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Tetrahedron Letters 44 (2003) 2869–2872

TETRAHEDRON LETTERS

The total synthesis of (–)-tetrahydrolipstatin

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Received 19 December 2002; accepted 14 February 2003

Abstract—Careful control during the bromolactonisation of β,γ-unsaturated acid **3** was required to afford regioselectively the *trans*-β-lactone **4** as the major diastereomer. Radical debromination of **4** followed by a three-step sequence of reactions afforded the lipase inhibitor (–)-tetrahydrolipstatin.

Tetrahydrolipstatin (**1**, Fig. 1) is a potent inhibitor of pancreatic lipase, and is currently marketed as an anti-obesity drug under the name Xenical®. It is a saturated derivative of lipstatin, which was isolated from *Streptomyces toxytricini* in 1987.[1] The biological activity of **1** is due to the presence of the *trans*-substituted β-lactone, which reacts to form a persistent ester linkage with the serine hydroxyl group in the active site of pancreatic lipase, thereby slowing the hydrolysis of triglycerides and the absorption of dietary fat by the small intestine.[2]

There has been considerable interest in **1** owing to the growing awareness of obesity related illness, and several syntheses have been reported. In each case, the synthesis of the β-lactone of **1** emerges as a major synthetic challenge. The majority of approaches[3] use Adams' conditions to achieve β-lactone ring formation from a β-hydroxy acid precursor, which requires establishment of the hydroxy acid stereochemistry prior to lactone formation.

From a strategic viewpoint, greater levels of efficiency would be expected in approaches that couple β-lactone formation with concomitant introduction of the required oxetanone stereochemistry and a number of innovative syntheses have capitalised on this tactic.[4] Our approach to the synthesis of **1**, which also aimed to exploit this efficiency, is outlined in Scheme 1. Tetrahydrolipstatin (**1**) could be obtained by a three-step sequence from the known hydroxy lactone **2**.[3e,h] This, in turn, could be derived from the β,γ-unsaturated acid **3** by a two-step sequence involving bromolactonisation to give **4** followed by radical debromination. Key to the success of this approach is control over the regioselectivity and stereoselectivity of the bromolactonisation reaction to afford the desired *trans*-β-lactone. A further challenge involves the radical reduction of the strained bromolactone **4**. Reported here is a novel, diastereoselective synthesis of **1** that successfully addresses these challenges as well as our observations concerning the influence of the reaction conditions on the diastereoselectivity of the pivotal bromolactonisation step.

Beginning with (2*E*,4*E*)-diene ester **5**,[5,6] hydrolysis using aqueous potassium hydroxide afforded diene acid

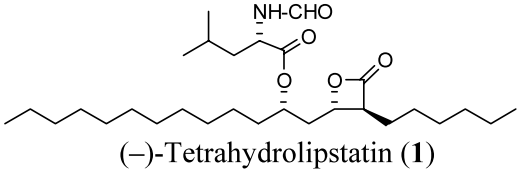
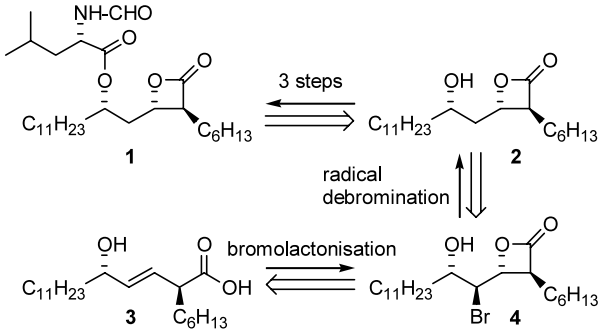


Figure 1. (–)-Tetrahydrolipstatin (**1**).



Scheme 1.

Keywords: (–)-tetrahydrolipstatin; bromolactonisation; β-lactone; radical dehalogenation.

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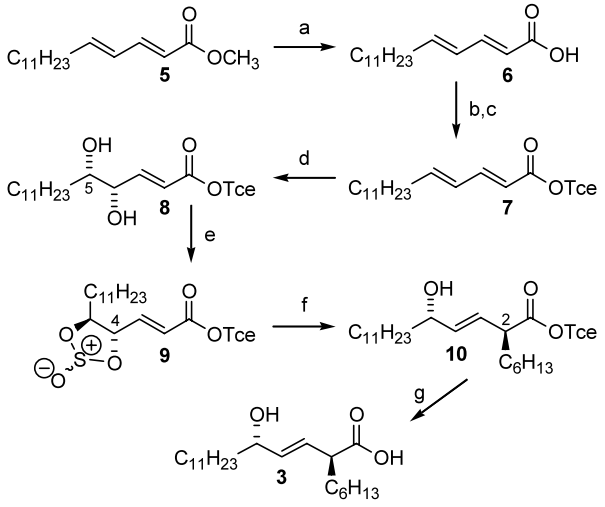
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00443-X

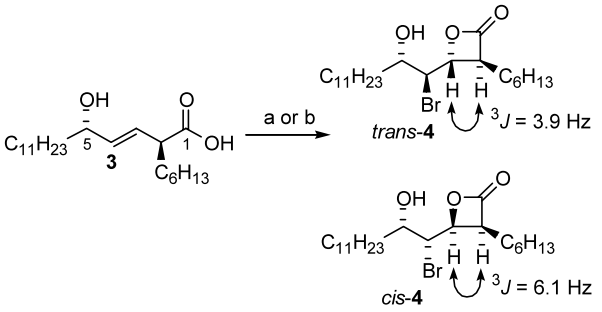
6 in 84% yield (Scheme 2). Acid **6** was carried on without further purification, with a one-pot conversion into the trichloroethyl (Tce) ester **7** achieved in 94% yield.[7] Sharpless asymmetric dihydroxylation was used to enantio- and regioselectively functionalise the diene **7**.[8] Using the commercially available AD-mix-α, methanesulfonamide and sodium bicarbonate in biphasic *tert*-butanol/water, dihydroxylation was achieved to afford the (4*S*,5*S*)-diol **8**. Treatment of **8** with thionyl chloride afforded an inseparable mixture of diastereomeric cyclic sulfites **9** in 92% yield that were carried on to the following step.[9]

The diorganocuprate reagent obtained from copper(I) cyanide, *n*-hexyllithium and boron trifluoride diethyl etherate was added to **9** by pre-cooled cannula (dry ice) to afford **10** in 85% yield as a single diastereomer. Alkylation at C2 occurs *anti* to the leaving group at C4 via an S_N' mechanism,[10] thus, the configuration at C4 and the *trans* double bond geometry of **9** combine to give the desired (2*S*,5*S*)-stereochemistry.[11] Deprotection of **10** was achieved upon treatment with zinc dust in acetic acid, affording unsaturated acid **3** in 74% yield.[7,12]

Bromolactonisation was initially carried out using the method of Barnett.[13] A solution of the acid **3** in a biphasic mixture of dichloromethane and 10% aqueous sodium bicarbonate was treated with bromine in carbon tetrachloride. These conditions afforded a quantitative yield of β-lactones in a 2:1 ratio of the *cis*-**4** to *trans*-**4** isomers, as determined by ^{1}H NMR integration of the product mixture, with no other isomers detected (Scheme 3). Identification of each isomer was readily achieved by examination of the characteristic ^{1}H NMR coupling constants associated with the protons on the



Scheme 2. *Reagents and conditions*: (a) 2 M KOH, THF, 22 h (84%); (b) $(COCl)_2$, DMF cat., CH_2Cl_2, 0–25°C, 1 h; (c) CCl_3CH_2OH, NEt_3, DMAP, rt, 20 h (94% over two steps); (d) AD-mix-α, $MeSO_2NH_2$, $NaHCO_3$, ^{t}BuOH/H_2O, 0°C, 25 h (58%); (e) $SOCl_2$, CCl_4, reflux, 22 h (92%); (f) CuCN, *n*-HexLi, THF, −78–25°C; then $BF_3{\cdot}OEt_2$, −78°C; then **9** (85%); (g) Zn, AcOH, rt, 4 h (74%).



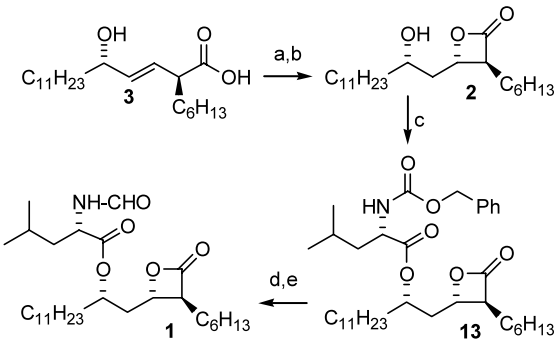
Scheme 3. *Reagents and conditions*: (a) 3 equiv. Br_2 in CCl_4, CH_2Cl_2/$NaHCO_3$, rt, 5 min, quant., 1:2 *trans*-**4**:*cis*-**4**; (b) 3 equiv. Br_2 in CCl_4, MeOH/$NaHCO_3$, rt, 20 s, quant., 5:1 *trans*-**4**:*cis*-**4**.

lactone ring. The observed coupling constants of 6.1 and 3.9 Hz for *cis*-**4** and *trans*-**4**, respectively, were in good agreement with the literature values.[14] A strong carbonyl absorption at 1830 cm^{-1} in the infrared spectrum was also consistent with the formation of β-lactone products.[15]

Obtaining high selectivity for the β-lactones in this system was gratifying as the bromolactonisation of β,γ-unsaturated carboxylic acids with 1,2-disubstituted double bonds typically affords mixtures of the β- and γ-lactone regioisomers.[16] The high level of regioselectivity is thought to arise due to the influence of the inductively withdrawing C5 hydroxyl group, which disfavours substitution at the adjacent C4 position of the bromonium ion intermediate that leads to γ-lactone products. However, the predominance of the *cis*-**4** was surprising, as ample literature precedent suggests that the *trans* isomer is usually the major product.[16] This suggests that in addition to exerting a positive influence on the regiochemistry of the bromolactonisation, the hydroxyl bearing C5 stereocentre may also influence the diastereoselectivity of the reaction.

Following extensive investigation of reaction parameters we made the fortuitous discovery that conducting the bromolactonisation reaction in methanol and 10% aqueous sodium bicarbonate solution afforded predominantly *trans*-**4** (Scheme 3). Optimised reaction conditions with a 20 s reaction time produced a quantitative yield of β-lactones, with >5:1 selectivity in favour of *trans*-**4**.

Attempted separation of the bromolactone isomers by column chromatography on silica resulted in substantial decomposition and low recovery of the lactone products enriched in *trans*-**4**. The crude mixture was therefore taken on to the following step. Radical debromination was carried out following the procedure of Crich and Mo[17] using tributyltin hydride in the presence of diphenyl diselenide and di-*tert*-butylperoxyoxalate (DBPO, CAUTION)[18,19] as a radical initiator. This provided a reliable debromination method and afforded a 63% yield of the *trans*-β-lactone **2** {$[\alpha]_D$ −16 (*c* 1.4, CH_2Cl_2); lit.[3h] $[\alpha]_D$ −15.3 (*c* 1.2, CH_2Cl_2)} over two steps from the β,γ-unsaturated acid **3** (Scheme 4).



Scheme 4. *Reagents and conditions*: (a) 3 equiv. Br_2 in CCl_4, $MeOH/NaHCO_3$, rt, 20 s, quant., 5:1 *trans*-**4**:*cis*-**4**; (b) DBPO, Ph_2Se_2, Bu_3SnH, PhMe, 0°C, 2.5 h (63% over two steps); (c) cbz-Leu, DCC, DMAP, CH_2Cl_2, DMAP, 1.5 h (87%); (d) H_2, 10% Pd–C, THF, rt, 3 h; (e) AcOCHO, ether, rt, 20 min (76% over two steps).

The product arising from debromination of the minor isomer, *cis*-**4**, was not observed and this may reflect the aforementioned instability of the *cis*-bromolactone or the greater ring strain associated with the *cis* isomer leading to more rapid radical β-scission and destruction of the lactone ring.

Hydroxylactone **2** was esterified with *N*-benzyloxycarbonyl-L-leucine using DCC and DMAP to afford **13** {$[\alpha]_D$ −23 (*c* 1.1, CH_2Cl_2); lit.[3e] $[\alpha]_D$ −23.86 (*c* 1.06, $CHCl_3$)} in 87% yield.[3e,h] Hydrogenolysis of the benzyloxycarbonyl protecting group was effected using 10% palladium on charcoal[3e,h] and the crude product was then treated with formic acetic anhydride[3e,h,20] to afford (−)-tetrahydrolipstatin **1** {$[\alpha]_D$ −32 (*c* 1.8, $CHCl_3$); lit.[1b] $[\alpha]_D$ −32 (*c* 1, $CHCl_3$)} in 76% yield over two steps. Spectral data (IR, ^1H and ^{13}C NMR) for synthetic (−)-**1** are identical to those reported.[3]

In summary, (−)-tetrahydrolipstatin **1** was synthesised in 12 steps and 11.3% overall yield from the unsaturated ester **5**. Excellent regioselectivity favouring β-lactones in the bromolactonisation reaction of **3** was afforded from the electronic bias associated with an allylic hydroxyl group. The diastereoselectivity of this reaction under standard conditions unexpectedly afforded the undesired *cis*-β-lactone as the major diastereomer. However, reversing the diastereoselectivity of this transformation to favour the required *trans*-β-lactone (>5:1) could be achieved through the judicious choice of experimental conditions.

Acknowledgements

We thank the University of Sydney for financial support.

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