Total Synthesis of Tetrahydrolipstatin and Stereoisomers via a Highly Regio- and Diastereoselective Carbonylation of Epoxyhomoallylic Alcohols

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Ⓢ *Supporting Information*

ABSTRACT: A concise enantioselective synthesis of tetrahydrolipstatin (THL) and seven stereoisomers has been achieved. The synthesis of THL was accomplished in 10 steps and 31% overall yield from an achiral ynone. Key to the success of the approach is the use of a bimetallic [Lewis acid]$^+$[Co(CO)$_4$]$^-$ catalyst for a late-stage regioselective carbonylation of an enantiomerically pure *cis*-epoxide to a *trans*-β-lactone. The success of this route to THL and its stereoisomers also demonstrated the practicality of the carbonylation catalyst for complex molecule synthesis as well as its functional group compatibility.
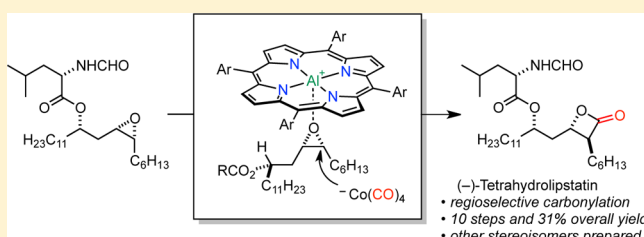
INTRODUCTION

Tetrahydrolipstatin (THL, **1**) is an over-the-counter anti-obesity drug that acts by inhibiting the absorption of dietary fats. THL is the saturated form of lipstatin (**2**), a natural product isolated from *Streptomyces toxytricini* in 1987.[1] Due to its greater stability, THL was chosen over lipstatin for pharmaceutical development. Both THL and lipstatin contain an α-alkylated β,δ-dihydroxy acid, which exists in the β-lactone form (Figure 1). The β-lactone in THL and lipstatin is believed
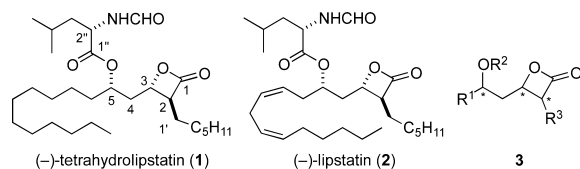
Figure 1. Tetrahydrolipstatin (THL, **1**), lipstatin (**2**), and analogues (**3**).

to ring-open and covalently bind to pancreatic lipase, which results in irreversible inhibition.[1a,2] In addition, THL and related β-lactones have been found to inhibit the thioesterase domain of fatty acid synthase (FAS),[3] the inhibition of which has been linked to anticancer activity.[4] More recently, THL has been shown to inhibit the *in vitro* growth of *Giardia duodenalis*, the causative parasite of the gastrointestinal disease giardiasis.[5]

Since the first synthesis of THL by Schneider,[6a] there have been numerous total[6−12] and formal syntheses of THL,[13] which have involved a diverse range of approaches. In terms of how they derive absolute stereochemistry, these approaches can be classified into the following categories: (1) chiral auxiliary,[6] (2) asymmetric aldol,[7] (3) asymmetric allylation/crotylation,[8] (4) asymmetric reductions,[9] (5) asymmetric resolutions,[10] (6) asymmetric oxidations,[11] and (7) chiron approach.[12] These routes include the elegant use of a chiral phosphate template,[9c] a tandem Mukaiyama aldol lactonization,[7e,i] an anti-aldol segment via a non-aldol route,[7h] and a Prins cyclization for stereocontrol.[10b]

As part of a larger effort aimed at the use of catalysis for the asymmetric synthesis and structure−activity relationship studies of biologically active natural products,[14] we became interested in the synthesis of THL (**1**) and related analogues **3** (Figure 1). We were particularly interested in the carbonylation of epoxides using bimetallic [Lewis acid]$^+$[Co(CO)$_4$]$^-$ catalysts, which has recently emerged as a reliable, direct route to β-lactones.[15] We have had success using this type of carbonylation catalyst for the synthesis of terminal β-lactones *en route* to natural products.[16] However, unsymmetrically disubstituted epoxides are prone to giving a mixture of regioisomeric β-lactones. Presumably this is because of an unselective S$_N$2-ring opening reaction in the case of electronically or sterically unbiased substrates (Scheme 1).

This problem has recently been addressed by the introduction of catalysts that can carbonylate racemic and enantioenriched *trans*-disubstituted epoxides to the corresponding *cis*-β-lactones with high and opposing regioselectivities.[17] We hypothesized that it would be possible to obtain the desired β-lactone isomer **3b** of THL and its analogues via regioselective carbonylation of protected *cis*-epoxyhomoallylic alcohols

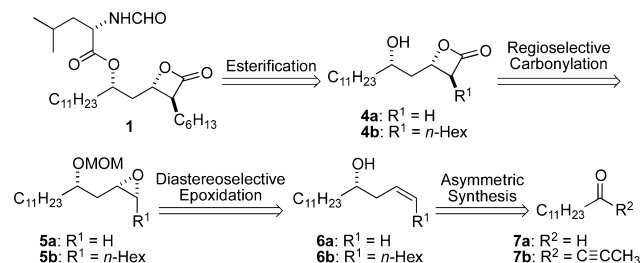**Scheme 1. Regioselective Carbonylation of Protected *cis*-Epoxyhomoallylic Alcohols**
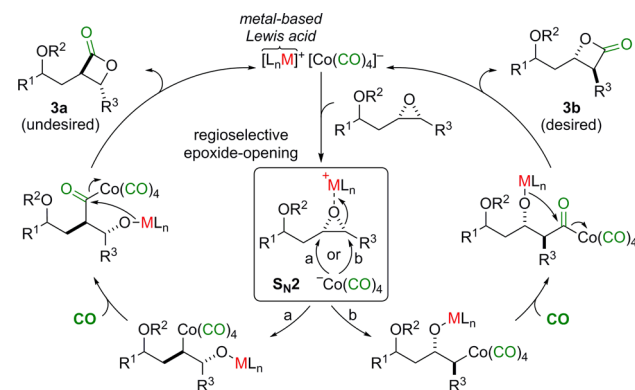
(Scheme 1). Herein, we disclose a new route for the synthesis of THL and seven stereoisomers using regioselective carbonylation of epoxides to form the β-lactone moiety. The fatty acid lipid portion of THL (**4b**) was prepared from protected *cis*-epoxyhomoallylic alcohol **5b** with all the lipid stereogenic centers in place via a *de novo* asymmetric route (Scheme 2).

Scheme 2. Retrosynthetic Analysis of THL (1)

Retrosynthetic Analysis. Retrosynthetically, we envisioned preparing THL from its lipid core **4b** and *N*-formyl-L-leucine (Scheme 2). Using a regioselective carbonylation reaction, the lipid portion of THL (**4b**) could be prepared either directly from *cis*-epoxyalcohol **5b** or from **5a** after alkylation of the terminal β-lactone **4a**. Epoxides **5a,b** could be prepared from a highly diastereoselective epoxidation of homoallylic alcohol **6a,b**, which in turn could be prepared from **7a,b** via asymmetric synthesis. Key to the success of this approach is the need for high regioselectivity in the carbonylation (**5** to **4**). Presumably, this could be accomplished with a high degree of confidence using terminal epoxide **5a**.[15a] However, the subsequent alkylation of terminal β-lactones such as **4a** is highly problematic.[10a,18] Consequently, a greater degree of synthetic efficiency would result from a regioselective carbonylation of a 2,3-disubstituted epoxide with all the requisite lipid carbons in place, i.e. **5b** to **4b**. Regioselective carbonylation of epoxides had very little precedence in the synthesis of complex molecules prior to our endeavors.[19]

We anticipated that the precise choice of hydroxyl protecting group in **5b** could be critical for the control of the carbonylation regioselectivity. At the outset, we chose a methoxymethyl group (MOM) for its potential to participate in chelated transition states. However, we were also interested in investigating the use of *N*-formyl-L-leucine, thus avoiding the need for a protecting group at this stage. This had the added advantage of testing the compatibility of the

[Lewis acid]$^+$[Co(CO)$_4$]$^-$ carbonylation catalyst with the Lewis basic and Brønsted acidic formamide functional group as well as the rather epimerizable α-amino ester group.

RESULTS AND DISCUSSION

Formal Synthesis of Tetrahydrolipstatin. To ensure success with this approach, we began our efforts with the synthesis of the diastereomeric terminal epoxides **10** and **12** (Scheme 3). The approach began with a Leighton allylation[20]

Scheme 3. Formal Synthesis of THL (1)[a]
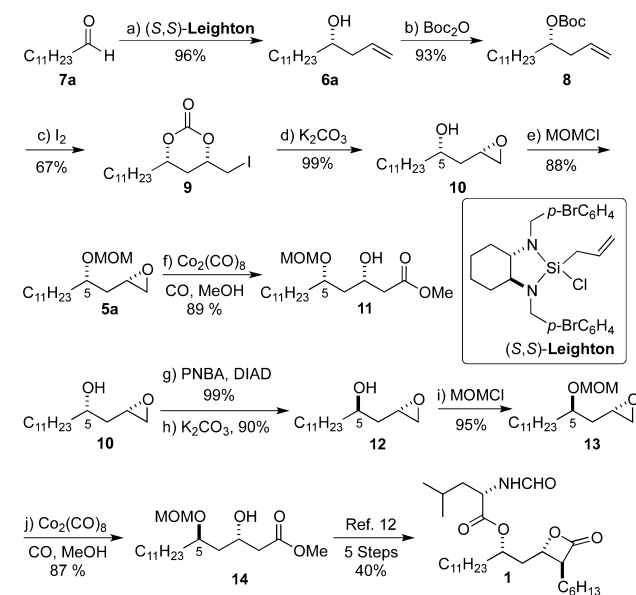
[a]Reagents and conditions: (a) (*S,S*)-**Leighton**, Sc(OTf)$_3$ (2.5 mol %), CH$_2$Cl$_2$, −10 °C, 96%, >95% ee; (b) Boc$_2$O, *n*-BuLi, THF, 0 °C, 93%; (c) I$_2$, MeCN, −20 °C, 67%; (d) K$_2$CO$_3$, MeOH, rt, 99%, >95% dr; (e) MOMCl, DIPEA, CH$_2$Cl$_2$, 0 °C, 88%; (f) Co$_2$(CO)$_8$ (10 mol %), 3-hydroxypyridine (20 mol %), CO (900 psi), MeOH, THF, 60 °C, 89%; (g) PNBA, DIAD, PPh$_3$, THF, 0 °C, 99%; (h) K$_2$CO$_3$, MeOH, 0 °C, 90%; (i) MOMCl, DIPEA, CH$_2$Cl$_2$, 0 °C, 95%; (j) Co$_2$(CO)$_8$ (10 mol %), 3-hydroxypyridine (20 mol %), CO (900 psi), MeOH, THF, 60 °C, 87%. DIAD = diisopropyl azodicarboxylate, PNBA = *p*-nitrobenzoic acid, MOMCl = chloromethyl methyl ether, DIPEA = *N,N*-diisopropylethylamine.

of dodecanal **7a** to give homoallylic alcohol **6a**. After Boc-protection of alcohol **6a**, the resulting *t*-butylcarbonate **8** was treated with iodine to form cyclic carbonate **9**. Hydrolysis of carbonate **9** led to *in situ* epoxidation to form **10**, which was then protected as a MOM ether **5a** (MOMCl/DIPEA). Alternatively, the stereochemistry at C5 in **10** was inverted using Mitsunobu conditions to give **12** after hydrolysis (PNBA/PPh$_3$/DIAD, K$_2$CO$_3$/MeOH), which was also protected as a MOM ether **13**. Epoxides **5a/13** underwent regioselective carbonylation to give β-hydroxy esters **11/14** when exposed to carbonylation conditions (CO, 10 mol % Co$_2$(CO)$_8$, 20 mol % 3-hydroxypyridine).[21] The synthesis of β-hydroxy ester **14** constitutes a formal synthesis of THL (**1**) as **14** has been previously transformed into THL via the *n*-hexyl α-alkylation of a dianion generated from **14**.[12]

Asymmetric Synthesis of *cis*-Epoxyhomoallylic Alcohol 19. With access to a formal synthesis of THL, we turned our focus to potentially more efficient approaches to THL, which involved carbonylation of the more challenging 2,3-

disubstituted *cis*-epoxide **5b**. The synthesis of epoxide **5b** required a practical asymmetric synthesis of epoxyhomoallylic alcohol **19** (Scheme 4). Our approach involved the novel

**Scheme 4. Synthesis of *cis*-Epoxyhomoallylic Alcohol 19[a]**
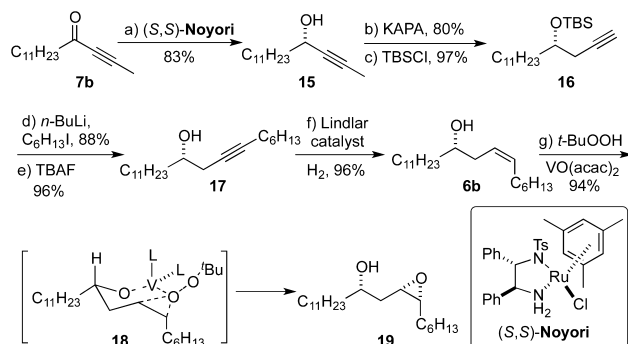
[a]Reagents and conditions: (a) (*S,S*)-**Noyori** (5 mol %), Et₃N, HCO₂H, rt, 83%, >95% ee; (b) H₂N(CH₂)₃NH₂, KH, 15 °C to rt, 80%; (c) TBSCl, imidazole, DMF, rt, 97%; (d) *n*-BuLi, HPMA, THF, −20 °C; C₆H₁₃I, −20 °C to rt, 88%; (e) TBAF, THF, rt, 96%; (f) Pd/CaCO₃, quinoline, H₂ (1 atm), MeOH, rt, 96%; (g) *t*-BuOOH, VO(acac)₂ (2 mol %), CH₂Cl₂, 0 °C, 94%, 92% dr. KAPA = potassium 3-aminopropylamide, TBSCl = *tert*-butyldimethylsilyl chloride, HMPA = hexamethyl phosphoramide, TBAF = tetra-*n*-butylammonium fluoride.

construction of the *Z*-homoallylic alcohol functionality via a Noyori reduction/alkyne zipper/Lindlar reduction sequence.[22] To establish the absolute stereochemistry for this route, we used a highly enantioselective (95% ee) Noyori asymmetric reduction[23] of achiral ynone **7b**, which could be prepared in one step from a known Weinreb amide. Using the alkyne zipper reaction,[24] the internal 2-alkyne in **15** was isomerized into a terminal alkyne and then TBS protected to give **16**. Alkylation of terminal alkyne **16** (*n*-BuLi then *n*-Hex-I, 88%) and TBAF-promoted deprotection of the TBS-ether provided the homopropargyl alcohol **17**. Partial hydrogenation of alkyne **17** using Lindlar conditions[25] (1 atm H₂, Pd/CaCO₃, quinoline, 96%) cleanly gave (*Z*)-olefin **6b**. Finally, a highly diastereoselective hydroxy-directed epoxidation of **6b** furnished **19** (*t*-BuOOH, 2 mol % VO(acac)₂, 94%, 92% dr) via putative intermediate **18**.[26]

Total Synthesis of Tetrahydrolipstatin. With the establishment of a practical and stereocontrolled synthesis of epoxide **19**, we began our investigation of the regioselectivity of the carbonylation reaction (Scheme 5). This study began with the protection of the alcohol as a MOM ether **5b** (MOMCl, 85%). To our delight, when the MOM-protected epoxide **5b** was subjected to carbonylation (1 mol % [ClTPPAl][Co(CO)₄], CO (900 psi)),[15f] a single regioisomer *β*-lactone **20** was formed, which was obtained in 81% isolated yield.

The synthesis of THL was easily finished via a four-step deprotection/acylation/deprotection/formylation procedure. Thus, the MOM group was removed with BF₃ etherate to give **4b** (83%). A DCC coupling of **4b** with *N*-Cbz-L-leucine installed the amino acid side chain in **21**. Finally, a two-step hydrogenolysis/formylation procedure both removed the Cbz group (1 atm H₂, Pd/C in AcOCHO) and installed the *N*-formyl group to give THL (**1**) without any epimerization (*vide infra*).[6f,7h] The synthetic THL produced had spectral (¹H, ¹³C NMR, IR) and optical properties (reported $[\alpha]_D^{20}$ = −33 (c =

**Scheme 5. Synthesis of THL (1): Carbonylation of MOM-Protected Epoxide 5b[a]**
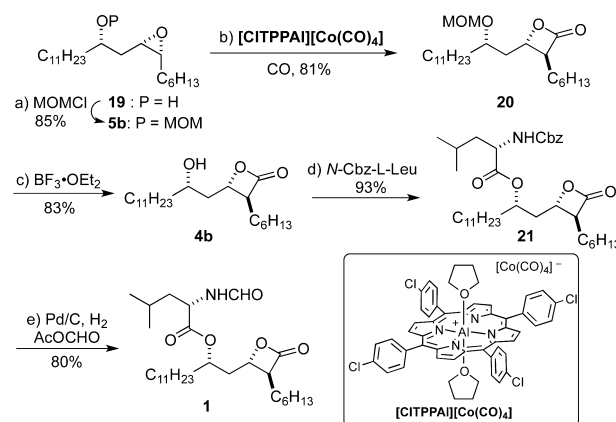
[a]Reagents and conditions: (a) MOMCl, DIPEA, CH₂Cl₂, 0 °C, 85%; (b) [ClTPPAl][Co(CO)₄] (1 mol %), CO (900 psi), THF, 50 °C, 81%; (c) BF₃·OEt₂, 1,2-ethanedithiol, CH₂Cl₂, 0 °C, 83%; (d) *N*-Cbz-L-leucine, DCC, DMAP, CH₂Cl₂, rt, 93%; (e) Pd/C (10% wt/wt, 10 mol %), H₂ (1 atm), AcOCHO, rt, 80%. ClTPP = *meso*-tetra(4-chlorophenyl) porphyrinato, DCC = *N,N′*-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine.

0.36, CHCl₃);[6b] synthetic $[\alpha]_D^{23}$ = −33.7 (c = 0.48, CHCl₃)) consistent with what have been reported in the literature.

Alternative Approach to THL. To test the functional group compatibility of the carbonylation catalyst, we explored alternatives to the MOM protecting group. In this vein, we looked at the use of the *N*-formyl-L-leucine ester group (i.e., **22**) (Scheme 6) as a replacement for the MOM ether. Along

Scheme 6. Synthesis of THL (1): A Late-Stage Carbonylation of Epoxide[a]
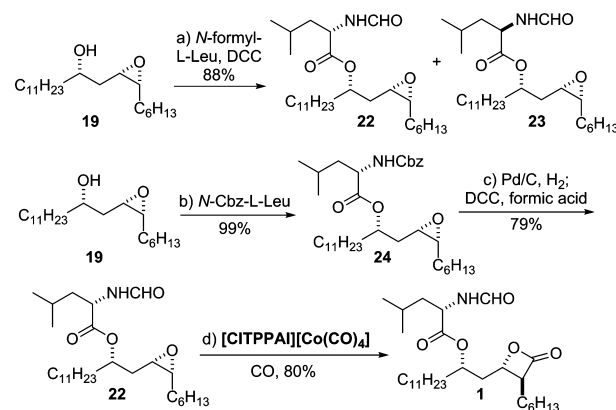
[a]Reagents and conditions: (a) *N*-formyl-L-leucine, DCC, DMAP, CH₂Cl₂, rt, 88%; (b) *N*-Cbz-L-leucine, DCC, DMAP, CH₂Cl₂, rt, 99%; (c) Pd/C (10% wt/wt, 10 mol %), H₂ (1 atm), THF, rt; DCC, formic acid, CH₂Cl₂, rt, 79%; (d) [ClTPPAl][Co(CO)₄] (2 mol %), CO (900 psi), THF, 50 °C, 80%.

with testing the functional group compatibility of the carbonylation conditions, this substitution also had the advantage of reducing steps.

We initially investigated the synthesis of epoxide **22** via the direct DCC coupling of *N*-formyl-L-leucine with **19**. Unfortunately, we were not able to find conditions under which the coupling occurred without appreciable amounts of epimeriza-

tion (i.e., **22** and **23** were isolated as a 6:4 mixture of epimers).[6f,7h] To circumvent the epimerization problem, we returned to the less epimerizable N-Cbz-protected L-leucine. Under the same DCC coupling procedure, N-Cbz-L-leucine coupled with **19** to afford ester **24** in 99% yield without any sign of epimerization.[6f] Exposure of **24** to the two-step hydrogenolysis/formylation conditions (1 atm H_2, Pd/C then HCO_2H/DCC) provided the desired epoxide **22** in 79% yield. Gratifyingly, under carbonylation conditions (2 mol % [ClTPPAl][Co(CO)$_4$], CO (900 psi)), epoxide **22** with an N-formyl-L-leucine side chain was cleanly transformed into THL (**1**) as the single regioisomer, which was obtained in excellent yield (80%) without any sign of epimerization.

Preparation of Other THL Stereoisomers. The successful synthesis of THL via late-stage regioselective carbonylation of epoxide **22** prompted us to explore the scope of this approach. In particular, we were interested in exploring its utility for the synthesis of various stereoisomers of THL.[27] To do this, we required access to a series of stereoisomeric epoxides with various groups at the C5 position. This was carried out from epoxyalcohol **19** and its enantiomer ent-**19**. Thus, the C5 diastereomer **26** with a MOM-protecting group was easily prepared from ent-**19** by means of a three-step Mitsunobu/hydrolysis/protection sequence in a 65% overall yield (Scheme 7).

Scheme 7. Synthesis of Diastereomer 26[a]
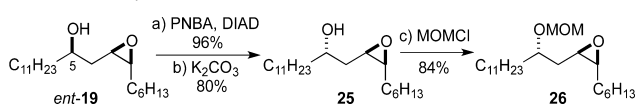
[a]Reagents and conditions: (a) PNBA, DIAD, PPh$_3$, THF, 0 °C, 96%; (b) K$_2$CO$_3$, MeOH, 0 °C, 80%; (c) MOMCl, DIPEA, CH$_2$Cl$_2$, 0 °C, 84%.

By both invertive and retentive acylation chemistry, the three epoxides with an N-formyl leucine side chain (**23**, **28**, and **30**) were prepared from epoxide **19** (Scheme 8). To circumvent the problem associated with epimerization during the DCC coupling with N-formyl leucine, we resorted to the use of N-Cbz-D-leucine in the coupling to form **27**, which could be readily converted into N-formyl amide **23** by hydrogenolysis followed by a DCC coupling with formic acid. In contrast to the DCC coupling with N-formyl leucine, the invertive Mitsunobu acylation of epoxide **19** with N-formyl leucine occurred with complete stereocontrol to give **28**. Epoxide **30** was also made from **19** via ester **29** by means of a three-step Mitsunobu acylation and hydrogenolysis N-Cbz to N-formyl group exchange (1 atm H_2, Pd/C then HCO_2H/DCC).

With related invertive and retentive acylation chemistry, three stereoisomeric epoxides (ent-**24**, ent-**29**, and **32**) and their enantiomers were made with the N-Cbz leucine side chain from epoxide ent-**19** (Scheme 9). To serve as a control group for the amide substitution, epoxide **31** with no amino-substitution was prepared by a Mitsunobu acylation with isohexanoic acid.

We next investigated the regioselectivity of the carbonylation with the various epoxide stereoisomers (Table 1). Exposure of the MOM-protected diastereomeric epoxide **26** to typical carbonylation conditions cleanly converted it into β-lactone **33** (entry 1, 88%) with complete regioselectivity. Similarly, clean conversion was found for the C2″ stereoisomeric epoxide **23**, which reacted to give β-lactone **34** as a single regio- and stereoisomer (entry 2, 77%). In contrast to changes in

Scheme 8. Synthesis of Stereoisomeric Epoxides from 19[a]
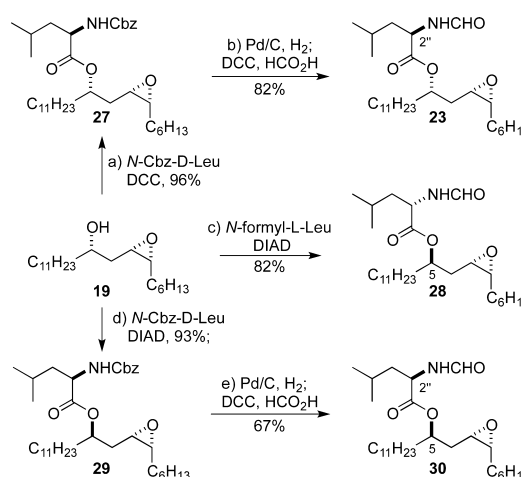
[a]Reagents and conditions: (a) N-Cbz-D-leucine, DCC, DMAP, CH$_2$Cl$_2$, rt, 96%; (b) Pd/C (10% wt/wt), H$_2$ (1 atm), THF, rt; DCC, formic acid, CH$_2$Cl$_2$, rt, 82%; (c) N-formyl-L-leucine, DIAD, PPh$_3$, THF, 0 °C to rt, 82%; (d) N-Cbz-D-leucine, DIAD, PPh$_3$, THF, 0 °C, 93%; (e) Pd/C (10% wt/wt), H$_2$ (1 atm), THF, rt; DCC, formic acid, CH$_2$Cl$_2$, rt, 67%.

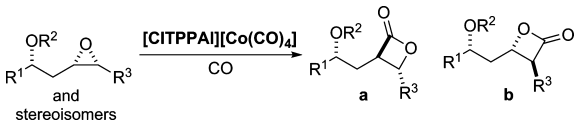**Scheme 9. Synthesis of Stereoisomeric Epoxides from ent-19**[a]
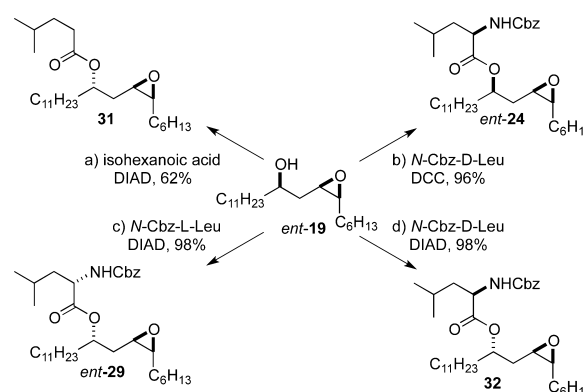
[a]Reagents and conditions: (a) isohexanoic acid, DIAD, PPh$_3$, THF, 0 °C, 62%; (b) N-Cbz-D-leucine, DCC, DMAP, CH$_2$Cl$_2$, rt, 96%; (c) N-Cbz-L-leucine, DIAD, PPh$_3$, THF, 0 °C, 98%; (d) N-Cbz-D-leucine, DIAD, PPh$_3$, THF, 0 °C, 98%.

stereochemistry at C2″, the inversion of the stereochemistry at C5 had a significant effect on the regioselectivity of the reaction (entries 3 and 4). Epoxide **28** with an N-formyl amide carbonylated to give β-lactones **35** in good yields of a 6:1 mixture of regioisomers. The C2″ epimeric epoxide **30** also carbonylated with lower regioselectivity to give β-lactones **36** in good yields of a 5:1 mixture of regioisomers. In addition to poor regioselectivities, epoxides **28** and **30** also required higher catalyst loadings.[28]

We hypothesized that the loss in regioselectivity for substrates **28** and **30** could be the result of hydrogen bonding interactions (Figure 2). This hydrogen bonding interaction in turn could lower the barrier for pathway **a** to the regioisomeric β-lactone. To test this hypothesis, we investigated the carbonylation of epoxides **31**, ent-**24**, ent-**29**, and **32**. When the N-formyl group was removed as in epoxide **31** (entry 5), the carbonylation occurred to give β-lactone **37** with complete

Table 1. Stereochemical Scope of Regioselective Carbonylation[a]

Entry	Epoxide	Major Regioisomer **b**	Ratio[b] **b:a**	Isolated Yield (%)
1	**26**	**33**	>99:1	88
2	**23**	**34**	>99:1	77
3	**28**	**35**	6:1	72
4	**30**	**36**	5:1	77
5	**31**	**37**	>99:1	53
6	*ent*-**24**	*ent*-**21**	>99:1	75
7	*ent*-**29**	*ent*-**38**	>99:1	80
8	**32**	*ent*-**39**	>99:1	74

[a]See Supporting Information for detailed reaction conditions for each entry. [b]Ratio determined by ^{1}H NMR spectroscopy; for entries 1, 2, and 5−8 regioisomer **a** was not observed.

Figure 2. Rationale for loss of regiocontrol for epoxides **28** and **30**.

Scheme 10. Synthesis of β-Lactones 35 and 36 from Known β-Lactone 4b[a]

[a]Reagents and conditions: (a) *N*-Cbz-L-leucine, DIAD, PPh₃, THF, 0 °C, 72%; (b) Pd/C (10% wt/wt), H₂ (1 atm), THF, rt; DCC, formic acid, CH₂Cl₂, rt, 63%; (c) *N*-Cbz-D-leucine, DIAD, PPh₃, THF, 0 °C, 82%; (d) Pd/C (10% wt/wt), H₂ (1 atm), THF, rt; DCC, formic acid, CH₂Cl₂, rt, 60%.

control of regioselectivity. Interestingly, when the *N*-formyl group was replaced with the less acidic *N*-Cbz group, the high regioselectivity returned. Thus, epoxides *ent*-**24**, *ent*-**29**, and **32** carbonylated to form β-lactones *ent*-**21**, *ent*-**38**, and *ent*-**39** as single regioisomers (entries 6−8; 75%, 80%, 74%, respectively).

In order to confirm the connectivity of unknown β-lactones **35**, **36**, **38**, and **39**, we prepared them independently from known β-lactone **4b** (Scheme 10). The β-lactone **4b** was converted into Cbz-protected leucine esters **38** and **39** via a Mitsunobu esterification. A hydrogenolysis/formylation reac-
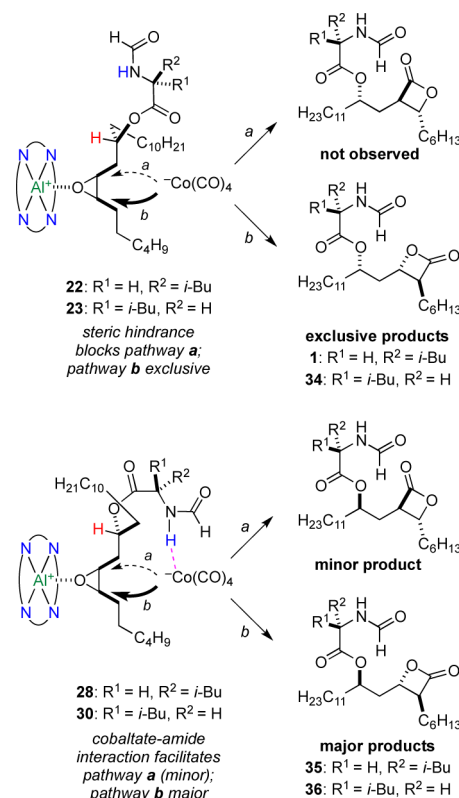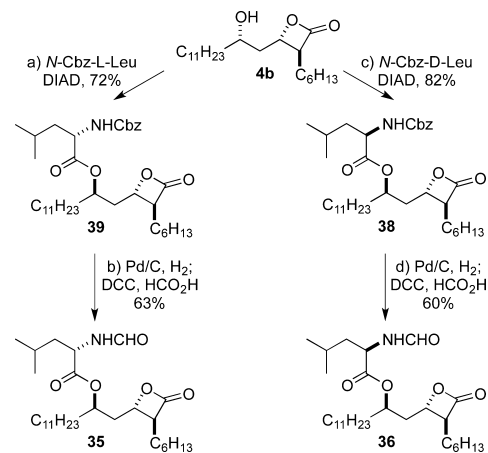
tion converted **38** and **39** into **36** and **35**, respectively, which had identical ^{1}H NMR spectra to the products prepared from the carbonylation reactions.

In support of the structure of the minor isomers formed from the carbonylation of epoxides **28** and **30** (entries 3 and 4; **35** and **36**), we carried out a thermolytic decarboxylation reaction on the product mixture **35** and presumed regioisomer **35a** (Scheme 11). Specifically, a 2:1 mixture of **35** and hypothesized **35a** was heated to 230 °C in a sealed tube under argon for 1

Scheme 11. Evidence for Minor Regioisomer 35a by Thermolysis[a]
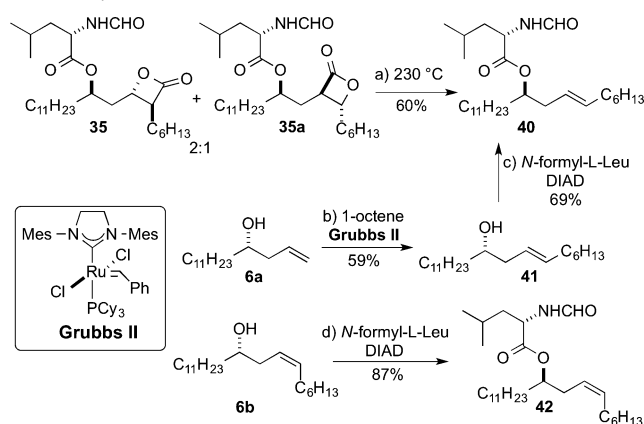
[a]Reagents and conditions: (a) 230 °C, 60%; (b) 1-octene, **Grubbs II**, CH₂Cl₂, reflux, 59%, E/Z = 6:1; (c) N-formyl-L-leucine, DIAD, PPh₃, THF, 0 °C, 69%; (d) N-formyl-L-leucine, DIAD, PPh₃, THF, 0 °C, 87%.

hour producing *trans*-olefin **40** as the sole product. The identity of olefin **40** was confirmed by its synthesis from homoallylic alcohol **41**, which in turn was made from terminal olefin **6a** using cross metathesis.[29] For comparison, *cis*-olefin **42** was prepared from **6b**, which was readily distinguishable from its *trans*-isomer **40** by ¹³C NMR spectra.

Synthesis of *ent*-THL and Its Stereoisomers. With the route established above, we synthesized the enantiomer of THL (*ent*-**1**), as well as the stereoisomers *ent*-**34**, *ent*-**35**, and *ent*-**36** (Scheme 12). The most direct route took advantage of the

Scheme 12. Synthesis of *ent*-THL (*ent*-1) and Its Stereoisomers[a]
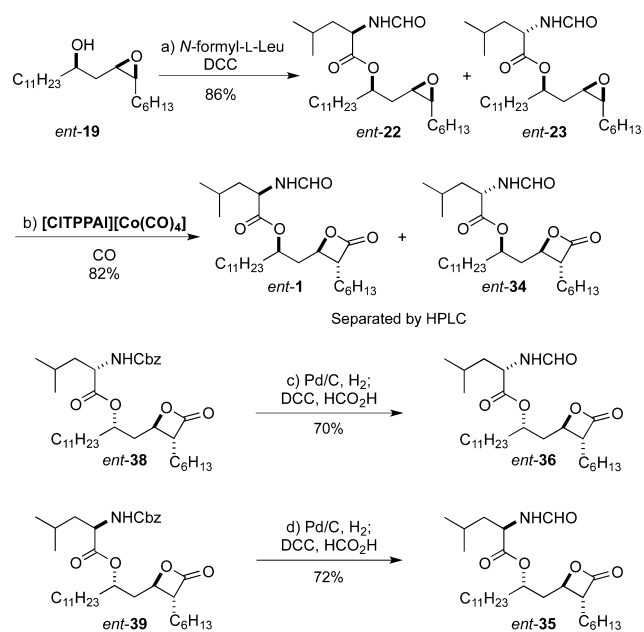
[a]Reagents and conditions: (a) N-formyl-L-leucine, DCC, DMAP, CH₂Cl₂, rt, 86%; (b) [ClTPPAl][Co(CO)₄] (2 mol %), CO (900 psi), THF, 50 °C, 82%; (c) Pd/C (10% wt/wt, 20 mol %), H₂ (1 atm), THF, rt; DCC, formic acid, CH₂Cl₂, rt, 70%; (d) Pd/C (10% wt/wt, 20 mol %), H₂ (1 atm), THF, rt; DCC, formic acid, CH₂Cl₂, rt, 72%.

epimerization that occurred during the DCC coupling of epoxide *ent*-**19** and N-formyl-L-leucine. Under these conditions, a mixture of *ent*-**22** and *ent*-**23** was afforded, which upon carbonylation were smoothly converted into a mixture of β-lactones *ent*-**1** and *ent*-**34**. Preparative HPLC was used to purify the two isomers, *ent*-**1** and *ent*-**34**. The remaining two enantiomers, *ent*-**35** and *ent*-**36**, were prepared by an analogous route to the synthesis of their enantiomers (**35** and **36**, Scheme 10). This was accomplished by a two-step hydrogenolysis/formylation procedure, which replaced the N-Cbz group with an N-formyl group in β-lactones *ent*-**38** and *ent*-**39**, cleanly providing *ent*-**36** and *ent*-**35**, respectively.

■ CONCLUSIONS

A concise enantioselective synthesis of THL has been achieved in 10 steps and 31% overall yield from achiral ynone **7b**. The route is amenable for the production of THL and seven stereoisomers. In addition, the route demonstrated the versatility and regioselectivity of the bimetallic [Lewis acid]⁺[Co(CO)₄]⁻ catalyzed carbonylation of enantiomerically pure *cis*-epoxides to *trans*-β-lactones. Further application of bimetallic carbonylation catalysts for the synthesis and medicinal chemistry studies of natural products will be reported in due course.

■ ASSOCIATED CONTENT

ⓈSupporting Information
Detailed experimental procedures, full characterization data, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
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