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Oxazoline *N*-Oxide-Mediated [2+3] Cycloadditions. Application to a Synthesis of (–)-Tetrahydrolipstatin

O. Dirat, C. Kouklovsky, and Yves Langlois*

Laboratoire de Synthèse des Substances Naturelles, Associé au CNRS, ICMO, bâtiment 410, Université de Paris-sud, 91405 Orsay, France

langlois@icmo.u-psud.fr

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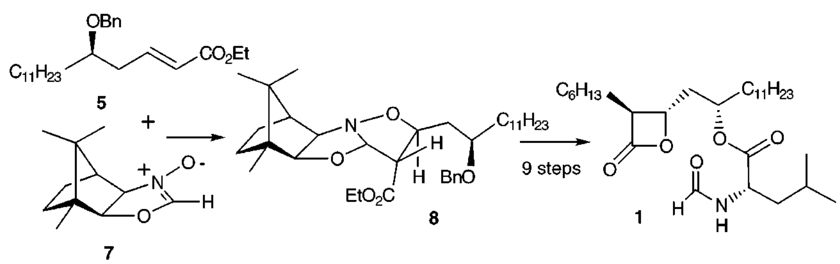
ABSTRACT

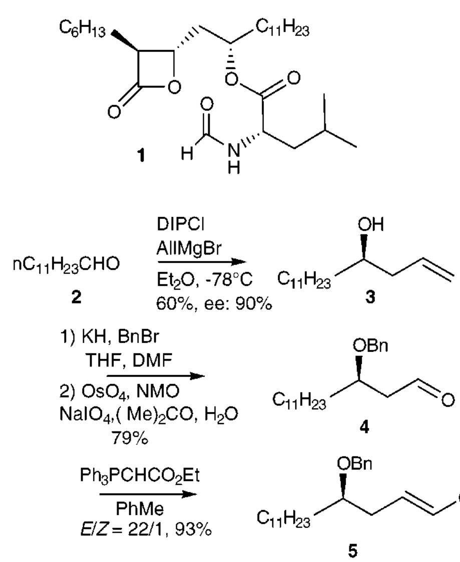


A [2+3] cycloaddition of camphor-derived oxazoline *N*-oxide to α,*β*-unsaturated ester afforded adduct 8. Tetrahydrolipstatin 1 was prepared from this compound in a nine-step sequence of reactions.

Tetrahydrolipstatin **1** is a potent inhibitor of pancreatic lipase[1] and has been marketed in several countries as an antiobesity drug. The biological activity of this compound attracted the interest of synthetic chemists, and many total syntheses of *β*-lactone **1** have already been published.[2] As an illustration of the potential of a new kind of asymmetric [2+3] cycloaddition using oxazoline *N*-oxides as dipoles,[3] we report in this paper a novel stereoselective synthesis of the title compound.

The known aldehyde **4** has been prepared in 90% ee and in 47% overall yield from the commercially available dodecanal **2** by a modification of Hanessian's scheme.[4] Wittig olefination gave rise to a 22:1 mixture of *E* and *Z* geometric isomers which after purification afforded (*E*)-α,*β*-unsaturated ester **5** in 93% yield (Scheme 1).[5]

Scheme 1



Cycloaddition of ester **5** to oxazoline *N*-oxide **7**, resulting from the condensation of aminoisoborneol hydrochloride **6**[3]

(1) Hochuli, E.; Kupfer, E.; Maurer, R.; Meister, W.; Mercadal, Y.; Schmidt, K. *J. Antibiot.* **1987**, *40*, 1086.

(2) Total syntheses: (a) Paterson, I.; Doughty, V. A. *Tetrahedron Lett.* **1999**, *40*, 393. (b) Fleming, I.; Lawrence, N. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2679. (c) For reviews on *β*-lactone synthesis, see: Pommier, A.; Pons, J.-M. *Synthesis* **1995**, 729. Yang, H. W.; Romo, D. *Tetrahedron* **1999**, *55*, 6403 (and references therein).

(3) For a review, see: (a) Langlois, Y. *Curr. Org. Chem.* **1998**, *2*, 1. (b) Kouklovsky, C.; Dirat, O.; Berranger, T.; Langlois, Y.; Tran Huu Dau, M.-E.; Riche, C. *J. Org. Chem.* **1998**, *63*, 5123. (c) Dirat, O.; Kouklovsky, C.; Langlois, Y. *J. Org. Chem.* **1998**, *63*, 6634.

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and trimethylorthoformate, was performed in toluene at 80 °C. The endo adduct **8** was isolated in 61% yield after chromatography along with less than 5% of the corresponding exo adduct and less than 5% of the adduct resulting from the cycloaddition with the minor *ent*-**5**. The configuration of the newly created asymmetric centers in **8** was deduced after NOESY experiments as illustrated in Figure 1. In

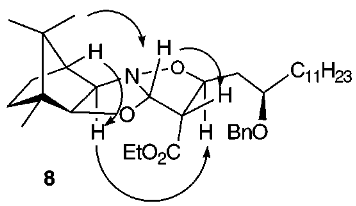
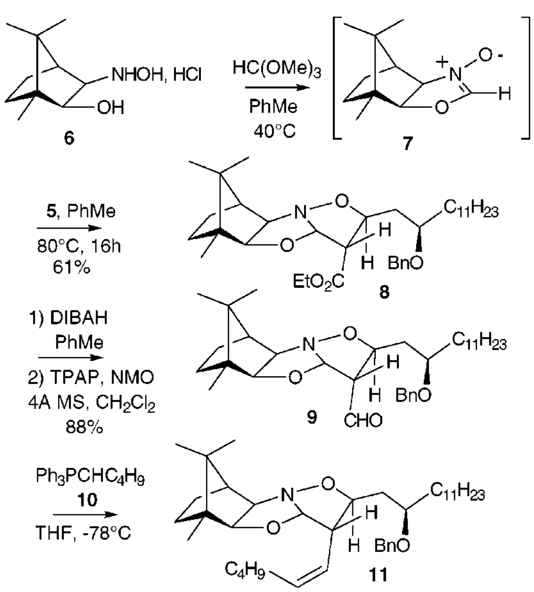


Figure 1.

agreement with semiempirical calculations, this cycloaddition is controlled by HOMO dipole−LUMO dipolarophile interactions.[3b]

Reduction−oxidation of the ester group in **8** gave rise to the aldehyde derivative **9** in 88% yield.[6] In the following step, the Wittig chain elongation was very sensitive to the presence of salt. When phophorane **10** was generated by deprotonation of the corresponding phosphonium bromide salt with ^{n}BuLi, NaHMDS, or KHMDS, the reaction was very slow and afforded compound **11** in poor yield. However, when **10** was generated with $NaNH_2$ in boiling THF followed by filtration of NaBr, the resulting solution reacted instantaneously with aldehyde **9** at −78 °C and gave rise to the expected compound **11** as the *Z* isomer (Scheme 2).

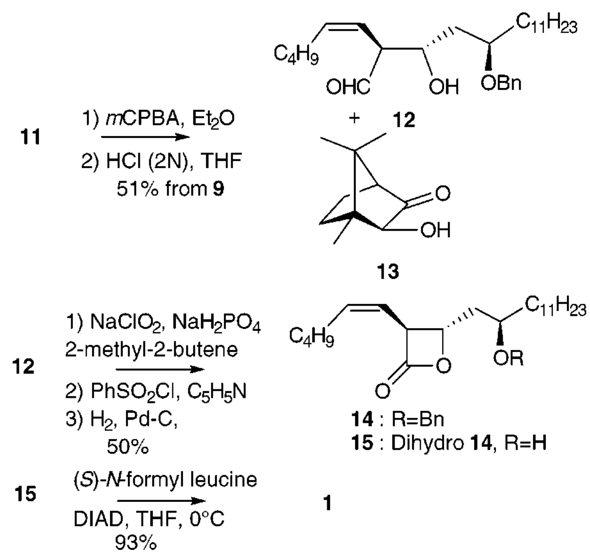
Scheme 2



Unexpectedly, this compound proved to be unstable and, for this reason, was subjected without purification[7] to oxidation−hydrolysis[3] affording the aldehyde **12**. γ,δ-Unsaturated aldehyde **12** was purified without isomerization or epimerization and was isolated in 51% overall yield from **9**. Ketol **13**, a precursor of aminoisoborneol hydrochloride **6**,[3] was recovered at this stage in 98% yield.

Oxidation of aldehyde **12** with buffered $NaClO_2$[8] was followed by β-lactone ring formation of the resulting acid with $PhSO_2Cl$ using the previously reported conditions.[9] The β-lactone **14** was thus isolated in 50% yield. Hydrogenation of the double bond with concomitant hydrogenolysis of the benzyloxy group gave rise nearly quantitatively to the known β-lactone **15**.[4,9] Compound **15** was finally coupled with (*S*)-*N*-formylleucine under Mitsunobu conditions (for this step, DIAD gave better results than DEAD) and afforded tetrahydrolipstatin **1**[10] in 93% yield (Scheme 3): mp 42 °C (mp[4,9] 40−42 °C); $[\alpha]^{20}_D = -32.0$ (*c* 0.74, $CHCl_3$); $[\alpha]^{20}_D$ [4,9] $= -33.0$ (*c* 0.79, $CHCl_3$).

Scheme 3



Following this strategy, the synthesis of tetrahydrolipstatin **1** was completed in 11 steps and 14% overall yield from the known aldehyde **4** and in 14 steps and 5.58% overall yield (81.4% for each step) from the commercially available

(4) ee was determined by ^1H NMR analysis of the corresponding *O*-acetylmandelate ester of alcohol **3**; see: Hanessian, S.; Tehim, A.; Chen, P. *J. Org. Chem.* **1993**, *58*, 7768.

(5) The same compound has been described under the racemic form: Oblin, L.; Parrain, J.-L.; Rajzmann, M.; Pons, J.-M. *J. Chem. Soc., Chem. Commun.* **1998**, 1619.

(6) Direct reduction of the ester **8** with DIBAH gave aldehyde **9** in 76% yield.

(7) Under these conditions, the Wittig resulting compound **11** was obtained in 80% yield as a crude product. As degradation occurred during purification, crude **11** was taken in the next reaction.

(8) Kraus, G. A.; Tashner, M. J. *J. Org. Chem.* **1980**, *45*, 1175.

(9) Barbier, P.; Schneider, F. *Helv. Chim. Acta* **1987**, *70*, 196.

(10) New compounds are characterized by ^1H and ^{13}C NMR spectra, HRMS, and optical rotation.

dodecanal **2**. This synthesis competes favorably with the previously reported ones.

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Supporting Information Available: Detailed experimental procedures and characterization data for compounds **3**−**15** and tetrahydrolipstatin **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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