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A short-step synthesis of *trans*-whisky lactone by an asymmetric Michael reaction

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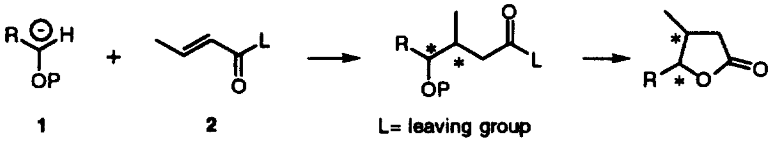
Abstract

trans-Whisky lactone **6** was synthesized enantioselectively in only six steps from readily available 2-trimethylsilyloxyfurans and 3-crotonoyl-1,3-oxazolidin-2-one using an asymmetric Michael reaction as the key step. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Multi-substituted γ-lactone substructures exist in many natural products and asymmetric syntheses of γ-lactones or their synthetic equivalents have received considerable attention.[1] Recently, highly enantioselective Lewis acid catalyzed asymmetric Michael reactions have been reported[2] and we expected that an asymmetric Michael reaction between the anion **1** bearing a protected hydroxy group and enoate **2** would provide a useful method for the synthesis of chiral γ-lactones (Eq. 1). However, anion **1** is a strong base and vitiates the Lewis acid catalyst. Therefore, an equivalent of **1** which is not basic but nucleophilic is required to perform this type of Michael reaction successfully in the presence of chiral Lewis acid catalyst.



1 **2** (1)

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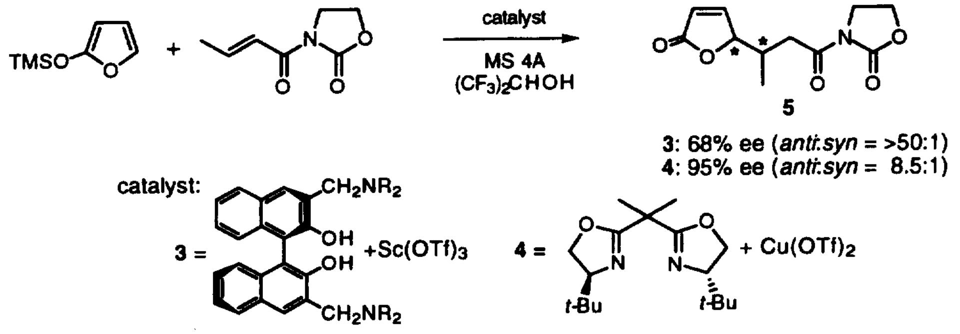
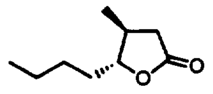
2. Results and discussion

It has been reported that 2-trimethylsilyloxyfurans react with various electrophiles including enoates, to give the corresponding C4-substituted butenolides.[3] This suggests that 2-trimethylsilyloxyfurans are good candidates for equivalents of **1**. Thus, we examined chiral Lewis acid promoted Michael additions of 2-trimethylsilyloxyfuran to oxazolidinone enoates and found that scandium–BINOL **3** or copper–bis(oxazoline) complex **4** serve as efficient catalysts for the present purpose.[4] Catalyst **3** shows high *anti*- and moderate enantioface selectivity, while complex **4** shows good *anti*- and high enantioface selectivity (Scheme 1). Advantages of using 2-trimethylsilyloxyfurans as nucleophiles are twofold: (i) they directly provide an acylated hydroxy group which can be readily cleaved under hydrolytic or reductive conditions; (ii) the resulting butenolide moiety can be further functionalized in various ways. Recrystallization of the obtained Michael adduct **5** gave enantiopure *anti*-adduct *anti*-**5** as a single isomer.



Scheme 1.

To demonstrate the efficiency of the present reaction for the synthesis of γ-lactone derivatives, we examined the enantiospecific conversion of Michael adduct *anti*-**5** to *trans*-whisky lactone, (3*S*,4*R*)-3-methyloctan-4-olide **6**. *trans*-Whisky lactone is found along with *cis*-whisky lactone in many liquors such as whisky, brandy and wine stored in oak barrels, because they are extracted from the barrels while maturing.[5,6]



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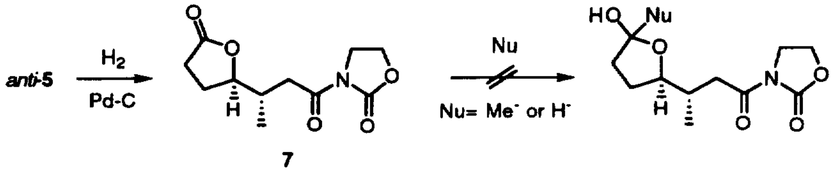
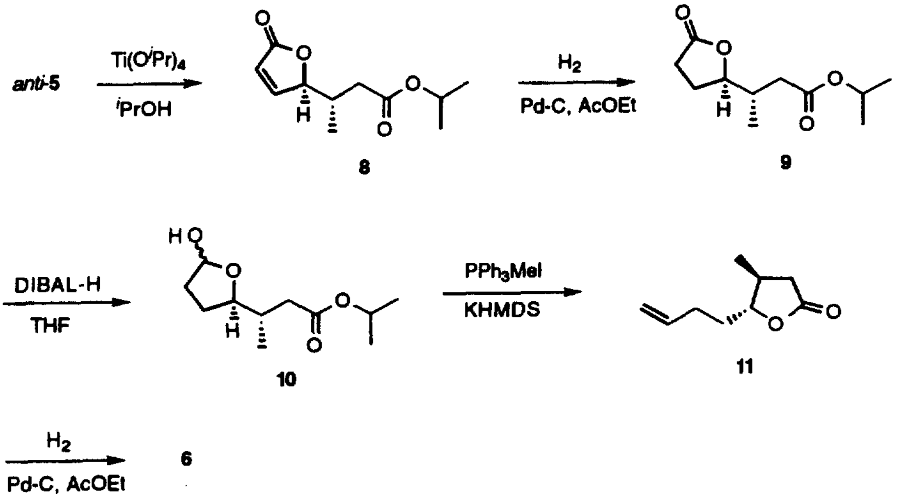
The necessary one-carbon elongation for the present conversion seemed to be executed by direct nucleophilic addition to saturated γ-lactone **7** or by its reduction and subsequent nucleophilic addition. Contrary to our expectation, treatment of compound **7** with methyllithium or with reducing agents such as lithium aluminum hydride or diisobutylaluminum hydride (DIBAL-H) gave complex mixtures, because the two functional groups (butenolide and imido groups) had similar reactivity toward these nucleophiles (Scheme 2). The reduction of *anti*-**5** with DIBAL-H also gave a complex mixture.



Scheme 2.

It is well known that esters are less reactive toward nucleophiles than lactones, due to the anomeric effect. Thus, we examined the selective conversion of the imido group to an acid or ester group but usual hydrolysis (LiOH or NaOH) or alcoholysis (K_2CO_3–MeOH) again gave complex mixtures. However, titanium alkoxide mediated alcoholysis[7] seemed to be a promising method for this conversion, because the imido group was expected to serve as a bidentate ligand and to coordinate to the titanium ion in preference to the lactone. As expected, treatment of *anti*-**5** with titanium tetraisopropoxide in 2-propanol selectively converted the imido group into the desired isopropyl ester **8** (Scheme 3), leaving the lactone group intact. The conversion of compound **8** into *trans*-whisky lactone **6** was completed in four steps. Compound **8** was hydrogenated in the presence of Pd/C to give γ-lactone **9**. DIBAL-H reduction of **9** in THF at −78°C occurred selectively at the lactone moiety, giving the corresponding lactol **10**, and the reduction of the isopropyl ester group was not observed under the present conditions. Lactol **10** was then subjected to Wittig reaction. The direct Wittig product, γ-hydroxy ester, was not isolated but it cyclized in situ to give γ-lactone **11** as a sole product. Hydrogenation of the terminal olefin in **11** in the presence of Pd/C gave *trans*-whisky lactone **6**. The specific rotation of **6** was $[\alpha]_D^{25}$ +82.1 (*c* 0.68, MeOH) [lit.[6h] $[\alpha]_D^{23}$ +79.5 (*c* 1.0, MeOH)].



Scheme 3.

In conclusion, we were able to show that the Michael addition products of 2-trimethylsiloxyfuran to enoates are useful synthetic precursors of γ-lactones by performing a short step synthesis of *trans*-whisky lactone. This demonstrates the high utility of the present asymmetric Michael reaction because various γ-lactone sub-structures exist in many natural products.

3. Experimental

All melting points are uncorrected. NMR spectra were recorded at 270 MHz on a JEOL EX-270 instrument. Signals are expressed as ppm downfield from tetramethylsilane used as an internal standard (δ value in $CDCl_3$) unless otherwise described. IR spectra were obtained with a SHIMADZU FTIR-8600 instrument. Optical rotation was measured with a JASCO DIP-360 automatic digital polarimeter. High resolution mass spectra (HRMS) were recorded on a JEOL JMS-SX/SX 102A instrument. Column chromatography was conducted on silica gel BW-820-MH, 70–200 mesh ASTM, available from Fuji

Silysia Chemical Ltd. Solvents were dried and distilled shortly before use. Reactions were carried out under an atmosphere of nitrogen or argon if necessary.

3.1. *3-[(3S,2′S)-3-(2′,5′-Dihydro-5′-oxo-2′-furyl)butanoyl]-1,3-oxazolidin-2-one* anti-*5*

The Michael reaction of 2-trimethylsilyloxyfuran and 3-crotonoyl-1,3-oxazolidin-2-one using catalyst **4** gave compound **5** of 95% ee together with a small amount of *syn*-isomer, according to the reported procedure.[4b] Crude **6** was recrystallized from hexane–AcOEt to give enantiomerically pure *anti*-**5** as a single isomer in 58% yield.

3.2. *(4S,5S)-6-Isopropoxycarbonyl-5-methyl-2-hexen-4-olide 8*

To a solution of *anti*-**5** (498 mg, 2.1 mmol) in *i*-PrOH (10 ml) was added titanium tetraisopropoxide (1.2 ml, 4.2 mmol) at room temperature. After being heated at 80°C for 2 h, the mixture was cooled to room temperature and quenched with 2 N HCl (10 ml). After vigorous stirring for 1 h, the mixture was extracted with ethyl acetate. The extract was dried over anhydrous $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (hexane:AcOEt=7:3) to afford unsaturated γ-lactone **8** (424 mg, 96% yield) as a colorless oil. $[\alpha]_D^{26}$ +23.3 (*c* 0.38, $CHCl_3$); ^1H NMR (270 MHz): δ 7.49 (dd, *J*=1.6 and 5.9 Hz, 1H), 6.15 (dd, *J*=2.3 and 5.9 Hz, 1H), 4.96–5.05 (m, 2H), 2.41 (dd, *J*=5.3 and 17.1 Hz, 1H), 2.45–2.40 (m, 1H), 2.21 (dd, *J*=9.2 and 17.1 Hz, 1H), 1.24 (d, *J*=6.3 Hz, 3H), 1.23 (d, *J*=6.3 Hz, 3H), 1.10 (d, *J*=6.6 Hz, 3H); IR (neat): 2979, 2937, 1755, 1728, 1375, 1263, 1165, 1107, 993, 968, 822 cm^{-1}. Found: C, 62.30; H, 7.63%. Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60%.

3.3. *(4R,5S)-6-Isopropoxycarbonyl-5-methylhexan-4-olide 9*

A solution of lactone **8** (400 mg 1.9 mmol) in AcOEt (20 ml) containing 10% Pd–C (80 mg) was stirred under H_2 (1 atm) at room temperature overnight. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated under reduced pressure to afford γ-lactone **9** (382 mg, 95% yield) as a colorless oil. $[\alpha]_D^{26}$ −31.2 (*c* 1.23, $CHCl_3$); ^1H NMR (270 MHz): δ 5.03 (hept, *J*=6.3 Hz, 1H), 4.29 (dt, *J*=6.3 and 8.3 Hz, 1H), 2.66–2.52 (m, 3H), 2.36–2.14 (m, 3H), 1.99–1.84 (m, 1H), 1.24 (d, *J*=6.3 Hz, 6H), 0.99 (d, *J*=6.6 Hz, 3H); IR (neat): 2980, 2937, 1778, 1728, 1460, 1421, 1375, 1265, 1184, 1109, 1022, 972, 916 cm^{-1}. Found: C, 61.67; H, 8.46%. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47%.

3.4. *(3S,4R)-3-Methyl-7-octen-4-olide 11*

To a solution of γ-lactone **9** (352 mg, 1.6 mmol) in THF (8 ml) was added diisobutylaluminum hydride (1.76 ml, 0.93 mol dm^{-3} in hexane) at −78°C. After being stirred for 2 h, the mixture was quenched with MeOH and gradually raised to room temperature. To the mixture was added saturated aqueous potassium sodium tartrate (2 ml). After vigorous stirring for 1 h, the organic layer was removed and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane:AcOEt=7:3) afforded lactol **10** (332 mg, 94% yield), which was immediately used for the next reaction.

To a suspension of methyltriphenylphosphonium iodide (185 mg, 0.46 mmol) in THF (4.5 ml) and HMPA (0.5 ml) was added potassium hexamethyldisilazide (0.85 ml, 0.5 mol dm^{-3} in toluene) at room temperature. After being stirred for 10 min, the yellow solution was cooled to −78°C and to this solution was added the above lactol **10** (71 mg, 0.33 mmol) in THF (1.0 ml). The reaction mixture was allowed to warm to room temperature and quenched with saturated aqueous NH_4Cl. The organic layer was removed and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (hexane:AcOEt=8:2) to afford γ-lactone **11** (37 mg, 73% yield). $[\alpha]_D^{26}$ +69.6 (*c* 0.71, $CHCl_3$); ^1H NMR (270 MHz): δ 5.81 (ddt, *J*=6.6, 10.2 and 16.8 Hz, 1H), 5.05 (dd, *J*=1.3 and 16.8 Hz, 1H), 5.01 (dd, *J*=1.3 and 10.2 Hz, 1H), 4.03 (dt, *J*=4.0 and 7.6 Hz, 1H), 2.74–2.61 (m, 1H), 2.34–2.13 (m, 4H), 1.82–1.58 (m, 2H), 1.13 (d, *J*=6.3, 3H); IR (neat): 2980, 2937, 1778, 1728, 1460, 1421, 1375, 1246, 1209, 1171, 993, 937, 916 cm^{-1}. Found: C, 70.48; H, 9.34%. Calcd for $C_9H_{14}O_2$: C, 70.09; H, 9.15%.

3.5. trans-*Whisky lactone 6*

A solution of γ-lactone **10** (30 mg 0.19 mmol) in AcOEt (3 ml) containing 10% Pd–C (8 mg) was stirred under H_2 (1 atm) at room temperature overnight. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to afford *trans*-whisky lactone **6** (28 mg, 93% yield) as a colorless oil. $[\alpha]_D^{26}$ +82.1 (*c* 0.68, $CHCl_3$). Its spectroscopic data (^1H NMR and IR) were the same as the reported ones in all respects.[6h]

Acknowledgements

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