

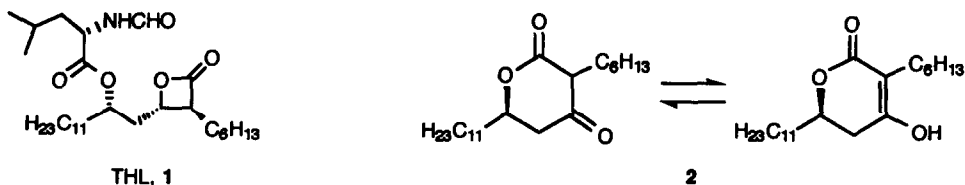
A New Route to β -Keto- δ -lactones: Practical Preparation of (R)-3-Hexyl-5,6-dihydro-4-hydroxy-6-undecyl-2H-pyran-2-one,¹ a Key Intermediate in the Asymmetric Synthesis of Tetrahydrolipstatin

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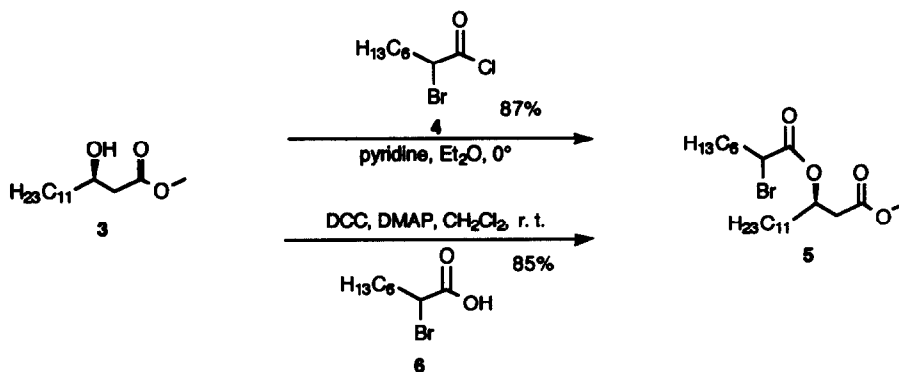
Abstract: A formal asymmetric synthesis of the anti-obesity drug tetrahydrolipstatin is reported. The advanced intermediate (R)-3-hexyl-5,6-dihydro-4-hydroxy-6-undecyl-2H-pyran-2-one is prepared in a brief sequence using a novel cyclization reaction. The sequence is also used to prepare other β -ketolactones.

Tetrahydrolipstatin (THL, 1) is a promising new drug for the treatment of obesity.² All of the syntheses reported thus far³ are unsuitable for commercial production of THL because of excessive length and/or the use of low temperature reactions. Herein we report a short preparation of (R)-3-hexyl-5,6-dihydro-4-hydroxy-6-undecyl-2H-pyran-2-one (2), an advanced intermediate in a synthesis of THL,^{3d} by a novel cyclization strategy which should be amenable to scale-up. We also report a brief study of the generality of the key cyclization reaction.



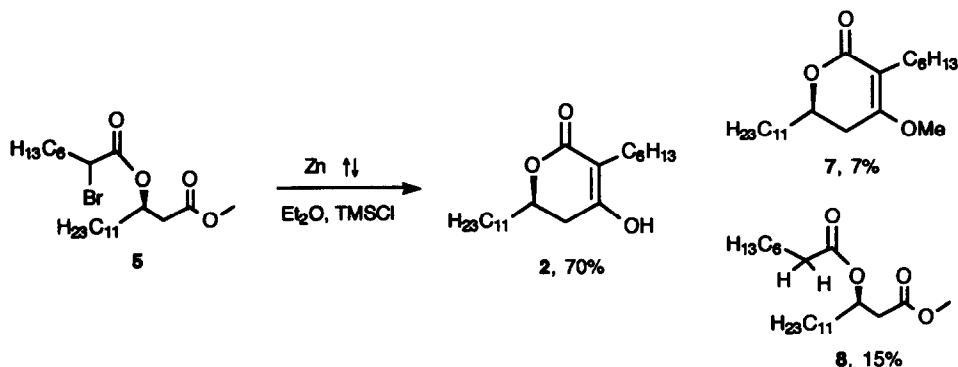
The preparation of lactone 2 began with esterification of methyl (R)-3-hydroxytridecanoate (3)⁴ with 2-bromooctanoyl chloride(4)⁵ to give bromodiester 5⁶ (Scheme I). Bromodiester 5 prepared by this method was used in the subsequent reaction without purification. Hydroxyester 3 could also be converted to bromodiester 5 by treatment with 2-bromooctanoic acid (6),⁷ N,N'-dicyclohexylcarbodiimide (DCC), and 4-dimethylaminopyridine (DMAP), following a known general procedure.⁸ In this case, the crude product was purified by silica gel chromatography (CH₂Cl₂/hexanes) to remove the byproduct N,N'-dicyclohexylurea.

Scheme I



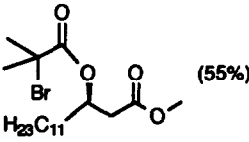
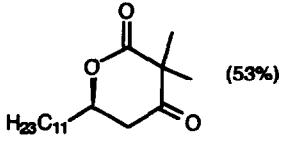
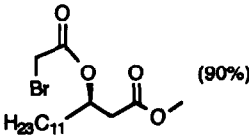
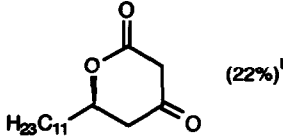
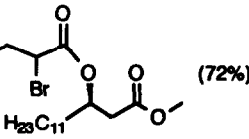
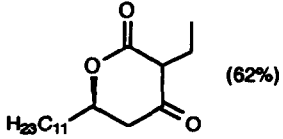
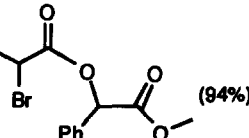
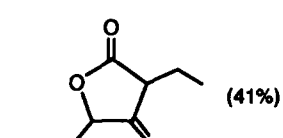
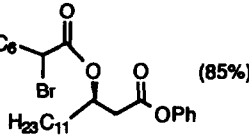
Pure bromodiester **5** (prepared by the route employing DCC/2-bromo-octanoic acid) was treated with zinc in a mixture of one part ether/four parts chlorotrimethylsilane (TMSCl) at reflux to give a mixture of mainly lactone **2** (existing in solution as a mixture of keto and enol tautomers) and small amounts of enol ether **7** and diester **8** (Scheme II) after acidic work-up. Radial chromatography (hexanes/ EtOAc) was used to separate the three components. It was later found that lactone **2** could be separated from enol ether **7** and diester **8** by simply triturating the crude product with hexanes followed by suction filtration. Lactone **2** purified in the latter manner (70% yield⁹) was a white waxy powder, $\text{mp} = 109 - 111^\circ\text{C}$ and $[\alpha]_D^{20} = -44.19^\circ$ ($c = 0.98\%$ in dioxane).¹⁰ All spectra were consistent with those published before.^{3d} The filtrate containing enol ether **7** and diester **8** from the above trituration could be hydrolyzed with aqueous HCl in ethyl acetate to give an additional 5% yield of lactone **2**.

Scheme II



The choice of solvent for the Scheme II cyclization reaction was crucial. With a lesser amount of or no TMSCl present, the reaction proceeded sluggishly and gave a much higher ratio of diester **8** to lactone **2**. Because further conversion to lactone **2** was not attained with the best solvent after extended periods at reflux, it was assumed that the intermediate zinc enolate of diester **8** (**9**) was being protonated during the reaction. The proton source may be lactone **2**, which arises from premature decomposition of the intermediate mixed ketal **10** (Scheme III). A large excess of TMSCl was chosen as an additive because not only would it activate the zinc,¹¹

Table 1. Synthesis of β -Ketolactones From Hydroxyesters and α -Bromoacyl Compounds^a

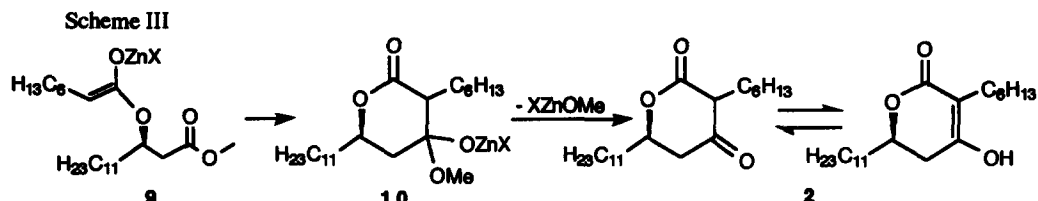
Reactants	Bromodiester (yield)	Lactone (yield)
2-bromoisobutyryl bromide and hydroxyester 3	 (55%)	 (53%)
bromoacetyl bromide and hydroxyester 3	 (90%)	 (22%) ^b
2-bromobutyryl bromide and hydroxyester 3	 (72%)	 (62%)
2-bromobutyryl bromide and (\pm)-methyl mandelate	 (94%)	 (41%)
acid 6 and phenyl (R)-3-hydroxytetradecanoate ^c	 (85%)	2 (67%)

^a Illustrative procedure for 2: A mixture of 744 mg (11.4 mmol) zinc and 1.03 g (2.22 mmol) 5 in 10 mL 1:4 v:v Et₂O : TMSCl was heated at reflux under N₂ with rapid stirring for 20 min. The mixture was cooled to r. t. and suction filtered through celite, washing with 10 mL Et₂O. The filtrate was cooled in an ice/H₂O bath and 10 mL H₂O was added with stirring. After 10 min, the mixture was poured into 100 mL tap H₂O and extraction with 3 X 50 mL Et₂O was performed. The combined organic layers were washed with 50 mL brine and dried over MgSO₄. The Et₂O was removed by rotary evaporation, giving 773 mg crude white solid. The solid was stirred with 15 mL hexanes for 30 min, followed by suction filtration and washing with 6.5 mL hexanes. The product obtained in this manner was a white waxy powder.

^b Also isolated were the methyl enol ether corresponding to 7 (13%) and the product of simple debromination corresponding to 8 (46%).

^c This compound was prepared by the following method: 1) hydrolysis of hydroxyester 3 with NaOH to yield the corresponding acid 2) hydroxyl group protection with *t*-butyldimethylsilyl chloride 3) phenyl ester formation with phenol/DCC 4) desilylation with tetrabutylammonium fluoride/HOAc.

but it was hoped that it would silylate the mixed ketal 10, thereby eliminating formation of lactone 2 until work-up.¹² After much experimentation, a mixture of ether/TMSCl (1:4) at reflux was found to give the best yield of lactone 2. These reaction conditions were applied to other bromodiester (synthesized as in Scheme 1),



producing a γ -lactone as well as δ -lactones (Table 1). We are aware of two isolated examples of this type of cyclization which produced γ -lactones.¹³

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9. A 61% yield of lactone **2** was obtained when crude bromodiester **5**, prepared by the route employing 2-bromooctanoyl chloride, was used.
10. Unpublished results of M. Karpf and M. Flück show that lactone **2** (prepared by a different route) has mp = 104.8 - 106.2 °C and $[\alpha]^{20}_D = -43.6^\circ$ (c = 1% in dioxane)
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12. The results may also be explained by assuming that diester **8** arose from incomplete cyclization of enolate **9** followed by quenching of the enolate during work-up. The role of TMSCl in this instance would be to silylate enolate **9** giving a silyl enol ether which may be more likely to cyclize.
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