An Enantioselective Synthesis of 3,4-Disubstituted Butyrolactones

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An enantioselective synthesis of γ-butyrolactones including a formal synthesis of (−)-methylenolactocin **1** is achieved by employing an enantioselective deprotonation of 3-phenylcyclobutanone as a key step.

γ-Butyrolactones with a wide range of substituents are often observed in nature and also are of biologically significance. Because of their importance as building blocks in natural products synthesis in addition to their interesting pharmacological activities, many efforts have been devoted to the synthesis of this type of compound in optically active forms.[1]

(−)-Methylenolactocin **1**, isolated from the culture filtrate of *Penicillium* sp. is a highly functionalized and isomerization-prone antitumour antibiotic[2] having a 4-pentyl-γ-butyrolactone structure as a basic skeleton and only one example for its synthesis involving an asymmetric [2 + 2] cycloaddition reaction as a key step, was recently reported by Greene and his coworkers.[3]

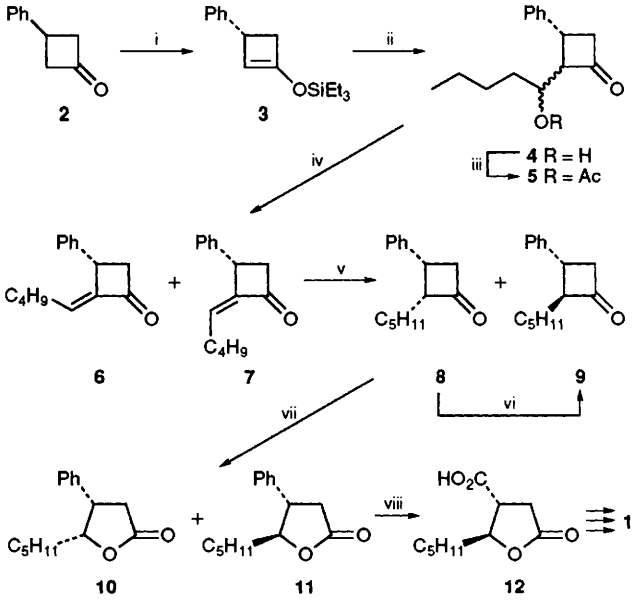
In conjunction with the synthesis of the physiologically active natural products by employing an enantioselective deprotonation strategy,[4] we have developed[5] a novel enantioselective synthesis of the 3-substituted γ-butyrolactone structure from prochiral cyclobutanone derivatives. As an extension of this work, we became interested in developing an efficient procedure for a synthesis of the 3,4-disubstituted γ-butyrolactones and report here a successful enantioselective synthesis of (−)-methylenolactocin **1**. Based on the results of our earlier work,[5] an enantioselective deprotonation of 3-phenylcyclobutanone **2** was carried out as follows. Treatment of 3-phenylcyclobutanone **2** with lithium (*S*,*S*′)-α,α′-dimethyldibenzylamide in dry tetrahydrofuran (THF) at −100 °C, followed by trapping of the resulting enolate with triethylsilyl chloride afforded the triethylsilyl enol ether **3** in 67% conversion yield with 92% enantiomeric excess (e.e.). Although difficulties were initially encountered in the introduction of an alkyl group at the 2-position of the enol ether, *e.g.* attempted stereoselective alkylation of **3** with 1-bromopent-2-ene or pentenyl bromide *via* the corresponding lithium or zinc enolate in appropriate solvents all failed, aldol reaction of the enol ether **3** with valeraldehyde in THF in the presence of tetrabutylammonium fluoride[6] gave possible four diastereoisomers **4** as an inseparable mixture in 75% yield. The expected stereoselectivity giving a *trans* isomer predominantly could not be observed in this aldol reaction unfortunately. Acetylation of the mixture **4** with acetic anhydride in the presence of a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) in pyridine and dichloromethane afforded the acetates **5** which on reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene underwent smooth conversion to provide the α,β-unsaturated ketones **6** and **7** in 46.7 and 23.3% yields, respectively.

The stereochemistry of these enones was easily determined based on their NMR spectra.† The olefinic proton of the *E*-enone **6** at δ 6.45 as a double-triplet was shifted downfield by 0.84 ppm, in relation to the position of that of the *Z*-enone **7** at δ 5.61 as a double-triplet, due to the presence of a deshielding effect of the neighbouring carbonyl group.

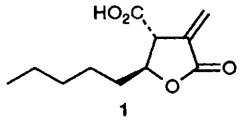
Catalytic reduction of the *E*-enone **6** over palladium on carbon under an atmospheric pressure of hydrogen afforded the *cis*- and *trans*-ketones **8** and **9** in quantitative yield, in a ratio of *ca.* 2:1, as an inseparable mixture, whereas the reduction of the *Z*-enone **7** furnished **8** and **9** in a ratio of *ca.* 1:2. Although the mixture of the *cis* and *trans* isomers was formed with disappointing ratio and could not be separated at this stage, the *cis*-isomer **8** was readily isomerized to the trans-isomer **9**, in a ratio of 20:1, by treatment with sodium hydride in THF in 88% yield. The stereoselective introduction of a suitable alkyl group at the desired position was thus achieved.

Baeyer–Villiger oxidation of the ketones **8** and **9** (20:1 v/v) in acetic acid and 30% hydrogen peroxide proceeded regioselectively to provide the lactone **11** together with its diastereoisomer **10** in 83.8 and 4.2% yields, respectively, which were easily separated by column chromatography on silica gel. Since the basic skeleton for methylenolactocin was constructed stereoselectively, we focused our attention on its further conversion into the natural product. Oxidation of the phenyl group of **11** with ruthenium tetroxide under the Sharpless's condition[7] afforded the carboxylic acid **12** quantitatively, mp 104–105 °C (decomp.) [lit.,[3] mp 105–107 °C (decomp.)], $[\alpha]_D$ −50.5 (*c* 0.4, $CHCl_3$) [lit.,[3] $[\alpha]_D$ −54 (*c* 0.5, $CHCl_3$)], whose spectroscopic data supported its structure. Since this compound has already been transformed into (−)-methylenolactocin **1** by methylenation,[3] this synthesis constitutes its formal synthesis.

In conclusion, we have described the methodology which permits the enantioselective construction of 3,4-disubstituted γ-butyrolactones from prochiral 3-substituted cyclobutanones. This methodology seems to be widely applicable to the chiral synthesis of various types of natural compounds.



Scheme 1 *Reagents and conditions*: i. lithium (*S*,*S*′)-α,α′-dimethyldibenzylamide, THF, −100 °C; then triethylsilyl chloride (67%); ii, valeraldehyde, Bu^n_4NF, THF, 0 °C (75%); iii, Ac_2O, pyridine, cat. DMAP, CH_2Cl_2, room temp. (82%); iv, cat. DBU, benzene, reflux (70%); v, H_2, 10% Pd–C, EtOH, room temp. (quant.); vi, cat. NaH, THF, 0 °C (88%); vii, 30% H_2O_2, AcOH, 0 °C (90%); viii, $RuCl_3$, HIO_4, CCl_4–MeCN–H_2O (1:1:2, v/v), room temp. (quant.)



Further development in this area is under progress in this laboratory.

Received, 1st September 1993; Com. 3/05246G

Footnote

† *Selected spectroscopic data* for **6**: ν_{max} ($CHCl_3$)/cm^{-1} 1740 and 1660; δ($CDCl_3$) 0.77 (3H, t, *J* 7.3 Hz, Me), 1.13–1.32 (4H, m), 1.87 (2H , dq, *J* 1.2 and 7.9 Hz, CH_2CH=C), 2.91 (1H, dd, *J* 6.1 and 17.1 Hz, 4-H), 3.45 (1H, dd, *J* 9.2 and 17.1 Hz, 4-H), 4.12–4.22 (1H, m, 3-H), 6.45 (1H, dt, *J* 2.4 and 7.9 Hz, CH=C), 7.23–7.35 (5H, m, aromatic protons); MS *m/z* 214 (M^+). $[\alpha]_D$ −115.9 (*c* 1.0, $CHCl_3$).

For **7**: ν_{max} ($CHCl_3$)/cm^{-1} 1740 and 1660; δ($CDCl_3$) 0.90 (3H, t, *J* 7.3 Hz, Me), 1.26–1.45 (4H, m), 2.57 (2H, dq, *J* 1.8 and 7.9 Hz, CH_2CH=C), 2.94 (1H, dd, *J* 6.1 and 17.7 Hz, 4-H), 3.38 (1H, dd, *J* 9.2 and 17.7 Hz, 4-H), 4.06–4.12 (1H, m, 3-H), 5.61 (1H, dt, *J* 2.4 and 7.9 Hz, CH=C), 7.21–7.35 (5H, m, aromatic protons); MS *m/z* 214 (M^+). $[\alpha]_D$ −69.6 (*c* 1.0, $CHCl_3$).

For **11**: ν_{max} ($CHCl_3$)/cm^{-1} 1770; δ($CDCl_3$) 0.85 (3H, t, *J* 7.3 Hz, Me), 1.23–1.51 (6H, m), 1.64–1.72 (2H, m), 2.74 (1H, dd, *J* 10.4 and 17.1 Hz, 2-H), 2.95 (1H, dd, *J* 8.5 and 17.1 Hz, 2-H), 3.30 (1H, dt, *J* 8.5 and 10.4 Hz, 3-H), 4.45 (1H, dt, *J* 6.1 and 8.5 Hz, 4-H), 7.22–7.41 (5H, m, aromatic protons). MS *m/z* 232 (M^+). $[\alpha]_D$ −25.6 (*c* 1.6, $CHCl_3$).

For **12**: ν_{max} ($CHCl_3$)/cm^{-1} 1780 and 1740; δ($CDCl_3$) 0.90 (3H, t, *J* 7.3 Hz, Me), 1.31–1.48 (6H, m), 1.72–1.83 (2H, m), 2.82 (1H, dd, *J* 9.8 and 17.7 Hz, 2-H), 2.95 (1H, dd, *J* 8.5 and 17.7 Hz, 2-H), 3.10 (1H, ddd, *J* 7.3, 8.5 and 9.8 Hz, 3-H), 4.62 (1H, dt, *J* 4.9 and 7.3 Hz, 4-H), MS *m/z* 200 (M^+). $[\alpha]_D$ −50.5 (*c* 0.4, $CHCl_3$).

References

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