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A stereoselective synthesis of (−)-tetrahydrolipstatin

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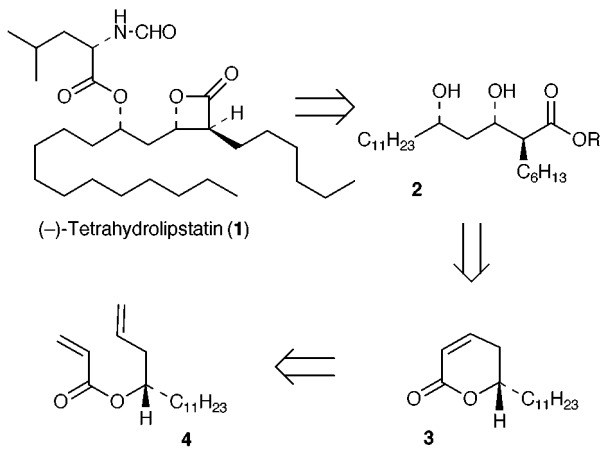
A stereoselective synthesis of (−)-tetrahydrolipstatin has been accomplished utilizing olefin metathesis of an acrylate ester as the key step.

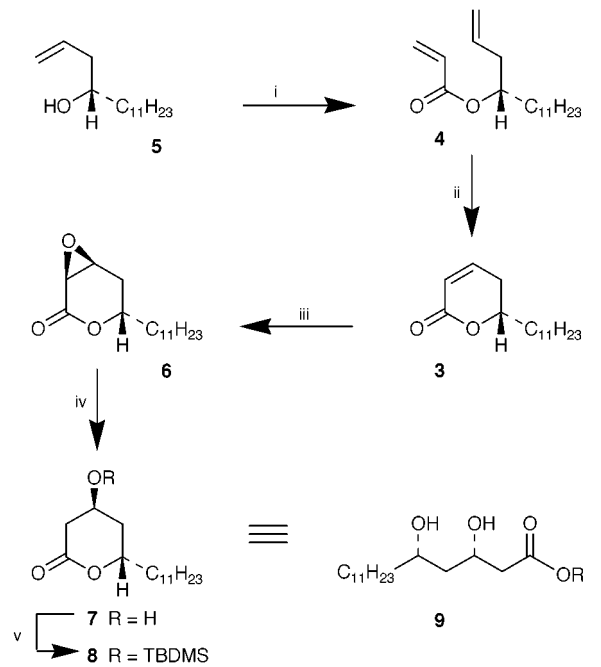
Tetrahydrolipstatin **1**, a member of the lipstatin class of β-lactone microbial agents, is a potent and irreversible inhibitor of pancreatic lipase.[1] The lipase enzyme is responsible for the digestion of fat in the diet of humans.[2] The strained β-lactone functionality of **1** is critical to its lipase inhibitory properties. The inactivation mechanism involves an irreversible acylation of the active site serine residue of pancreatic lipase by the β-lactone 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 (−)-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 (−)-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 β-lactone 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-hydroxy-lactone **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]

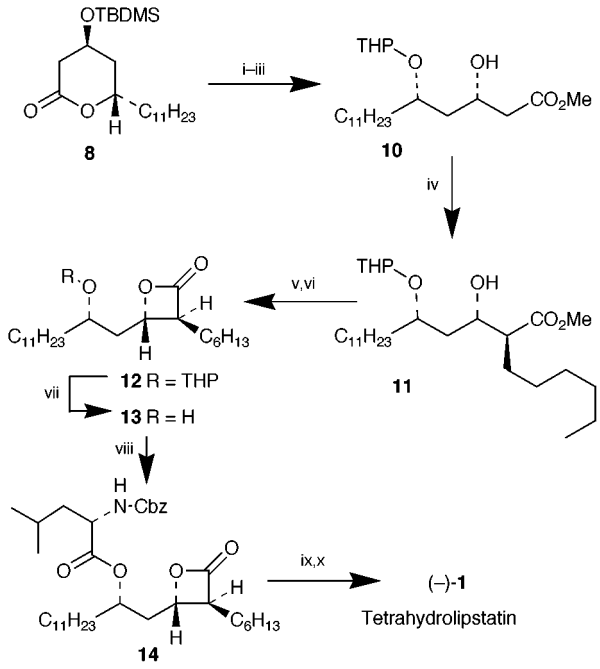
The β-hydroxy lactone **7** was first protected as a TBDMS ether **8** by treatment with TBDMSCl and Pr^i_2NEt in DMF at



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%).

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 (−)-tetrahydrolipstatin **1** [$[\alpha]_D^{23}$ −33.8, (*c* 1.4, $CHCl_3$); lit.,[1] $[\alpha]_D^{23}$ −34.45, (*c* 1, $CHCl_3$)]. 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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13 Alkylation of the corresponding β-hydroxy ester containing an *anti*-δ-benzyloxy 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.

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