Pergamon

Tetrahedron Letters 40 (1999) 393–394

TETRAHEDRON LETTERS

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

Ian Paterson* and Victoria A. Doughty

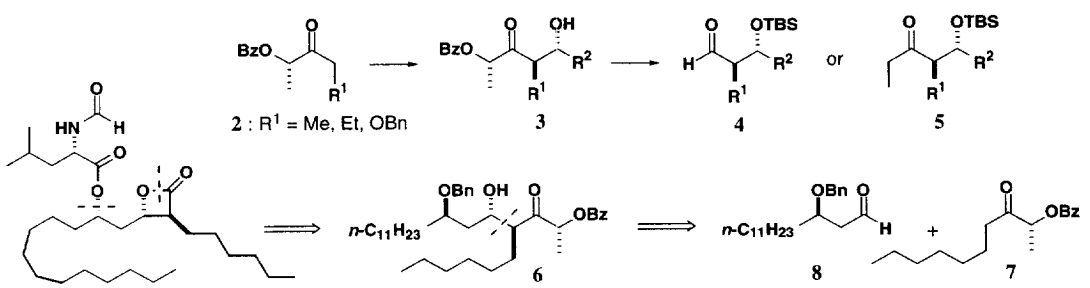
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

Received 7 October 1998; accepted 26 October 1998

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**).

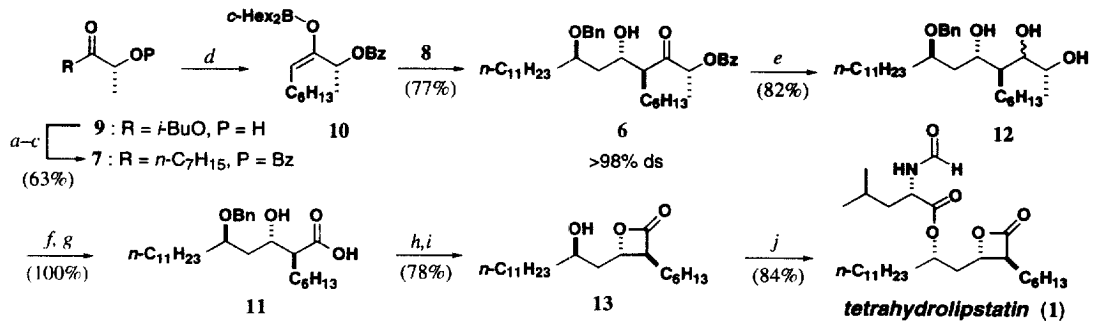
We have previously shown that the boron-mediated aldol reactions of α-benzoyloxy ketones, as in **2** → **3**, proceed with up to 200:1 diastereoselectivity.[5,6] After appropriate manipulation of the lactate-derived auxiliary, the asymmetric synthesis of a variety of *anti*-configured aldehydes and 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**).



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).

PII: S0040-4039(98)02321-1



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.

Acknowledgement: We thank the EPSRC and Knoll Pharmaceuticals for support (CASE Studentship to VAD) and Dr Robert Norrie (Knoll Pharmaceuticals) for a gift of the alcohol precursor to aldehyde **8**.

References and Notes

1. (a) Weibel, E. K.; Hadvary, P.; Hochuli, E.; Kupfer, E.; Lengsfeld, H. *J. Antibiot.* **1987**, *40*, 1081. (b) Hochuli, E.; Kupfer, E.; Maurer, R.; Meister, W.; Mercadel, Y.; Schmidt, K. *J. Antibiot.* **1987**, *40*, 1086.
2. (a) Hadvary, P.; Lengsfeld, H.; Wolfer, H. *Biochem. J.* **1988**, *256*, 357. (b) Borgström, B. *Biochim. Biophys. Acta* **1988**, *962*, 308.
3. (a) Barbier, P.; Schneider, F. *Helv. Chim. Acta* **1987**, *70*, 196. (b) Barbier, P.; Schneider, F.; Widmer, U. *Helv. Chim. Acta* **1987**, *70*. 1412. (c) Barbier, P.; Schneider, F. *J. Org. Chem.* **1988**, *53*, 1218. (d) Pons, J.; Kocienski, P. J. *Tetrahedron Lett.* **1989**, *30*, 1833. (e) Fleming, I.; Lawrence, N. J. *Tetrahedron Lett.* **1990**, *31*, 3645. (f) Chadha, N. K.; Batcho, A. D.; Tang, P. C.; Courtney, L. F.; Cook, C. M.; Wovkulich, P. M.; Uskokovic, M. R. *J. Org. Chem.* **1991**, *56*, 4714. (g) Case-Green, S. C.; Davies, S. G.; Hedgecock, C. J. R. *Synlett* **1991**, 781. (h) Hanessian, S.; Tehim, A.; Chen, P. *J. Org. Chem.* **1993**, *58*, 7768. (i) Pommier, A.; Pons, J.; Kocienski, P. J.; Wong, L. *Synthesis* **1994**, 1294. (j) Giese, B.; Roth, M. *J. Braz. Chem. Soc* **1996**, *7*, 243. (k) Fleming, I.; Lawrence, N. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2679.
4. Paterson, I.; Hulme, A. N. *J. Org. Chem.* **1995**, *60*, 3288.
5. (a) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639. (b) Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083. (c) Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994**, *35*, 9087.
6. For some applications, see: (a) Paterson, I.; Wallace, D. J. *Tetrahedron Lett.* **1994**, *35*, 9477. (b) Paterson, I.; Feβner, K.; Finlay, M. R. V. *Tetrahedron Lett.* **1997**, *38*, 4301.
7. All new compounds gave spectroscopic data in agreement with the assigned structures.
8. Williams, M. J.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
9. Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.