, stereoselective epoxidation and regioselective epoxide reduction followed by its elaboration to **1**.

As depicted in Scheme 1, we planned to construct the blactone ring from the corresponding β-hydroxy acid derivative **2**. The elaboration of the *syn*-1,3-diol functionality and stereoselective introduction of the C-2 alkyl chain in **2** would be achieved from the α, β - unsaturated δ-lactone **3**. The intermediate **3** would be derived from ring-closing metathesis of the corresponding acrylate ester **4**. Recently, a number of convenient syntheses of various α,β-unsaturated γ- and δ-lactones have been reported involving ring closing metathesis of acrylates utilizing Grubbs' catalyst.[6] The broad synthetic utility of Grubbs' catalyst is now well established.[7] The key starting material, homoallylic alcohol **5** was prepared in multigram quantities by Keck's enantioselective allylation of dodecanal employing a catalytic amount (10 mol%) of (*R*)-BINOL and $Ti(OPr^i)_4$ to furnish **5** in 90% yield.[8] The optical purity of the alcohol **5** [92% ee, $[\alpha]_D^{23}$ – 6.3 (*c* 1.23, $CHCl_3$)] was obtained by formation of the Mosher ester and ^{19}F NMR analysis.[9] Reaction of **5** with acryloyl chloride (1.2 equiv.) and Et_3N (3 equiv.) in the presence of a catalytic amount of DMAP in CH_2Cl_2 provided the acrylate ester **4** in 91% yield after silica gel chromatography (Scheme 2). Olefin metathesis of **4** with commercially available Grubbs' catalyst (10 mol%) in the presence of $Ti(OPr^i)_4$ (0.3 equiv.) in refluxing CH_2Cl_2 (0.007 M solution) for 15 h afforded the α,β-unsaturated δ-lactone **3** in 93% yield. Consistent with our earlier report, exposure of

acrylate ester **4** to Grubbs' catalyst (10 mol%) in CH_2Cl_2 for 15 h in the absence of $Ti(OPr^i)_4$ resulted in low conversion of lactone **3** (50% by ^1H NMR) with a substantial amount of unreacted starting material remaining.[6b] Epoxidation of lactone **3** was carried out with alkaline H_2O_2 in MeOH at 23 °C for 1 h. Acidification, extractive work-up followed by azeotropic removal of the water by heating in benzene furnished the epoxide **6** as a single isomer. Epoxidation of **3** proceeded stereoselectively from the less hindered β-face.[10] Exposure of epoxide **6** to PhSeSePh and $NaBH_4$ in Pr^iOH at 0 °C in the presence of AcOH resulted in regioselective reduction of the epoxide to afford the β-hydroxy-lactone **7** in 83% yield (from **3**) after silica gel chromatography.[11] Thus, the sequence of reactions involving olefin metathesis, stereoselective epoxidation and regioselective epoxide reduction constitute an effective protocol for the *syn*-1,3-diol synthon **9**. For introduction of the C-2 alkyl chain, attempted direct alkylation of the β-hydroxylactone **7** under a variety of reaction conditions was unsuccessful. Therefore, the elaboration of the C-2 side chain was carried out by an alternate route using Seebach's asymmetric alkylation of β-hydroxy esters.[12]

The β-hydroxy lactone **7** was first protected as a TBDMS ether **8** by treatment with TBDMSCl and Pr^i_2NEt in DMF at 23 °C for 12 h. Lactone **8** was converted to β-hydroxy ester **10** in a three step sequence involving (i) opening of the lactone ring by exposure to Et_3N in MeOH at 23 °C for 12 h, (ii) protection of the resulting δ-hydroxy methyl ester as THP ether, and (iii) removal of the TBDMS group by treatment with Bu_4NF in THF in the presence of AcOH at 23 °C for 5 h (60% from **7**). The C(2) hexyl side chain was then introduced by an asymmetric alkylation of the β-hydroxy ester **10** (Scheme 3). Thus, methyl ester **10** was treated with LDA (2.2 equiv.) in the presence of HMPA (5 equiv.) in THF at −78 °C and the reaction mixture was warmed to −50 °C for 2 h. The resulting dianion was cooled to −78 °C and reacted with hexyl iodide (2 equiv.) at −78 to 0 °C for 6 h to afford the alkylated product **11** in 85% yield (based upon 30% recovery of starting material). The removal of the THP ether group in **11** revealed excellent diastereoselectivity (ratio 22:1 by ^{13}C NMR).[13] The stereochemical course of such alkylation processes has been well-established previously.[12]

Saponification of ester **11** with aqueous LiOH followed by exposure of the resulting acid to $PhSO_2Cl$ in pyridine at 0 °C for 8 h, as described by Barbier and Schneider, afforded the β-lactone **12** in 84% yield (from **11**).[5k] The removal of the THP group by treatment with PPTS in EtOH at reflux furnished the (5*S*)-hydroxy β-lactone **13** [$[\alpha]_D^{23}$ – 14.4 (*c* 1.2, $CHCl_3$)] as a single isomer. Attempted esterification with *N*-formylleucine under a variety of conditions failed to provide satisfactory results. To complete the synthesis, *N*-formylleucine was introduced by an alternate protocol as described by Uskokovic *et al.*[5g] Esterification of **13** with Cbz-leu and DCC in the presence of DMAP provided the Cbz derivative **14** in 95% yield.[14] Catalytic hydrogenation of **14** over 10% Pd-C followed by *N*-formylation of the resulting amine with formic acetic anhydride in THF at 23 °C for 1 h furnished the synthetic (2)-tetrahydrolipstatin **1** [$[\alpha]_D^{23}$ – 33.8 (*c* 1.4, $CHCl_3$); lit.,[1] $[\alpha]_D^{23}$ – 34.45, (*c* 1, CHCl3)]. Spectral data (IR and 400 MHz ^1H NMR) for the synthetic tetrahydrolipstatin are identical to those reported for the natural product.[1]

In summary, an asymmetric synthesis of (—)-tetrahydrolipstatin has been accomplished. A number of key features of this synthesis are noteworthy; a Keck enantioselective allylation of dodecanal, olefin metathesis of an acrylate ester to an unsaturated δ-lactone, elaboration of this lactone to a *syn*-1,3-diol synthon and Seebach's asymmetric alkylation of a β-hydroxy ester.

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Notes and references

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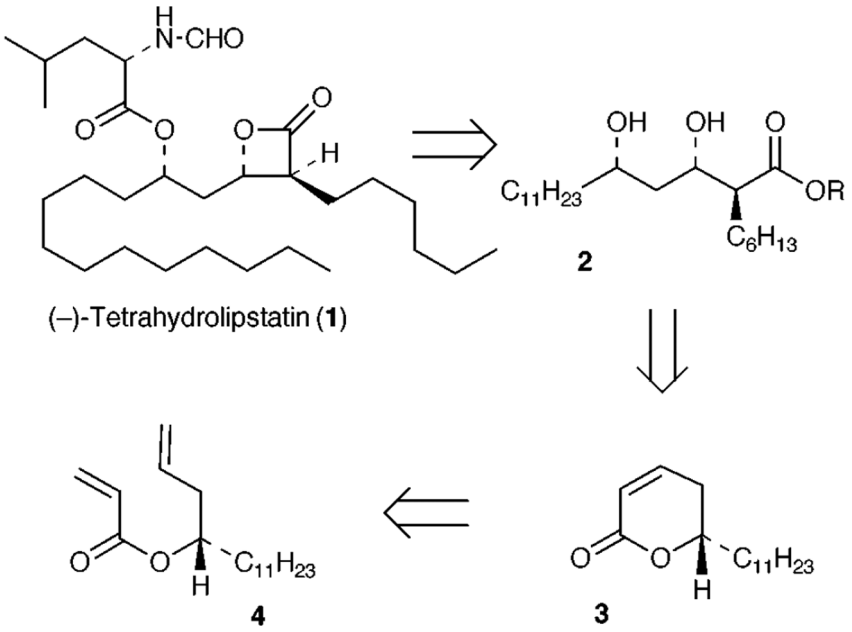
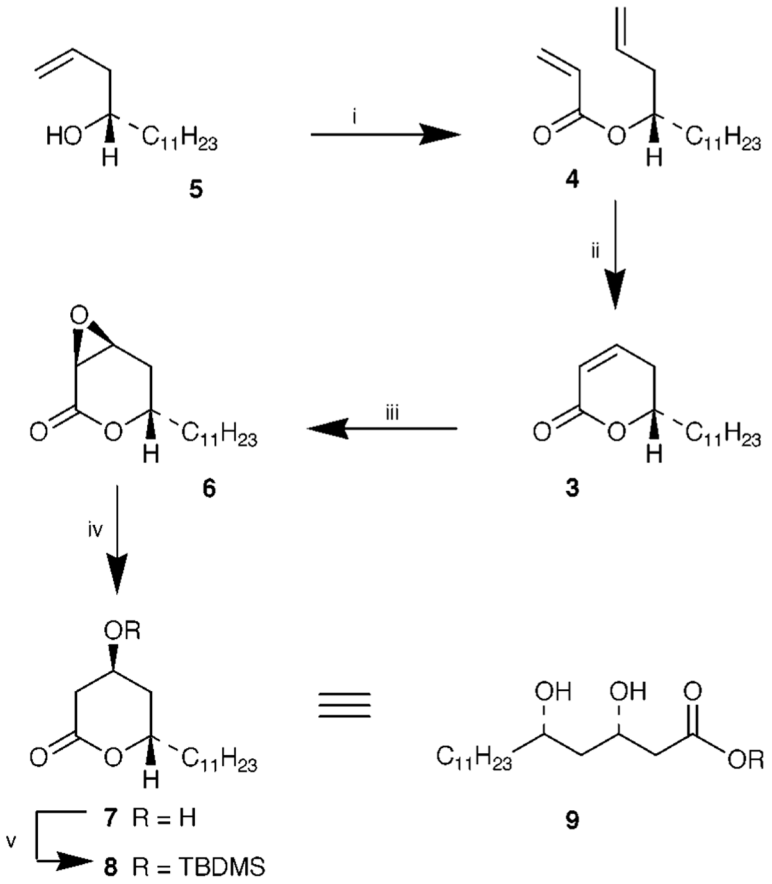
13. Alkylation of the corresponding b-hydroxy ester containing an anti-dbenzyloxy group proceeded with excellent diastereoselectivity (40+1). [ref. 5(e)]. Thus, the stereochemistry of the remote alkoxy group has little influence on the stereochemical outcome of this alkylation process.
14. All new compounds gave satisfactory spectroscopic and analytical results.

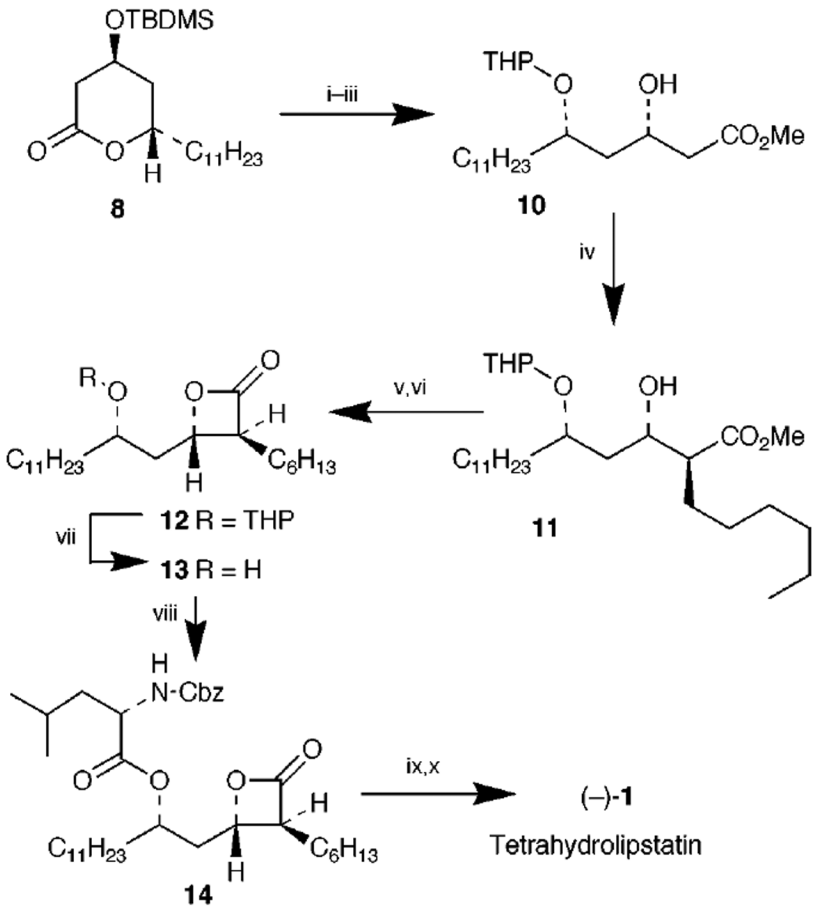


Scheme 1.



Scheme 2.

Reagents and conditions: i, CH_2=CHCOCl, Et_3N, DMAP, 23 °C (91%); ii, $(PCy_3)_2Cl_2Ru$=CHPh (10 mol%), $Ti(OPr^i)_4$ (0.3 equiv.), CH_2Cl_2, 40 °C (93%); iii, aq. NaOH, H_2O_2, 23 °C; iv, PhSeSePh, $NaBH_4$, Pr^iOH, AcOH, 0 °C (83%); v, TBDMSCl, Pr^i_2NEt, DMF, 25 °C (98%).



Scheme 3.

Reagents and conditions: i, Et_3N, MeOH, 23 °C, 12 h (75%); ii, DHP, PPTS, 8 h; iii, Bu_4NF, THF, AcOH, 25 °C, 5 h (60% from **7**); iv, LDA, HMPA, $C_6H_{13}I$, THF, −78 to 0 °C, 6 h (70% conversion, 85%); v, aq. LiOH, 25 °C, 12 h, H^+; vi, $PhSO_2Cl$, Py, 0 °C, 8 h (84% from **11**); vii, PPTS, EtOH, reflux, 3 h (90%); viii, Cbz-Leu, DCC, DMAP (95%); ix, H_2, Pd-C, 12 h; x, AcOCHO, THF, 25 °C, (87%).