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A SYNTHESIS OF (-)-TETRAHYDROLIPSTATIN

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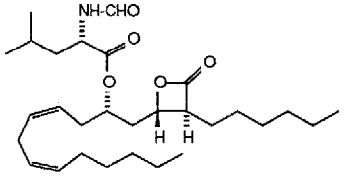
Abstract. A Lewis acid-catalysed [2+2]-cycloaddition of *n*-hexyl trimethylsilyl ketene (**4**) to (3*R*)-3-(benzyloxy)-tetradecanal (**3**) is the key step in a synthesis of the ß-lactone moiety of the antiobesity agent (-)-tetrahydrolipstatin (**2**).

Lipstatin (**1**) and its tetrahydro derivative (**2**)[1] are potent, selective, and irreversible inhibitors of pancreatic lipase which, in some species, results in a marked reduction in dietary fat absorption. There is considerable commercial interest in the antiobesity activity of tetrahydrolipstatin (**2**) since chronic treatment of animals with a moderately high fat diet causes a decrease in weight even though energy intake increases during treatment[2]. Several approaches to (-)-tetrahydrolipstatin have been reported recently by workers at Hofmann-La Roche & Co[3-5]. We now describe an alternative approach to (-)-(**2**) in which a [2+2]-cycloaddition of the stable trimethylsilyl-substituted ketene (**4**) to the aldehyde (**3**) is a key step.



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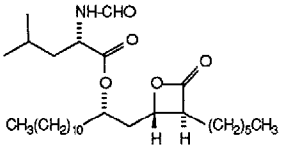

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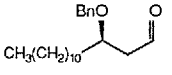

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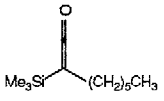
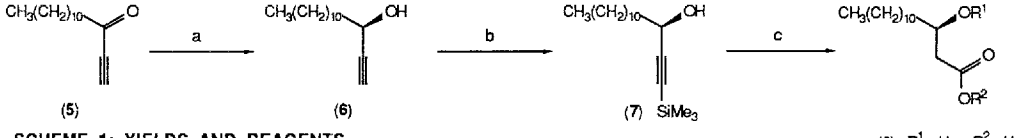


(4)

A. Synthesis of (3*R*)-3-(Benzyloxy)-tetradecanal (3)(Scheme 1). The synthesis of aldehyde (**3**) began with an enantioselective reduction[6] of the ynone (**5**)(78% yield; 84% e.e.) using *R*-Alpine-Borane®. The resultant alkynol (**6**) was converted to the 1-trimethylsilyl derivative (**7**) which underwent smooth



(5) (6) (7) SiMe$_3$

SCHEME 1: YIELDS AND REAGENTS

(a) 78% *R*-Alpine-Borane (1.4 eq) (neat), 0°C to RT, 8h;
(b) 89% n-BuLi (2.4 eq)/ THF, -78°C followed by Me_3SiCl (2.6 eq), -20°C to RT; 1.4M H_2SO_4;
(c) 55% dicyclohexylborane (2 eq) / THF, 0°C followed by NaOH, H_2O_2, 40-50°C;
(d) 85% HCl / MeOH, 2h, RT;
(e) 81% benzyltrichloroacetimidate (1.2 eq), triflic acid (0.1 eq) / CH_2Cl_2-cyclohexane, 10°C-RT;
(f) 78% DiBALH (1.1 eq) / CH_2Cl_2, -78°C.

d → (8) R^1=H R^2=H; → (9) R^1=H R^2=Me
e → (10) R^1=Bn R^2=Me
f → (3)

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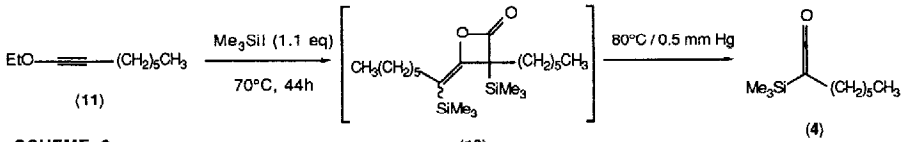
hydroboration-oxidation[7] to the ß-hydroxyacid (**8**). Further functional group manipulation (3 steps, 54% overall) served to convert (**8**) to the desired (3*R*)-3-(benzyloxy)-tetradecanal (**3**)(81% e.e.) which was identical by high field ^{1}H NMR with the data previously reported for (**3**) by the Hofmann-La Roche group[4].

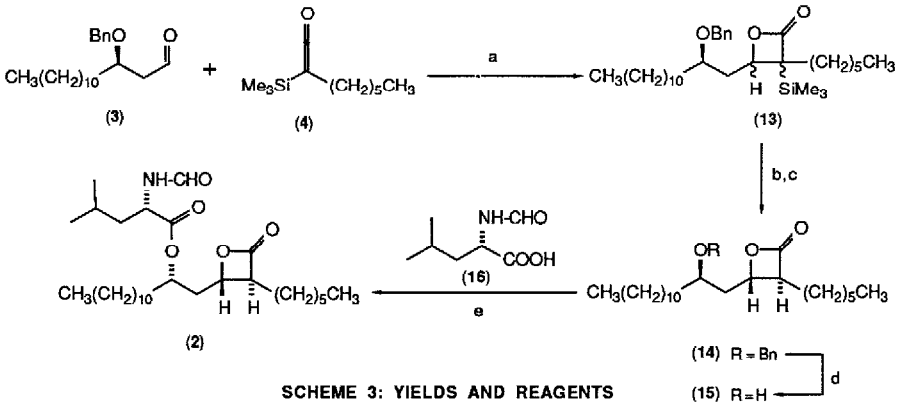
B. Synthesis of *n*-Hexyl Trimethylsilyl Ketene (4)(Scheme 2). After much experimentation, a procedure of Sakurai and co-workers[8] was adapted for the synthesis of the silylketene (**4**). Thus, reaction of a neat mixture of 1-ethoxy-1-octyne[9](1.0 eq) with Me_3SiI (1.1 eq) at 70°C for 44 h gave a diastereoisomeric mixture of dimeric products tentatively assigned the structure (**12**)[10]. IR analysis of the course of the reaction revealed a gradual decrease in the absorbtion at 2285 cm^{-1} due to acetylene (**11**) with the formation of (**12**) (1790 cm^{-1}) and ketene (**4**) (2090 cm^{-1}). The ketene absorbtion then gradually diminished with a concomitant increase in the absorbtion at 1790 cm^{-1}. *When the ketene absorbtion had disappeared,* excess Me_3SiI was removed *in vacuo*, and the residual dimer thermolysed at 80°C/0.5 mm Hg to give the desired silylketene (**4**) in 50% yield from (**11**). The silylketene (**4**) was quite stable and could be stored for protracted periods at -20°C.



SCHEME 2

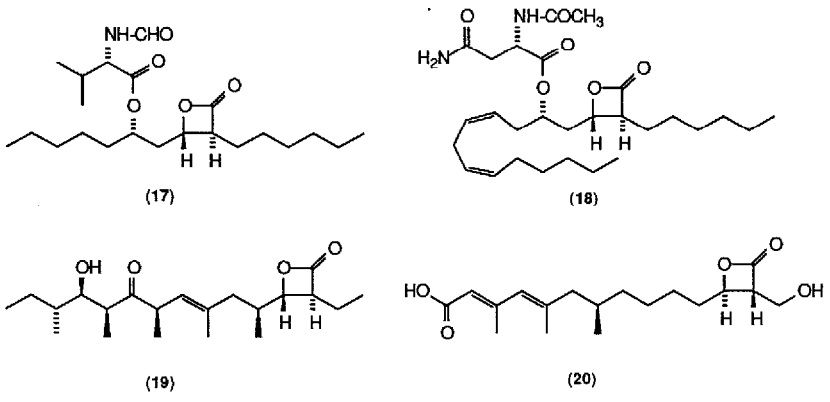
C. Synthesis of Tetrahydrolipstatin (2)(Scheme 3). The fulcrum of our synthetic plan was a diastereoselective [2+2]-cycloaddition of the trimethylsilylketene (**4**) to the aldehyde (**3**) which, in analogous systems, is well-precedented in the work of Brady and co-workers[11]. In the presence of a catalytic amount of boron trifluoride etherate, rapid and clean cycloaddition took place at -15°C to give a mixture of diastereomeric cycloadducts (**13**). Desilylation with Bu_4NF (84%) revealed a mixture of 4 diastereoisomers from which the major component, the desired ß-lactone (**14**), was easily isolated in 55-61% yield by column chromatography. The remaining 3 diastereoisomers were obtained in 45-39% combined yield. Hydrogenolysis of the benzyl protecting group in (**14**) followed by Mitsunobu esterification using (*S*)-N-formylleucine (**16**) gave (-)-tetrahydrolipstatin (**2**) [25% overall yield from (**3**) and (**4**)]: m.p. 40-41°C (pentane)[Lit.[3] m. p. 41-42.5°C]; α_D (24°C) -31.2° (c. 0.5, $CHCl_3$)[Lit.[4] α_D (20°C) -33°C (c. 0.36, $CHCl_3$)]; IR (CCl_4): 1839, 1740, and 1695 cm^{-1}; partial ^{1}H NMR (360 MHz, $CDCl_3$): 8.22 (1H, s, NH-CHO), 6.03 (1H, d, J 8.7 Hz, NH), 5.02 (1H, m, $CH_3(CH_2)_{10}$-CH-O), 4.68 (1H, ddd, J 8.5, 8.5, 4.5 Hz, CH-NH), 4.29 (1H, ddd appearing as a symmetrical 5-line m, lactone O-CH), 3.21 (1H, ddd, J 7.8, 7.8, 4.0 Hz, lactone O=C-CH), 2.17 (1H, J 14.8, 7.2, 7.2 Hz, O-CH-CH$_A$H$_B$-CH-O); 2.00 (1H, ddd, J 14.8, 4.2, 4.1 Hz, O-CH-CH$_A$H$_B$-CH-O); ^{13}C NMR (67.5 MHz, $CDCl_3$): 172.1 (s), 171.0 (s), 160.8 (d), 75.0 (d), 72.9 (d), 57.2 (d), 49.8 (d), 41.7, 38.9, 34.2, 32.1, 31.6, 29.8 (2C), 29.7, 29.6, 29.5, 29.1, 27.8, 26.9, 25.3 (all t), 25.0 (d), 23.0 (q), 22.9 (t), 22.7 (t), 21.9 (q), 14.3 (q), 14.2 (q).

Conclusion. The stability of trimethylsilyl ketenes has long been appreciated[12] but seldom exploited[13]. In the present work we have substantially improved the synthesis of alkyl trimethylsilyl ketenes and shown that they undergo clean and efficient cycloaddition with ß-alkoxy-substituted aldehydes to provide a concise and diastereoselective synthesis of ß-lactones. This methodology should be applicable to the synthesis of other ß-lactone esterases such as Valilactone (**17**)[14], Esterastin (**18**)[15], Ebelactone B (**19**)[16] and L-659,699 (**20**) (an inhibitor of cholesterol biosynthesis)[17].



SCHEME 3: YIELDS AND REAGENTS

(a) 83% BF_3-Et_2O / Et_2O, -15° to 5°C, 3h;
(b) 84% TBAF(1.1 eq) / THF, -80°C, 1 min;
(c) 55% Column chromatography on silica gel, Et_2O-hexane (2.5 : 97.5);
(d) 88% H_2, Pd-C / THF, 8h, RT;
(e) 73% Ph_3P(1.2 eq), DEAD(1.3 eq), (**16**)(1.3 eq) / THF, 0°C to RT.



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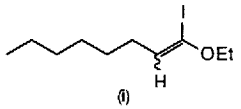
9. 1-Ethoxy-1-octyne (**11**) was prepared as follows: To a solution of ethoxyacetylene (4.56 g, 65 mmol) in THF (70ml) cooled to -80°C was added dropwise n-BuLi (46 ml of a 1.6M solution in hexanes). After 1h at -80°C, HMPA (24.9 ml, 143 mmol) was added, followed 15 min later by a solution of 1-iodohexane (11.02 g, 52 mmol) in THF (10 ml). The cooling bath was removed and the mixture stirred at ambient temperature overnight before being quenched with water. Normal extractive workup then provided (**11**) (6.88 g, 86%) as a colourless oil after kugelrohr distillation (b.p. 80-90°C (bath)/1mmHg) having spectroscopic data identical to those reported: C. C. McCarney, R. S. Ward, and D. W. Roberts, *Tetrahedron*, 1976, **32**, 1189.
10. Preparation of *n*-hexyl trimethylsilyl ketene (**4**): 1-ethoxy-1-octyne (**11**)(1.540 g, 10.0 mmol) was added to iodotrimethylsilane [prepared *in situ* from hexamethyldisilane (0.966 g, 6.6 mmol) and iodine (1.523 g, 6.0 mmol)] and the mixture heated at 70°C for 44 h. The excess Me_3SiI was then removed *in vacuo* (70°C/20 mm Hg, 15 min) and the residue, composed of the dimer (**12**) and enol ether (**i**) (20-30%), heated at 80°C/0.5 mm Hg in a kugelrohr apparatus. The desired ketene (**4**) (0.99 g, 5.0 mmol, 50%) distilled as a clear, colourless oil: IR (film): 2090 and 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): 1.92 (2H, t, J 7 Hz), 1.25-1.55 (8H, m), 0.90 (3H, t, J 6.9 Hz), 0.16 (9H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$): 182.6 (s), 31.8 (t), 31.7 (t), 29.0 (t), 22.8 (t), 22.2 (t), 22.2 (t), 14.2 (q), 13.0 (s), -0.7 (q).



(i)

The enol ether (**i**) was identified from the following spectroscopic data: IR (film): 1635 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): 5.32 (1H, t, J 7.3 Hz), 3.72 (2H, q, J 7.1 Hz), 2.08 (2H, dt, J 7.1, 7.5 Hz), 1.18-1.4(8H, m), 0.89 (3H, t, J 7); ^{13}C NMR (67.5 MHz, $CDCl_3$) 127.5 (s), 112.2 (d), 69.7 (t), 31.8 (t), 29.3 (t), 28.9 (t), 28.9 (t), 28.5 (t), 14.3 (q), 14.0 (q); LRMS m/z 282(M^+, 20%), 211(20), 183(29), 155 (M-I, 67), 127(37), 109(78), 85(85), 67(36), 55(72), 43(53), 29(100).
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