

Asymmetric Synthesis of (–)-Tetrahydrolipstatin: An *anti*-Aldol-Based Strategy

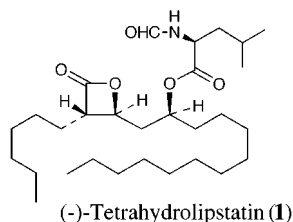
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ABSTRACT



A stereoselective synthesis of (–)-tetrahydrolipstatin is described. The synthesis involves an asymmetric ester derived titanium enolate *anti*-aldol reaction, a nitro-aldol reaction to append the C-2' C₁₁ side chain, and a diastereoselective reduction of a β -hydroxy ketone to an *anti*-1,3-diol functionality followed by its elaboration to (–)-tetrahydrolipstatin.

Tetrahydrolipstatin (**1**), a β -lactone, triglyceride mimic, is the saturated analogue of lipstatin, which was isolated from *Streptomyces toxytricini* in 1987.¹ It is a potent and irreversible inhibitor of pancreatic lipase.^{1b} Recently, (–)-tetrahydrolipstatin has been marketed in several countries as an antiobesity agent under the name Xenical. The key to the biological activity of **1** is the β -lactone moiety, featuring *anti*-stereochemistry about the ring. The lactone has been shown to bind irreversibly to an active site serine of pancreatic lipase.² Due to its biological properties, tetrahydrolipstatin has been the subject of immense synthetic activity since its isolation.³

As part of our continuing interest in tetrahydrolipstatin,^{3b} we herein report a novel, diastereoselective synthesis of (–)-tetrahydrolipstatin. The key steps include an asymmetric ester derived titanium enolate *anti*-aldol reaction, a nitro-aldol reaction to append the C-2' C₁₁ side chain, and a diastereo-

selective reduction of a β -hydroxy ketone to an *anti*-1,3-diol functionality. As shown in Figure 1, the key structural

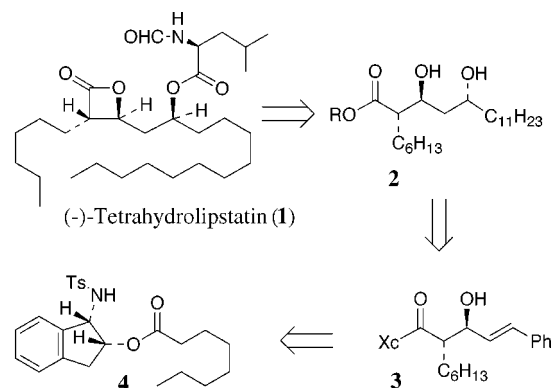


Figure 1.

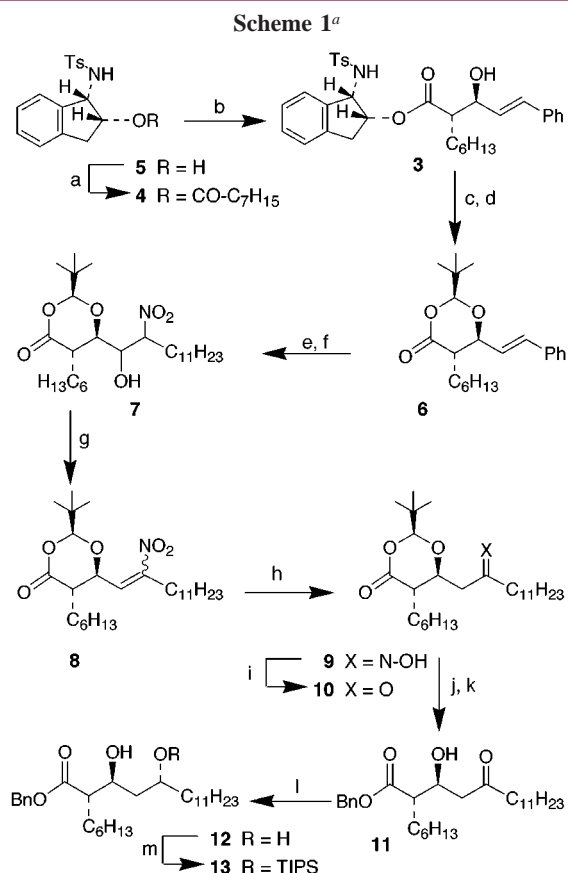
element is the sensitive β -lactone, which we envision closing late in the synthesis. The key intermediate **2** can be prepared

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from *anti*-aldol adduct **3**. The *anti*-selective aldol reaction of ester **4** and *trans*-cinnamaldehyde will provide **3**. Stereocontrolled generation of such *anti*-aldol fragments has been described by us recently.⁴

Thus, ester **4** is made from the known *N*-tosyl-1-amino-2-indanol⁴ by coupling with octanoyl chloride in the presence of pyridine in CH₂Cl₂ at 23 °C for 2 h in 92% yield after silica gel chromatography (Scheme 1). The titanium enolate



^a (a) C₇H₁₅COCl, pyridine, CH₂Cl₂, 23 °C, 92%; (b) TiCl₄, *i*Pr₂NEt, CH₂Cl₂, 0 °C to 23 °C, then Bu₂BOTf, *trans*-cinnamaldehyde, CH₂Cl₂, -78 °C, 60%; (c) LiOOH, THF-H₂O (3:1), 0 °C to 23 °C, 92%; (d) 4 Å MS, Me₃CCHO, TMSO*i*Pr, TMSOTf, CH₂Cl₂, -78 °C to -20 °C, 79%; (e) O₃, CH₂Cl₂, -78 °C, then Ph₃P, -78 °C to 23 °C, 84%; (f) *n*Bu₄N⁺F⁻, C₁₂H₂₅NO₂, DMF, 23 °C, 82%; (g) DCC, CuCl, CH₃CN, 60 °C, 80%; (h) Zn, AcOH, THF, 0 °C, 50%; (i) CAN, HNO₃, EtOH, -45 °C, 77%; (j) 4 N HCl, THF, 23 °C, 98%; (k) CsCO₃, MeOH-H₂O (6:1) then BnI, DMF, 23 °C, 60%; (l) Me₄NB(OAc)₃H, AcOH-CN₃CN (1:1), -40 °C, 99%; (m) TIPSOTf, 2,6-lutidine, CH₂Cl₂, -78 °C, 96%.

was formed by treatment of ester **4** with TiCl₄ (1.2 equiv) in CH₂Cl₂ at 0–23 °C for 15 min followed by addition of *N,N'*-diisopropylethylamine (4 equiv) at 23 °C and stirring of the resulting brown solution for 2 h. The resulting enolate was cooled to -78 °C, and *trans*-cinnamaldehyde precomplexed with Bu₂BOTf (1.5 equiv) was added to provide the *anti*-aldol adduct **3** in 60% yield, as a mixture of *anti*- and *syn*-diastereomers (6.1:1).^{4a} The mixture was separated by silica gel chromatography (20% ethyl acetate in hexanes as

the eluent), and diastereomerically pure **3** was subsequently utilized for the synthesis. In a one-pot procedure, when the above Ti-enolate was cooled to -78 °C and reacted with excess *trans*-cinnamaldehyde (4 equiv) in the presence of additional TiCl₄ (2.2 equiv) and *N,N'*-diisopropylethylamine (6 equiv), aldol adduct **3** was obtained exclusively in 38% yield. However, attempts to further improve the yield were unsuccessful.

Saponification of ester **3** was carried out by exposure to aqueous lithium hydroperoxide in THF at 23 °C for 40 h affording the corresponding β-hydroxy acid in 92% yield. The chiral template **5** was fully recovered. Attempts to protect the resulting β-hydroxy acid as a *tert*-butyl-1,3-dioxan-4-one using pivalaldehyde and a variety of Brønsted acids (CSA, PPTS, TsOH) in the presence of 4 Å molecular sieves led only to recovered starting material.

Dioxanone **6** was however prepared efficiently utilizing the protocol described by Crich et al.⁵ Thus, reaction of the resulting β-hydroxy acid with pivalaldehyde, isopropoxytrimethylsilane, and TMSOTf in the presence of 4 Å molecular sieves at -78 to -20 °C for 16 h afforded the 1,3-dioxane derivative **6** as an 11:1 mixture of diastereomers (by ¹H and ¹³C NMR) in 79% yield after silica gel chromatography. This mixture was directly used for the subsequent reaction. The relative stereochemistry of **6** was established by NOESY experiments. As shown in Figure 2,

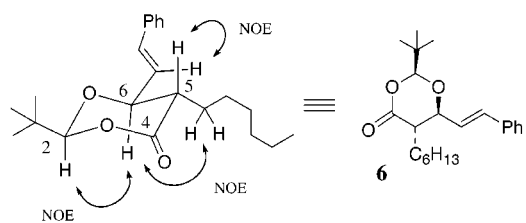


Figure 2.

an NOE was observed between the ring C-6 hydrogen and the C-5 alkyl chain. Also, NOEs were detected between the ring C-5 hydrogen and the adjacent vinylic hydrogen and between the ring C-2 and C-6 hydrogens.

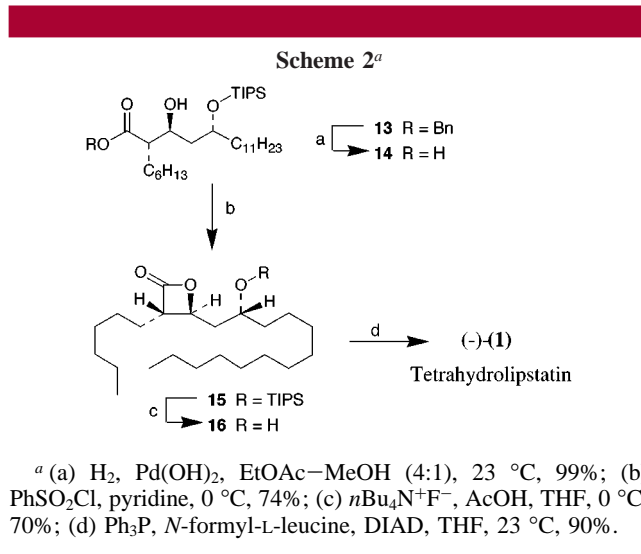
Ozonolysis of **6** in CH₂Cl₂ at -78 °C followed by reductive workup with Ph₃P yielded the corresponding

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aldehyde. The aldehyde was treated with 1-nitrododecane⁶ in DMF at 23 °C for 24 h in the presence of a catalytic amount (10 mol %) of $n\text{Bu}_4\text{N}^+\text{F}^-$ to provide the corresponding nitro aldol products **7** as a mixture of diastereomers in 82% isolated yield. The resulting mixture of diastereomers without further separation was then subjected to Seebach's dehydration conditions with DCC and CuCl in acetonitrile at 60 °C for 18 h.⁷ The nitroalkene **8** was isolated as a mixture (*E/Z*, 1:1.7) of isomers in 80% yield. The nitroalkene was then reduced to oxime **9** with zinc and acetic acid in THF at 0 °C for 15 min.⁸ The resulting oxime **9** was oxidatively hydrolyzed with ceric ammonium nitrate in the presence of nitric acid in ethanol at -45 °C to provide ketone **10** as a single isomer.^{9,10}

Attempts to reduce this ketone directly under a variety of reaction conditions resulted in a mixture of diastereomers with low selectivity (ca. 1.2:1 by ¹H NMR). We have therefore elected to utilize Evans' hydroxyl directed stereocontrolled reduction of β -hydroxy ketones to deliver the C-2' stereocenter diastereoselectively.¹¹ Thus, dioxanone **10** was first hydrolyzed using Seebach's conditions to provide the free β -hydroxy acid.¹² The resulting acid was esterified with CsCO_3 and benzyl iodide to furnish benzyl ester **11** in 59% yield (two steps). β -Hydroxy ketone **11** was then subjected to *anti*-selective reduction using Evans' protocol.¹¹ Treatment of **11** with $\text{Me}_4\text{NB}(\text{OAc})_3\text{H}$ in a mixture (1:1) of MeCN and AcOH at -40 °C for 24 h provided the *anti*-1,3-diol **12** diastereoselectively (selectivity 22:1 by 500 MHz ¹H NMR and ¹³C NMR analysis) in near quantitative yield. The mixture was used directly for the next reaction. Selective protection of the more accessible C-5 hydroxyl group was carried out with TIPSOTf and 2,6-lutidine in CH_2Cl_2 at -78 °C for 2.5 h to obtain the monoprotected TIPS ether **13** as a single isomer (by ¹H and ¹³C NMR) in 96% yield. However, the use of TBSOTf for this protection was much less selective; the corresponding C-5 and C-3 monoprotected silyl ethers were formed as a 3:1 mixture.

Protected ether **13** was converted to tetrahydrolipstatin as shown in Scheme 2. Catalytic hydrogenation of **13** in a



mixture of ethyl acetate and methanol (4:1) in the presence of Pearlman's catalyst provided β -hydroxy acid **14** in 99% yield. Exposure of the acid to PhSO_2Cl in pyridine at 0 °C for 48 h afforded β -lactone **15** in 74% isolated yield. The removal of the TIPS protecting group was effected by treatment of **15** with $n\text{Bu}_4\text{N}^+\text{F}^-$ and AcOH in THF at 0 °C for 4 h to provide the known lactone **16** ($[\alpha]^{23}_{\text{D}} -42$ (*c* 0.19, CHCl_3); lit.^{3m} $[\alpha]^{20}_{\text{D}} -41.4$ (*c* 0.5, CHCl_3)) in 70% yield.³ⁿ To complete the synthesis, lactone **16** was exposed to known^{3a} Mitsunobu esterification conditions using *N*-formyl-L-leucine, Ph_3P , and diisopropyl azodicarboxylate to furnish (-)-tetrahydrolipstatin **1** ($[\alpha]^{23}_{\text{D}} -33$ (*c* 0.06, CHCl_3); lit.^{3m} $[\alpha]^{20}_{\text{D}} -33$ (*c* 0.36, CHCl_3)) in 90% yield. Spectral data (IR, ¹H NMR and ¹³C NMR) for synthetic (-)-**1** are identical to that reported for the natural product.

In conclusion, a diastereoselective synthesis of (-)-tetrahydrolipstatin is described. The key steps involve an asymmetric ester derived titanium enolate *anti*-aldol reaction, a nitro aldol reaction, and a diastereoselective reduction of a β -hydroxy ketone. Three of the four asymmetric centers (C-3, C-4, and C-2') of (-)-**1** were set by asymmetric synthesis. The current route is easily amenable to the synthesis of other stereoisomers and structural variants of (-)-tetrahydrolipstatin.

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Supporting Information Available: ¹H NMR and ¹³C NMR spectra for compounds **3**–**16**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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