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Total Synthesis of (-)-Tetrahydrolipstatin by the Tandem Mukaiyama-aldol Lactonization**

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Abstract: (-)-Tetrahydrolipstatin **1** was synthesized in three steps and 33.8% overall yield from aldehyde **6** by tandem Mukaiyama-aldol lactonization, which offered a concise, efficient and highly diastereoselective route to this antiobesity drug. We also presented a resolution method for preparation of the crucial intermediate, *β*- (*t*-butyldimethylsilyloxy)tetradecanal.

Keywords: Tetrahydrolipstatin, tandem Mukaiyama-aldol lactonization, asymmetric synthesis, (*R*)-*β*-hydroxy tetradecanal, resolution.

(-)-Tetrahydrolipstatin (orlistat, **1**), the saturated derivative of lipstatin, which was isolated from *streptomyces toxytricini* in 1987[1], is a potent, selective and irreversible pancreatic lipase inhibitor. Recently, (-)-tetrahydrolipstatin has been marketed as antiobesity drug by Hoffman-La Roche[2], and used widely in the clinic under the name Xenical®. Due to its unusual biological activity, (-)-tetrahydrolipstatin **1** has attracted much attention on its total synthesis, and many asymmetric synthetic strategies have been published in recent years[3]. In connection with our interest in new antiobesity drugs of orlistat analogues, a concise, efficient and highly diastereoselective route to synthesize **1** is needed. Some of the published strategies were based on the asymmetric aldol reaction to construct the protected *anti*-*β*-hydroxy acid **2**, and then lactonization to give the *anti*-*β*-lactone (**Scheme 1**)[3d-f]. Compared with the strategy in **Scheme 1**, tandem aldol lactonization is concise and favorable to access the *β*-lactone moiety. Here, we report our asymmetric synthesis of **1** by using tandem Mukaiyama aldol-lactonization, which afforded the *anti*-*β*-lactone in one step from protected *β* chiral aldehyde.

Schick and coworkers reported a protocol of tandem aldol lactonization, in which 1-acylbenzotriazole was used as activated carboxylic acid derivative and *β*-lactone was obtained in one step[4], and precursor of **1** was synthesized following this method[3b]. Phenyl and thiophenyl esters were also employed in tandem aldol lactonization for synthesis of *β*-lactone[5]. However, in this one-step *β*-lactone synthesis, the diastereo-

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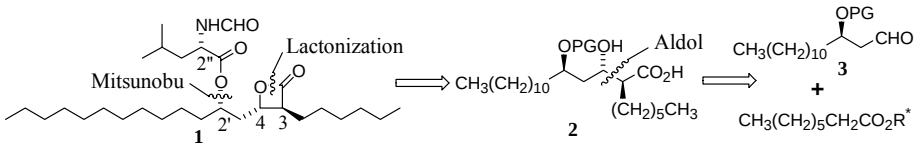
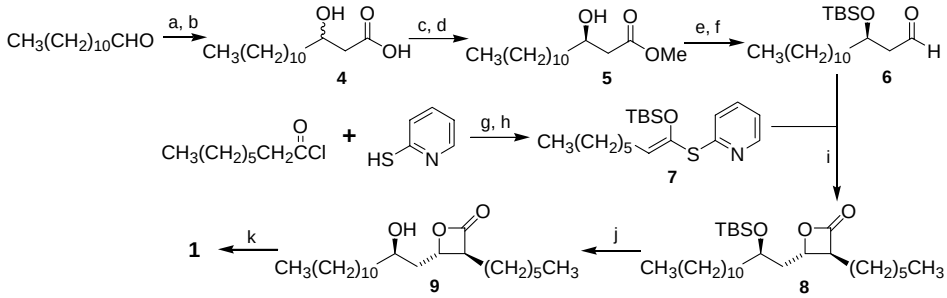
** Dedicated to Prof. Dr. Dieter Enders in RWTH Aachen on occasion of his 60th birthday.

Scheme 1



Scheme 2



Reagents and conditions: a) $BrCH_2CO_2Et$, Zn, C_6H_6/Et_2O, 92%; b) 20% NaOH, reflux, 80%; c)resolution with quinine, 30%; d) MeOH, H_2SO_4, reflux, 94%;e)DMF, TBSCl, imidazole, 0°C to rt, 96%; f) DIBAL-H, CH_2Cl_2, -78°C, 90%; g) CH_2Cl_2, pyridine, DMAP, 0°C to rt, 95%; h) LiHMDS, DMF, Et_3N, TBSCl, THF, 65%; i) $ZnCl_2$, CH_2Cl_2, 3 days, rt; j) aq. HF, CH_3CN, 0°C to rt, 45% for 2 steps; k) N-formyl-L-leucine, PPh_3, DIAD, THF, 0°C to rt, 75%.

selectivities were not so good. Romo *et al.* presented a highly diastereoselective route to *β*-lactone by condensation of ketene thioacetals with aldehydes, and the reaction was named tandem Mukayama-aldol lactonization[6]. The reaction was conducted in dichloromethane at room temperature, catalyzed by zinc chloride, and gave almost exclusively the *trans*-*β*-lactone in moderate to good yields[6]. We herein report our formal synthesis of **1** by using the Romo's tandem Mukaiyama-aldol lactonization strategy, and a new route to access the protected (*R*)-*β*-hydroxy tetradecanal (**Scheme 2**).

Benzyl or *t*-butyldimethylsilyl (TBS) protected (*R*)-*β*-hydroxy tetradecanal was prepared mainly by two methods: (1) asymmetric hydrogenation of *β*-ketone ester gave (*R*)-*β*-hydroxy ester, after protection of the hydroxy group, reduction by DIBAL-H afforded the desired aldehyde[3e-f]; (2) asymmetric allylation of dodecanal gave (*R*)-homoallylic alcohol, after protection, ozonolysis provided the desired aldehyde[3g-h]. We now report a complementary route from dodecanal (**Scheme 2**). Reformatsky reaction of dodecanal with ethyl bromoacetate and hydrolysis gave racemic *β*-hydroxy tetradecanic acid **4**, which was resolved by quinine in acetonitrile to offered the *R* configuration acid with $[\alpha]_D^{20}$ -16.2 (*c* 1, $CHCl_3$) (lit.[7] $[\alpha]_D^{20}$ -16.2 (*c* 1, $CHCl_3$)). After esterification and protection with TBSCl, and by DIBAL-H reduction the desired aldehyde **6** was obtained.

Thiopyridyl ketene acetal **7** was prepared from octanoyl chloride according to Romo's procedure[6a]. Tandem Mukaiyama-aldol lactonization with **6** and **7** proceeded smoothly to give the *β*-lactone **8** as a 10:1 (*trans/cis*) mixture of diastereomers[8], the major isomer possessed the desired stereochemistry. It is necessary that the reaction

mixture should be treated with $CuBr_2$ to clean the ketene thioacetal and thiol ester during the workup[9], and after desilylation **8** was obtained. It can be used for next step without further purification. *trans*-β-Lactone **9** was obtained in 45% yield for the two steps, and the stereochemistry of *trans*-fused lactone was confirmed by the coupling constants of H-3 and H-4 ($J_{2,3}$ = 4.17 Hz). Mitsunobu reaction with N-formyl-L-leucine gave the target molecular **1** in 75% yield, which displayed identical spectral and physical properties[10] with that of the natural product[1b] and reported data[3g-h].

In conclusion, (-)-tetrahydrolipstatin was synthesized in three steps and 33.8% overall yield from *β*-(*t*-butyldimethylsilyloxy)tetradecanal by tandem Mukayama-aldol lactonization, which offered a concise, efficient and highly diasteroselective route to this antiobesity drug. We also presented a resolution method for preparation of the crucial intermediate, *β*-(*t*-butyldimethylsilyloxy)tetradecanal.

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10. Spectral and physical data of **1**: m.p. 41−43 °C; $[\alpha]_D^{20}$ -34.1 (*c* 1, $CHCl_3$) (lit[3h]. m.p. 42 °C; $[\alpha]_D^{20}$ -32 (*c* 0.74, $CHCl_3$)); IR (KBr) *v*: 3332, 2956, 2921, 2853, 1823, 1731, 1709, 1667, 1525, 1384, 1260, 1202 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm) 0.86 (t-like, 6H, 2×CH_3), 0.95 (d, 6H, *J* = 5.56 Hz, H-5", H-6"), 1.15−1.85 (m, 33H), 1.98 (ddd, 1H, *J* = 4.47, 4.47, 14.92 Hz, one of H-4), 2.14 (ddd, 1H, *J* = 7.57, 7.57, 14.90 Hz, one of H-4), 3.20 (ddd, 1H, *J* = 4.10, 7.30, 7.70 Hz, H-2), 4.27 (ddd, 1H, *J* = 4.10, 4.84, 7.94 Hz, H-3), 4.66 (ddd, 1H, *J* = 4.67, 8.65, 8.60 Hz, H-2"), 5.02 (m, 1H, H-5), 6.01 (d, 1H, *J* = 8.49 Hz, NH), 8.20 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm) 171.92, 170.62, 160.56, 74.72, 72.76, 57.11, 49.70, 41.62, 38.75, 34.08, 31.89, 31.46, 29.68, 29.59, 29.52, 29.41, 29.30, 28.94, 27.65, 26.70, 25.09, 24.93, 22.83, 22.65, 22.48, 21.93, 21.79, 14.06, 13.95; ESI-MS *m/z* (%): 496.5 ($[M+H]^+$).

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