J. Braz. Chem. Soc., Vol. 7, No. 5, 243-246, 1996.
Printed in Brazil.

0103 – 5053 $6.00 + 0.00

Article

Diastereoselective Radical Addition as a Key-Step in the Synthesis of Tetrahydrolipstatin

Bernd Giese*, Martin Roth

Institut für Organische Chemie der Universität Basel, St. Johanns Ring 19, CH-4056 Basel, Switzerland

Received: July 11, 1996

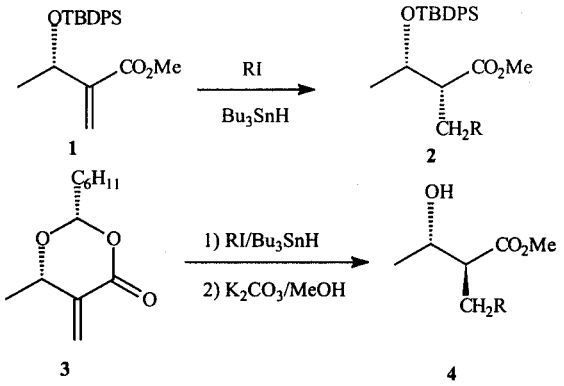
A tetraidrolipstatina foi sintetizada utilizando como etapa chave uma adição radicalar estereosseletiva.

Tetrahydrolipstatin was synthesized using a stereoselective radical addition as key-step.

Keywords: *tetrahydrolipstatin, allylic strain, stereoselective radical addition*

Introduction

Recently, we have observed that A-strain can govern the stereochemistry of radical reactions[1].



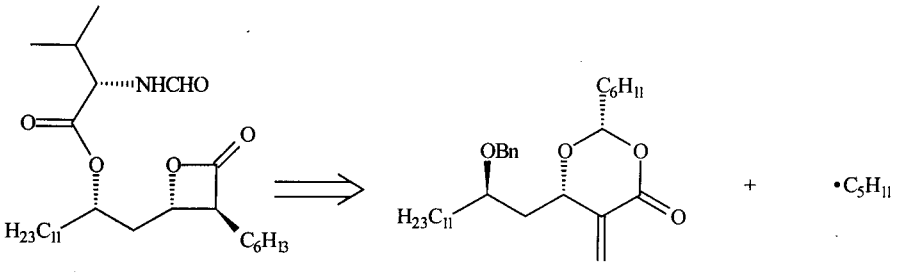
Scheme 1.

Thus, acyclic alkene **1** gives *syn* product **2** whereas the cyclic alkene **3** mainly yields *anti* product **4**[2]. We have now applied this concept to the synthesis of tetrahydrolipstatin **5**, a lipase inhibitor that was developed by the company Hoffmann-La Roche[3].

Our retrosynthetic approach of **5** involves cyclic alkene **6a** as key-intermediate. Addition of pentyl radical $C_5H_{11}^{\bullet}$ to **6a** and stereoselective hydrogen abstraction should introduce the hexyl substituent of tetrahydrolipstatin with the right stereochemistry.

Results and Discussion

The cyclic acetal **6** was synthesized starting from β-keto ester **7**. Asymmetric hydrogenation[4] of **7** in the presence of ruthenium(II) BINAP led to β-hydroxy ester **8** in 97% yield (ee = 95%) which, after benzylation[5] of the hydroxyl group (91%), was subsequently reduced with DIBAL[6] to yield the corresponding aldehyde **9** (95%). The chain elongation was

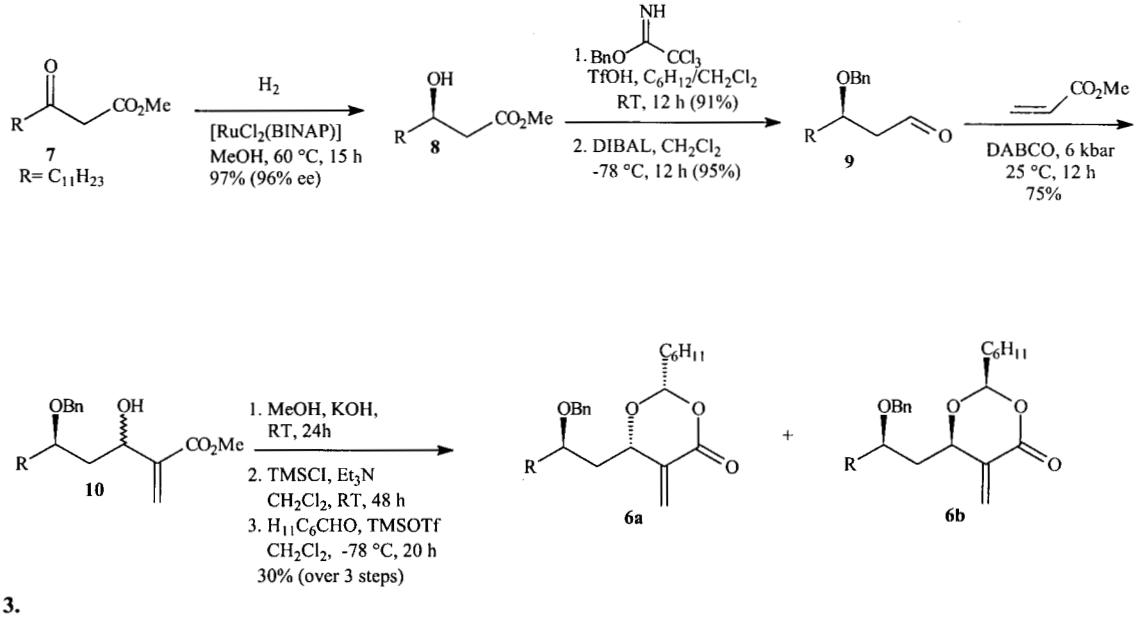


Scheme 2.

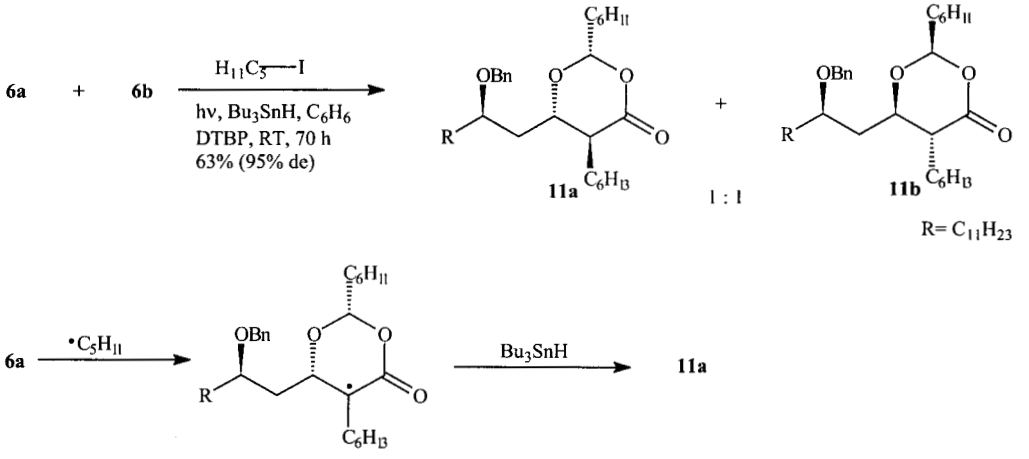
performed by means of a high-pressure (5 kbar) Baylis-Hillman[7] reaction of **9** with methyl acrylate in the presence of 10 mol% DABCO[8]. The reaction was carried out in neat phase and yielded **10** (75%) in racemic form. Saponification led to the corresponding β-hydroxy acid which was bis-silylated and subsequently treated with cyclohexylcarbaldehyde to form the cyclic acetals **6a,b** in 30% yield over the 3 steps[9].

The key-step of the synthesis consisted in the introduction of the hexyl substituent by radical addition of *n*-pentyl iodide to the double bond of **6**. The reaction was carried out in the presence of tributyltin hydride under irradiation (150 W sun lamp) for 3 days. Only two diastereomers **11a,b** were obtained in 63% yield and could be separated by flash chromatography on silica gel. NOE experiments confirmed the structure of the products and showed that the H-abstraction by radical **12** occurs stereoselectively to form the *anti* product **11a** as predicted from our model studies[10]: Due to allylic strain, the hexyl substituent adopts a conformation in which the *Si*-face of radical **12** is shielded and H-abstraction occurs from the *Re*-face.

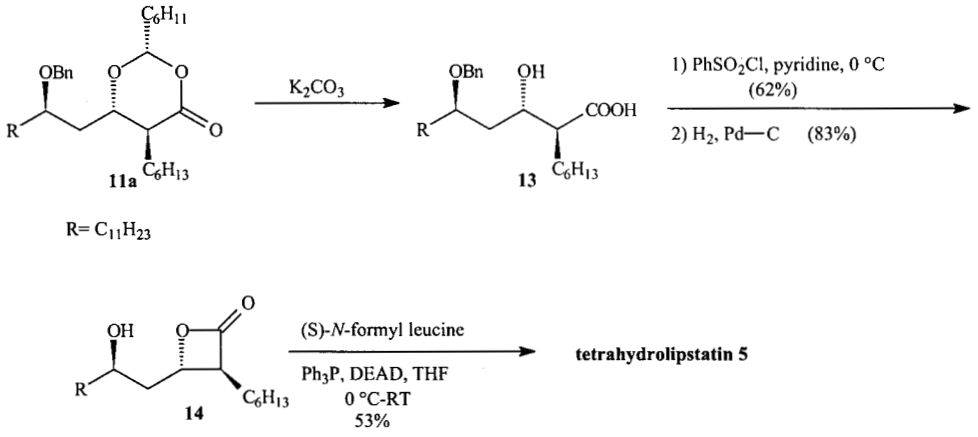
Hydrolysis of acetal **11a** in the presence of K_2CO_3 yielded quantitatively β-hydroxy acid **13** which was converted to tetrahydrolipstatin **5** in 3 steps following literature procedure[3g]: formation of the β-lactone in the presence of phenylsulfonyl chloride (72%), followed by deprotection of the benzyl ether by hydrogenolysis (75%), and subsequent esterification of the hydroxyl function with (*S*)-*N*-formyl leucine (53%) under Mitsunobu conditions. The configuration of the product was confirmed by comparison of its NMR data with those of an authentic sample and by independent synthesis of **11a**.



Scheme 3.



Scheme 4.



Scheme 5.

Experimental

Radical addition of pentyl iodide to **6a,b**. *Synthesis of (2S,5S,6S,2'R)- and (2R,5R,6S,2'R)-2'-cyclohexyl-5-hexyl-6-(2-benzyloxytridecyl)-1,3-dioxan-4-one* **11a** *and* **11b**

Compound **6a,b** (70 mg, 0.144 mmol) and *n*-iodopentane (278 mg, 1.4 mmol) were solved in dry benzene (1 mL) at 20 °C and argon was passed through the solution for 15 min. The mixture was then irradiated with a 150 W tungsten lamp. During irradiation, a solution of tributyltin hydride (144 µl, 0.432 mmol) and di-*tert*-butyl peroxide (37 µl, 0.144 mmol) in dry benzene (1 mL) was added within 2 h by syringe pump addition. The reaction mixture was further irradiated for 70 h then diethyl ether (10 mL) was added and the solution was treated with potassium fluoride (500 mg, 8.64 mmol) in water (5 mL). The mixture was stirred for 48 h at room temperature and during this time a white precipitate appeared. This was filtered off, the organic phase was separated and dried over $MgSO_4$. After removal of the solvent under vacuum, the crude product was purified by flash chromatography on silica gel (eluent: pentane/AcOEt 95:5) to give 47 mg (0.085 mmol, 63%) of **11a,b**. The two diastereomers (2*S*,3*S*,5*R*) **11a** and (2*R*,3*R*,5*R*) **11b** were formed in a 1:1 ratio and could be separated by flash chromatography (silica gel, eluent: pentane/AcOEt, 95:5).

11a: ^{1}H-NMR (400 MHz, $CDCl_3$), δ 7.35–7.20 (m, 5H), 4.75 (d, J = 5.04 Hz, 1H), 4.64 (d, J = 11.81 Hz, 1H), 4.36 (d, J = 11.66 Hz, 1H), 3.78 (dt, J = 1.17 Hz, 1H), 3.65 (m, 1H), 2.37 (dt, J = 5.2 Hz, 1H), 1.90–1.50 (m, 30H), 1.26 (broad s, 18H), 0.88 (t-like, 2 x 3H); ^{13}C-NMR (121 MHz, $CDCl_3$) δ 171.2, 138.9, 128.4, 127.9, 127.7, 105.5, 74.9, 74.8, 71.5, 46.7, 42.2, 39.7, 34.2, 31.9, 31.6, 29.9, 29.7, 2 x 29.6, 29.5, 29.4, 27.9, 26.62, 26.57, 26.3, 26.2, 25.6, 25.5, 25.0, 22.7, 22.6, 14.12, 14.06. **11b**: ^{1}H-NMR (400 MHz, $CDCl_3$), δ 7.35–7.20 (m, 5H), 5.0 (d, J = 4.9 Hz, 1H), 4.5 (d, J = 2.5 Hz, 2H), 3.79 (dt, J = 3.0, 9.0 Hz, 1H), 3.6 (m, 1H), 2.5 (dt, J = 9.9, 5.2 Hz, 1H), 1.90–1.50 (m, 30H), 1.26 (broad s, 18H), 0.88 (t-like, 2 x 3H); ^{13}C-NMR (121 MHz, $CDCl_3$) δ 170.2, 138.7, 128.3, 127.7, 127.6, 105.4, 75.5, 75.2, 70.8, 46.7, 42.2, 37.7, 33.7, 31.9, 30.9, 29.6, 29.5, 29.3, 28.2, 26.7, 26.5, 26.1, 25.3, 22.7, 22.6, 14.12, 14.06.

Anal. calcd. for $C_{36}H_{50}O_4$ (546.79): C 77.65, H 10.86; found: C 77.66, H 10.77.

Acknowledgments

This work was supported by the *Swiss National Science Foundation*. The authors thank Prof. F.G. Klärner for giving them the opportunity to carry out the high pressure experiments in his laboratory.

References

1. Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996.
2. Bulliard, M.; Zeitz, H.-G.; Giese, B. *Synlett* **1991**, 423.
3. For other syntheses of tetrahydrolipstatin see: a) Barbier, P.; Schneider, F. *Helv. Chim. Acta* **70**, 196 (1987); b) Barbier, P.; Schneider, F.; and Widmer, U. *Helv. Chim. Acta* **1987**, *70*, 1412; c) Pons, J.M.; Kociensky, P. *Tetrahedron Lett.* **1989**, *30*, 1833; d) Fleming, I.; Lawrence, N.J. *Tetrahedron Lett.* **1990**, *31*, 3645; e) Case-Green, S.C.; Davies, S.G.; Hedgecock, C.J.R. *Synlett* **1991**, 781; 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) Hanessian, S.; Tehim, A.; Chen, P. *J. Org. Chem.* **1993**, *58*, 7768.
4. Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.
5. U. Widmer, *Synthesis* **1987**, 568.
6. Zarkharkin, L.I.; Khorlina, I.M. *Tetrahedron Lett.* **1962**, 619.
7. a) Baylis, A.B.; Hillman, M.E.D. German Patent 2 155 113, *Chem. Abstr.* **1972**, *77*, 34174q; b) Drewes,

S.E.; Roos, G.H.P. *Tetrahedron* **1988**, *44*, 4653; for a review see: Basavaiah, D.; Rao, P.D.; Hyma, R.S. *Tetrahedron* **1996**, *52*, 8001.

8. The best diastereoselective excess that we could obtain for the Baylis-Hilman reaction under high pressure was 30%. In this case the reaction was carried out in the presence of quinidine as chiral base under 11 kbar pressure in CH_2Cl_2 at 25 °C for 12 h.
9. a) Seebach D.; Zimmermann, J. *Helv. Chim. Acta* **1986**, *69*, 1147; b) Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448.
10. Giese, B.; Damm, W.; Witzel, T.; Zeitz, H.-G. *Tetrahedron Lett.* **1993**, *34*, 7053.