# Asymmetric Synthesis of (–)-Tetrahydrolipstatin from a β-Hydroxy-δ-oxo Sulfoxide

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**Abstract:** An asymmetric synthesis of (–)-tetrahydrolipstatin is described. A palladium-catalyzed regioselective oxidation of an alkene to a ketone, highly diastereoselective reduction of a β-hydroxy ketone, selective oxidation of a diol, and modular synthesis are the key features of the synthesis.

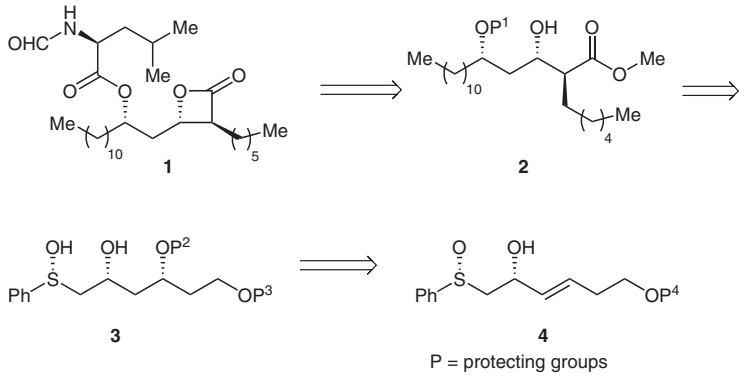
**Key words:** asymmetric synthesis, sulfoxide, palladium, tetrahydrolipstatin, Frater–Seebach alkylation

Tetrahydrolipstatin (THL, **1**), the stable saturated derivative of lipstatin that was isolated from *Streptomyces toxytricini*,[1] is a potent irreversible inhibitor of pancreatic lipase.[2] The β-lactone moiety of THL reacts with the serine hydroxyl group present in the active site of lipases forming an ester bond, thereby slowing the hydrolysis of triglycerides and thus blocks the absorption of dietary fat. It is currently marketed as an anti-obesity drug under the name of Xenical®. The important biological properties and its unique structural features have led to total syntheses by a number of groups adopting varied strategies.[3]

As part of our continuing interest in exploring sulfoxide chemistry,[4] we report herein a diastereoselective and novel synthesis of (–)-tetrahydrolipstatin. The salient features of the reported synthesis are (a) the use of (*R*)-methyl phenyl sulfoxide as the only original source of chirality, (b) a regioselective Wacker-type oxidation of an unsaturated sulfoxide using a Pd catalyst, (c) a diastereoselective reduction of a β-hydroxy ketone, and (d) its modularity. As depicted in Scheme 1, we envisioned closing the β-lactone ring late in the synthesis. The key intermediate **2** can be prepared by Frater–Seebach alkylation from a triol derivative **3** which can be obtained from allyl alcohol **4**.

The synthesis commenced by condensing the lithium anion of (*R*)-methyl phenyl sulfoxide[5] **5** with the unsaturated ester[6] **6** following Solladie's protocol[7] to furnish β-keto sulfoxide **7** {$[\alpha]_D^{25}$ +51 (*c* 0.7, $CHCl_3$)}. Diastereoselective reduction of **7** using DIBAL-H in the presence of anhydrous $ZnCl_2$[8] yielded allyl alcohol **4** {P = 4-$MeOC_6H_4CH_2$ (PMB), >95% de, $[\alpha]_D^{25}$ +62.6 (*c* 2.3, $CHCl_3$)}. The Wacker-type oxidation of **4** proceeded cleanly under the standard conditions[9] developed by us to afford β-hydroxy ketone **8** {$[\alpha]_D^{25}$ +84.9 (*c* 0.35, $CHCl_3$)}.[10] Diastereoselective *syn* reduction of **8** using $NaBH_4$ in the presence of $Et_2BOMe$[11] furnished diol **9** {$[\alpha]_D^{25}$ +56 (*c* 2.25, $CHCl_3$)}.[10] Acetylation of **9** furnished the diacetate **10**. Attempted introduction of the decyl chain exploiting the ene reaction[12] on the intermediate resulting from a Pummerer reaction on diacetate **10** met with failure probably due to competing activation of the PMB group by $SnCl_4$ resulting in its deprotection and other side reactions (Scheme 2).

Exploring an alternative route, the diol **9** was protected as the acetal **3** {$P^1$, $P^2$ = 4-$MeOC_6H_4CH$, $[\alpha]_D^{25}$ +34.4 (*c* 1.4, $CHCl_3$)} by DDQ oxidation of the PMB group under anhydrous conditions.[13] Compound **3** on Pummerer reaction followed by a one-pot hydrolysis, and reduction of the resulting intermediate afforded the diol **11** {$[\alpha]_D^{25}$ –21.8 (*c* 1.3, $CHCl_3$)}. Selective tosylation of the primary hydroxy




**Scheme 1**

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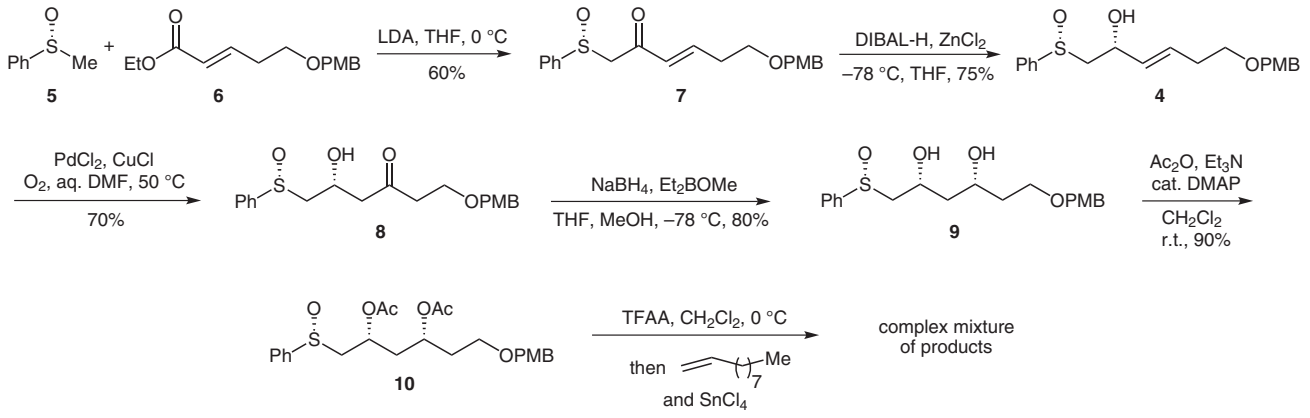
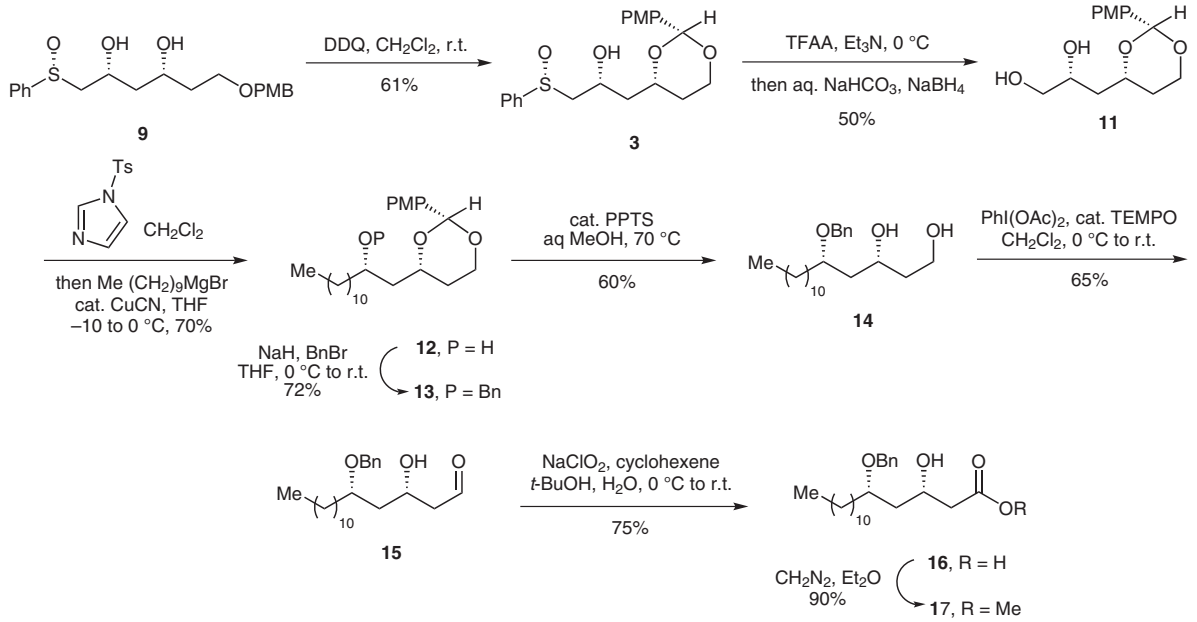



**Scheme 2**

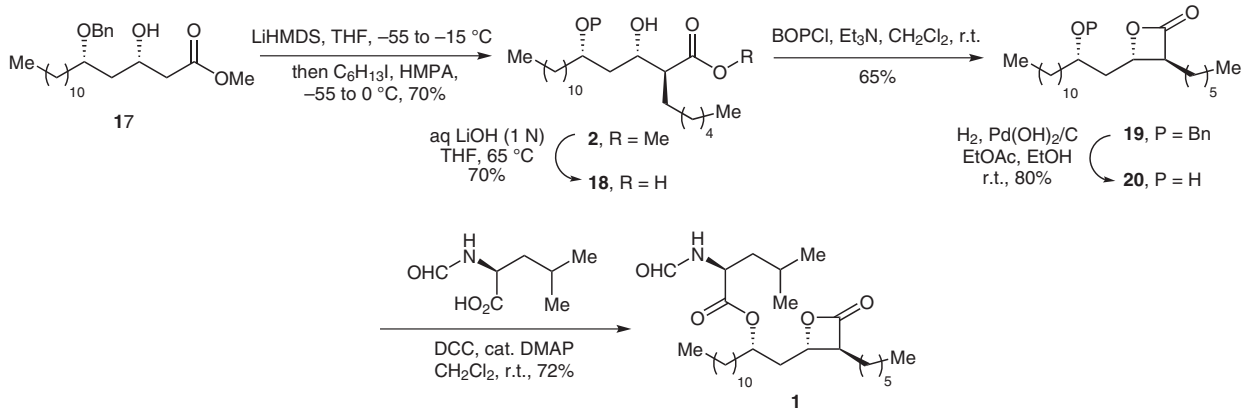
group using *N*-Ts imidazole followed by treatment of the tosylate with decylmagnesium bromide in the presence of CuCN in an one-pot operation[14] furnished the triol derivative **12** {$[\alpha]_D^{25}$ –14.9 (*c* 1.1, $CHCl_3$)}.[10] The secondary hydroxy group in **12** was protected as its benzyl ether **13** {$[\alpha]_D^{25}$ –14 (*c* 0.3, $CHCl_3$)} and the acetal hydrolyzed under mild acidic conditions to yield diol **14** {$[\alpha]_D^{25}$ +25.3 (*c* 2.65, $CHCl_3$)}. Selective oxidation of the primary in the presence of the secondary hydroxy group was effected using $PhI(OAc)_2$/Tempo[15] to furnish the corresponding aldehyde **15** {$[\alpha]_D^{25}$ +2.6 (*c* 1.05, $CHCl_3$)}. Subsequent oxidation to the acid **16** using Pinnick protocol[16] and esterification with ethereal diazomethane yielded ester **17** {$[\alpha]_D^{25}$ +27.5 (*c* 1, $CHCl_3$), Scheme 3}.

The synthesis of THL was completed employing a straightforward sequence of known reactions. Diastereoselective alkylation of **17** employing Frater–Seebach protocol[17] afforded the hexyl derivative **2** {P = Bn, $[\alpha]_D^{25}$ +19.2 (*c* 1.25, $CHCl_3$)} in good yield (dr >90:10). Hydrolysis of the ester using aq 1 N LiOH afforded the hydroxy acid **18** {$[\alpha]_D^{25}$ +14 (*c* 0.53, $CHCl_3$)}, β-lactone formation using BOPCl[18] proceeded cleanly to yield compound **19** {$[\alpha]_D^{25}$ –4 (*c* 0.97, $CHCl_3$)} identical to the product reported by Kumaraswamy and co-workers.[3r] Debenzylation and esterification[19] using *N*-formyl leucine furnished (–)-THL {$[\alpha]_D^{25}$ –31 (*c* 0.1, $CHCl_3$; lit.[3d] $[\alpha]_D^{25}$ –33.04 (*c* 0.79, $CHCl_3$)} with physical characteristic in complete agreement to those reported in the literature[3d] (Scheme 4).

In summary, we have described a diastereoselective route to THL. The key steps include the Wacker-type oxidation of an alkene to a ketone regioselectively, stereoselective *syn* reduction of β-hydroxy ketone, and diastereoselective Frater–Seebach alkylation. The synthesis is flexible and alkyl chains of variable lengths can be introduced at two positions using an advanced intermediate to access analogues of THL.




**Scheme 3**




**Scheme 4**

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(6) The unsaturated ester **6** was prepared by a three-step sequence. Selective protection of 1,3-propane diol as its *p*-methoxybenzyl ether followed by Swern oxidation and Wittig olefination afforded **6** in 40% overall yield.

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(10) **Synthesis of Compound 8**
A suspension of $PdCl_2$ (352 mg, 1.98 mmol) and CuCl (1.96 g, 19.8 mmol) in a mixture of DMF and $H_2O$ (1:1, 20 mL) was stirred under an $O_2$ atmosphere for 1 h. A solution of allyl alcohol **4** (7.13 g, 19.8 mmol) in DMF and $H_2O$ (1:1, 10 mL) was added to the above, and the reaction mixture was stirred at 50 °C for 4 h. The reaction mixture was extracted with $Et_2O$ (3 × 75 mL), washed successively with $H_2O$ (2 × 20 mL), brine (20 mL), and dried over anhyd $Na_2SO_4$. Evaporation of the solvent in vacuo afforded the crude product which was purified by column chromatography using 60% EtOAc–hexane as the eluent to furnish β-hydroxy ketone **8** (5.21 g, 13.9 mmol) in 70% yield as a viscous oil. TLC: $R_f$ = 0.15 (70% EtOAc–hexane); $[\alpha]_D$ +84.9 (*c* 0.35, $CHCl_3$). IR (neat): 3138, 2925, 2657, 1630, 1384, 1245, 1088, 1029, 754 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): δ = 7.67–7.59 (m, 2 H), 7.56–7.48 (m, 3 H), 7.16 (d, *J* = 8.8 Hz, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 4.52 (quin, *J* = 5.9 Hz, 1 H), 4.39 (s, 2 H), 3.78 (s, 3 H), 3.66 (t, *J* = 5.9 Hz, 2 H), 2.98–2.73 (m, 4 H), 2.66 (t, *J* = 5.9 Hz, 2 H). $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 208.62, 159.34, 143.63, 131.33, 129.93, 129.43, 129.35, 123.99, 113.87, 72.91, 64.73, 61.99, 55.28, 49.02, 43.67. ESI–MS: 399 $[M + Na]^+$. ESI–HRMS: *m/z* $[M + Na]^+$ calcd for $C_{20}H_{24}O_5NaS$: 399.1242; found: 399.1240.
**Synthesis of Compound 9**
To a solution of β-hydroxy ketone **8** (5.21 g, 13.9 mmol) in THF (110 mL) cooled at –78 °C was added diethylmethoxyborane (1 M in THF, 15.4 mL, 15.4 mmol) followed by MeOH (28 mL), and stirred for 30 min. Then solid $NaBH_4$ (577 mg, 15.3 mmol) was added in three portions and the mixture stirred for 2 h at the same temperature. The reaction was quenched using a mixture of pH 7 phosphate buffer (20 mL), MeOH (30 mL), and 30% (w/v) $H_2O_2$ soln (10 mL). This mixture was allowed to warm to r.t. and stirred at r.t. for further 18 h. The organic solvent was evaporated in vacuo,

and the aqueous layer was extracted with $Et_2O$ (3 × 75 mL). The combined organic layers were washed with brine (20 mL) and dried over anhyd $Na_2SO_4$. Evaporation of the solvent in vacuo yielded the crude product, which was purified by column chromatography using 65% EtOAc–hexane as the eluent to afford the *syn* 1,3-diol **9** (3.82 g, 10.1 mmol) in 73% yield as a viscous oil. TLC: $R_f$ = 0.2 (70% EtOAc–hexane); $[\alpha]_D$ +56 (*c* 2.25, $CHCl_3$). IR (neat): 3386, 2923, 2856, 2362, 1611, 1512, 1441, 1303, 1246, 1175, 1088, 1030, 820, 753, 691, 503 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.67–7.62 (m, 2 H), 7.55–7.46 (m, 3 H), 7.18 (d, *J* = 8.3 Hz, 2 H), 6.82 (d, *J* = 8.3 Hz, 2 H), 4.41 (s, 2 H), 4.36–4.24 (m, 1 H), 3.78 (s, 3 H), 3.69–3.53 (m, 3 H), 3.03 (dd, *J* = 7.6, 12.8 Hz, 1 H), 2.80 (dd, *J* = 4.5, 12.8 Hz, 1 H), 1.86–1.62 (m, 4 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 159.37, 143.86, 131.21, 129.84, 129.36, 124.08, 113.93, 77.01, 73.05, 71.54, 68.43, 63.42, 55.28, 42.71, 29.68. ESI–MS: 401 $[M + Na]^+$. ESI–HRMS: *m/z* $[M + Na]^+$ calcd for $C_{20}H_{26}O_5NaS$: 401.1398; found: 401.1405.

**Synthesis of Compound 12**

To a suspension of NaH (60% in Nujol, 310 mg, 7.7 mmol) in anhyd THF (10 mL), cooled at 0 °C, was added a solution of diol **11** (810 mg, 3.1 mmol) in THF (20 mL) dropwise. The mixture was gradually allowed to warm to r.t. and further stirred for 1 h at the same temperature. It was then recooled at 0 °C and *N*-Ts-Imd (686 mg, 3.1 mmol) was added in three equal potions over a period of 20 min. The mixture was warmed to r.t. and stirred for 40 min, then CuCN (55 mg, 0.61 mmol) was added. After stirring for an additional 5 min, the mixture was cooled at –10 °C, and a freshly prepared solution of decylmagnesium bromide (0.7 M in $Et_2O$, 13.3 mL, 9.31 mmol) was added via syringe. The reaction mixture was kept at the same temperature for 2 h and then allowed to warm to 0 °C gradually over a period of 1 h. The reaction was quenched by the addition of aq sat. $NH_4Cl$ solution (10 mL) and diluted with $Et_2O$ (65 mL). The separated organic phase was washed with $H_2O$ (2 × 25 mL) and brine (25 mL). The aqueous layers were re-extracted with $Et_2O$ (2 × 25 mL), and the combined organic layers were dried over anhyd $Na_2SO_4$. Evaporation of the solvent in vacuo furnished the crude residue which was purified by column chromatography using 10% EtOAc–hexane as the eluent to afford triol **12** (846 mg, 2.1 mmol) in 70% yield as a viscous oil. TLC: $R_f$ = 0.5 (20% EtOAc–hexane); $[\alpha]_D$ –14.9 (*c* 1.1, $CHCl_3$). IR (neat): 3447, 2922, 2853, 1634, 1459, 558 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 9.1 Hz, 2 H), 6.82 (d, *J* = 9.1 Hz, 2 H), 5.45 (s, 1 H), 4.22 (dd, *J* = 4.5, 12.1 Hz, 1 H), 4.13–4.02 (m, 1 H), 3.92 (dt, *J* = 2.3, 12.1 Hz, 1 H), 3.86–3.80 (m, 1 H), 3.78 (s, 3 H), 1.92–1.23 (m, 24 H), 0.88 (distorted t, *J* = 6.8 Hz, 3 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 159.83, 130.67, 127.15, 113.57, 101.07, 78.10, 71.36, 66.98, 55.32, 42.77, 37.66, 31.56, 29.72, 29.69, 29.42, 25.51, 22.76, 14.22. ESI–MS: 393 $[M + H]^+$. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{24}H_{40}O_4Na$: 415.2824; found: 415.2804.

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