An Approach to the Synthesis of (−)-Lipstatin by Wittig Reaction and Lewis Acid-promoted [2 + 2] Cycloaddition

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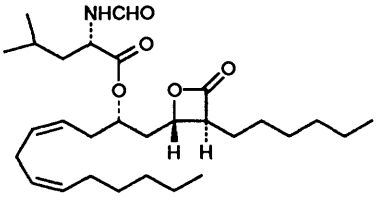
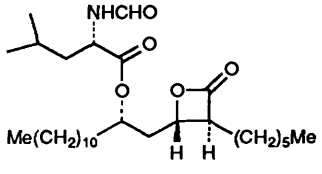
The β-lactone moiety of (−)-lipstatin **1**, a potent inhibitor of pancreatic lipase, is prepared *via* a Lewis acid-promoted [2 + 2] cycloaddition between hexyltrimethylsilyl ketene **3** and the (*Z*,*Z*)-dienic aldehyde **4**, obtained from hexanal by two stereoselective Wittig reactions.

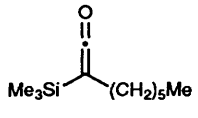
Several natural β-lactone derivatives have considerable medicinal potential. Among them, lipstatin **1**, a β-lactone isolated from *Streptomyces toxytricini*,[1] is a potent and irreversible inhibitor of pancreatic lipase, which is essential for dietary fat absorption.[2,3] Therefore, lipstatin **1** and its tetrahydro derivative **2** are promising candidates for the treatment of obesity.[4] Although several syntheses of tetrahydrolipstatin **2** can be found in the literature,[5–7] no synthesis of lipstatin **1** itself has yet been published. As part of a program on β-lactone chemistry, we report here the first approach to the synthesis of (−)-lipstatin **1**. Our strategy involves a Lewis acid promoted [2 + 2] cycloaddition between hexyltrimethylsilyl ketene **3** and the (*Z*,*Z*)-dienic aldehyde **4** to build the β-lactone moiety. Such a reaction had proved to be efficient in the synthesis of tetrahydrolipstatin **2**.[7]



Lipstatin **1**



Tetrahydrolipstatin **2**



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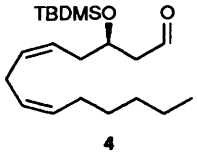

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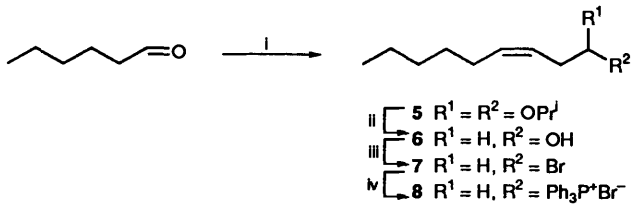
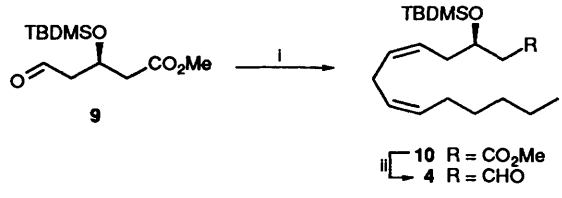
Synthesis of the Dienal **4**.—The synthesis began with the stereoselective Wittig three-carbon homologation of hexanal with (3,3-diisopropoxypropyl)triphenylphosphonium bromide salt[8] which led quantitatively to the (*Z*)-β,γ-unsaturated diisopropyl acetal **5**. The latter was then deprotected[8] yielding the corresponding β,γ-unsaturated aldehyde, which was not isolated but directly reduced, with $LiAlH_4$ in tetrahydrofuran (THF), into the allylic alcohol **6** (72% yield over the two steps). Bromination of **6** with Ph_3PBr_2–Py in MeCN led to the allylic bromide **7** (90%)[9] which was then quantitatively transformed into the corresponding phosphonium bromide salt **8** (Scheme 1).



Scheme 1 *Reagents and conditions:* i, $Ph_3P^+(CH_2)_2CH(OPr^i)_2Br^-$, $NaN(SiMe_3)_2$, THF, −100 °C to room temp., 12 h (100%); ii, *p*-TsOH/H_2O–THF, 10 min, reflux, then $LiAlH_4$, THF, −90 to −20 °C, 2.5 h (72%); iii, Ph_3PBr_2–Py, MeCN, −7 °C to room temp., 1 h (90%); iv, PPh_3, MeCN, reflux, 48 h (100%)

Finally, a Wittig reaction between scalemic aldehyde **9** (78% e.e.)[10] and phosphonium bromide salt **8** led to the (*Z*,*Z*)-dienic β-silyloxy methyl ester **10** (86% yield) which, with diisobutylaluminium hydride (DIBAH) in dichloromethane at −90 °C, underwent clean reduction to the (*Z*,*Z*)-dienic aldehyde **4** (93% yield) (Scheme 2).



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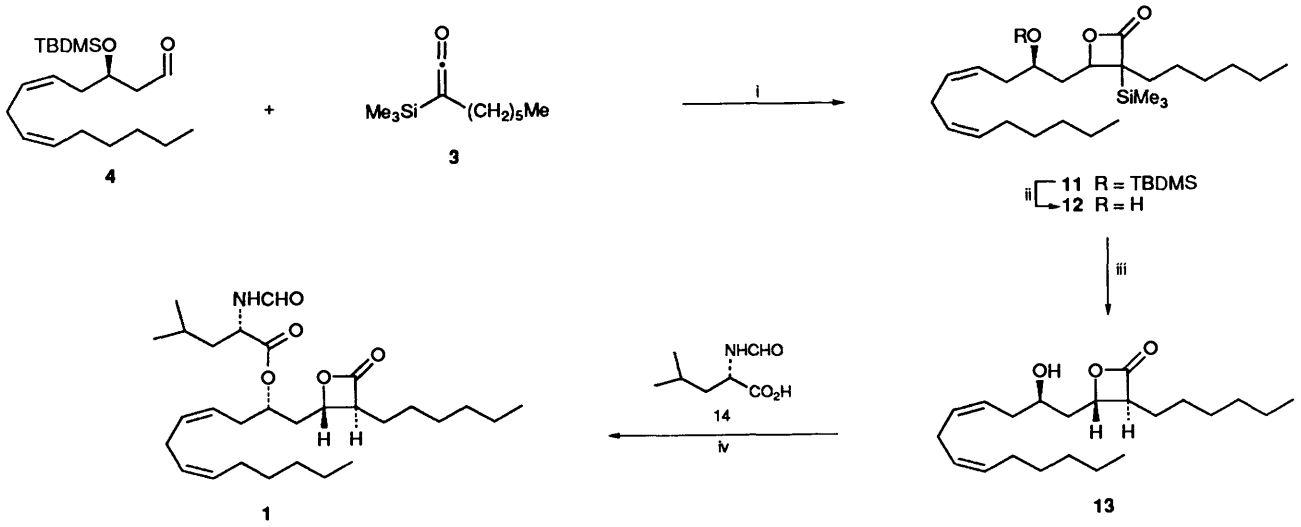
Scheme 2 *Reagents and conditions:* i, **8**, $NaN(SiMe_3)_2$, THF, −100 °C to room temp., 12 h (86%); ii, DIBAH, CH_2Cl_2, −90 °C, 1 h (93%)

Synthesis of (−)-*Lipstatin* **1**.—The ketene **3**, prepared as described earlier,[7] and the aldehyde **4**, in the presence of a stoichiometric amount of ethyldichloroaluminium (1 mol dm^{-3} solution in hexanes) in diethyl ether (−40 to −20 °C), underwent [2 + 2] cycloaddition to give a mixture of diastereoisomeric (75:15:10 ratio) β-lactones **11** (81% yield) (see Experimental section). The *tert*-butyldimethylsilyl protective group was removed with 40% aq. HF in MeCN yielding the lactones **12** with 77% yield. Desilylation of **12**, with tetrabutylammonium fluoride (TBAF) in THF, produced *trans*-β-lactone **13** (70% yield) (see Experimental section) which, under Mitsunobu esterification conditions [diethyl azodicarboxylate (DEAD), PPh_3] and in the presence of (*S*)-*N*-



Scheme 3 *Reagents and conditions:* i, $EtAlCl_2$, Et_2O, −50 to −20 °C, 1 h (81%); ii, HF 40% aq., MeCN, 0 °C to room temp., 12 h (77%); iii, TBAF, THF, −78 °C, 15 min (70%); iv, (*S*)-*N*-formylleucine **14**, PPh_3, DEAD, THF, 0 °C to room temp., 1.5 h (50%)

formylleucine **14**, led to (−)-lipstatin **1** (50% yield)* (Scheme 3).

In conclusion, we have developed an approach to the synthesis of (−)-lipstatin **1** in which the relative stereochemistry of the β-lactone ring is determined by favourable 1,3-asymmetric induction in the diastereoselective [2 + 2] cycloaddition and the absolute stereochemistry is determined by Baker's yeast reduction used to create the reference stereogenic centre in the synthon **9**. Furthermore, we have provided further evidence of (a) the value of silyl-stabilised ketenes as synthetic reagents and their ability to react cleanly with a carbonyl moiety in the presence of a carbon–carbon double bond, and (b) the efficiency and high *Z*-stereoselectivity of the double-Wittig chain-extension for the synthesis of (*Z*,*Z*)-1,4-dienes. Further investigation of the scope and stereochemistry of the cycloaddition is currently underway.

Experimental

4-{(4Z,7Z)-2-[1,1-*Dimethylethyl*(*dimethyl*)*silyloxy*]*trideca*-4,7-*dienyl*}-3-*trimethylsilyl*-3-*hexyloxetan*-2-*one* **11**.—To a solution of **4** (3.05 g, 9 mmol) in diethyl ether (70 cm^3), cooled to −40 °C under argon, $EtAlCl_2$ (12.6 cm^3 of a 1 mol dm^{-3} solution in hexanes; 12.6 mmol) was added dropwise. The solution was then stirred for 15 min at the same temperature before a solution of **3** (3.00 g, 15 mmol) in diethyl ether (20 cm^3) was added to it. The reaction mixture was allowed to warm to −20 °C over 2.5 h while the advancement of the reaction was monitored by TLC. Once the reaction was over, standard work-up [hydrolysis with 100 cm^3 of ice–water, extraction with diethyl ether (3 × 50 cm^3) and drying ($MgSO_4$) of the extract] led to the crude material. Flash chromatography on silica gel with pentane–diethyl ether (97:3) as the eluent yielded the mixture of β-lactones **11** (3.94 g, 81%); ν_{max}(film)/cm^{-1} 1815, 1260 and 850; major isomer δ_H(200 MHz; $CDCl_3$) 5.53–5.24 (4 H, m), 4.64 (1 H, dd, *J* 11.5 and 1.6), 3.91 (1 H, m), 2.78 (2 H, t, *J* 6.3), 2.30 (2 H, m), 2.03 (2 H, m), 1.72 (2 H, m), 1.40–1.20 (16 H, m), 0.92 (9 H, s), 0.93–0.86 (6 H, m), 0.20 (9 H, s) and 0.11 (6 H, s); major isomer δ_C(50.3 MHz; $CDCl_3$) 174.3 (s), 130.8 (d), 130.7 (d), 127.3 (d), 124.7 (d), 75.6 (d), 68.4 (d), 54.4 (s), 39.3 (t), 36.2 (t), 31.6 (t), 30.5 (t), 29.6 (t), 29.4 (t), 27.3 (t), 26.2 (t), 25.9 (q), 22.6 (t), 22.5 (t), 18.1 (s), 14.1 (q), −1.4 (q), −4.1 (q) and −4.9 (q).

4-[(4Z,7Z)-2-*Hydroxytrideca*-4,7-*dienyl*]-3-*hexyloxetan*-2-*one* **13**.—To a solution of **12** (369 mg, 0.87 mmol) in THF (15 cm^3), cooled to −90 °C under argon, a solution of TBAF (250 mg, 0.96 mmol) in THF (2 cm^3) was added dropwise. After the mixture had been stirred at the same temperature for 15 min, the reaction was quenched with water (10 cm^3). Extraction with diethyl ether (3 × 15 cm^3), drying ($MgSO_4$) of the extract, and concentration of the latter under reduced pressure gave crude *trans* β-lactone **13** (213 mg, 70%). This was easily separated from other diastereoisomers, including traces of a *cis*-isomer, by flash chromatography on silica gel with pentane–diethyl ether (75:25) as the eluent; $[\alpha]_D^{27}$ −37 (*c* 2 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3480, 1825 and 1120; δ_H(200 MHz; $CDCl_3$) 5.59 (1 H, m), 5.45–5.20 (3 H, m), 4.47 (1 H, m), 3.81 (1 H, m), 3.22 (1 H, td, *J* 7.4 and 4.0), 2.78 (2 H, t, *J* 6.8), 2.27 (2 H, m), 2.10–1.65 (8 H, m), 1.44–1.20 (12 H, m) and 0.85 (6 H, m); δ_C(50.3 MHz; $CDCl_3$) 171.7 (s), 132.6 (d), 130.9 (d), 127.0 (d), 124.3 (d), 75.6 (d), 67.9 (d), 56.6 (d), 41.3 (t), 36.0 (t), 31.6 (t), 29.3 (t), 29.0 (t), 27.7 (t), 27.3 (t), 26.8 (t), 25.8 (t), 22.61 (t), 22.57 (t), 14.11 (q) and 14.08 (q); *m*/*z* 332 (M^+ − H_2O) (Found: *m*/*z* 332.270. Calc. for $C_{22}H_{36}O_2$: 332.2715).

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References

1 E. K. Weibel, P. Hadvary, E. Hochuli, E. Kupfer and H. Lengsfeld, *J. Antibiot.*, 1987, **40**, 1081.
2 E. Hochuli, E. Kupfer, R. Maurer, W. Meister, Y. Mercadal and K. Schmidt, *J. Antibiot.*, 1987, **40**, 1086.
3 For the absolute configuration of (−)-lipstatin **1**, see: P. Barbier and F. Schneider, *Helv. Chim. Acta*, 1987, **70**, 196.
4 S. Hogan, A. Fleury, P. Hadvary, H. Lengsfeld, M. K. Meier, J. Triscari and A. C. Sullivan, *Int. J. Obes.*, 1987, **11** (suppl. 3), 35.
5 P. Barbier, F. Schneider and U. Widmer, *Helv. Chim. Acta*, 1987, **70**, 1412

* (−)-Lipstatin **1** (a pale yellow oil)[1] is present as the major isomer of an inseparable 10:1 mixture of diastereoisomers. ^1H NMR (400 MHz), ^{13}C NMR (100.6 MHz) and IR spectra are in agreement with the literature.[2] However, in order to establish unambiguously the obtention of (−)-lipstatin **1**, the mixture was hydrogenated;[2] (−)-tetrahydrolipstatin **2** was obtained as the major product, purified by crystallization (pentane) and fully characterized, m.p. 40–41 °C (lit.,[3] m.p. 41–42.5 °C); [illegible]

6 P. Barbier and F. Schneider, *J. Org. Chem.*, 1988, **53**, 1218; I. Fleming and N. J. Lawrence, *Tetrahedron Lett.*, 1990, **31**, 3645; N. K. Chadha, A. D. Batcho, P. C. Tang, F. F. Courtney, C. M. Cook, P. M. Wovkulich and M. R. Uskokovic, *J. Org. Chem.*, 1991, **56**, 4714; S. C. Case-Green, S. G. Davies and C. J. R. Hedgecock, *Synlett*, 1991, 781.
7 J.-M. Pons and P. Kocienski, *Tetrahedron Lett.*, 1989, **30**, 1833.
8 J. Viala and M. Santelli, *Synthesis*, 1988, 395.
9 J. Sandri and J. Viala, *Synth. Commun.*, 1992, **22**, 2945.
10 F. Bennett, D. W. Knight and G. Fenton, *J. Chem. Soc., Perkin Trans. 1*, 1991, 519.

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