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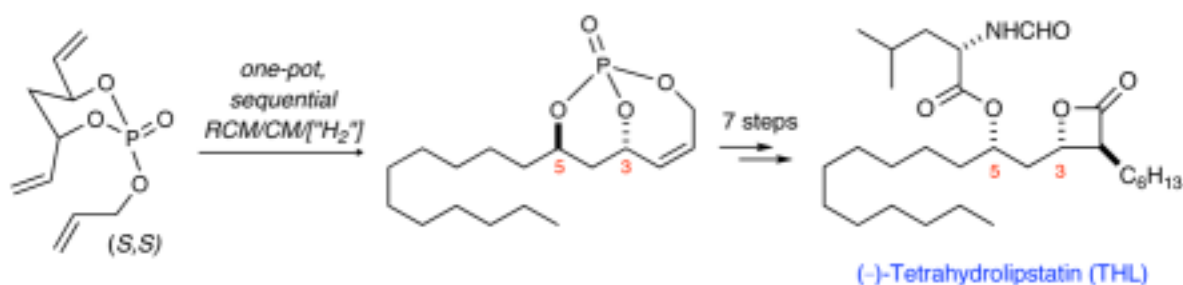
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## A Concise, Phosphate-Mediated Approach to the Total Synthesis of (-)-Tetrahydrolipstatin

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### Abstract



An efficient synthesis of (-)-tetrahydrolipstatin (THL) is reported. This method takes advantage of a phosphate tether-mediated, one-pot, sequential RCM/CM/hydrogenation protocol to deliver THL in 8 total steps from a readily prepared (*S,S*)-triene. The strategy incorporates selective cross metathesis, regio-selective hydrogenation, regio- and diastereoselective cuprate addition and Mitsunobu inversion for installation of the C5 formamide ester subunit.

(-)-Tetrahydrolipstatin (THL, **1**) is an anti-obesity drug marketed under generic name Orlistat<sup>®</sup> and is a stable saturated form of the naturally occurring lipstatin (**2**) (Figure 1). Lipstatin is a protein-reactive natural product and an irreversible pancreatic lipase inhibitor which was first isolated in 1987 from *Streptomyces toxytricini*.<sup>1</sup> The biological activity inherent to this family of molecules is based on the reactivity of the  $\beta$ -lactone moiety which is readily acylated by the pancreatic lipase enzyme. This process ultimately inhibits the enzyme reactivity aimed at hydrolyzing triglycerides to produce free fatty acids which are then readily absorbed into the dietary system.<sup>1b,2</sup>

Recently, the discovery of selective inhibition of thioesterase activity of fatty acid synthase (FAS) in cancer cells has elevated the potential of Orlistat<sup>®</sup> as an anticancer drug.<sup>3,4</sup> The inhibition of FAS stops both endothelial cell proliferation and angiogenesis and ultimately delays tumor progression in a variety of cancer cells. This promising activity highlights the broad and interesting biological profile of Orlistat<sup>®</sup> and has prompted renewed synthetic efforts and corresponding biology of THL, lipstatin and analogs thereof.<sup>4,5</sup> Herein we report a concise total synthesis of (-)-tetrahydrolipstatin via a strategy utilizing a phosphate-tether-mediated, one-pot, sequential RCM/CM/hydrogenation pathway of triene (*S,S*)-**7**.<sup>6</sup> Overall, the reported

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 Supporting Information Available Experimental details and spectroscopic data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

synthetic route comprises 9 total steps from the readily prepared diene diol-(*S,S*)-**8** and highlights the utility of phosphate tethered processes and one-pot, multi-step operations.

The first total synthesis of THL was achieved in 1987 by Schneider and coworkers utilizing Wittig olefination and an aldol condensation as key steps in a non-stereoselective process.<sup>7</sup> Numerous total syntheses,<sup>8</sup> formal syntheses<sup>9</sup> and synthetic analogues have followed this initial report, with the majority of synthetic pathways comprised of 14–25 steps. The shortest routes to THL reported to-date range from 10–12 steps using an array of synthetic strategies, including, (i) a 12-step *anti*-aldol approach,<sup>8i</sup> (ii) a 12-step diastereoselective allylation and crotylation sequence utilizing allyl/crotyltrifluoroborates,<sup>8n</sup> (iii) a 10-step tandem Mukaiyama-aldol lactonization,<sup>8o</sup> and (iv) a 12-step Prins cyclization approach.<sup>8q</sup> Other noteworthy strategies include substrate-controlled stereoselective hydrogenation to install the C2-C3 stereocenters,<sup>7c</sup> Lewis acid-catalyzed [2+2] cycloaddition,<sup>8f</sup> *anti*-aldol approach,<sup>8h</sup> substrate-controlled [2+3] cycloaddition,<sup>8j</sup> and diastereoselective aldol reaction with an embedded iron chiral auxiliary.<sup>8t</sup>

The route reported herein is highlighted in the retrosynthetic analysis shown in Scheme 1. THL (**1**) can be readily derived from  $\beta$ -lactone intermediate **3** via simple silyl deprotection and Mitsunobu esterification.<sup>7a</sup>  $\beta$ -Lactone **3** in turn can be synthesized from diol **4** via a 3-step sequence of TIPS-protection, ozonolysis/oxidation and lactonization. Diol **4** is obtained from **5** via diastereo-selective cuprate addition and phosphate tether removal under reductive conditions. Bicyclic phosphate **5** is in turn derived from (*S,S,P<sub>S</sub>*)-**6** via cross-metathesis and regioselective hydrogenation. The bicyclic phosphate, (*S,S,P<sub>S</sub>*)-**6**,<sup>10</sup> can be produced in a straightforward 2-step sequence from desymmetrization of the pseudo-*C*<sub>2</sub>-symmetric triene (*S,S*)-**7** using an RCM/phosphate tether method inspired by Burke and coworkers.<sup>11</sup> Triene (*S,S*)-**7** is readily prepared from the *C*<sub>2</sub>-symmetric *anti*-diene diol (*S,S*)-**8**<sup>12</sup> in one step using phosphoramidite chemistry. Optimization was envisioned for a one-pot, sequential RCM/CM/hydrogenation sequence that would access **5** directly from triene (*S,S*)-**7**.

Initially, a linear approach was followed for the synthesis of **5** from bicyclic phosphate (*S,S,P<sub>S</sub>*)-**6**,<sup>13,14</sup> which was synthesized via RCM desymmetrization of triene (*S,S*)-**7** using [(IMesH<sub>2</sub>)(PCy<sub>3</sub>)(Cl)<sub>2</sub>Ru=CHPh; cat-**B**]<sup>15</sup> (Scheme 2). Cross metathesis of phosphate (*S,S,P<sub>S</sub>*)-**6** and 1-undecene, a type I olefin,<sup>16</sup> using cat-**C**<sup>17</sup> gave desired product **9** with > 99:1 *E:Z* selectivity. Regioselective hydrogenation of the *exo*-cyclic olefin under mild conditions (*o*-nitrobenzenesulfonyl hydrazine (*o*-NBSH), Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>)<sup>18</sup> via an *in situ* generated diimide afforded desired product **5** in 85% yield.<sup>10b</sup>

The development of a one-pot, RCM/CM/hydrogenation sequence was next investigated (Schemes 3 and 4). Recently a number of tandem and sequential protocols involving metathesis have followed the seminal report by Grubbs and coworkers.<sup>19</sup> Initially, a one-pot, sequential CM/hydrogenation procedure was investigated using CH<sub>2</sub>Cl<sub>2</sub> as a common solvent with no workup after the metathesis event. This CM/hydrogenation sequence proceeded smoothly yielding the desired hydrogenated product **5** in 53% yield with an average of 73% yield for each step (Scheme 3).

To further streamline the process, we optimized the previously reported two-step protocol for synthesizing triene **7** from the corresponding diene-diol **8**<sup>6a</sup> using a one-step process employing allyl tetraisopropylphosphoro-diamidite in the presence of tetrazole, followed by oxidation with *m*-CPBA. This method provided the desired triene **7** in 64% yield (Scheme 4).<sup>20</sup> An RCM/CM/hydrogenation sequence from triene **7** was next investigated. Starting with triene (*S,S*)-**7**,<sup>5</sup> RCM in the presence of cat-**B** and subsequent CM with cat-**C**, followed by hydrogenation with *o*-NBSH, gave the desired hydrogenated product **5** in 40% yield along with 7% of the hydrogenated product of unreacted (*S,S,P<sub>S</sub>*)-**6** phosphate [5:1 ratio].<sup>21</sup> Overall, this method

represents an average yield of 74% for each step. Moreover, it simplifies the synthesis of **5** to a 2-step protocol from diene-diol (*S,S*)-**8**.

With **5** in place, 7-steps were required to complete the total synthesis of THL (**1**) (Scheme 5).  $S_N2'$  addition on *endo*-cyclic olefin with *in situ* generated organocuprate reagent followed by methylation with  $TMSCHN_2$  proceeds with high regio- and diastereoselectivity giving desired monocyclic phosphate **10**.<sup>6</sup> The phosphate tether was next removed under reductive conditions with the use of two equivalents of  $LiAlH_4$  affording diol **4** with all the desired stereocenters that are carried through until the last step of the sequence where inversion of the C5 stereocenter is carried out with Mitsunobu esterification. Selective silyl protection of the sterically more accessible C5 alcohol in **4** gave the desired silylether adduct **11** in 80% yield.<sup>22</sup> Conversion to carboxylic acid **12** was accomplished via ozonolysis/Pinnick oxidation protocol affording **12** in an overall 93% yield. The TIPS-protected  $\beta$ -lactone **3** was next readily accessed via lactonization of  $\beta$ -hydroxy carboxylic acid **12** in the presence of BOPCI through a mixed anhydride intermediate. Ensuing TIPS-deprotection under mild basic conditions (HF-pyr) followed by esterification with *N*-formyl-L-leucine under Mitsunobu inversion conditions (DIAD,  $PPh_3$ ) developed by Schneider<sup>7a</sup> afforded the desired final product tetrahydrolipstatin (**1**) in 94% yield with all matching characterization of the reported data.<sup>7</sup>

In conclusion, a successful synthesis of (–)-tetrahydrolipstatin has been developed that incorporates a phosphate tether approach starting from diene-diol (*S,S*)-**8**. Overall, a 9-step route from diene-diol (*S,S*)-**8** employing a phosphorodiamidite coupling and one-pot, sequential RCM/CM/hydrogenation sequence has been developed. Current efforts are focused on further optimization of the aforementioned one-pot, sequential RCM/CM/hydrogenation process, phosphorodiamidite coupling as well as additional phosphate tether approaches towards bioactive natural products containing 1,3-*anti*-diol subunits. The use of this one-pot, sequential RCM/CM-/hydrogenation sequence towards the synthesis of other bioactive natural products is ongoing and will be reported in due course.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

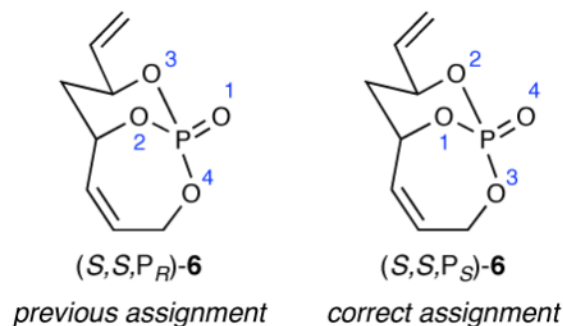
## Acknowledgments

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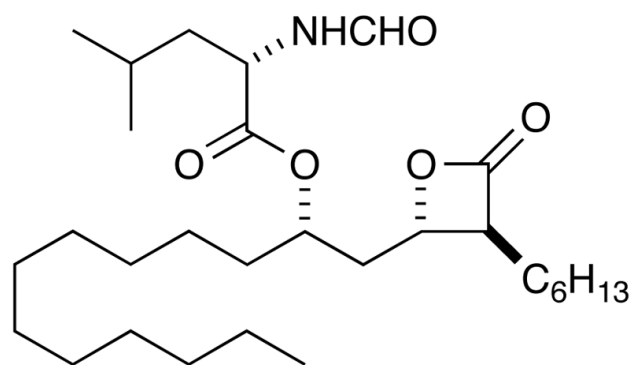
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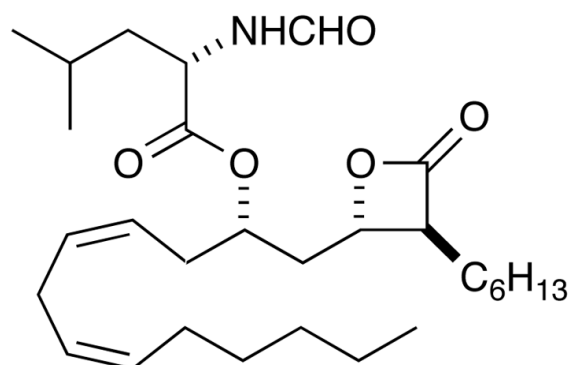
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14. We previously assigned the stereochemical descriptor at phosphorus in (S,S,P<sub>S</sub>)-6 as P<sub>R</sub> (see reference 6b). Workers at Chemical Abstracts Service kindly noted that Cahn-Ingold-Prelog priority rules dictate that “Contributions by d-orbitals to bonds of quadriligant atoms are neglected”, and hence the P=O in 6 should be treated as a P–O with assignment of least priority, see page 391 in Cahn RS, Ingold C, Prelog V. *Angew Chem Int Ed* 1966;5:385–415.



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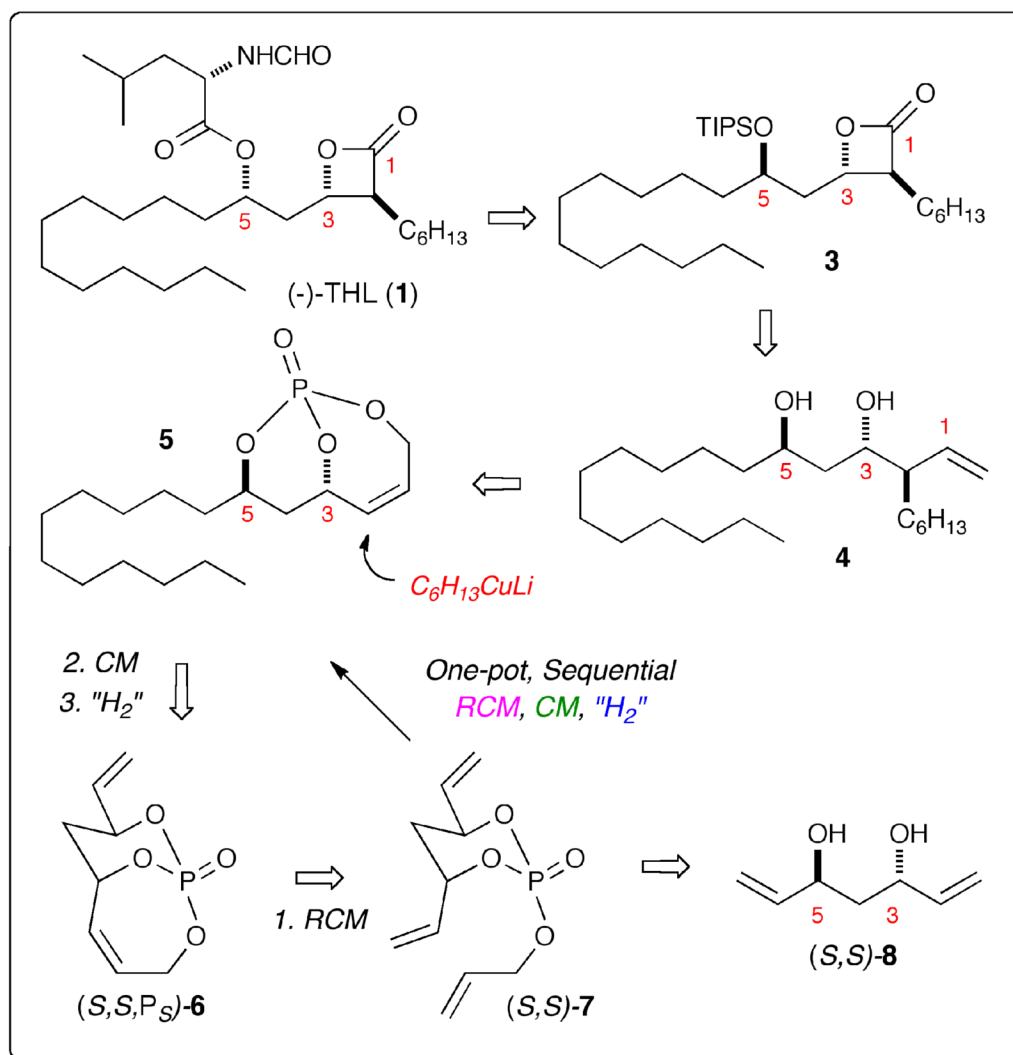


(-)-tetrahydrolipstatin (1)

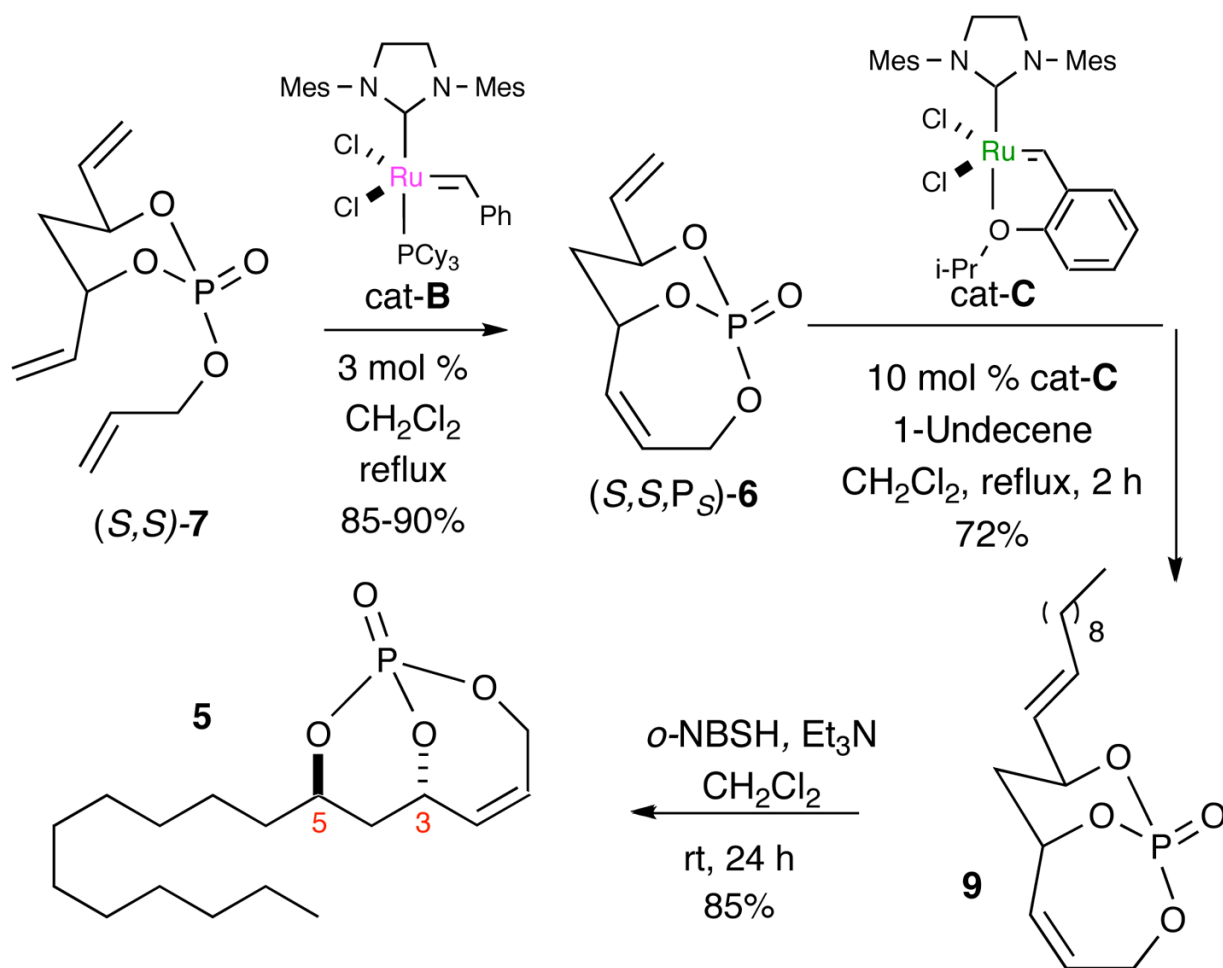


(-)-lipstatin (2)

**Figure 1.**  
(-)-Tetrahydrolipstatin and (-)-Lipstatin

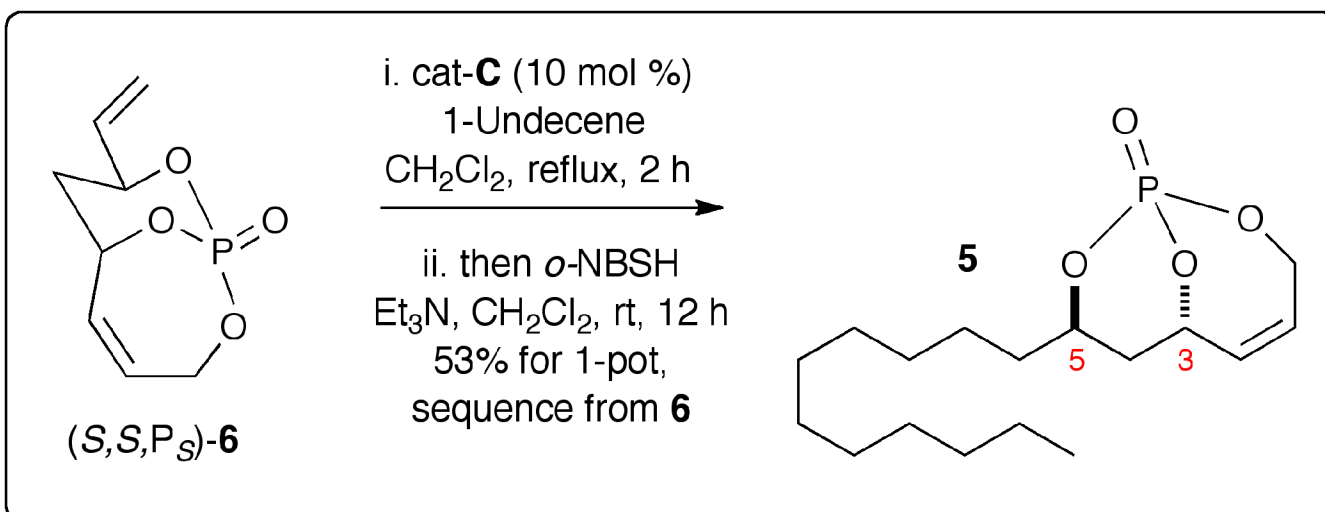


**Scheme 1.**  
Retrosynthetic Analysis of (-)-Tetrahydrolipstatin

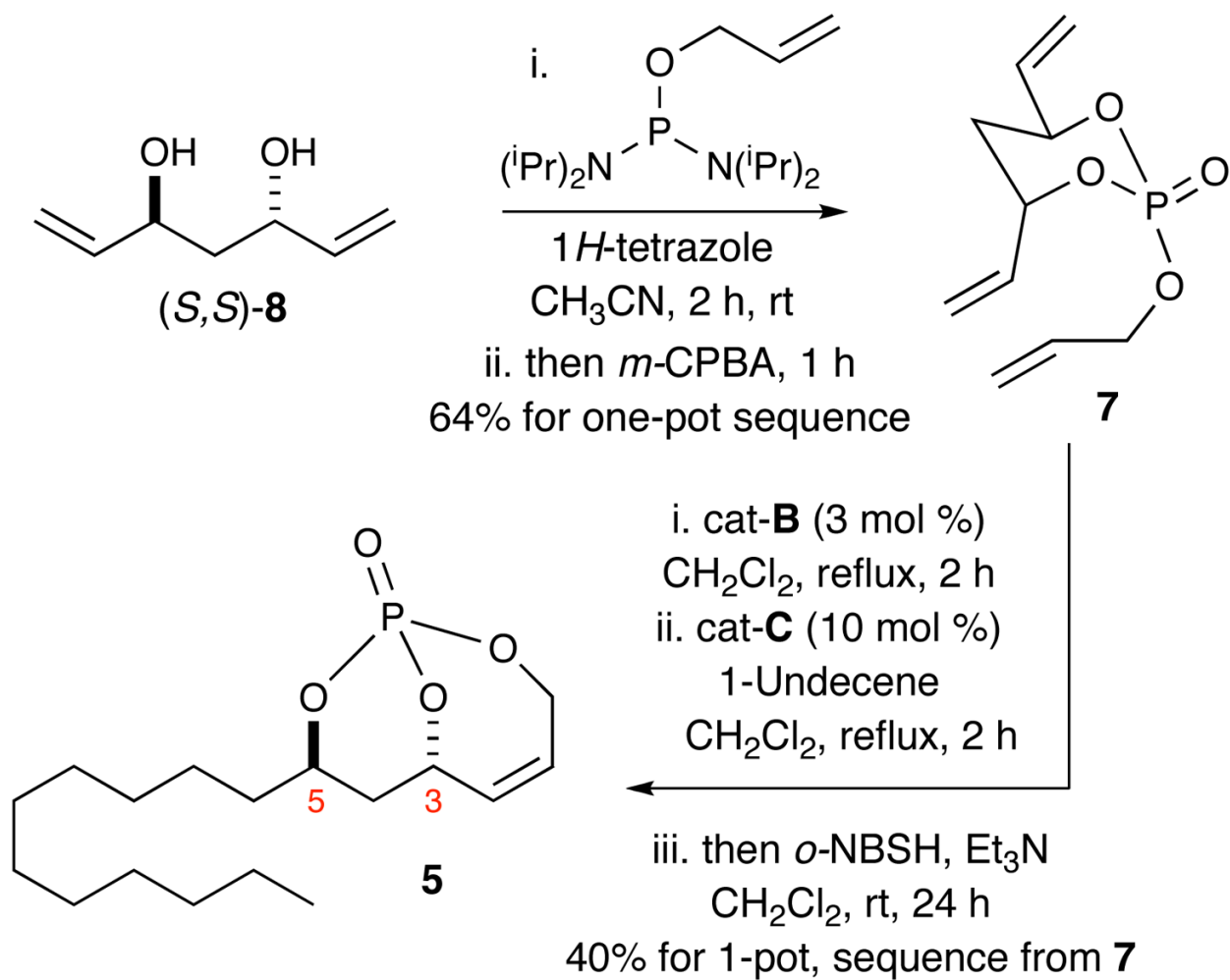


**Scheme 2.**  
Stepwise RCM, CM and hydrogenation sequence

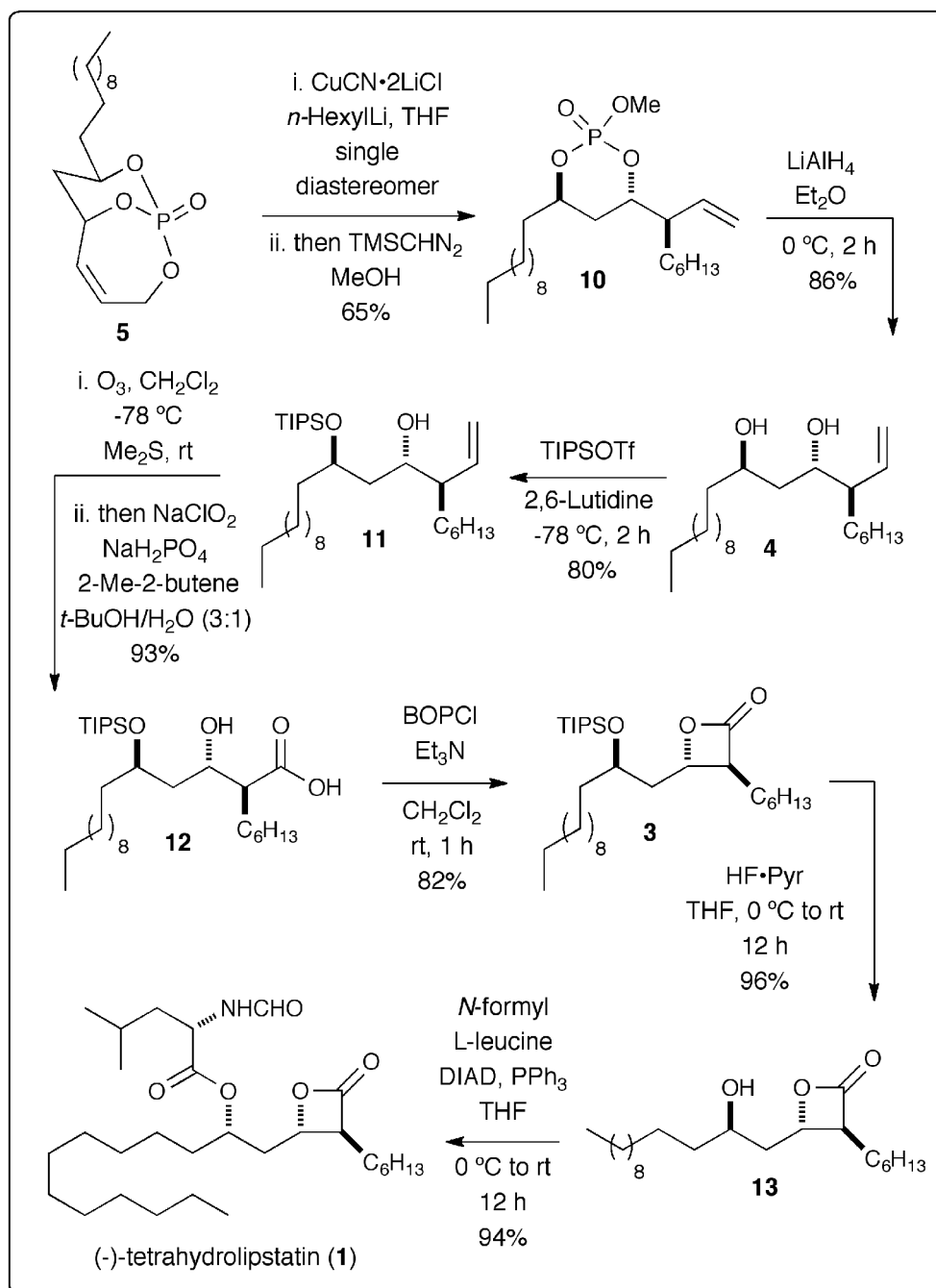




**Scheme 3.**  
One-pot, Sequential CM/Hydrogenation Pathway



**Scheme 4.** Phosphorodiamidite coupling and One-Pot, Sequential RCM/CM/Hydrogenation Sequence.



**Scheme 5.**  
 Total Synthesis of (-)-Tetrahydrolipstatin (1)