Asymmetric Total Synthesis of *ent*-Tetrahydrolipstatin from an Epoxy Alkenol

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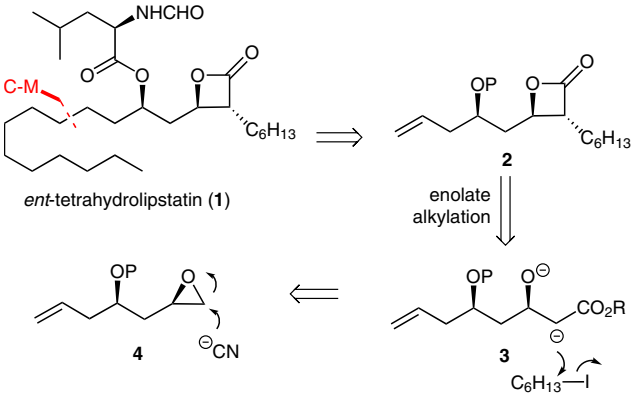
Abstract: A highly efficient asymmetric total synthesis of *ent*-tetrahydrolipstatin (THL) was accomplished from the known epoxy alkenol. The β-lactone portion of THL was synthesized by the epoxide opening with cyanide and stereoselective enolate alkylation method. The side chain was introduced by cross metathesis of the alkene part with 1-decene. Coupling with a protected leucine completed the synthesis of *ent*-tetrahydrolipstatin.

Key words: enolate alkylation, epoxides, metathesis, *ent*-tetrahydrolipstatin, total synthesis

Tetrahydrolipstatin (THL), the first FDA-approved anti-obesity drug (Orlistat®),[3] is a hydrogenated form of the naturally occurring lipstatin which was isolated from *Streptomyces toxytricini*.[1] Both THL and lipstatin are known as potent inhibitors of pancreatic lipases.[2] The β-lactone moiety of THL reacts with the serine hydroxyl group in the active site of pancreatic lipase, thus the absorption of dietary fat is blocked. Recent studies show that THL also has antitumor activity acting as a novel inhibitor of the thioesterase domain of fatty acid synthase (FAS), which is strongly linked to tumor progression in cancer cells.[4] Due to these important biological properties and its unique structural features, several synthetic efforts have been devoted for the synthesis of THL.[5,6]

Synthetic approaches for THL are essentially focused on the stereoselective constructions of the *trans*-β-lactone ring system possessing two stereogenic centers and the stereocenter at the δ-position. Herein, we report a concise asymmetric total synthesis of THL based on the epoxide-opening–enolate alkylation–cross-metathesis strategy. Over the past few years, we have developed efficient asymmetric routes[7] for the synthesis of natural products possessing 1,3-diol moieties starting from the optically pure epoxide **4** which is readily prepared by Jacobsen's hydrolysis kinetic resolution (HKR) method.

Asymmetric total synthesis of *ent*-THL could be readily accessed by the epoxide opening–enolate alkylation–cross-metathesis strategy starting from the epoxide **4** (Scheme 1). Introduction of the cyano group by epoxide opening followed by stereoselective alkylation of the dianionic enolate could efficiently set up the three stereogenic centers of THL. Subsequent β-lactone formation, chain elongation by cross metathesis, and final coupling with a protected leucine would furnish *ent*-THL (**1**). In this strategy, the lipophilic side chain is introduced by cross metathesis at the final stage, which could allow us easy access to the different lipophilic groups in the synthesis of THL derivatives.



Scheme 1 Retrosynthesis analysis of *ent*-THL (**1**)

Firstly, the known epoxy alkenol **5**[7] was protected with a benzyl group and then reacted with KCN (2 equiv) in a DMF–H_2O (3:1) solution under refluxing conditions[8] to synthesize the β-hydroxy nitrile **6**. Subsequent hydrolysis of nitrile to the corresponding carboxylic acid found to be difficult. Typical acidic and basic conditions for the hydrolysis of the nitrile failed to yield the desired acid. Either formation of the corresponding amide under mild conditions or decomposition under strong conditions was observed. Fortunately, the hydrolysis reaction of **6** turned out to be efficient when sodium peroxide (NaOONa) is used in H_2O under mild conditions.[9] Thus we obtained the β-hydroxy carboxylic acid **7** in 93% yield. Following protection of **7** with AcCl in MeOH provided the β-hydroxy ester **8** (Scheme 2).

With the β-hydroxy ester in hand, we then attempted dianionic alkylation reaction to introduce the C(2) *n*-hexyl side chain. Literature procedures for the diastereoselective dianionic alkylation of β-hydroxy ester[10] were screened. Thus, the β-hydroxy methyl ester **8** was treated with 2.5 equivalents of base (LiHMDS or LDA) at low temperature, then *n*-hexyl iodide in HMPA was added. In general, the alkylation reactions using LiHMDS gave low yields of the desired product. Alkylation reactions with the dianion generated by LDA gave better yields. Optimal

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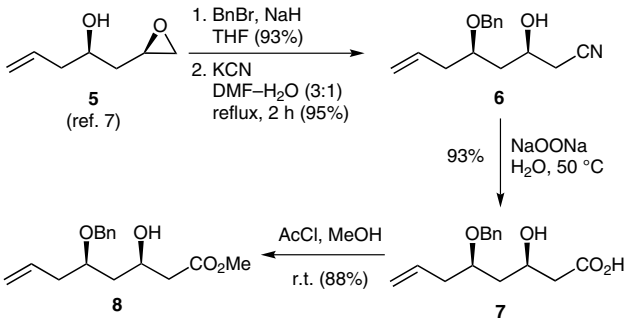
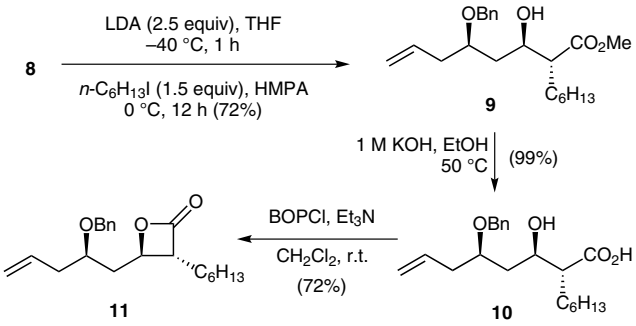


Scheme 2 Synthesis of the β-hydroxy ester **8**

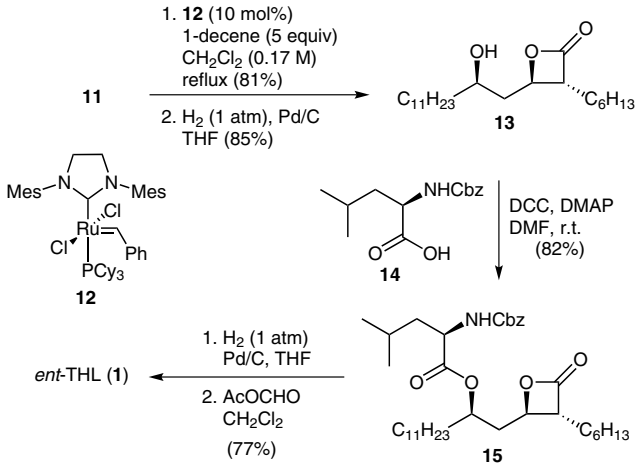
yield for the alkylation was achieved when the dianion was generated with 2.5 equivalents of LDA in THF at –40 °C for one hour as shown in Scheme 3. The desired alkylated product **9** was obtained in 72% yield based on the recovered starting material (53% of isolated yield) with excellent diastereoselectivity.[11] Saponification of ester **9** with aqueous KOH, followed by treatment with BOPCl,[12] gave the β-lactone **11** in 72% (Scheme 3).



Scheme 3 Synthesis of the β-lactone **11**

In the known literature synthesis of THL utilizing the dianion alkylation strategy,[6] the *n*-hexyl chain is introduced after the incorporation of the long lipophilic chain. However, in this synthesis, we first set up all three stereogenic centers before the chain elongation. For the introduction of the lipophilic part, the cross metathesis–hydrogenation sequence was employed. Reaction of **11** with five equivalents of 1-decene in the presence of second-generation Grubbs catalyst **12** (10 mol%) under refluxing dichloromethane and subsequent hydrogenation of the isomeric alkenes with H_2–Pd/C produced the extended alkyl chain. Under the reaction conditions, the benzyl protecting group at the δ-hydroxy group was also removed to yield the known lactone compound **13** {$[\alpha]_D^{20}$ +15.85 (*c* 0.79, $CHCl_3$); lit.[6e] $[\alpha]_D^{20}$ –16.3 (*c* 1.05, $CHCl_3$) for *ent*-**13**}.

To complete the synthesis, final esterification of the *N*-formylleucine was attempted using DCC/DMAP. However, significant epimerization was observed to give mainly two isomers as reported in the literature.[6r,13] Instead, DCC-mediated coupling with the Cbz-protected leucine (**14**) provided the Cbz derivative **15** {$[\alpha]_D^{20}$ +24.20 (*c* 0.61, $CHCl_3$); lit.[6e] $[\alpha]_D^{20}$ –23.86 (*c* 1.06, $CHCl_3$)} in 82% with no epimerization (Scheme 4). Deprotection of the Cbz group by catalytic hydrogenation followed by formylation with formic acetic anhydride completed the total synthesis of *ent*-THL (**1**).[14] The spectral data of **1** are identical to those reported for the natural product with the opposite optical rotation value {$[\alpha]_D^{20}$ +30.66 (*c* 0.36, $CHCl_3$); lit.[5a] $[\alpha]_D^{20}$ –33 (*c* 0.36, $CHCl_3$)}.



Scheme 4 Completion of total synthesis of *ent*-THL (**1**)

In summary, we have completed a concise asymmetric total synthesis of *ent*-tetrahydrolipstatin starting from the known epoxy alkenol **5** in 12 steps. Epoxide opening with cyanide, diastereoselective dianionic alkylation, and cross-metathesis reactions were employed in the key steps. In this synthesis, the lipophilic side chain ($C_{11}H_{23}$) was introduced at a relatively late stage utilizing cross-metathesis reaction after rapid construction of three stereogenic centers.

Acknowledgment

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

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(14) **Spectral Data for *ent*-Tetrahydrolipstatin (1)**
R_f = 0.32 (silica gel, hexane–EtOAc = 7:3); $[\alpha]_D^{20}$ +30.66 (*c* 0.36, $CHCl_3$); mp 41–42 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 5.93 (d, *J* = 8.0 Hz, 1 H), 5.04–5.02 (m, 1 H), 4.71–4.67 (m, 1 H), 4.31–4.27 (m, 1 H), 3.23–3.21 (m, 1 H), 2.19–2.15 (m, 1 H), 2.03–1.98 (m, 1 H), 1.87–1.54 (m, 7 H), 1.29–1.25 (m, 26 H), 0.98–0.94 (m. 6 H), 0.90–0.86 (m, 6 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.1, 170.9, 160.8, 74.9, 72.9, 57.2, 49.8, 41.7, 38.9, 34.2, 32.1, 31.6, 29.8, 29.7, 29.6, 29.5, 29.1, 27.8, 26.9, 25.2, 25.1, 23.0, 22.8, 22.7, 21.9, 14.3, 14.2. IR (film): 3353, 3025, 2954, 2924, 2855, 1825, 1733, 1699, 1652, 1521, 1456, 1386, 1273, 1250, 1195, 1126, 877, 815, 761 cm^{-1}. HRMS: *m*/*z* calcd for $C_{29}H_{54}NO_5[M + H]^+$: 496.4002; found: 496.4004.

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