Diastereoselective Construction of 2,2,6-Trisubstituted Tetrahydropyrans by Intramolecular Alkylation Reaction of Lithium Enolates Generated from α-Alkoxy Carboxylates

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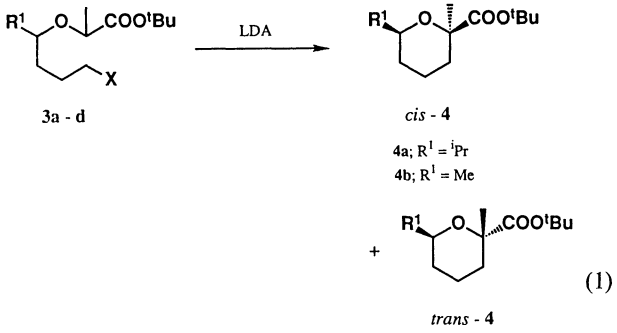
Synopsis. The intramolecular alkylation reaction of enolates of *t*-butyl α-alkoxy carboxylates in THF–HMPA proceeded stereoselectively to afford 2,2,6-trisubstituted tetrahydropyrans with high cis-selectivity.

Concerning stereoselective construction of oxacyclic compounds, the intramolecular alkylation reaction of lithium enolates of α-alkoxy carboxylic acid esters has been recently reported from our laboratory to give the corresponding 2,2,5-trisubstituted tetrahydrofurans with high stereoselectivity.[1] This concept was successively applied to the diastereoselective ring formation of tetrahydropyrans. Although the prevalence of the tetrahydropyrans subunits in numerous polyether and ionophore natural products has prompted the development of many methods for the stereoselective preparation of tetrahydropyrans via carbon–oxygen bond formations,[2] the stereoselective ring formation of tetrahydropyrans via cabon–carbon bond formation has been scarcely reported because of its difficulty from polycyclization process.[3] Thus, the novel route for the construction of tetrahydropyrans via stereoselective intramolecular alkylation reaction of lithium enolates of α-alkoxy carboxylic acid esters was examined.

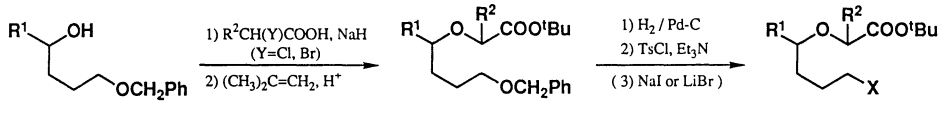
The substrates for the cyclization were prepared by the following scheme: The substitution reaction of α-halo acid by sodium alkoxides of δ-benzyloxy alcohols **1**, followed by esterification, gave α-alkoxy carboxylic acid esters **2**. Hydrogenolysis of benzyl group in **2** and the transformation of the resulted hydroxyl group into the leaving group gave the precursors **3** for the cyclization reaction.

Firstly the cyclization of the α-alkoxy carboxylic acid esters **3a** possessing iodine as a leaving group was examined. The ester **3a** was treated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −20 °C and the mixture was allowed to be warmed to room temperature. However, the cyclized tetrahyropyran **4** was disappointedly not obtained and the olefinic product resulted from elimination of hydrogen iodide was obtained as a main product. On the other hand, utilizing α-alkoxy carboxylic acid ester **3b** with tosyloxy group instead of iodine as a leaving group, the cyclized tetrahydropyrans, *t*-butyl ester of *cis*- and *trans*-2-methyl-5-isopropyl-2-tetrahydropyrancarboxylate (**4a**),[4] were able to be obtained in totally 21% yield. By the analysis of capillary gas chromatography, *cis*-isomer was predominantly formed in a ratio of 81 : 19 (Entry 1). When the reaction was carried out in a 4 : 1 mixture of THF and hexamethylphosphoric triamide (HMPA), it was found that the stereoselectivity was dramatically enhanced and only *cis*-**4a** was obtained in 54% yield (Entry 2). It appeared that the alkylation reaction using ω-bromo carboxylic acid ester **3c** also gave tetrahydropyrans, but the stereoselectivity was lower than the case of ω-tosyloxy ester **3b** (Entry 3). Furthermore, the cyclization of α-alkoxy carboxylic acid ester **3d** in THF-HMPA also proceeded stereoselectively to afford *cis*-**4b** in a ratio of 91 : 9 (Entry 4).



(1)

In addition to the cyclization reaction of α-alkoxy carboxylic acid esters to 2,2,6-trisubstituted tetrahydropyrans, the substitution reaction of the cyclized 2,6-disubstituted tetrahydropyran was examined. The treatment of lithium enolate generated from 2,6-disubstituted tetrahydropyran **5** with methyl iodide in THF–HMPA, gave *trans*-**4a** mainly (*cis* : *trans*=29 : 71).



1 2 3

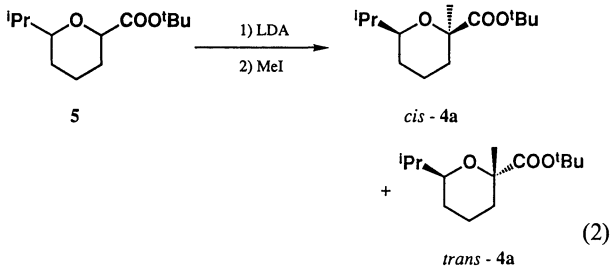
3a; R^1 = ^{i}Pr, R^2 = Me, X = I
3b; R^1 = ^{i}Pr, R^2 = Me, X = OTs
3c; R^1 = ^{i}Pr, R^2 = Me, X = Br
3d; R^1 = Me, R^2 = Me, X = OTs
3e; R^1 = ^{i}Pr, R^2 = H , X = OTs

Scheme 1.

Table 1. Cyclization of Ester Enolates of *t*-Butyl α-Alkoxy Carboxylates **3**

Entry	R^1	R^2	X	Solvent	Temp/°C	*T*/h	Yield/%	*cis*:*trans*[a]
1	*i*Pr	Me	OTs (**3b**)	THF	−20—r.t.	15	21	81: 19
2	*i*Pr	Me	OTs (**3b**)	THF-HMPA	−20—r.t.	19	54	>99:<1
3	*i*Pr	Me	Br (**3c**)	THF-HMPA	−60	4	57	81: 19
4	Me	Me	OTs (**3d**)	THF-HMPA	−20—r.t.	11	40	91: 9

a) The ratios were determined by capillary GLC (SE-30). *cis*: *c*-6-alkyl-*r*-2-ester; *trans*: *t*-6-alkyl-*r*-2-ester.



(2)

The stereochemistry of *cis*-**4a** was determined by the measurement of its ^1H–^1H NOE experiments in which irradiation of C_2-methyl substituent resulted in a 31% enhancement of the H_6 signal. The tetrahydropyrans *cis*-**4b** and *trans*-**4b** were converted to the corresponding tetrahydropyran-2-methanols **6** by the reduction with $LiAlH_4$, respectively, and the data of ^{13}C NMR spectra of *cis*- and *trans*-**6** were identical with that reported.[5]

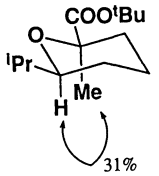
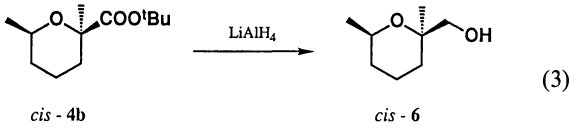


Fig. 1.



(3)

Thus, the intramolecular alkylation reaction of enolates of α-alkoxy carboxylates in THF–HMPA proceeded stereoselectively to afford 2,2,6-trisubstituted tetrahydropyrans with high *cis*-selectivity. It is possible to yield optically active tetrahydropyran derivatives by the use of a chiral alkoxy ester which is easily derived from easily available both enantiomers of δ-hydroxy ester.[6]

Experimental

The IR spectra were measured on a JASCO IR-810 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a JEOL JNX-PMX 60si spectrometer and a Hitachi R-90H spectrometer with tetramethylsilane as an internal standard. The NOE spectrum was measured on a JEOL GX-400 spectrometer. The MS spectra were taken on a JMS-DX303 spectrometer and a JMS-SX102A spectrometer. All experiments were carried out under an argon atmosphere unless otherwise noted.

6-Benzyloxy-2-methyl-3-hexanol (1) (R^1=*i*Pr): To a suspension of magnesium metal 1.7 g (70 mg atm) in THF (40 ml) was added in a THF (20 ml) solution of 1-benzyloxy-3-bromopropane 13.6 g (59 mmol) for 40 min and the mixture was heated under reflux for 1 h. This Grignard reagent was added dropwise to a solution of isobutyraldehyde 4.3 g (60 mmol) in THF (25 ml) at −78 °C, and the reaction mixture was allowed to be warmed to room temperature for 4 h. The reaction was quenched by sat. aq NH_4Cl and extracted with AcOEt. The combined extracts were dried over Na_2SO_4, and evaporated under reduced pressure. Purification of the residue by silica-gel column chromatography [hexane–AcOEt=2 : 1 (v/v) as an eluent] gave alcohol **1** (R^1=*i*Pr) (9.1 g, 68%). IR (KBr) 3420, 3020, 2940, 1460, 1380, 1100 cm^{-1}; ^1H NMR (CCl_4) δ=7.23 (5H, s), 4.44 (2H, s), 3.43 (3H, m), 2.17 (1H, br s), 1.53 (5H, m), 0.87 (6H, d, *J*=6 Hz). Found: *m*/*z* 223.1706. Calcd for $C_{14}H_{23}O_2$: M+H, 223.1698.

***t*-Butyl 2-[(4-Benzyloxy-1-isopropylbutyl)oxy]propionate (2)** (R^1=*i*Pr, R^2=Me): To a suspension of NaH 7.2 g (300 mmol) in THF (110 ml) was added a THF (30 ml) solution of 6-benzyloxy-2-methyl-3-hexanol 6.7 g (30 mmol) and, after the evolution of hydrogen, a THF (10 ml) solution of 2-bromopropionic acid 9.1 g (60 mmol). The reaction mixture was heated under reflux for 6 h and cooled to 0 °C. After quenching the reaction by the addition of H_2O, the aqueous layer was washed with Et_2O and the ethereal wash was discarded. The aqueous layer was acidified to pH 3 with 2 equiv HCl and extracted with Et_2O. The combined ethereal extracts were washed with brine, dried over Na_2SO_4. and evaporated in vacuo to give 9.6 g (quant.) of 2-[(4-benzyloxy-1-isopropylbutyl)oxy]propionic acid. Next, in a sealed bottle 2-methyl-1-propene 5.0 g (88 mmol), a CH_2Cl_2 (18 ml) solution of the acid 6.7 g (30 mmol) and 5 drops of concd H_2SO_4 was added, and the mixture was vigorously stirred for 12 h at room temperature. To the reaction mixture was added triethylamine (2 ml) and H_2O, and the mixture was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel [hexane–AcOEt=3 : 1 (v/v) as an eluent] provided 6.8 g (95%) of the corresponding *t*-butyl ester. IR (KBr) 3025, 2975, 1740, 1455, 1365, 1110 cm^{-1}; ^1H NMR (CCl_4) δ=7.21 (5H, s), 4.41 (2H, s), 3.80 (1H, q, *J*=7 Hz), 3.50—2.90 (3H, m), 2.12—1.45 (5H, m), 1.42 (9H, s), 1.25 (3H, d, *J*=6 Hz), 0.88 (6H, d, *J*=7 Hz). Found: *m*/*z* 351.2496. Calcd for $C_{21}H_{35}O_4$ M+H, 351.2535.

***t*-Butyl 2-[(4-Hydroxy-1-isopropylbutyl)oxy]propionate:** Under hydrogen atmosphere, 10% Pd–C (200 mg) was added to an EtOH (10 ml) solution of ester **2** (R^1=*i*Pr, R^2=Me) 2.0 g (5.6 mmol) and the mixture was vigorously stirred overnight. The catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was purified by silica-gel column chromatography [hexane–AcOEt=2 : 1 (v/v) as an eluent] to give 1.2 g (79%) of the desired alcohol. IR (KBr) 3500, 2930, 1740, 1400, 1120 cm^{-1}; ^1H NMR (CCl_4) δ=3.87 (1H, q, *J*=7 Hz), 3.41—2.90 (3H, m), 2.03 (1H, br s), 1.83—1.45 (5H, m), 1.42 (9H, s), 1.27 (3H, d, *J*=7 Hz), 0.88 (6H, d, *J*=7 Hz). Found: *m*/*z* 261.2058. Calcd for $C_{14}H_{29}O_4$: M+H, 261.2065.

***t*-Butyl 2-[(4-Tosyloxy-1-isopropylbutyl)oxy]propionate (3b):** To a solution of *t*-butyl 2-[(4-hydroxy-1-isopropylbutyl)-oxy]propionate 820 mg (3.1 mmol) in CH_2Cl_2 (15 ml) was added *p*-tosyl chloride 715 mg (3.8 mmol) and triethylamine 1.5 ml (11 mmol) and the mixture was stirred overnight. The

reaction was quenched by the addition of H_2O and the product was extracted with AcOEt. The combined organic layers were washed with 2 equiv HCl, brine and dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel [hexane–AcOEt=5 : 1 (v/v) as an eluent] to yield 1.1 g (85%) of the tosylate **3b**. IR (KBr) 3025, 2930, 1740, 1370, 1120 cm^{-1}; ^1H NMR (CCl_4) δ=7.67 (2H, d, J=8 Hz), 7.23 (2H, d, J=8 Hz), 4.21—3.55 (3H, m), 3.21—2.90 (1H, m) 2.43 (3H, s), 2.03—1.50 (5H, m), 1.42 (9H, s), 1.23 (3H, d, J=7 Hz), 0.83 (6H, d, J=7 Hz). Found: m/z 437.1959. Calcd for $C_{21}H_{34}O_6SNa$: M+Na,, 437.1974.

Tosylates **3d** and **3e** were also prepared by the same procedure. The spectral data are shown below.

***t*-Butyl 2-[(4-Tosyloxy-1-methylbutyl)oxy]propionate (3d):** IR (KBr) 3000, 2950, 1750, 1375, 1190 cm^{-1}; ^1H NMR (CCl_4) δ=7.75 (2H, d, J=8 Hz), 7.29 (2H, d, J=8 Hz), 4.07—3.33 (4H, m), 2.45 (3H, s), 2.03—1.20 (4H, m), 1.43 (9H, s), 1.31 (3H, dd, J=8.8 Hz), 1.08 (3H, dd, J=7.7 Hz).

***t*-Butyl 2-[(4-Tosyloxy-1-isopropylbutyl)oxy]acetate (3e):** IR (KBr) 3000, 2950, 1750, 1375, 1190 cm^{-1}; ^1H NMR (CCl_4) δ=7.73 (2H, d, J=8 Hz), 7.27 (2H, d, J=8 Hz), 4.02, (2H, t, J=6 Hz), 3.78 (2H, s), 3.20—2.93 (1H, m), 2.37 (3H, s), 1.96—1.20 (5H, m), 1.42 (9H, s), 0.85 (6H, dd, J=7.7 Hz). Found: m/z 423.1838. Calcd for $C_{20}H_{32}O_6SNa$: M+Na,, 423.1817.

Stereoselective Cyclization Reaction of α-Alkoxy Carboxylic Acid Ester 3b in THF–HMPA (Entry 2): To a THF (8 ml) solution of diisopropylamine 153 mg (1.5 mmol) was added butyllithium (1.5 mmol in hexane) at −20 °C, and the solution was stirred for 30 min at the same temperature. A solution of **3b** 207 mg (0.5 mmol) in HMPA (2 ml) was added slowly and the reaction mixture was allowed to be warmed to r.t. for 2 h, followed by being stirred for 17 h at r.t. The reaction was quenched by sat. aq NH_4Cl, and extracted with Et_2O. The extracts were washed with H_2O and brine, dried over Na_2SO_4, and evaporated under reduced pressure. Purification by TLC on silica gel [hexane–Et_2O=5 : 1 (v/v) as an eluent] gave the cyclization product **4a** in 54% yield (66 mg). From the analysis by capillary gas chromatography (SE-30), only *cis*-isomer *cis*-**4a** was detected.

***t*-Butyl 6-Isopropyl-2-methyl-2-tetrahydropyrancarboxylate (4a):** *cis*-Isomer, IR (KBr) 2975, 2900, 1760, 1380, 1170 cm^{-1}; ^1H NMR (CCl_4) δ=3.43—2.94 (1H, m), 2.00—1.40 (7H, m), 1.43 (9H, s), 1.32 (3H, s), 0.88 (6H, dd, J=7.7 Hz). Found: m/z 141.1303. Calcd for $C_9H_{17}O$: M−$CO_2{}^t$Bu, 141.1280. *trans*-isomer, IR (KBr) 2975, 2900, 1760, 1380, 1170 cm^{-1}; ^1H NMR (CCl_4) δ=3.40—2.83 (1H, m), 2.11—1.40 (7H, m), 1.43 (9H, s), 1.25 (3H, s), 0.90 (6H, dd, J=6.6 Hz). Found: m/z 141.1287. Calcd for $C_9H_{17}O$: M−$CO_2{}^t$Bu, 141.1280.

The cyclization of α-alkoxy carboxylic acid ester **3d** was also carried out by the same procedure.

***t*-Butyl 2,6-Dimethyl-2-tetrahydropyrancarboxylate (4b):** *cis*-Isomer, IR (KBr) 2960, 2920, 1760, 1150, 1120 cm^{-1}; ^1H NMR (CCl_4) δ=3.88—3.18 (1H, m), 1.78—1.30 (6H, m), 1.44 (9H, s), 1.30 (3H, s), 1.12 (3H, d, J=6 Hz). Found: m/z 113.0944. Calcd for $C_9H_{17}O$: M−$CO_2{}^t$Bu, 113.0965. *trans*-isomer, IR (KBr) 2960, 2920, 1760, 1150, 1120 cm^{-1}; ^1H NMR (CCl_4) δ=3.80—3.17 (1H, m), 1.85—1.30 (6H, m), 1.45 (9H, s), 1.24 (3H, s), 1.09 (3H, d, J=6 Hz). Found: m/z 113.0981. Calcd for $C_7H_{13}O$: M−$CO_2{}^t$Bu, 113.0965.

The Substitution Reaction of Tetrahydropyran 5: The tetrahydropyrancarboxylate **5** was prepared from α-alkoxy carboxylic acid ester **3e** by the same procedure described above (30%).

***t*-Butyl 6-Isopropyl-2-tetrahydropyrancarboxylate (5):** IR (KBr) 2950, 1755, 1370, 1160 cm^{-1}; ^1H NMR (CCl_4) δ=4.30—2.77 (2H, m), 2.10—1.20 (6H, m) 1.43 (9H, s), 0.98 (6H, dd, J=6.6 Hz). Found: 227.1775. Calcd for $C_{13}H_{23}O_3$: M−H, 227.1647. Next, to a THF (5 ml) solution of diisopropylamine 150 mg (1.47 mmol) was added butyllithium (1.40 mmol in hexane) at −20 °C and stirred for 30 min. To the mixture, a THF (1.5 ml) solution of **5** 91 mg (0.40 mmol) was added slowly. After the addition of HMPA (2 ml), the reaction mixture was cooled to −78 °C and a THF (1.5 ml) solution of methyl iodide 264 mg (1.85 mmol) was added to this solution. The reaction was gradually warmed to the room temperature and stirred overnight. After quenching by sat. aq NH_4Cl, the organic materials were extracted with ether and combined extracts were dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by preparative TLC on silica gel [hexane–Et_2O=5 : 1 (v/v) as an eluent] to afford *cis*-**4a** and *trans*-**4a** in a ratio of 29 : 71.

The Reduction of Tetrahydropyrancarboxylate *cis*-4b with $LiAlH_4$: To a suspension of $LiAlH_4$ 18 mg (0.47 mmol) in Et_2O (5 ml) was added a Et_2O (2 ml) solution of *cis*-**4b** 71 mg (0.33 mmol) at 0 °C and the mixture was stirred for 12 h at r.t. The reaction was quenched by the addition of sat. aq Na_2SO_4 (0.14 ml). The resulted solid was removed by the filtration through a celite pad and the filtrate was concentrated in vacuo. The distillation of the residue afforded 18 mg (38%) of the corresponding *cis*-alcohol *cis*-**6** (90 °C/35 mmHg (bath temp)) (1 mmHg=133.322 Pa).

2,*c*-6-Dimethyl-2-tetrahydropyran-*r*-2-methanol (*cis*-**6**): IR (KBr) 3300, 2930, 1455, 1380, 1085, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.87—3.30 (3H, m), 2.23 (1H, t, J=6 Hz), 1.83—1.20 (6H, m), 1.12 (3H, s), 1.06 (3H, d, J=6 Hz); ^{13}C NMR ($CDCl_3$) δ=73.91, 71.53, 66.58, 33.47, 29.94, 22.55, 19.41, 18.22.[5a]

The reduction of *trans*-**4b** was also carried out by the same procedure.

2,*t*-6-Dimethyl-2-tetrahydropyran-*r*-2-methanol (*trans*-**6**): IR (KBr) 3430, 2930, 1455, 1380, 1085, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.10—3.03 (3H, m), 1.95—1.33 (7H, m), 1.16 (3H, s), 1.10 (3H, d, J=6 Hz); ^{13}C NMR ($CDCl_3$) δ=73.60, 66.80, 62.68, 32.71, 32.04, 26.76, 22.61, 19.80.[5a,b]

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4) *cis*-**4a** means *c*-6-isopropyl-*r*-2-ester; *trans*-**4a** means *t*-6-isopropyl-*r*-2-ester.

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