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Stereoselective syntheses of (−)-tetrahydrolipstatin via Prins cyclisations

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Abstract—Stereoselective syntheses of (−)-tetrahydrolipstatin have been achieved via two divergent approaches through Prins cyclisations as the key steps. PCC mediated oxidative cleavage, Frater alkylation, Keck allylation, Sharpless asymmetric epoxidation and allylic cleavage were the other key steps employed.

(−)-Tetrahydrolipstatin (THL), a potent and irreversible lipase inhibitor, 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. Due to its biological activity, THL has been the target of several synthetic chemists.[2] In our ongoing program on the utilisation of the highly stereoselective Prins cyclisation reaction, a well established method for constructing multi-substituted tetrahydropyrans,[3] for the synthesis of polyketide motifs,[4] we have undertaken the total synthesis of (−)-THL.

The retrosynthetic analysis is outlined in Scheme 1. Not surprisingly, our first disconnection involved cleavage of the (*S*)-*N*-formyl amino acid portion to reveal the key triketide fragment **2** and acid **3**. It was envisioned that **2** could be obtained in two different ways. First, we speculated that the alkyl stereocentre could be created by controlled alkylation on **4** which could be easily obtained from lactone **5** which in turn is available through Prins cyclisation from simple homoallylic alcohol **6** and dodecanal. We also envisioned that the triketide **2** could be obtained, via allylic cleavage, from tetrasubstituted pyran **7** which in turn could be accessed from homoallylic alcohol (HAA) **8** and *trans*-2-hexenal. Homoallylic alcohol **8** would be easily obtained from chiral allylated **9** or from Sharpless asymmetric epoxidation product **10**.

Our first approach is outlined in Scheme 2. Cu mediated regioselective opening[5] of (*R*)-benzyl glycidyl ether **11**[6] with vinyl magnesium bromide resulted in HAA **6**. Prins cyclisation of HAA **6** with dodecanal in the presence of TFA followed by hydrolysis of the resulting trifluoroacetate gave trisubstituted pyran **12**.[3a,4a] Protection of the secondary alcohol as the TBS ether **13** using TBSCl, imidazole and catalytic DMAP followed by cleavage of the primary benzyl ether using Na in ammonia produced pyranyl methanol **14**. PCC mediated oxidative cleavage[4a,7] of **14** in refluxing benzene provided triketide δ-lactone **5**. Methanol addition to the lactone was carried out in the presence of TEA and resulted in the corresponding δ-hydroxy ester which without work-up but after removal of MeOH under reduced pressure, was protected as its MOM ether **15** in the presence of DIPEA and MOMCl in DCM. Attempts to isolate the intermediate MeOH addition product were unsuccessful as it cyclised back to lactone **5**. Cleavage of the silyl ether in **15** using TBAF in THF yielded β-hydroxy ester **4**. The dianion of **4**, formed on treatment with LDA in THF, was alkylated with hexyl iodide to give **16** as the predominant diastereomer in 75% yield after a flash column chromatography.[8] The crude reaction product revealed ~2% of the other diastereomer.

Hydroxy ester **16** was transformed into β-lactone **18** by hydrolysis of the ester group using LiOH followed by treatment of acid **17** with $PhSO_2Cl$ in the presence of pyridine in THF. β-Lactone **18** on cleavage of the MOM ether with $BF_3{\cdot}OEt_2$ and ethane dithiol[9] in DCM produced alcohol **2** which on esterification with (*S*)-*N*-formyl leucine **3** under Mitsunobu conditions[10]

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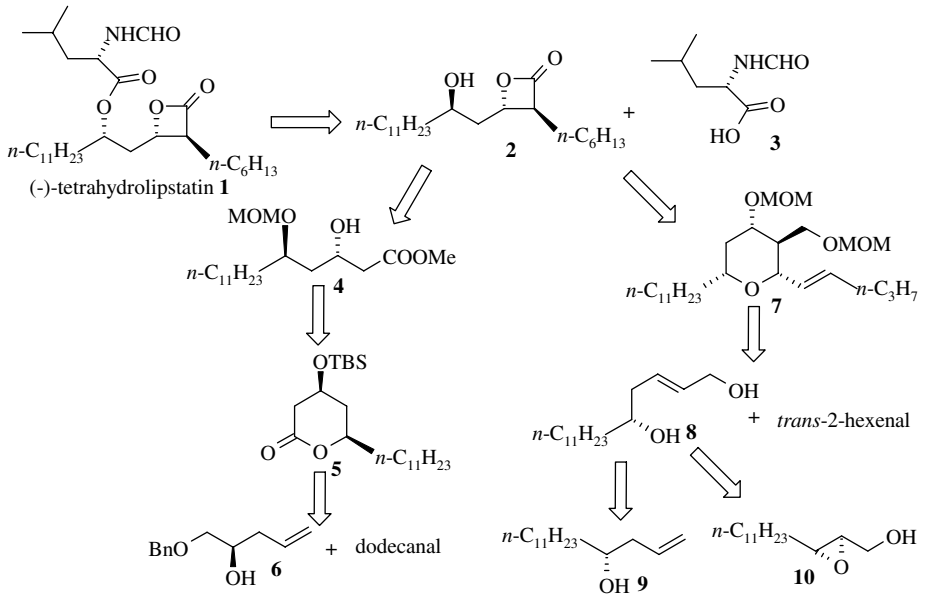
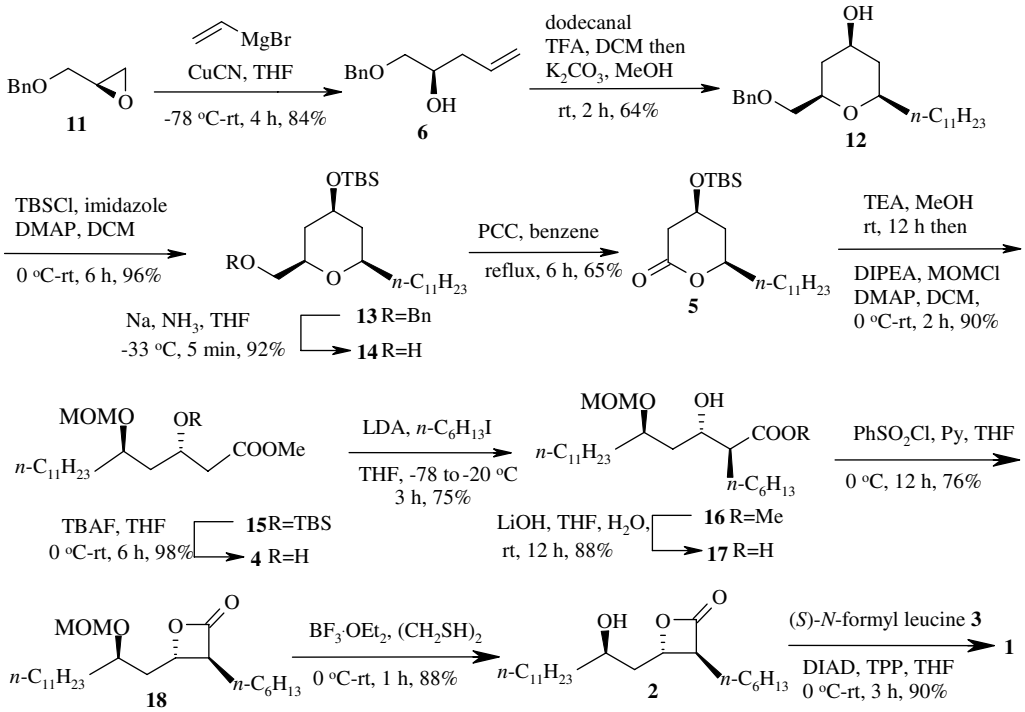


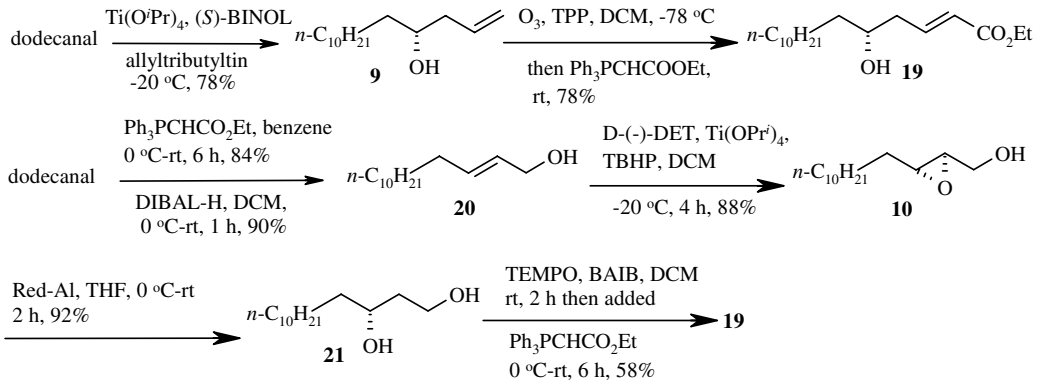
Scheme 1.



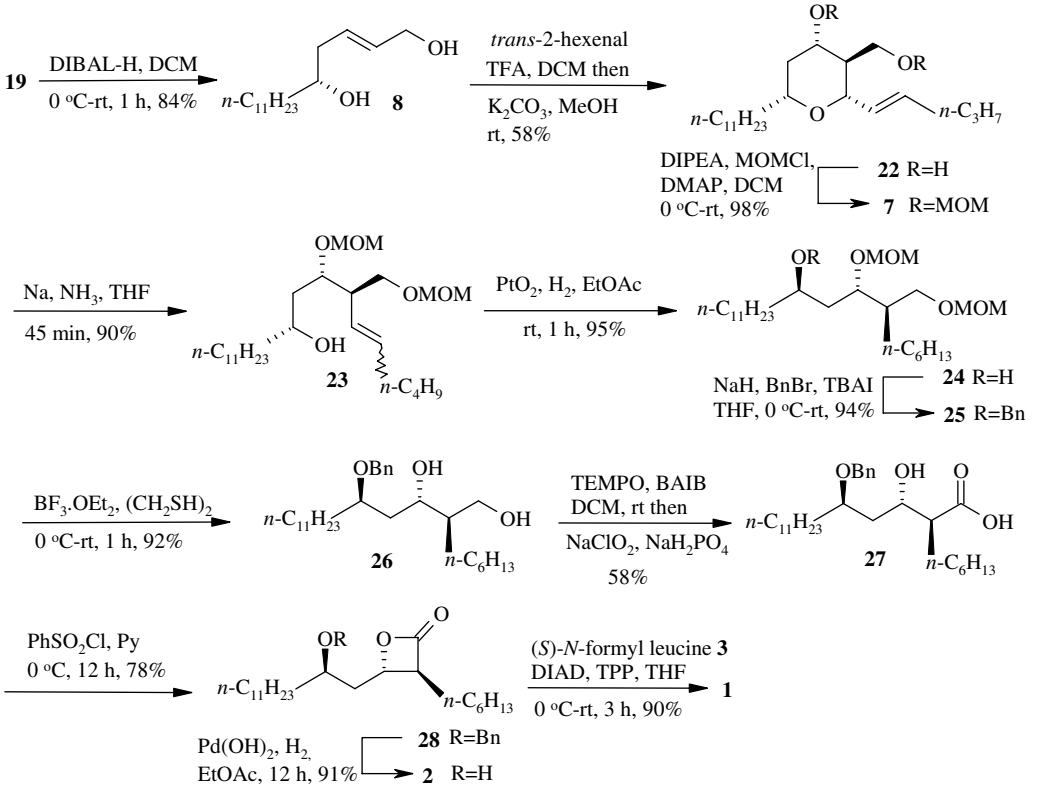
Scheme 2.

furnished (−)-THL **1**. The spectral and physical data of **1** were in good agreement with those reported.[11]

An alternative strategy, devised for the synthesis of (−)-THL **1**, is delineated in Schemes 3 and 4. The strategy again utilised the Prins cyclisation installing the key alkyl centre and a hydroxy group in a highly stereocontrolled manner. Thus, Keck allylation[12] of dodecanal gave HAA **9** which on subjection to one-pot ozonolysis–Wittig olefination[13] with the stable ylide, ethoxycarbonylmethylenetriphenylphosphorane furnished the α,β-unsaturated ester **19**. An alternative method was also successful for the conjugated ester **19**. Two-carbon homologation of dodecanal using ethoxycarbonylmethylenetriphenylphosphorane in benzene gave a conjugated ester which on reduction with DIBAL-H yielded allyl alcohol **20**. Sharpless asymmetric epoxidation[14] of **20** with D-(−)-DET produced epoxy alcohol **10**. Regioselective reduction of the epoxide using Red-Al yielded 1,3-diol **21** which on one-pot chemoselective oxidation of the primary hydroxy group using TEMPO and bis(acetoxy)iodobenzene (BAIB) in DCM and two-carbon Wittig homologation



Scheme 3.



Scheme 4.

on addition of the stable ylide, ethoxycarbonylmethylene-triphenylphosphorane resulted in hydroxy ester **19**.[15]

DIBAL-H mediated reduction of conjugated ester **19** led to the allylic alcohol **8**. Prins cyclisation of **8** with *trans*-2-hexenal using TFA in DCM followed by hydrolysis of the crude trifluoroacetate with K_2CO_3 in MeOH resulted in tetrasubstituted pyran **22**. Pyran **22** was converted in to its di-MOM ether **7** in the presence of DIPEA, MOMCl and catalytic DMAP in DCM which on subjection to Na in ammonia, underwent allylic cleavage to yield acyclic alcohol **23** as a 1:1 mixture of diastereomers with respect to the migrated double bond.[4b] However, reduction of the double bond with PtO_2 in EtOAc yielded a single diastereomer of **24**. Protection of the free hydroxy group as its benzyl ether **25** using NaH, BnBr and catalytic TBAI followed by deprotection of the MOM ether linkages with $BF_3{\cdot}OEt_2$ and ethane dithiol in DCM produced diol **26**.[9] Chemoselective oxidation of the primary alcohol with TEMPO and BAIB in DCM followed by further oxidation of the resulting crude aldehyde with NaH_2PO_4 and $NaClO_2$ furnished hydroxy acid **27**.[15] Treatment of **27** with $PhSO_2Cl$ in pyridine yielded beta-lactone **28** which on benzyl ether cleavage with $Pd(OH)_2$ in EtOAc followed by esterification with (*S*)-*N*-formyl leucine **3** under Mitsunobu conditions completed the total synthesis of (−)-THL **1**, whose spectral and physical data were again in good agreement with those reported.[11]

Thus, we have achieved the total synthesis of (−)-THL **1** via Prins cyclisation using two divergent routes from

completely different starting materials showing the convenience of the strategy. The total syntheses of similar polyketide molecules using this strategy are currently being pursued.

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11. Selected data for compound **1**: White solid, R_f 0.14 (20% ethyl acetate/hexane); mp 39–41 °C (lit.[2a,b] mp 40–42 °C); $[\alpha]_D^{20}$ −32.0 (*c* 0.96, $CHCl_3$) (lit.[2a,b] $[\alpha]_D^{20}$ −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): 1832, 1740, 1691 cm^{-1}.
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