Enantioselective Synthesis of *trans*-Whisky Lactone by Using Newly Developed Asymmetric Ring Expansion Reaction of Oxetane as a Key Step

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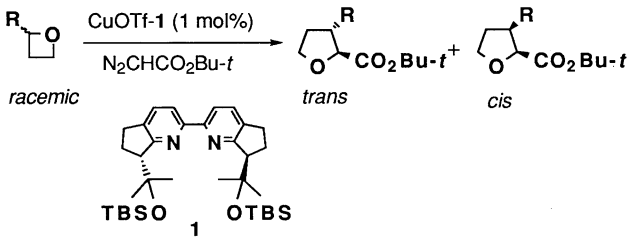
A mixture of optically active 3-substituted *cis*- and *trans*-tetrahydrofuran-2-carboxylates which was prepared in one step from readily available (±)-2-alkynyloxetane, was converted into *trans*-whisky lactone (**2**) in a straightforward manner.

Recently we developed a highly enantiospecific ring expansion of oxetanes catalyzed by chiral bipyridine (**1**)-copper complex (Scheme 1).[1] Since various oxetanes are readily available from 1,3-diols, this methodology provides a new entry to the synthesis of optically active tetrahydrofurans. To explore the utility of this reaction in the synthesis of natural products, we examined the enantioselective synthesis of *trans*-whisky lactone (**2**) by using the ring expansion reaction as a key step.

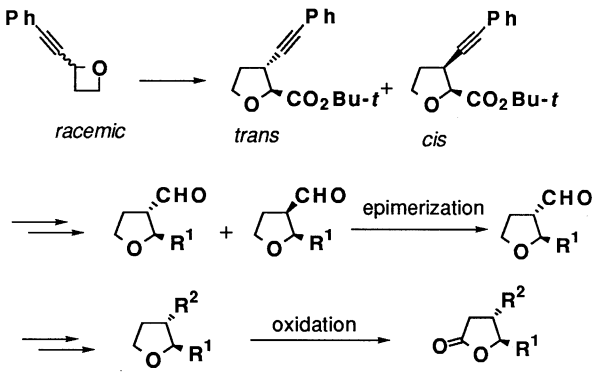


Scheme 1.

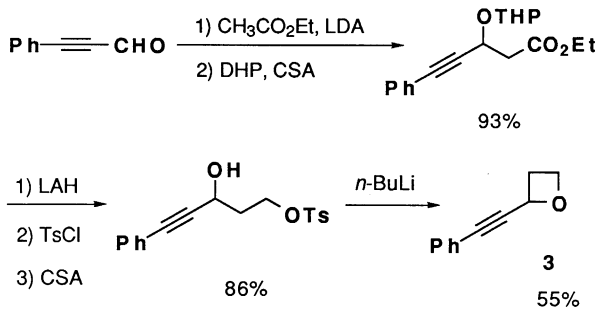
It has already been demonstrated that the reactions of (*R*)- and (*S*)-2-substituted oxetanes with diazoacetate in the presence of catalyst **1** provide respective (2*S*,3*S*)-*cis*- and (2*S*,3*R*)-*trans*-tetrahydrofuran-2-carboxylates enantiospecifically.[1] Therefore the reaction of (±)-2-substituted oxetane gives a mixture of *trans*- and *cis*-tetrahydrofuran-2-carboxylate derivatives which are diastereomeric at C3-carbon. Accordingly, if the desired sense of epimerization at C3 is possible at an appropriate stage, (±)-oxetane is readily converted into optically active 2,3-disubstituted tetrahydrofuran derivative which is amenable to further functionalization such as oxidation giving γ-lactone. Along this line, (±)-2-alkynyloxetane was subjected to asymmetric ring expansion reaction toward the synthesis of *trans*-whisky lactone (**2**), since alkynyl group was considered to be a chemical equivalent of aldehyde group (Scheme 2).

trans-Whisky lactone (**2**) is found along with *cis*-whisky lactone in whisky, brandy and wine stored in oak barrel, because they are extracted from the barrels under maturing.[2] Although several syntheses of optically active *trans*-whisky lactone have been reported, most of them used stoichiometric amount of chiral sources as starting materials or chiral auxiliaries,[3] except for a few examples.[4] Our synthesis of **2** started from (±)-2-(phenylethynyl)oxetane (**3**), which was prepared in 6 steps from propargyl aldehyde in a conventional manner (Scheme 3).

Treatment of **3** with equimolar amount of *t*-butyl diazoacetate in the presence of catalytic amount of Cu-**1** complex[1] at room temperature gave a 1:1 mixture of *trans*- and



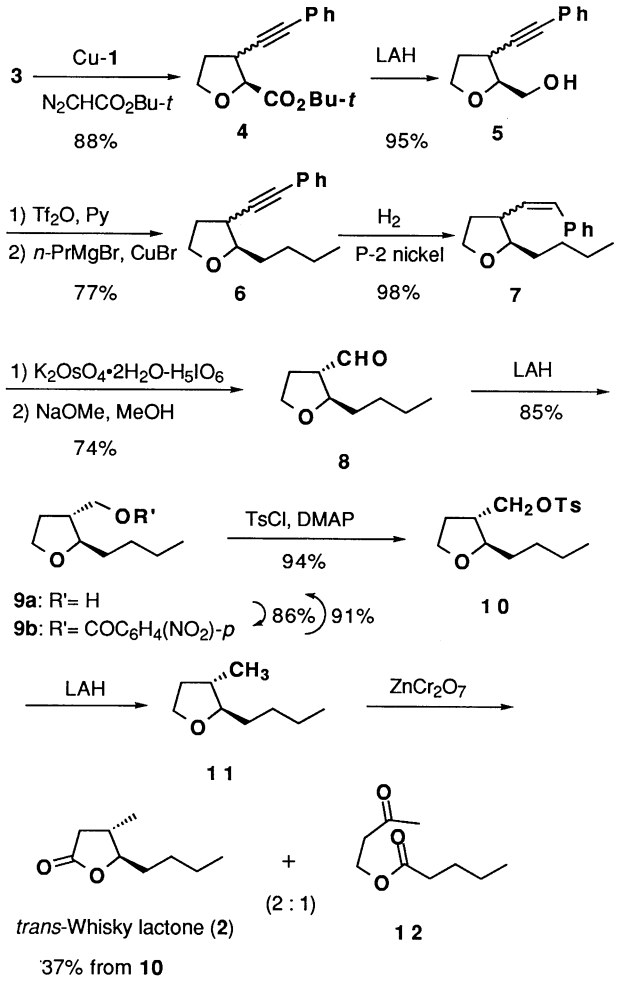
Scheme 2.



Scheme 3.

cis-t-butyl tetrahydrofuran-2-carboxylates (**4**, 75 and 71% ee, respectively[1b]), which were subjected to lithium aluminum hydride reduction (LAH) without separation to give alcohol **5** (Scheme 4). Three carbon extension was effected according to Kotsuki's procedure[5] (Tf_2O, pyridine, then CuBr, *n*-PrMgBr) to give compound **6**. Hydrogenation of **6** with P2-Ni[6] as a catalyst gave *cis*-olefin **7** exclusively (No *trans*-isomer was detected by ^1H NMR (270 MHz) analysis). Oxidative cleavage of double bond under modified Lemieux-Johnson conditions[7] (cat. K_2OsO_4, H_5IO_6) and subsequent epimerization at C-3 carbon with NaOMe gave preferentially *trans*-aldehyde **8** (*trans* : *cis* = 95 : 5) which was used for the next reaction without separation. In this procedure, no epimerization due to β-alkoxy elimination was detected. LAH reduction of aldehyde **8** followed by *p*-nitrobenzoylation afforded **9b**. The optical purity of **9b** was determined to be 73% ee by HPLC analysis using DAICEL (Chiralcel, OJ). This compound **9b** was subjected to recrystallization from hexane at -20 °C. The resulting crystals showed the reduced optical purity of 49% ee, but **9b** obtained from the filtrate showed the considerably improved optical purity of 89% ee. This procedure was repeated and **9b** of 98% ee was obtained in 33% yield. This material was used for the next

reaction. Reductive cleavage of *p*-nitrobenzoyl group with LAH, followed by tosylation of the resulting alcohol afforded tosylate **10**. Reduction of **10** with LAH gave **11**. The RuO_4 oxidation of **11** with aqueous $NaIO_4$ as a terminal oxidant gave no desired γ-lactone but 4-ketocarboxylic acid exclusively. However, the oxidation with $ZnCr_2O_7$[8] gave **2** preferentially, which was separated from the undesired side product **12** and a trace amount of *cis*-whisky lactone by gel permeation chromatography. Compound **2** gave the satisfactory spectroscopic data which were identical with that reported by Ebata *et al.*[3j] The specific rotation of **2** was $[\alpha]_D^{25}$ +81.8° (*c* 0.41, MeOH) [Lit.[3j] $[\alpha]_D^{23}$ +79.5° (*c* 1.0, MeOH)]. The minor side product **12** was considered to be generated by the sequence, i) oxidation of α-methine carbon, ii) dehydration, and iii) oxidative cleavage of the resulting double bond.



Scheme 4.

In summary, we have accomplished enantioselective synthesis of *trans*-whisky lactone by using the newly developed asymmetric ring expansion as a key step. This result demonstrates the utility of this reaction in organic synthesis.

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References and Notes

† Research Fellow of the Japan Society for the Promotion of Science.

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