Synthesis of Enantiomerically Pure *β*-Lactones by the Tandem Aldol−Lactonization. A Highly Efficient Access to (3*S*,4*S*)-3-Hexyl-4-[(2*S*)-2-hydroxytridecyl]oxetan-2-one, the Key Intermediate for the Enzyme Inhibitors Tetrahydrolipstatin and Tetrahydroesterastin†,[1]

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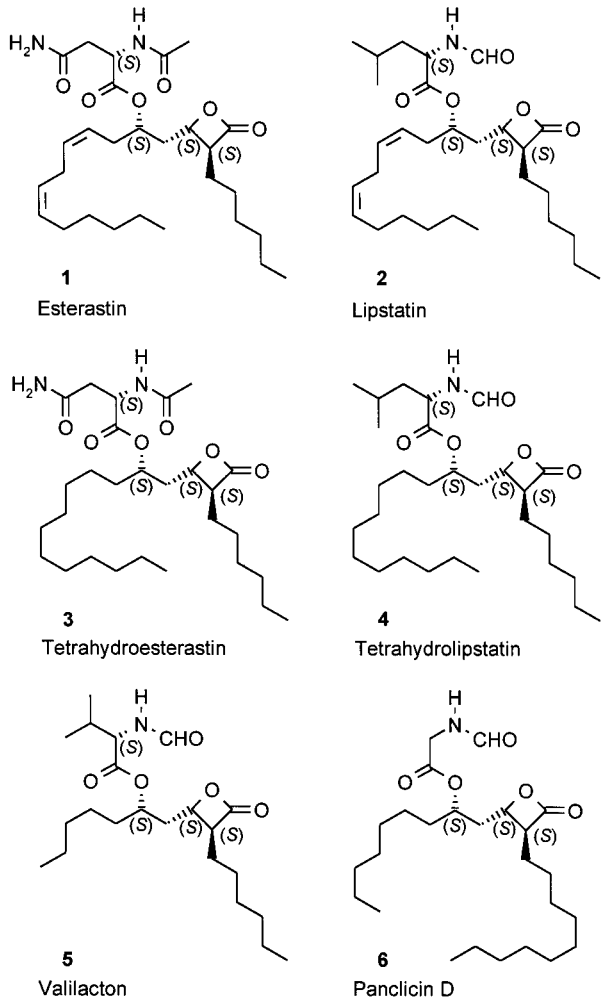
During the last 20 years it has become evident that (3*S*,4*S*)-3-alkyl-4-[(2*S*)-2-hydroxyalkyl]oxetan-2-ones esterified in the side chain with various *N*-formylated or *N*-acetylated α-amino acids form a steadily growing family of structurally closely related esterase and lipase inhibitors of microbial origin. Whereas the 4-alkyl side chains of esterastin (**1**)[2] and lipstatin (**2**)[3,4] are unsaturated, the 4-alkyl side chains of valilactone (**5**)[5] and of the recently detected panclicins (**6**, panclicin D)[6] are fully saturated. The saturated derivatives of **1** and **2**, tetrahydroesterastin (**3**)[2,7] and tetrahydrolipstatin (**4**),[3,7−10] exhibit comparable pharmacological properties, but are more stable than the parent compounds. Especially tetrahydrolipstatin (**4**) is now approved as an antiobesity agent.[11] Due to its promising pharmacological properties, this lipase inhibitor has served during the past decade as a target for the demonstration of the usefulness and versatility of new *β*-lactone syntheses.[7,12−19]

Chart 1



A common feature of these syntheses is the construction of a (3*S*,4*S*)-oxetan-2-one with *trans*-orientated alkyl groups and an (*S*)- or (*R*)-configured hydroxy group in the 2-position of the 4-alkyl chain. The configuration of the hydroxy group determines whether the final esterification with an α-amino acid derivative requires inversion or retention of the configuration of this stereogenic center.

On the basis of the one-step tandem aldol−lactonization of lithium enolates of activated carboxylic acid derivatives with aldehydes, developed in this laboratory during the last five years,[1,20] we now are able to present

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† This paper is dedicated to Professor Sigfrid Schwarz, Jenapharm, on the occasion of his 65th birthday.

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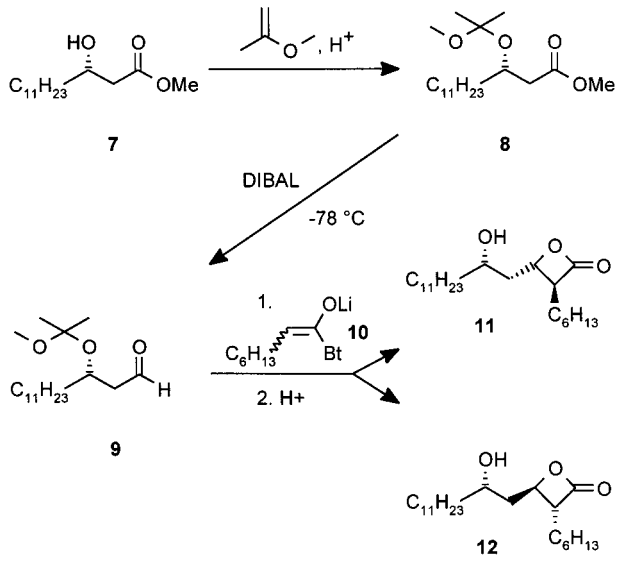
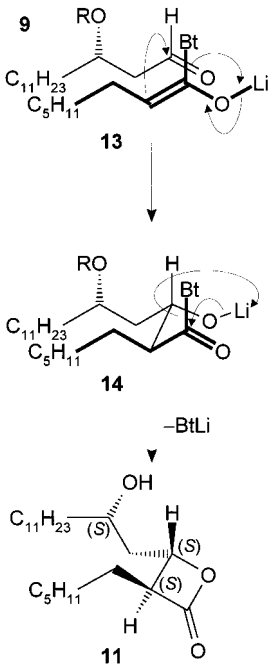
Scheme 1



Scheme 2



a very efficient three-step procedure for the synthesis of (3*S*,4*S*)-3-hexyl-4-[(2*S*)-2-hydroxytridecyl]oxetan-2-one (**11**), the common intermediate for the enzyme inhibitors **3** and **4**, starting from methyl (*S*)-3-hydroxytetradecanoate (**7**).

According to the protocol of the tandem aldol−lactonization, methyl (*S*)-3-hydroxytetradecanoate (**7**)[21] was treated with an excess of 2-methoxypropene[22] in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate and converted into the *O*-protected ester **8**. This was reduced with diisobutylaluminum hydride to the aldehyde **9** and then reacted with the amide enolate generated from 1-octanoylbenzotriazole **10**[20] and lithium hexamethyldisilazide. During the acidic workup, the very labile *O*-protecting group was spontaneously split off, and a 4:1 mixture of the diastereomeric oxetan-2-ones **11** and **12** was obtained. Separation by flash chromatography and recrystallization from pentane/hexane afforded both oxetan-2-ones in diastereomerically pure form. The structure of these two diastereoisomers with *anti*-arrangement of the side chains could be unambiguously assigned on the basis of their ^{1}H NMR spectra and comparison with published data.[18] The isolated yield of **11** amounted to 35%, the yield of **12** to about 5% (related to methyl (*S*)-3-hydroxytetradecanoate).

In comparison to the known syntheses for the oxetan-2-ones **11** and **12** the synthesis outlined here is extremely short. It requires only three steps from methyl 3-hydroxytetradecanoate, a starting material used also in several earlier multistep reactions.[13,15,18,19] The number of steps could be reduced by application of the tandem aldol−lactonization and the use of the very labile 2-methoxyprop-2-oxy protecting group, which does not require an additional deprotection step.

The protocol of the tandem aldol−lactonization requires an activated carboxylic acid derivative such as an *S*-phenyl ester,[23] a phenyl ester,[24] or a benzotriazolide[20] for the spontaneous intramolecular cyclization. Inexpensive chiral leaving groups of this type could not be found so far. The synthesis of lactones such as **11** or **12** according to this protocol can therefore not be based on double diastereoselection. It is restricted to simple diastereoselection based only on the directing influence of the stereogenic center of the *O*-protected 3-hydroxy aldehyde. Nevertheless, the overall economy of the process seems to be much better than that of processes requiring chiral auxiliaries for double stereoselection,[13,15] α-silyl ketenes for the construction of the hexyl side chain,[18] or sophisticated organometallic reagents.[14,15]

The preferential formation of the desired oxetan-2-one **11** from the *O*-protected aldehyde **7** may be explained on the basis of the Zimmerman−Traxler model.[25] It seems to be reasonable that the *Re*-face of the aldehyde is attacked by the *Re*-face of the α-methine group of the (*E*)-enolate **13** as depicted in Scheme 2. Only this approach gives rise to the chairlike transition state **14** with the two alkyl side chains in equatorial position and allows by elimination of lithium benzotriazolide the subsequent formation of the oxetan-2-one **11** with the side chains in *anti*-position. It seems to be possible that the lithiation of the benzotriazolide **10** forms the required (*E*)-enolate **13** with high selectivity. It was already observed in an earlier investigation that the application of benzotriazolides in the tandem aldol−lactonization exhibits a higher *anti*-selectivity than the application of the corresponding phenyl esters.[20]

A consideration of the Zimmerman−Traxler model allows understanding of the preferred formation of the (3*S*,4*S*)-oxetan-2-one starting from the (*S*)-configured aldehyde **9**. The 2-methoxyprop-2-oxy group protects the *Si*-face of the aldehyde against an attack by the amide enolate **13**, thus disfavoring the formation of the undesired *anti*-oxetan-2-one **12**.

As a consequence of the preferred formation of the (3*S*,4*S*)-configured oxetan-2-one starting from methyl

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(3*S*)-hydroxytetradecanoate (**7**), the final conversion of **11** into tetrahydrolipstatin (**4**) by esterification of the hydroxy group can be performed with formyl leucin without prior conversion of the configuration.[14−16] Regarding the molecular economy, this is a further advantage of the outlined procedure.

With the synthesis of a 4:1 mixture of the (3*S*,4*S*)- and (3*R*,4*R*)-oxetan-2-ones **11** and **12** from (*S*)-3-(2-methoxyprop-2-oxy)tetradecanal **9** and the lithium enolate of 1-octanoylbenzotriazole **10**, we were able to demonstrate that the tandem aldol−lactonization affords enantiomerically pure *β*-lactones with an acceptable diastereoselectivity. From the four possible diastereoisomers only the two *anti*-compounds were formed with a distinct preference of the diastereoisomer **11**, useful as common intermediate for the synthesis of the enzyme inhibitors tetrahydroesterastin (**3**) and tetrahydrolipstatin (**4**). Using 2-methoxypropene for the protection of the hydroxy group, methyl (*S*)-3-hydroxytetradecanoate could be converted in three steps into the intermediate **11** with an isolated yield of 35%.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 500 or 125 MHz, respectively, with HMDS as internal standard in $CDCl_3$, if not stated otherwise. Flash chromatography was performed on silica gel 60 (0.04−0.063 mm, E. Merck). The reactions with diisobutylaluminum hydride and butyllithium were carried out in an atmosphere of dry argon. Methyl (*S*)- and (*R*)-3-hydroxytetradecanoate were supplied by Hoffmann-La Roche, Basel. All other chemicals were purchased from Fluka or Aldrich.

Methyl (*S*)-3-(2-Methoxyprop-2-oxy)tetradecanoate (8). Pyridinium *p*-toluenesulfonate (200 mg) was added to an ice cold solution of the methyl ester **7** (10.32 g, 40 mmol) in 2-methoxypropene (40 mL). After being stirred for 5−10 min, the reaction mixture was extracted first with a saturated aqueous solution of sodium hydrogen carbonate (2 mL) and then with water (2 × 2 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residual colorless oil (12.96 g, 98%) was used in the next step without further purification. $[\alpha]^{25}_D$ +10.01 (*c* = 0.5 in hexane); ^{1}H NMR (DMSO-d_6, 75 MHz) *δ* 0.86 (t, *J* = 7 Hz, 3H), 1.24−1.46 (m, 26H), 2.42−2.47 (m, 2H), 3.09 (s, 3H), 3.58 (s, 3H), 4.03−4.05 (m, 1H); ^{13}C NMR (DMSO-d_6) *δ* 13.9, 22.0, 22.1, 24.3, 24.9, 28.7, 28.9, 28.97, 28.98, 29.0, 30.9, 31.3, 35.1, 40.2, 48.5, 51.2, 67.7, 100.4, 171.6. Anal. Calcd for $C_{19}H_{38}O_4$: C, 69.05; H, 11.59. Found: C, 69.00; H, 11.63.

(*S*)-3-(2-Methoxyprop-2-oxy)tetradecanal (9). Diisobutylaluminum hydride (10.7 mL, 60 mmol) dissolved in toluene (30 mL) was precooled to −70 °C and added during 1 h at a temperature of −70 °C to a solution of the crude ester **8** (12.96 g, 40 mmol) in toluene (100 mL), obtained according to the foregoing described procedure. After complete addition the mixture was stirred for an additional 30 min, diluted with methanol (15 mL), and allowed to warm to room temperature. A saturated aqueous solution of sodium chloride (40 mL) was added and the precipitate removed by filtration over a pad of fine sand. The filter cake was washed with ethyl acetate (5 × 15 mL). Filtrate and washings were combined. The aqueous phase was separated and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with water (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residual colorless oil (13.7 g, containing still traces of toluene) was used in the next step without further purification. $[\alpha]^{25}_D$ +4.89 (*c* = 0.5 in hexane); ^{1}H NMR (DMSO-d_6) *δ* 0.86 (t, *J* = 7 Hz, 3H), 1.24−1.69 (m, 26H), 3.08 (s, 3H), 4.17−4.21 (m, 1H), 9.67 (t, *J* = 2 Hz, 1H). The signal of the 2-CH_2-group is hidden by the signals of DMSO; ^{13}C NMR (DMSO-d_6) *δ* 13.9, 22.1, 24.5, 24.9, 25.0, 28.7, 28.9, 28.97, 29.00, 29.04, 31.3, 35.6, 48.5, 48.9, 66.3, 100.5, 202.8. Anal. Calcd for $C_{18}H_{36}O_4$: C, 71.95; H, 12.08. Found: C, 72.05; H, 12.28.

(3*S*,4*S*)-3-Hexyl-4-[(2*S*)-2-hydroxytridecyl]oxetan-2-one (11) and (3*R*,4*R*)-3-Hexyl-4-[(2*S*)-2-hydroxytridecyl]-oxetan-2-one (12). The crude aldehyde **9** (13.7 g, prepared from 40 mmol of **7**) was dissolved in dry THF (10 mL) and cooled to −50 °C. The solution was then added within 1 h to a solution of the lithium enolate of the benzotriazolide **10**,[20] maintaining the temperature of the reaction mixture by cooling with a slurry of ethanol in liquid nitrogen at −95 to −100 °C. After complete addition, the mixture was kept at this temperature for 30 min and allowed to warm to room-temperature overnight. Aqueous HCl (2 N) (50 mL) was added under cooling with ice water, and the mixture was stirred for 20 min. Diethyl ether (20 mL) was added. The aqueous phase was separated and extracted with diethyl ether (3 × 25 mL). The organic phase and the extracts were combined, washed with brine (2 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (350 g) with hexane/ethyl acetate (3 L, 4:1) as eluent afforded the more polar oxetan-2-one **11** and the less polar oxetan-2-one **12** (overall yield of **11** and **12**: 7.66 g, 54%), which were finally purified by recrystallization from pentane/hexane (1:1).

11:[14−16] yield 4.93 g, 35% (related to methyl ester **7**), colorless crystals, mp 63−64 °C; $[\alpha]^{22}_D$ −14.66 (*c* 0.4 in $CHCl_3$); ^{1}H NMR (300 MHz) *δ* 0.84−0.90 (m, 6H), 1.26−2.07 (m, 33H), 3.28−3.35 (m, 1H), 3.76−3.80 (m, 1H), 4.44−4.50 (m, 1H); ^{13}C NMR *δ* 14.1, 14.2, 22.6, 22.7, 25.5, 26.9, 27.9, 29.0, 29.4, 29.59, 29.63 (2 signals), 29.69, 29.71, 31.6, 32.0, 37.7, 41.2, 56.9, 69.4, 76.4, 171.7. Anal. Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94. Found: C, 74.68; H, 11.94.

12:[7,13,18] yield 0.65 g, 5% (related to methyl ester **7**), colorless crystals, mp 57−59 °C; $[\alpha]^{22}_D$ +40.74 (*c* 0.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 0.86−0.90 (m, 6H), 1.26−1.97 (m, 33H), 3.23−3.29 (m, 1H), 3.74−3.85 (m, 1H), 4.47−4.53 (m, 1H); ^{13}C NMR *δ* 14.1, 14.2, 22.6, 22.7, 25.5, 26.8, 27.8, 29.0, 29.4, 29.55, 29.62 (two signals), 29.68, 29.70, 31.6, 32.0, 38.2, 41.9, 56.7, 68.6, 75.7, 172.0. Anal. Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94. Found: C, 74.66; H, 11.94.

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