Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 49 (2008) 327–330

Enantioselective total synthesis of (−)-tetrahydrolipstatin using Oppolzer's sultam directed aldol reaction

G. Kumaraswamy* and B. Markondaiah

Organic Division III, Fine Chemicals Laboratory, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 3 October 2007; revised 30 October 2007; accepted 7 November 2007
Available online 13 November 2007

Abstract—A highly practical and concise stereoselective total synthesis of (−)-tetrahydrolipstatin is achieved using Oppolzer's sultam directed aldol reaction as the key step.

Natural products such as lipstatin **1a**, valilactone **1c**, esterastin **1d** and the lipstatin derivative, tetrahydrolipstatin **1b,** possessing a *trans*-β-lactone moiety, inhibit gastric and pancreatic lipases by blocking the hydrolysis of triglycerides. Among these, tetrahydrolipstatin, a reduced form of lipstatin is identified as an antiobesity agent, being the first over-the-counter weight-loss medication and approved by the FDA under the trade name Xenical (Fig. 1).[1]

Of late, these *trans*-β-lactones have generated renewed interest among synthetic chemists due to the recent findings that they are specific inhibitors of fatty acid synthase (FAS-TE), an approved drug target for anticancer activity.[2] The postulated mechanism for this potent inhibitory activity is due to irreversible covalent binding to an active site serine of pancreatic lipase. Owing to the significant activity of these molecules, a number of approaches have been reported for their synthesis.[3]

Chiral auxiliary mediated asymmetric C–C bond formation as the key step has been used extensively for the synthesis of various biologically active compounds.[4] Recently, we developed an efficient method for the synthesis of belactosin C and its congeners possessing the *trans*-β-lactone moiety using *D*-(2*R*)-sultam as a chiral auxiliary for generating *anti* and *syn* diastereomers. This

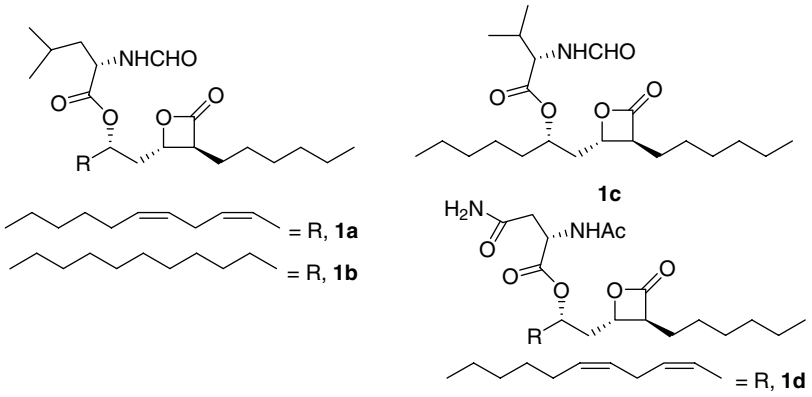
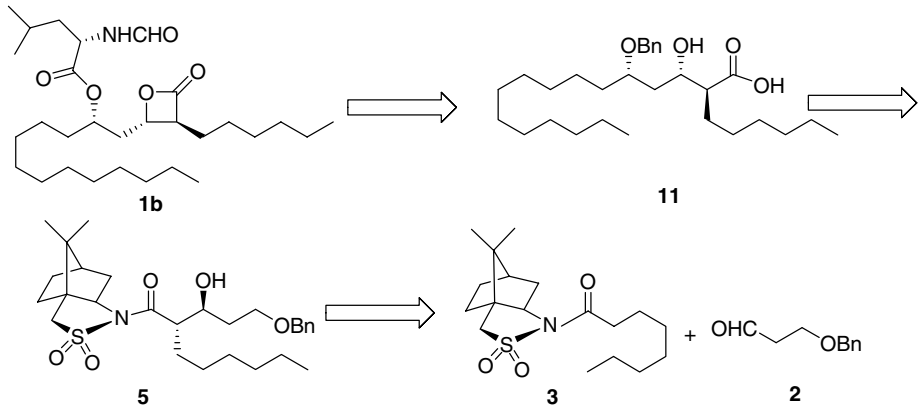


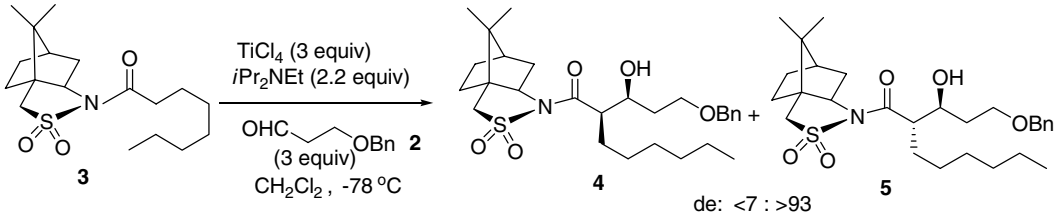
Figure 1.

Keywords: *trans*-β-Lactone; Tetrahydrolipstatin; *D*-(2*R*)-Sultam; Antiobesity agent; Pancreatic lipases; Anticancer activity.
* Corresponding author. Tel.: +91 40 27193154; fax: + 91 40 27193275; e-mail: gkswamy_iict@yahoo.co.in

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.051



Scheme 1.



Scheme 2.

process is significant in that the Lewis acid employed leads to different enantiomers depending on the stoichiometry.[5] This prompted us to consider the same methodology for the synthesis of (−)-tetrahydrolipstatin **1b** and our retrosynthetic approach is shown in Scheme 1.

We began our study following the previously developed protocol[5] (Scheme 2). Acylsultam **3** was treated with 1 equiv of $TiCl_4$ and 1.2 equiv of diisopropylethylamine at −78 °C and the resulting mixture was stirred for 1.5 h followed by the addition of 3 equiv of benzyloxypropanal **2**. As expected, after work-up, the *syn*-aldol **4** was isolated as the major product in 75% yield.

In another reaction, the Ti-enolate was generated at −78 °C using 1 equiv of acylsultam **3**, 2 equiv of $TiCl_4$ and 1.2 equiv of diisopropylethylamine and the sultam-enolate was quenched with 3 equiv of benzyloxypropanal **2**. The expected *anti*-aldol was isolated in 40% yield. However, reaction with 3 equiv of $TiCl_4$ and 2.2 equiv of diisopropylethylamine under otherwise identical conditions, not only showed improved de (**4**:**5**, <7:>93) but also increased the yield in favour of the *anti*-aldol **5** (Table 1).

The formation of *anti*-aldol **5** can be rationalized on the basis of open transition state $A^{\#}$ as proposed by Oppolzer and Lienard (Fig. 2).[4a]

Reductive cleavage of *anti*-aldol adduct **5** with LAH gave the 1,3-diol[6] in 75% yield. This was protected with 2,2-DMP/CSA in CH_2Cl_2 to afford **6** in 90% yield. Debenzylation of **6** in Li/Liq NH_3 gave the corresponding alcohol in 82% yield, which was oxidized with IBX in DMSO to give the aldehyde **7**. The Grignard reagent generated using undecyl bromide and Mg in THF at 0 °C, was added to aldehyde **7** to furnish the corresponding alcohol as a diastereomeric mixture. This was subjected to oxidation with IBX in DMSO to give the corresponding ketone[7] **8** in 90% yield. A highly *syn* stereoselective 1,3-asymmetric reduction was carried out using LiI–LAH in ether at −100 °C to provide the desired 1,3-*syn* product **9** in 80% yield (*syn*:*anti*

Table 1. Study of varying the amounts of $TiCl_4$ and iPr_2NEt and the effect on the *syn*:*anti* ratio in the reaction of acylsultam **3** and benzyloxypropanal **2** (3 equiv)

Entry	$TiCl_4$ (equiv)	iPr_2NEt (equiv)	Ratio **4**:**5**[a] de	Yield[b,c] (%)
1	1	1.2	95:5	75
2	2	1.2	10:90	40
3	3	2.2	<7:>93	58

[a] The de was determined from the ^1H NMR spectrum of the crude residue. The stereochemical assignment of the major diastereomer was made by analogy with our previous work.[5]
[b] Yields refer to the major isomer after column chromatography.
[c] All reactions were carried out at −78 °C.

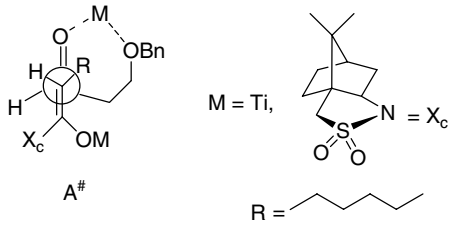
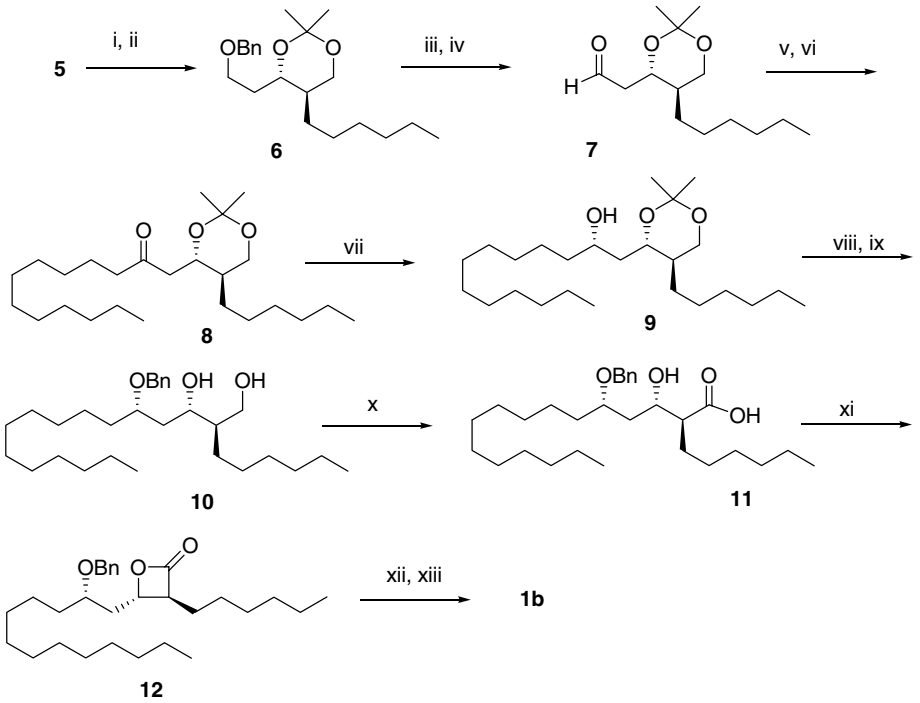


Figure 2.



Scheme 3. Reagents and conditions (i) LAH/ether, 0 °C to rt, 3 h, 75%; (ii) CSA, 2,2-DMP, CH_2Cl_2, 0 °C, 6 h, 90%; (iii) Li, NH_3, THF, 1 h, 82%; (iv) IBX, DMSO, CH_2Cl_2, rt, 4 h, 90%; (v) Mg, undecyl bromide, THF, 0 °C to rt, 12 h, 70%; (vi) IBX, DMSO, CH_2Cl_2, rt, 4 h, 90%; (vii) LiI, LAH, ether, −100 °C, 30 min, 80%; (viii) BnBr, NaH, THF, 0 °C to reflux, 6 h, 80%; (ix) 1 N HCl/THF (1:1) 0–60 °C, 3 h, 88%; (x) TEMPO, BAIB, CH_2Cl_2, rt, 2 h; then $NaClO_2$, 20%$NaH_2PO_4{\cdot}2H_2O$, *t*-BuOH, 0 °C to rt, 4 h, 90%; (xi) BOPCl, Et_3N, CH_2Cl_2, 23 °C, 1 h, 75%; (xii) $Pd(OH)_2/C$, H_2, EtOAc/EtOH (9:1), 12 h, 92%; (xiii) DCC, DMAP, (*S*)-*N*-formyl leucine, CH_2Cl_2, rt, 24 h, 80%.

85:15[8]). The hydroxy group was protected as its benzyl ether using NaH/BnBr and a catalytic amount of TBAI, and the acetonide cleaved with 1 N HCl/THF (1:1) at 0–60 °C to give the corresponding diol[9] **10** in 88% yield. Chemoselective oxidation of **10** with TEMPO and bis(acetoxy)iodobenzene (BAIB) in CH_2Cl_2 followed by further oxidation of the resulting aldehyde with perchlorite/dihydrogen orthophosphate furnished the β-hydroxy acid[10] **11** in 90% yield (Scheme 3).

The β-hydroxy acid **11** was lactonized with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) to furnish the known β-lactone **12** in 75% yield. Debenzylation of this β-lactone with $Pd(OH)_2/C$, H_2 in EtOAc/EtOH (9:1) gave the corresponding alcohol in 92% yield. Finally, the free alcohol of β-lactone **12** was coupled with (*S*)-*N*-formylleucine using DCC/ DMAP[11] in CH_2Cl_2 to give (−)-tetrahydrolipstatin **1b** in 80% yield.[12] The analytical data of **1b** was in full agreement with the reported data for the natural product.[3a]

In conclusion, we have developed a concise stereoselective total synthesis of (−)-tetrahydrolipstatin using Oppolzer's sultam directed aldol reaction as the key step. Application of this methodology to synthesize various cis and trans-substituted β-lactones to study their activity profiles is under progress.

Acknowledgements

We are grateful to Dr. J. S. Yadav, Director, IICT, for his constant encouragement. Thanks are also due to Dr. T. K. Chakraborty for his support. B.M. is thankful to UGC (New Delhi) for awarding the fellowship.

Supplementary data

Experimental procedures and spectral data of **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11**, **12** and **1b** and copies of the spectra of **4**, **5**, **9**, **12** and **1b**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.051.

References and notes

1. (a) Weibel, E. K.; Hadvary, P.; Hochuli, E.; Kupfer, E.; Lengsfeld, H. *J. Antibiot.* **1987**, *40*, 1081–1085; (b) Hochuli, E.; Kupfer, E.; Maurer, R.; Meister, W.; Mercadal, Y.; Schmidt, K. *J. Antibiot.* **1987**, *40*, 1086–1091.
2. (a) Kridel, S. J.; Axelrod, F.; Rozenkrantz, N.; Smith, J. W. *Cancer Res.* **2004**, *64*, 2070; (b) Knowles, L. M.; Axelrod, F.; Browne, C. D.; Smith, J. W. *J. Biol. Chem.* **2004**, *279*, 30540.
3. (a) Barbier, P.; Schneider, F.; Widmer, U. *Helv. Chim. Acta* **1987**, *70*, 1412–1418; (b) Barbier, P.; Schneider, F.; Widmer, U. *Helv. Chim. Acta* **1987**, *70*, 196–202; (c) Barbier, P.; Schneider, F. *J. Org. Chem.* **1988**, *53*, 1218–1221; (d) Dirat, O.; Kouklovsky, C.; Langlois, Y. *Org. Lett.* **1999**, *1*, 753–755; (e) Ghosh, A. K.; Liu, C. *Chem. Commun.* **1999**, 1743–1744; (f) Paterson, I.; Doughty, V. A. *Tetrahedron Lett.* **1999**, *40*, 393–394; (g) Wedler, C.; Costisella, B.; Schick, H. *J. Org. Chem.* **1999**, *64*, 5301–5303; (h) Parsons, P. J.; Cowell, J. K. *Synlett* **2000**, 107–109; (i) Ghosh, A. K.; Fidanze, S. *Org. Lett.* **2000**, *2*, 2405–2407; (j) Bodkin, J. A.; Humphries, E. J.; McLeod,

M. D. *Aust. J. Chem.* **2003**, *56*, 795–803; (k) Bodkin, J. A.; Humphries, E. J.; McLeod, M. D. *Tetrahedron Lett.* **2003**, *44*, 2869–2872; (l) Thadani, A. N.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 8051–8055; (m) Polkowska, J.; Lukaszewicz, E.; Kiegiel, J.; Jurczak, J. *Tetrahedron Lett.* **2004**, *45*, 3873–3875; (n) Yadav, J. S.; Vishweahwar Rao, K.; Sridhar Reddy, M.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4393–4395; (o) Yadav, J. S.; Vishweahwar Rao, K.; Prasad, A. R. *Synthesis* **2006**, 3888–3894; (p) Yadav, J. S.; Sridhar Reddy, M.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4995–4998.

4. (a) Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* **1993**, *34*, 4321–4324; (b) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747; (c) Oppolzer, W.; Christian, S.; Ines, R.; Bernardinelli, G. *Tetrahedron Lett.* **1991**, *32*, 61–64; (d) Corey, E. J.; Li, W.; Reichard, G. A. *J. Am. Chem. Soc.* **1998**, *120*, 2330–2336; (e) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2167–2172; (f) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047–1049; (g) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392–393; (h) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883; (i) Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374–2375; (j) Benjamin, H.; Danny, M. G.; Patrick, P.; Filisaty, V. *Tetrahedron: Asymmetry* **2006**, *17*, 1152–1155; (k) Saumen, H.; Aswini, K.; Ananta, K.; Snehadrinarayan, K. *Chem. Commun.* **2007**, 2408–2410.
5. Kumaraswamy, G.; Padmaja, M.; Markondaiah, B.; Nivedita, J.; Sridhar, B.; Kiran, M. U. *J. Org. Chem.* **2006**, *71*, 337–340.
6. Jorge, G.-F.; Juan, M.; Miguel, C.; Marco, J. M. *Org. Lett.* **2006**, *8*, 2695–2698.
7. Sabitha, G.; Sudhakar, K.; Reddy, N. M.; Rajkumar, M.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *14*, 6567–6570.
8. (a) Yuji, M.; Makoto, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1809–1812; (b) Yuji, M.; Makoto, S.; Akio, T.; Makoto, S. *Tetrahedron Lett.* **1988**, *29*, 5419–5422.
9. Kumaraswamy, G.; Markondaiah, B. *Tetrahedron Lett.* **2007**, *48*, 1707–1709.
10. Vatele, J.-M. *Tetrahedron Lett.* **2006**, *47*, 715–718.
11. Yikang, Wu.; Ya-ping, S. . *J. Org. Chem.* **2006**, *71*, 5748–5751.
12. *Spectral data of* **1b**: $[\alpha]_D^{25}$ −31.3 (*c* 0.001, $CHCl_3$) (lit.[3a] $[\alpha]_D^{20}$ −33 (*c* 0.65, $CHCl_3$)). ^1H NMR (200 MHz, $CDCl_3$): δ 8.22 (1H, s), 6.02 (1H, d, $J = 8.5$ Hz), 5.02 (1H, m), 4.68 (1H, m), 4.28 (1H, m), 3.22 (1H, dt, $J = 7.6$, 3.7 Hz), 2.25–2.11 (1H, m), 2.02 (1H, m), 1.80–1.15 (33H, m), 0.95 (6H, d, $J = 5.2$ Hz), 0.87 (6H, distorted t); ^{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, 31.8, 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; IR (KBr): 3447, 2925, 2855, 1822, 1670, 1461, 1213, 1122, 759 cm^{-1}; ESIMS: *m/z* 518 ($M+Na^+$); HRMS ($M+Na^+$) calcd for $C_{29}H_{53}NO_5Na$ 518.3821, found 518.3827.