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

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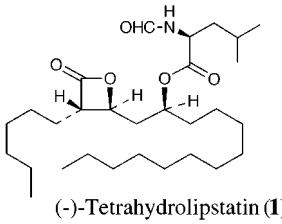
ABSTRACT



(-)-Tetrahydrolipstatin (**1**)

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′ C_{11} 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′ C_{11} side chain, and a diastereoselective reduction of a *β*-hydroxy ketone to an *anti*-1,3-diol functionality. As shown in Figure 1, the key structural

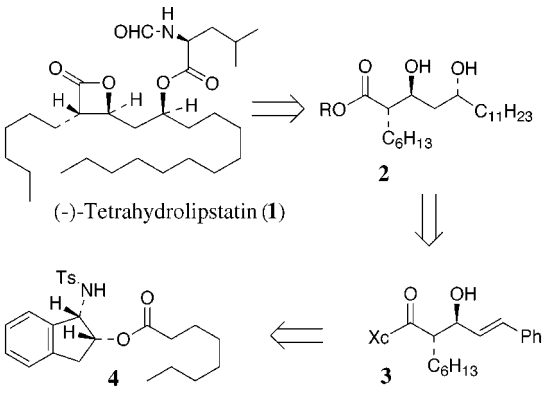


Figure 1.

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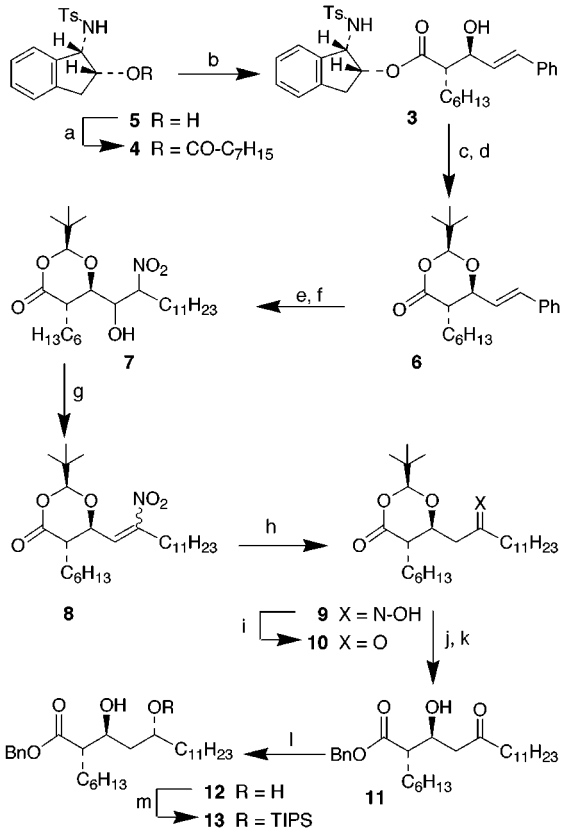
from *anti*-aldol adduct **3**. The *anti*-selective aldol reaction of ester **4** and *trans*-cinnamaldehyde will provide **3**. Stereocontrolled generation of such *anti*-aldol fragments has been described by us recently.[4]

Thus, ester **4** is made from the known *N*-tosyl-1-amino-2-indanol[4] by coupling with octanoyl chloride in the presence of pyridine in CH_2Cl_2 at 23 °C for 2 h in 92% yield after silica gel chromatography (Scheme 1). The titanium enolate

Scheme 1[a]



[a] (a) $C_7H_{15}COCl$, pyridine, CH_2Cl_2, 23 °C, 92%; (b) $TiCl_4$, *i*Pr_2NEt, CH_2Cl_2, 0 °C to 23 °C, then Bu_2BOTf, *trans*-cinnamaldehyde, CH_2Cl_2, −78 °C, 60%; (c) LiOOH, THF−H_2O (3:1), 0 °C to 23 °C, 92%; (d) 4 Å MS, Me_3CCHO, TMSO*i*Pr, TMSOTf, CH_2Cl_2, −78 °C to −20 °C, 79%; (e) O_3, CH_2Cl_2, −78 °C, then Ph_3P, −78 °C to 23 °C, 84%; (f) *n*$Bu_4N^+F^-$, $C_{12}H_{25}NO_2$, DMF, 23 °C, 82%; (g) DCC, CuCl, CH_3CN, 60 °C, 80%; (h) Zn, AcOH, THF, 0 °C, 50%; (i) CAN, HNO_3, EtOH, −45 °C, 77%; (j) 4 N HCl, THF, 23 °C, 98%; (k) $CsCO_3$, MeOH−H_2O (6:1) then BnI, DMF, 23 °C, 60%; (l) $Me_4NB(OAc)_3H$, AcOH−CN_3CN (1:1), −40 °C, 99%; (m) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 96%.

was formed by treatment of ester **4** with $TiCl_4$ (1.2 equiv) in CH_2Cl_2 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 Bu_2BOTf (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 $TiCl_4$ (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 ^{13}C 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,

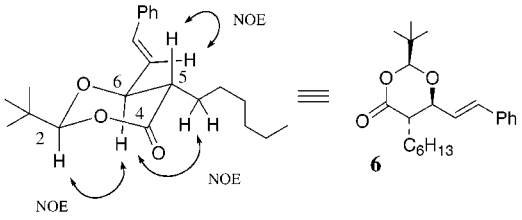


Figure 2.

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 CH_2Cl_2 at −78 °C followed by reductive workup with Ph_3P yielded the corresponding

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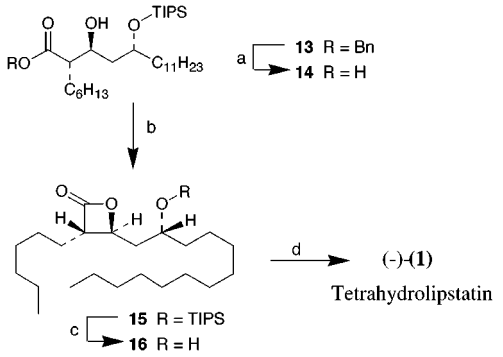
aldehyde. The aldehyde was treated with 1-nitrododecane[6] in DMF at 23 °C for 24 h in the presence of a catalytic amount (10 mol %) of nBu$_4$N$^+$F$^-$ to provide the corresponding nitro aldol products **7** as a mixture of diastereomers in 82% isolated yield. The resulting mixture of diastereomers 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 ^{1}H 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 Me$_4$NB(OAc)$_3$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 ^{1}H NMR and ^{13}C 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 ^{1}H and ^{13}C 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 nBu$_4$N$^+$F$^-$ and AcOH in THF at 0 °C for 4 h to provide the known lactone **16** ([α]$^{23}_D$ −42 (*c* 0.19, $CHCl_3$); lit.[3m] [α]$^{20}_D$ −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** ([α]$^{23}_D$ −33 (*c* 0.06, $CHCl_3$); lit.[3m] [α]$^{20}_D$ −33 (*c* 0.36, $CHCl_3$)) in 90% yield. Spectral data (IR, ^{1}H NMR and ^{13}C NMR) for synthetic (−)-**1** are identical to that reported for the natural product.

Scheme 2[a]



[a] (a) H_2, $Pd(OH)_2$, EtOAc−MeOH (4:1), 23 °C, 99%; (b) $PhSO_2Cl$, pyridine, 0 °C, 74%; (c) nBu$_4$N$^+$F$^-$, AcOH, THF, 0 °C, 70%; (d) Ph_3P, *N*-formyl-L-leucine, DIAD, THF, 23 °C, 90%.

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: ^{1}H NMR and ^{13}C 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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