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Stereoselective synthesis of (−)-tetrahydrolipstatin via a radical cyclization based strategy☆

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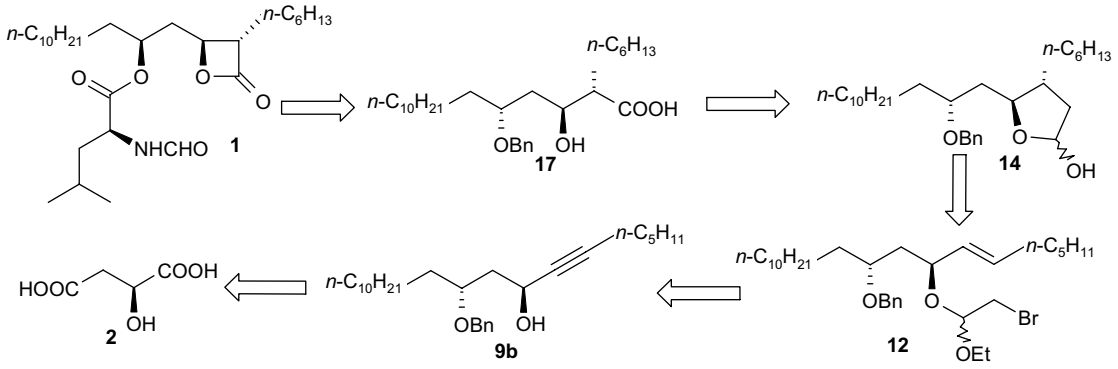
Abstract—An efficient and flexible approach for the total synthesis of (−)-tetrahydrolipstatin is described. The main features of the synthetic strategy are a stereocontrolled radical cyclization and the successful utilization of commercially available *S*-malic acid.

(−)-Tetrahydrolipstatin (THL) **1**, a β-lactone, is a potent and irreversible inhibitor of pancreatic lipase and is the saturated analogue of lipstatin isolated from *Streptomyces toxytricini* in 1987.[1] Recently, THL has been marketed in several countries as an anti-obesity agent under the name Xenical. The key to the biological activity of the lipstatins is the β-lactone moiety, featuring trans-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, THL has been the subject of much synthetic activity since its isolation.[3]

Our retrosynthetic analysis is outlined in Scheme 1. THL **1** would be obtained via a three-step sequence from the known β-hydroxy acid **17**. We envisioned that degradation of **14** could be effected by elimination then ozonolysis. The lactol **14** would be obtained from the propargylic alcohol **9b** through bromoacetal formation and stereoselective radical cyclization, a key step in this approach. The propargylic alcohol **9b** in turn would be obtained from commercially available *S*-malic acid by carbon extension at one end and Grignard addition to the other.

The starting material, 1,3-benzylidine-protected triol **3**, was obtained from commercially available *S*-malic acid as reported[4] in 65% overall yield. O-Tosylation and copper-mediated C–C bond formation with *n*-decylmagnesium bromide resulted in **4**.[5] This compound could



Scheme 1.

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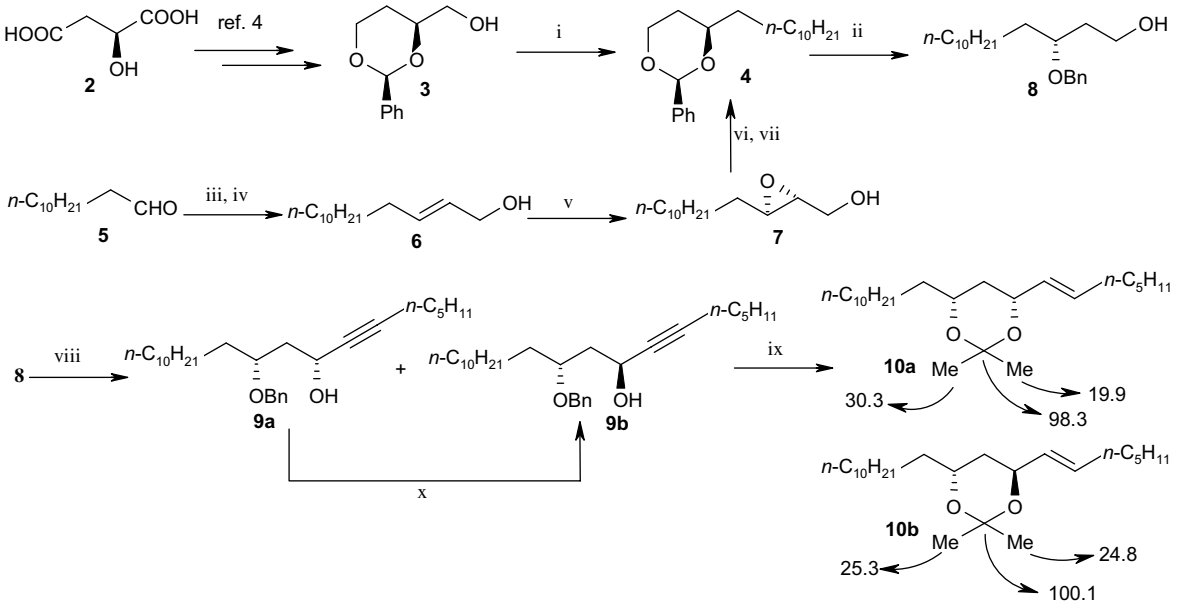
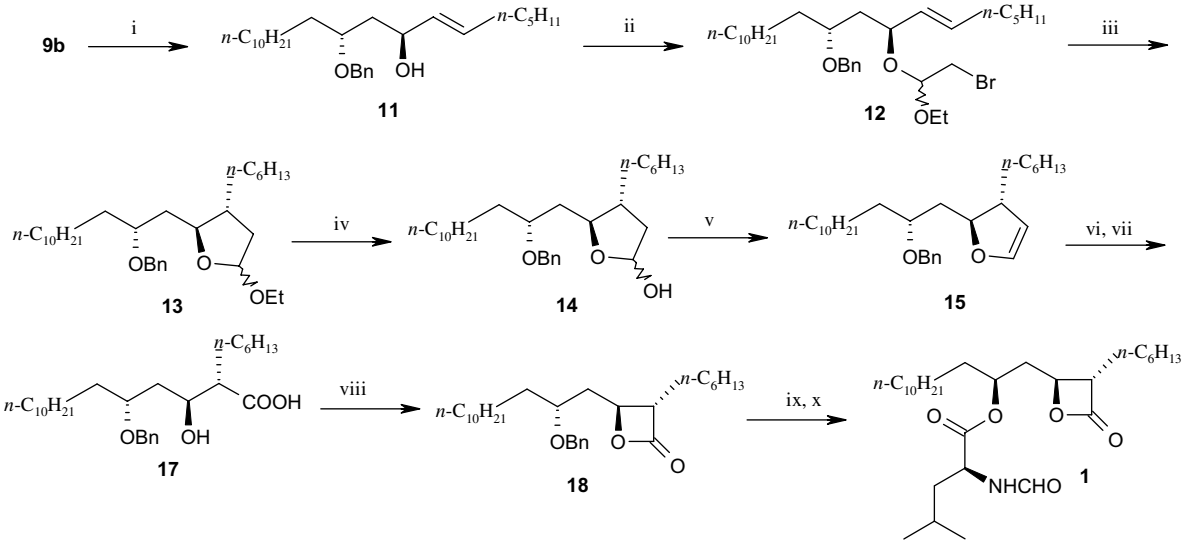
also be obtained from alcohol **3** via conversion to the corresponding triflate and copper-mediated Grignard displacement.[6] Compound **4** was also available in a three-step sequence from dodecanal **5** via Wittig olefination with (ethoxycarbonylmethylene)triphenylphosphorane in benzene, yielding an α,β-unsaturated ester which on reduction with DIBAL-H in DCM gave allyl alcohol **6**. Sharpless epoxidation of **6** with D-(−)-DET gave epoxy alcohol **7** which on reductive and regioselective opening with Red-Al gave a 1,3-benzylidene-protected by reaction with benzaldehyde dimethyl acetal, yielding **4**. Reductive and regioselective opening of benzylidine acetal **4** was easily carried out using DIBAL-H to produce **8**.[7] Oxidation of **8** under Swern conditions[8] followed by hept-1-yn-1-yl Grignard addition resulted in *cis* and *trans* propargylic alcohols **9a** and **9b** in a 1:1



Scheme 2. Reagents and conditions: (i) (a) TsCl, Et_3N, DCM, 0 °C–rt, 2 h or Tf_2O, 2,6-lutidine, DCM, 0 °C–rt; (b) *n*-$C_{10}H_{21}MgBr$, CuBr, THF, 0 °C–rt, 4 h, 72%; (ii) DIBAL-H, DCM, −78 °C, 69%; (iii) Ph_3PCHCO_2Et, benzene, rt, 6 h; (iv) DIBAL-H, DCM, −78 °C, 83%; (v) D-(−)-DET, $Ti(^iOPr)_4$, TBHP, DCM, −20 °C, 83%; (vi) Red-Al, THF, 0 °C–rt, 86%; (vii) PTSA, $PhCH(OMe)_2$, DCM, 0 °C–rt, 79%; (viii) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C then *n*-$C_7H_{12}MgBr$, THF, 0 °C–rt, 82%; (ix) (a) $LiAlH_4$, THF, 0 °C–rt, 85%; (b) Li, liq. NH_3, 2 min, 94%; (c) 2,2-DMP, acetone, PTSA, rt, 4 h, 76%; (x) DEAD, TPP, *p*-nitrobenzoic acid, THF, 0 °C–rt, 88%.



Scheme 3. Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C–rt, 85%. (ii) NBS, ethyl vinyl ether, DCM, 0 °C–rt, 4 h, 90%. (iii) AIBN, *n*-Bu_3SnH, dry toluene, reflux, 2 h, 92%. (iv) 80% AcOH in H_2O, 60 °C 6 h. (v) MsCl, Et_3N, −22 °C–rt-reflux, 92%. (vi) O_3, TPP, DCM, −78 °C–rt. (vii) $NaClO_2$–H_2O, 10% NaOH, 10 °C–rt, 86%. (viii) $PhSO_2Cl$, pyridine, 0 °C–rt, 78%. (ix) Pd/C, THF, rt, 4 h, 90%. (x) DEAD, TPP, *N*-formyl-L-leucine, 0 °C–rt, 65%.

ratio. To assign the stereochemistry we converted both isomers to the corresponding acetonides **10a** and **10b** in a three-step sequence (Scheme 2).

Reduction with LAH in THF and debenzylation with Li in NH_3 generated the corresponding 1,3-diols which on treatment with 2,2-DMP in acetone produced acetonides **10a** and **10b**. ^{13}C NMR analyses of these acetonides clearly revealed the stereochemistry of the diastereomers.[9]

The unrequired diastereomer **9a** was converted into **9b** under standard Mitsunobu conditions to give **9b** in 72% overall yield.[10] Reduction of propargyl alcohol **9b** with LAH in THF resulted in *trans* allyl alcohol **11** which on treatment with NBS and ethyl vinyl ether yielded bromoacetal **12** as an epimeric mixture at the newly created acetal centre.[11] The key step, stereocontrolled radical cyclization, was easily effected by treating the bromoacetal **12** with a refluxing mixture of *n*-Bu_3SnH and catalytic AIBN in toluene to produce the thermodynamically stable isomer **13**.[12] Cyclic ethyl acetal **13**, when treated with 80% AcOH in H_2O resulted in lactol **14**.[13] Mesylation of lactol **14** and in situ elimination was achieved by treatment with mesyl chloride and TEA in DCM under reflux conditions[14] to yield cyclic vinyl ether **15**, which on ozonolytic oxidative cleavage produced aldehyde **16** which was subjected to oxidation,[15] without purification, with $NaClO_2$ and 10% NaOH solution to furnish β-hydroxy acid **17**. The β-lactone ring was formed using $PhSO_2Cl$ in pyridine, followed by debenzylation and esterification with (*S*)-*N*-formyl leucine under Mitsunobu conditions[8] furnished (−)-THL **1** (Scheme 3). The spectroscopic and physical data of **1** were in good agreement with those reported in the literature.[16]

In conclusion, an efficient total synthesis of THL **1**, with high diastereoselectivity has been achieved. We constructed the key intermediate **4** in two different ways showing the flexibility of the route.

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16. Selected data for compound **1**: A white solid, R_f0.14 (20% ethyl acetate/hexane); mp 39–41 °C (lit.[3a] mp 40–42 °C;) $[\alpha]_D^{20}$ −32.6 (*c* 0.96, $CHCl_3$) (lit.[3a] $[\alpha]_D^{20}$ −33 (*c* 0.65, $CHCl_3$)). ^1H NMR (200 MHz, $CDCl_3$): δ 8.22 (s, 1H), 6.02 (d, 1H, $J = 8.5$ Hz, NH), 5.02 (m, 1H), 4.68 (m, 1H), 4.28 (m, 1H), 3.22 (dt, 1H, $J = 7.6$, 3.9 Hz), 2.25–2.11 (m, 1H), 2.02 (m, 1H), 1.80–1.15 (m, 33H), 0.95 (d, 6H, $J = 5.2$ Hz), 0.87 (distorted t, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 170.8, 160.7, 74.8, 72.6, 56.9, 49.7, 41.4, 38.7, 34.0, 31.9, 31.2, 29.6, 29.5, 29.4, 29.3, 29.2, 28.8, 27.7, 26.8, 25.2, 24.9, 22.8, 22.7, 22.5, 21.7, 14.1, 14.0. ESIMS: *m/z* 496 [M+H]. IR (KBr): 1835, 1740, 1695 cm^{-1}. HRMS *m/z* calcd for $C_{29}H_{54}NO_5$ $(M^+ + H)^+$ 496.4004, found 496.3987.