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Anti-Aldol Reactions of Lactate-Derived Ketones. Application to the Synthesis of (–)-Tetrahydrolipstatin.

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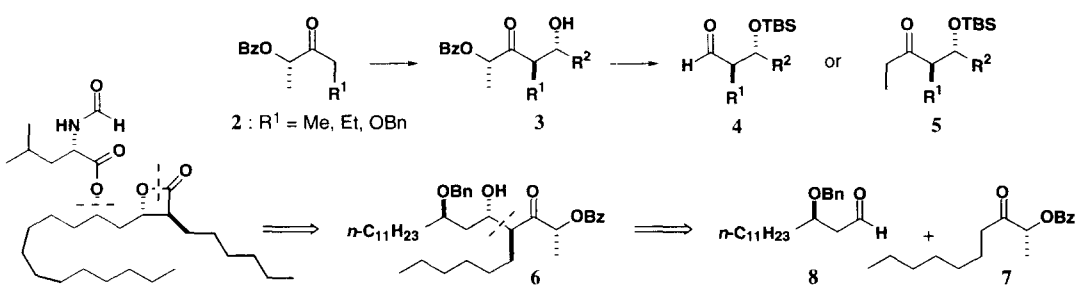
Abstract: (–)-Tetrahydrolipstatin (**1**) was prepared with a high level of stereocontrol (>98% ds) by employing a boron-mediated, *anti*-selective, aldol coupling between the (*R*)-lactate-derived ketone **7** and the aldehyde **8**.

The β-lactone tetrahydrolipstatin (**1**),[1] which acts as a potent inhibitor of pancreatic lipases,[2] is used clinically as an anti-obesity drug (marketed by Roche under the name Xenical) to block the digestion of dietary fat in overweight patients. A number of total syntheses of tetrahydrolipstatin have been reported, adopting a variety of strategies for achieving stereocontrol.[3] As part of our interest in β-lactone enzyme inhibitors,[4] we now report a novel asymmetric synthesis of (–)-tetrahydrolipstatin using an *anti*-selective aldol coupling as the key step (**Scheme 1**).

We have previously shown that the boron-mediated aldol reactions of α-benzoyloxy ketones, as in **2** → **3**, proceed with up to 200:1 diastereoselectivity.[5,6] After appropriate manipulation of the lactate-derived auxiliary, the asymmetric synthesis of a variety of *anti*-configured aldehydes and ketones, *e.g.* **4** and **5**, can be realised. Following this method, a short synthesis of (–)-tetrahydrolipstatin (**1**) should be feasible by preparing the β-hydroxy ketone **6** from (*R*)-2-(benzoyloxy)decan-2-one (**7**) and (*R*)-3-(benzyloxy)tetradecanal (**8**).



tetrahydrolipstatin (**1**)

Scheme 1

The enantiomerically pure ketone **7** was prepared (**Scheme 2**[7]) in 3 steps (63%) from (*R*)-(+)-isobutyl lactate (**9**) in an analogous fashion to that described previously for **2**.[5a] This involved initial Weinreb amide formation,[8] followed by addition of *n*-$C_7H_{15}MgBr$ in THF and benzoylation of the intermediate α-hydroxy ketone. Using our standard conditions (*c*-Hex_2BCl, Me_2NEt, Et_2O), the (*E*)-enol borinate **10** was generated from ketone **7** and combined with the known,[3a-c,h] enantiomerically pure, aldehyde **8** (prepared by Swern oxidation of the corresponding alcohol). On oxidative work-up, this led to the isolation of the required *anti* aldol adduct **6**[7] in 77% yield with >98% diastereoselectivity. As expected, the influence of the chiral enolate component in this reaction overwhelmed any intrinsic facial bias from the aldehyde **8**. Notably, no impairment in stereocontrol was observed using the long alkyl chain in ketone **7** (propionaldehyde also underwent aldol addition with >98% ds).

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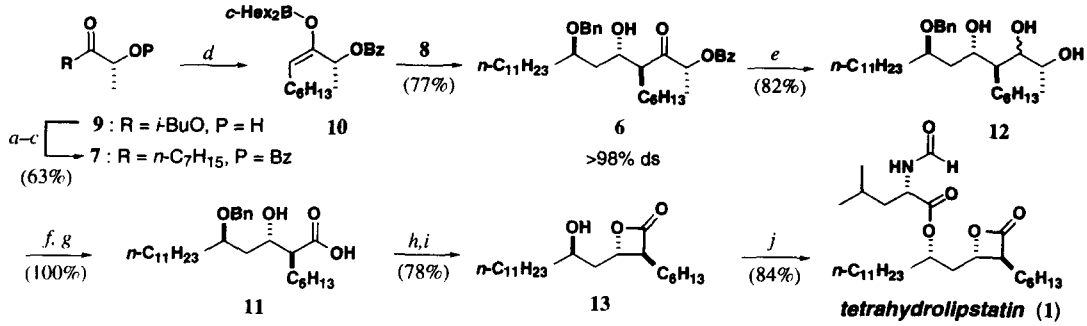

Scheme 2: (*a*) MeONHMe.HCl, ^{i}PrMgCl, THF, –20 → 0 °C, 1.5 h. (*b*) $C_7H_{15}MgBr$, 0 → 20 °C, THF, 4 h. (*c*) Bz_2O, DMAP, $^{i}Pr_2NEt$, 3 d. (*d*) $^{c}Hex_2BCl$, Me_2NEt, Et_2O, 0 °C, 2 h; **8**, –78 °C, 4 h; H_2O_2, NaOH, MeOH, 0 °C, 2 h. (*e*) $LiAlH_4$, Et_2O, –78 → 20 °C, 30 min. (*f*) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 0 °C, 1 h. (*g*) $NaClO_2$, $Na_2H_2PO_4$, 2-methyl-2-butene, ^{t}BuOH, H_2O, 24 h. (*h*) $PhSO_2Cl$, py, 0 °C, 10 min, 4 °C, 24 h. (*i*) H_2, Pd/C, EtOAc, 20 °C, 4 h. (*j*) PPh_3, (*S*)-*N*-formylleucine, DEAD, THF, 0 °C, 4 h.

In previous work,[5] the β-hydroxy group of the aldol adduct was generally silyl protected before conversion into the aldehyde (*cf.* **3** → **4**, **Scheme 1**). For tetrahydrolipstatin, we wished to obtain the β-hydroxy acid **11** without the need for protection. This synthetically useful transformation could be achieved smoothly in 3 steps (82%) by first reducing **6** with $LiAlH_4$ in Et_2O to give the triols **12**. Oxidative glycol cleavage using $Pb(OAc)_4$ then generated the β-hydroxy aldehyde, which was further oxidised[9] with buffered $NaOCl_2$ to give the acid **11**.

Having set up the required stereochemistry in **11**, the remainder of the synthesis paralleled that reported previously.[3a-c,h] The β-lactone ring was formed using $PhSO_2Cl$, followed by debenzylation to give the alcohol **13**, which was coupled with (*S*)-*N*-formyl leucine under Mitsunobu conditions to give (–)-tetrahydrolipstatin (**1**), $[\alpha]_D^{20}$ –34.6 (*c* 0.96, $CHCl_3$), in 65% yield. This had spectroscopic and physical data in agreement with that reported in the literature. Following this route, the synthesis of (–)-tetrahydrolipstatin was completed in 10 steps and 26% overall yield from (*R*)-(+)-isobutyl lactate. This versatile aldol methodology using lactate-derived ketones should be generally applicable to the asymmetric synthesis of other *trans*-disubstituted β-lactones.

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