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Diastereoselective Synthesis of 2,5-Substituted Tetrahydrofurans by Intramolecular Alkylation of an Ester Enolate

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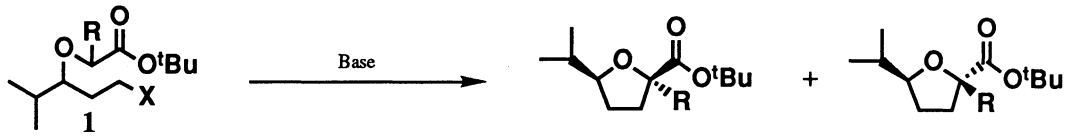
Highly diastereoselective cyclization is carried out by the intramolecular alkylation of an ester enolate of *t*-butyl α-alkoxyacetates. The addition of lithium salt enhances the diastereoselectivity of the reaction to afford 2,2,5-trisubstituted tetrahydrofurans.

The synthesis of polyether antibiotics and other complex targets containing oxacyclic subunits still requires easier preparative methods for the stereocontrolled construction of oxacyclic compounds. Although many syntheses of 2,5-substituted tetrahydrofurans were reported,[1] a satisfactory method of stereochemical control has been reported only concerning a carbon-oxygen bond formation. For example, a cyclization of an epoxy alcohol derived from an unsaturated ketone has been demonstrated to yield 2,5-substituted tetrahydrofuran.[2] A conceptually different approach to such oxacyclic systems by a carbon-oxygen bond formation has been developed, which involves electrophilic cyclization of an unsaturated alcohol using iodine.[3] In addition, it has been demonstrated that ring contraction of 2-alkyl-5-bromotetrahydropyrans can be used to prepare 2,5-substituted tetrahydrofurans exploiting a carbon-oxygen bond formation reaction.[4] On the other hand, synthesis of tetrahydrofuran derivatives achieved by a carbon-carbon bond formation has been reported, which includes the insertion of carbenes obtained from diazocarbonyl compounds into inactivated aliphatic carbon-hydrogen bonds.[5,6] Here we wish to report a novel route using a carbon-carbon bond formation by intramolecular alkylation of an ester enolate of α-alkoxyacetate derivatives.

The substrates of *t*-butyl ester of 2-(3-substituted propyloxy)acetic acid derivatives (**1**) were prepared by coupling 1,3-diol derivative[7] with the corresponding α-halocarboxylic acid followed by esterification with isobutene and the substitution of the leaving group at the terminal branches.[8] When *t*-butyl (4-methyl-1-tosyloxypentane-3-yloxy)acetate (**1a**) was treated with 1 equiv. of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78 - 0 °C for 5 h, the corresponding cyclization product was obtained in 58% yield, but the diastereoselectivity was not sufficiently high (*cis* : *trans* = 2 : 1). As listed in Table 1, several substrates and conditions were examined to improve the diastereoselectivity, and introduction of a methyl group at the α-position of the ester was found to enhance the diastereoselectivity (entries 1-3 vs. 4-16). Furthermore, the



a : R = H, X = OTs **b** : R = H, X = I **c** : R = Me, X = OTs *cis* -**2** *trans* -**2**

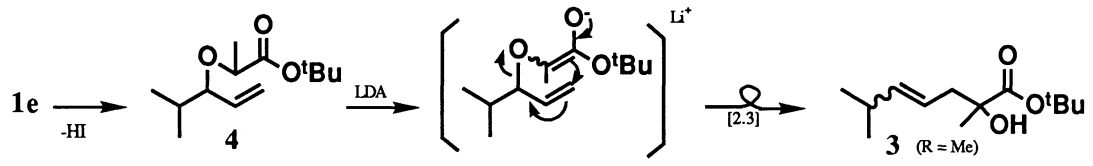
d : R = Me, X = Br **e** : R = Me, X = I

Table 1. Cyclization of ester enolate of *t*-butyl alkoxyacetates

Entry	Substrate	Base (equiv.)	Solvent	Additive (equiv.)	Temp/°C	Yield of **2**/%	*cis* : *trans*
1	**1a**	LDA (1)	THF		-78 - 0	58	67 : 33[c]
2	**1b**	LDA (1)	THF		-78 - 0	59	67 : 33[c]
3	**1b**	LDA (1)	THF-DMPU[a]		-78	62	67 : 33[c]
4	**1c**	LDA (3)	THF		-78 - 0	62	86 : 14
5	**1c**	LDA (3)	THF-HMPA[a]		-78 - 0	64	73 : 27
6	**1d**	LDA (3)	THF		-78 - 0	85	72 : 28
7	**1d**	LDA (3)	THF-HMPA[a]		-78 - 0	70	74 : 26
8	**1e**	LDA (3)	THF		-78 - 0	47 (10)[b]	75 : 25
9	**1e**	KHMDS (3)	THF		-78 - 0	10 (79)[b]	
10	**1e**	LDA (3)	THF-HMPA[a]		-78 - 0	49 (12)[b]	97 : 3
11	**1e**	LDA (3)	THF-DMPU[a]		-78	65	93 : 7
12	**1e**	LDA (1.5)	THF-HMPA[a]		-78 - 0	42 (15)[b]	52 : 48
13	**1e**	LDA (1.5)	THF-HMPA[a]	LiI(3)	-78 - 0	49 (39)[b]	92 : 8
14	**1e**	LDA (1.5)	THF-DMPU[a]	LiI(3)	-78	80	94 : 6
15	**1e**	LDA (1.5)	THF	LiCl(3)	-78	70	26 : 74
16	**1d**	LDA (1.5)	THF	LiCl(3)	-78	90	28 : 72

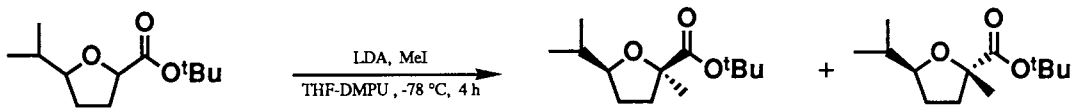
a) The ratio of THF:cosolvent is 4 : 1. b) Parentheses show the yield of **3**. c) The ratios were determined by ^{1}H-NMR analyses.

diastereoselectivity was improved when the iodide **1e** was chosen as substrate, and when the reaction was carried out in a mixture of THF and hexamethylphosphoric triamide (HMPA) (entries 4-8, and 10). *t*-Butyl 2-hydroxy-2,6-dimethyl-4-heptenate (**3**, R=Me), however, was simultaneously obtained as a by-product resulting from the elimination of hydrogen iodide to afford *t*-butyl 2-(4-methylpent-1-en-3-yloxy)propionate (**4**) followed by the [2.3]-Wittig rearrangement of the lithium enolate of **4** (entries 8 and 10). When N,N'-dimethylpropyleneurea (DMPU)[9] was used instead of HMPA as a cosolvent and the reaction mixture was kept at -78 °C, no formation of **3** was observed (entry 11). As for the bases used, LDA was superior to other bases, such as potassium hexamethyldisilazide (KHMDS)[10] (entry 8 vs. 9). It is noteworthy that a decrease of stereoselectivity was observed when 1.5 equiv. of LDA was used (entry 12). The addition of an excess lithium salt,[11] especially lithium iodide, however, was effective to enhance the stereoselectivity (entries 13 and 14). Interestingly, in the reaction of *t*-butyl 2-(1-iodo-4-methylpentane-3-yloxy)propionate (**1e**) in the presence of an excess lithium cation derived from lithium chloride in a THF solution at -78 °C, *trans*-**2** (R=Me) was obtained in a ratio of 74 : 26 in



70% yield (entry 15). In this case dehydroiodination product **4** was obtained in 15% yield. In order to suppress the elimination, the bromide **1d** was used as a substrate, to afford *trans*-**2** (R=Me) in a ratio of 72 : 28 in 90% yield (entry 16).

On the other hand, the methylation of enolate of *t*-butyl 5-isopropyltetrahydro-furan-2-carboxylate (2, R=H) with methyl iodide afforded *trans*-**2** (R=Me) in a ratio of 64 : 36 in 72% yield.



2 (R = H) *cis* -**2** (R = Me) *trans* -**2** (R = Me)

A typical reaction procedure for the preparation of *t*-butyl 2-methyl-5-isopropyltetrahydrofuran-2-carboxylate (**2**, R=Me) is as follows: To a THF (5 ml) solution of LiI (1.5 mmol) was added diisopropylamine (0.75 mmol) under an argon atmosphere at rt, and the mixture was cooled to 0 °C. Then butyllithium (0.75 mmol in hexane) was added, and the solution was stirred at the same temperature for 30 min followed by the addition of DMPU (2 ml). After cooling to -78 °C, a THF (3 ml) solution of *t*-butyl 2-(1-iodo-4-methylpentane-3-yloxy)propionate (**1e**) (0.5 mmol) was added to the mixture. Then stirring was continued for 5 h at -78 °C, and the reaction was quenched by addition of sat. aqueous NH_4Cl. Extraction with ethyl acetate and purification by silica-gel column chromatography (AcOEt-Hexane) gave *t*-butyl *cis*-**2**-methyl-5-isopropyltetrahydrofuran-2-carboxylate (**2**, R=Me) and the *trans*-isomer (total yield 80%) in a ratio of 96 : 4. *Cis*-**2** (R=Me)[12] ^{1}H-NMR (CCl_4) δ 3.86 - 3.52 (1H, m), 2.53 - 1.52 (5H, m), 1.47 (9H, s), 1.33 (3H, s), 0.96 (3H, d, J = 7 Hz), 0.82 (3H, d, J = 7 Hz); IR (film) 2980, 2880, 1735, 1375, 1160, 1130 cm^{-1}. The diastereomeric ratio was determined by capillary GLC analysis (Column, SE-30 50m; Temp, 150 °C).

In this way, the present method employing a carbon-carbon bond formation by intramolecular alkylation of an ester enolate provides a new stereoselective approach for constructing 2,2,5-trisubstituted tetrahydrofurans.

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8) General procedure for the preparation of *t*-butyl α-alkoxyacetates: 1-Benzyloxy-4-methyl-3-pentanol was condensed with chloroacetic acid using excess sodium hydride in THF (reflux, overnight). Then the crude product was esterified with isobutene (H^+, CH_2Cl_2, rt, 3 h). Deprotection of benzyl ether of *t*-butyl (1-benzyloxy-4-methylpentane-3-yloxy)acetate was achieved by hydrogenolysis (H_2, 10% Pd-C, EtOH, rt, 4 h). Finally, tosylation with *p*-toluenesulfonyl chloride in the presence of Et_3N (CH_2Cl_2, rt, 5 h) gave *t*-butyl (4-methyl-1-tosyloxypentane-3-yloxy)acetate (**1a**) in 40 - 50% overall yield; ^{1}H-NMR (CCl_4) δ 7.79 (2H, d, J = 8 Hz), 7.32 (2H, d, J = 8 Hz), 4.51 - 4.00 (2H, m), 3.84 (2H, s), 3.49 - 3.05 (1H, m), 2.45 (3H, s), 2.05 - 1.70 (3H, m), 1.43 (9H, s) and 0.90 (6H, d, J = 7 Hz); IR (film) 2970, 2930, 1750, 1370, 1180 cm^{-1}. Other esters were prepared by a similar method, *i.e.*, the corresponding bromide was obtained by the reaction of the tosylate with lithium bromide (DMF, rt, 1 h, 95%), and the iodide by the treatment of the corresponding tosylate with sodium iodide (Me(Et)C=O, rt, 5 h, 90%): **1b** ^{1}H-NMR (CCl_4) δ 3.93 (2H, s), 3.58 - 3.00 (3H, m), 2.14 - 1.68 (3H, m), 1.46 (9H, s), 0.91 (6H, d, J = 6.5 Hz); IR (film) 2970, 2930, 1750, 1370, 1230,1160, 1130 cm^{-1}: **1c** ^{1}H-NMR (CCl_4) δ 7.77 (2H, d, J = 8 Hz), 7.35 (2H, d, J = 8 Hz), 4.23 (2H, t, J = 7 Hz), 4.00 - 3.60 (1H, m), 3.40 - 3.02 (1H, m), 2.47 (3H, s), 2.10 - 1.56 (3H, m), 1.42 (9H, s), 1.27 (3H, d, J = 7 Hz), 0.85 (6H, d, J = 7 Hz); IR (film) 2960, 2920, 1750, 1370, 1180 cm^{-1}: **1d** ^{1}H-NMR (CCl_4) δ 4.10 - 3.07 (4H, m), 2.21 - 1.75 (3H, m), 1.46 (9H, s), 1.28 (3H, d, J = 7 Hz), 0.88 (6H, d, J = 7 Hz); IR (film) 2970, 2930, 1750, 1370, 1240 cm^{-1}: **1e** ^{1}H-NMR (CCl_4) δ 3.81 (1H, q, J = 6 Hz), 3.36 - 3.05 (3H, m), 2.09 - 1.58 (3H, m), 1.43 (9H, s), 1.29 (3H, d, J = 6 Hz), 0.91 (6H, d, J = 7 Hz); IR (film) 2970, 2920, 1750, 1370, 1220, 1160, 1130 cm^{-1}.

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