Stereoselective Alkylation of Lithium Enolates Generated from *t*-Butyl Esters of 4-Alkyl-Substituted 5-Hydroxypentanoic Acids

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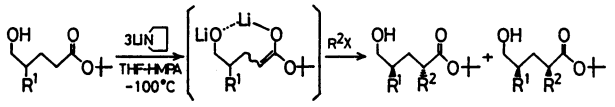
Synopsis. Alkylation of lithium enolates generated from *t*-butyl esters of 4-alkyl-substituted 5-hydroxypentanoic acid by treatment with lithium pyrrolidinide in THF-HMPA proceeded stereoselectively to afford the corresponding *anti*-α-alkylated esters.

Concerning remote chiral induction directed by a hydroxyl group, we reported that the lithium enolates of *t*-butyl 5-hydroxy carboxylates react with electrophiles such as alkyl halides, ketones and oxaziridines, giving the corresponding 2-substituted products with high diastereoselectivities.[1] In these reactions remote chiral induction (1,4-relationship) is considered to be efficiently controlled by the formation of a lithium chelate, therefore, we successively applied this concept to the stereoselective preparation of 2,4-disubstituted 5-hydroxypentanoates based on the following consideration.

When a 4-alkyl-substituted 5-hydroxypentanoate **1** is treated with lithium amide in tetrahydrofuran (THF) and hexamethylphosphoric triamide (HMPA), it is expected that the (*E*)-enolate would be generated stereoselectively[2] and would form an 8-membered chelate **2**,[1] which would successively react with alkylating reagents in a stereoselective manner.



1 **2** **3** **4**

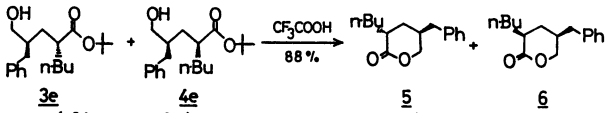
According to the above hypothesis, the enolization of 5-hydroxypentanoates **1A—C**, which have methyl, allyl or benzyl group as a 4-substituent, and the successive reaction with alkylating reagents were examined. The hydroxy ester **1** was treated with 3 molar amounts of lithium pyrrolidinide[3] in THF-HMPA at −100 °C for 1 h, and then the alkylation was performed at the temperature. The diastereoselectivities in these reactions are summarized in Table 1. Generally a good diastereoselectivity is observed and the 4-substituent slightly affects the selectivity. That is, in the case that the substituent is allyl or benzyl group, a higher selectivity is observed as compared with that in reaction of the methyl substituted ester **1A**.

Table 1. Diastereoselectivity in the Alkylation of **1**

R^1	R^2-X	3 : 4	Total yield/%
Me	Me_2SO_4	80 : 20[a]	78
CH_2=$CHCH_2$	Me_2SO_4	85 : 15[a]	81
CH_2=$CHCH_2$	$PhCH_2Br$	90 : 10[b]	96
$PhCH_2$	Me_2SO_4	90 : 10[b]	80
$PhCH_2$	*n*-BuI[c]	91 : 9[d]	76

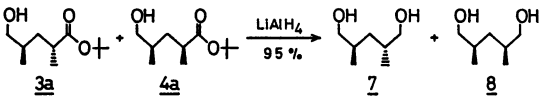
a) The ratio was determined by GLPC (PEG-HT). b) The ratio was determined by HPLC (Waters RESOLVE). c) After the addition of *n*-BuI, the reaction mixture was stirred for 1 h at −100 °C and gradually warmed to −78 °C.

The alkylated product **3e** was readily converted to the *trans*-2,4-disubstituted 5-pentanolide **5** by treatment with trifluoroacetic acid at room temperature. On the othe hand, an attempt to prepare the *trans*-pentanolide **5** from a cyclic compound such as 4-benzyl-5-pentanolide by the alkylation of the corresponding lithium enolate with butyl iodide failed, resulting in the formation of almost equal amounts of the both isomers (**5** : **6**=59 : 41). Therefore, the present reaction affords a stereoselective method for the preparation of *trans*-2,4-disubstituted pentanolide.



3e (91 : **4e** 9) **5** (91 : **6** 9)

The relative stereochemistry was confirmed by the transformation of **3a** to *dl*-2,4-dimethyl-1,5-pentanediol **7**. The mixture of **3a** and **4a** was reduced with lithium aluminum hydride to the diol **7** and **8** (4 : 1 mixture, respectively). The authentic *meso*-diol **8** was prepared from *meso*-2,4-dimethylglutaric anhydride, and the ^{13}C NMR spectrum of the authentic **8**[4] was identical with that of the minor isomer **8** obtained by the reduction of the mixture of **3a** and **4a**.



3a (4 : **4a** 1) **7** **8**

In conclusion, *anti*-2,4-disubstituted 5-hydroxy pentanoates **3** are prepared by the stereoselective remote alkylation of the 5-hydroxy esters **1**. The products **3** are considered to be useful synthetic intermediates, because the two different terminal oxygen functions can be effectively used for further transformation.

Experimental

Preparation of *t*-Butyl 5-Hydroxy-4-methylpentanoate (1A). To a THF (90 mL) solution of diisopropylamine (5.27 g, 52 mmol) was added butyllithium (49.6 mL in hexane, 52 mmol) at −78 °C under an argon atmosphere and stirred for 15 min. To the mixture was added a THF (10 mL) solution of ethyl propionate (5.28 g, 52 mmol) and stirred for 1 h at −78 °C. Then a THF (10 mL) solution of *t*-butyl acrylate (5.31 g, 41 mmol) was added to the mixture.[5] After being stirred for 1 h at the temperature, the reaction was quenched with sat. aqueous NH_4Cl and extracted with chloroform. The combined organic extracts were dried over Na_2SO_4, and condensed under reduced pressure. Purification by column chromatography on silica gel (hexane: ethyl acetate=15 : 1, volume ratio) gave the pure Michael

adduct, *t*-butyl 4-ethoxycarbonylpentanoate (6.66 g, 70%). IR (neat) 1730 cm^{-1}. ^1H NMR (CCl_4) δ=1.13 (3H, d, J=6.6 Hz), 1.24 (3H, t, J=7.0 Hz), 1.42 (9H, s), 1.52—1.95 (2H, m), 1.95—2.57 (3H, m), 4.01 (2H, q, J=7.0 Hz).

Next, to a THF (250 mL) solution of lithium aluminum hydride (3.29 g, 87 mmol) was slowly added a THF (20 mL) solution of the above Michael adduct (6.65 g, 29 mmol) at −78 °C under an argon atmosphere, and stirred for 8 h. The mixture was quenched with sat. aqueous Na_2SO_4 (25 mL) and the resulting precipitate was filtered off. The condensed filtrate was purified by column chromatography on silica gel (hexane : ethyl acetate=3 : 1, volume ratio) to give **1A** (2.97 g, 55%), bp 95 °C (bath temp)/2 mmHg (1 mmHg=133.322 Pa). IR (neat) 3430, 1730 cm^{-1}. ^1H NMR (CCl_4) δ=0.90 (3H, d, J=6.0 Hz), 1.20—1.80 (3H, m), 1.43 (9H, s), 2.03—2.53 (3H, m), 3.21—3.53 (2H, m).

4-Alkyl-substituted 5-hydroxy esters **1B** and **1C** were prepared by the method of Yamaguchi.[6] The spectra data are shown below.

***t*-Butyl 4-Benzyl-5-hydroxypentanoate (1C):** Bp 147 °C (bath temp)/2 mmHg. IR (neat) 3430, 1720 cm^{-1}. ^1H NMR (CCl_4) δ=1.20—1.71 (3H, m), 1.27 (9H, s), 1.92—2.28 (2H, m) 2.28—2.57 (3H, m), 3.28 (2H, d, J=4.0 Hz), 7.06 (5H, s).

***t*-Butyl 4-Hydroxymethyl-6-heptenoate (1B):** Bp 120 °C (bath temp)/2 mmHg. IR (neat) 3450, 1725, 1640 cm^{-1}. ^1H NMR δ=1.21—1.80 (3H, m), 1.43 (9H, s), 1.91—2.49 (4H, m), 2.68 (1H, br s), 3.40 (2H, d, J=5.6 Hz), 4.68—5.14 (2H, m), 5.31—6.07 (1H, m).

Stereoselective Alkylation of 1C with Dimethyl Sulfate. To a THF solution of lithium pyrrolidinide (1.67 mmol), which was prepared from pyrrolidine (173 mg, 2.44 mmol) and butyllithium (1.64 M hexane solution (1 M=1 mol dm^{-3}), 1.02 mL) at −78 °C, was added HMPA (0.58 mL, 3.33 mmol) at 0 °C under an argon atmosphere, and cooled to −100 °C. A THF (3 mL) solution of *t*-butyl 4-benzyl-5-hydroxypentanoate (**1C**, 147 mg, 0.56 mmol) was added to the mixture and stirred for 1 h at that temperature. Then a THF (3 mL) solution of dimethyl sulfate (251 mg, 1.99 mmol) was added to the mixture. After being stirred for 1 h at −100 °C, the reaction was quenched with sat. aqueous NH_4Cl and extracted with ether. The combined ether extracts were washed with water and brine, dried over Na_2SO_4, and condensed under reduced pressure. Purification by column chromatography (silica gel, hexane : ethyl acetate=10 : 1, volume ratio) gave *t*-butyl *anti*-4-benzyl-5-hydroxy-2-methylpentanoate (**3d**) and the *syn*-isomer **4d** (total 124 mg, 80%) in the ratio of 90 : 10, respectively.

The preparations of **3a,b,c,e** were carried out by the same procedure. All the alkylated products were isolated as a mixture of the *anti* and *syn* isomers **3** and **4**, which were not able to be separated by column chromatography or TLC. The following spectral data were for a mixture of the *anti* and *syn* isomers (91:9—80:20, respectively).

***t*-Butyl *anti*-5-Hydroxy-2,4-dimethylpentanoate (3a) and the *syn*-Isomer 4a:** IR (neat) 3430, 1720 cm^{-1}. ^1H NMR (CCl_4) δ=0.87 (3H, d, J=6.0 Hz), 0.99 (2.4H, d, J=7.0 Hz, anti), 1.00 (0.6H, d, J=7.4 Hz, syn), 1.20—1.98 (3H, m), 1.42 (9H, s), 2.03—2.60 (1H, m), 3.18—3.41 (3H, m).

***t*-Butyl *anti*-4-Hydroxymethyl-2-methyl-6-heptenoate (3b) and the *syn*-Isomer 4b:** IR (neat) 3430, 1725, 1640 cm^{-1}. ^1H NMR (CCl_4) δ=0.93—2.61 (6H, m), 1.09 (3H, d, J=7.0 Hz), 1.43 (9H, s), 2.97 (1H, br s), 3.27—3.55 (2H, m), 4.70—5.16 (2H, m), 5.35—6.09 (1H, m).

***t*-Butyl *anti*-2-Benzyl-4-hydroxymethyl-6-heptenoate (3c) and the *syn*-Isomer 4c:** IR (neat) 3430, 1720, 1640 cm^{-1}. ^1H NMR (CCl_4) δ=0.77—2.93 (8H, m), 1.26 (9H, s), 2.62 (1H, br s), 3.31—3.55 (2H, m), 4.70—5.13 (2H, m), 5.30—5.93 (1H, m), 7.06 (5H, s).

***t*-Butyl *anti*-4-Benzyl-5-hydroxy-2-methylpentanoate (3d) and the *syn*-Isomer 4d:** IR (neat) 3420, 1725 cm^{-1}. ^1H NMR (CCl_4) δ=1.06 (3H, d, J=6.8 Hz), 1.19—2.92 (6H, m), 1.36 (9H, s), 2.76 (1H, br s), 3.23—3.53 (2H, m), 7.02 (5H, s).

***t*-Butyl *anti*-2-(2-Benzyl-3-hydroxypropyl)hexanoate (3e) and the *syn*-Isomer 4e:** IR (neat) 3450, 1725 cm^{-1}. ^1H NMR (CCl_4) δ=0.63—2.63 (15H, m), 1.23 (8.2H, s, anti), 1.30 (0.8H, s, syn), 2.07 (1H, br s), 3.17—3.43 (2H, m), 7.07 (5H, s).

Transformation of the α-Alkylated Ester 3e to the Lactone 5. A mixture of **3e** and **4e** (total 123 mg, 0.39 mmol) was dissolved in trifluoroacetic acid (2 ml), and stirred for 2 h. After evaporation of the trifluoroacetic acid in vacuo, the residue was purified by preparative TLC on silica gel (hexane : ethyl acetate=3 : 1, volume ratio) to afford *trans*-4-benzyl-2-butyl-5-pentanolide (**5**) and the *cis*-isomer **6** (total 95 mg, 88%) in the ratio of 91 : 9, respectively. The isomeric ratio was determined by HPLC (Waters RESOLVE). *trans*-4-Benzyl-2-butyl-5-pentanolide and the *cis*-isomer: IR (neat) 1735 cm^{-1}. ^1H NMR (CCl_4) δ=0.65—2.73 (15H, m), 3.55—4.27 (2H, m), 6.83—7.10 (5H, m).

2,4-Dimethyl-1,5-pentanediol (7 and 8): Under an argon atmosphere, to a THF (3 mL) solution of lithium aluminum hydride (50 mg, 1.32 mmol) was added a THF (3 mL) solution of *t*-butyl 5-hydroxy-2,4-dimethylpentanoate (**3a** and **4a**, 110 mg, 0.54 mmol, anti : syn=4 : 1) at 0 °C, and the mixture was stirred at room temperature overnight. The mixture was quenched with sat. aqueous Na_2SO_4 (0.4 mL) and the resulting precipitate was filtered off. The condensed filtrate was purified by preparative TLC (ethyl acetate) to furnish the diol (68 mg, 95%). IR (neat) 3300 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.63—2.06 (4H, m), 0.87 (6H, d, J=6.4 Hz), 2.76—3.93 (2H, m), 3.37 (4H, d, J=6.0 Hz). ^{13}C NMR ($CDCl_3$) δ=16.55 (*dl*), 17.74 (meso), 32.91 (*dl*), 33.21 (meso), 37.03 (*dl*), 37.19 (meso), 67.58 (meso), 68.61 (*dl*).

The ^{13}C NMR spectrum of the minor isomer of diols was agreed with that of the authentic *meso*-diol obtained by the Allinger's method.[4]

References

1) K. Narasaka, Y. Ukaji, and K. Watanabe, *Bull. Chem. Soc. Jpn.*, **60**, 1457 (1987).

2) R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).

3) The alkylation reaction was examined by using some lithium amides such as lithium diisopropylamide, lithium diethylamide, lithium dimethylamide and lithium pyrrolidinide, and the best anti selectivity was observed when lithium pyrrolidinide was employed as a base.

4) N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 232 (1959).

5) M. Yamaguchi, M. Tsukamoto, and I. Hirao, *Chem. Lett.*, **1984**, 375.

6) M. Yamaguchi, K. Shibato, and I. Hirao, *Tetrahedron Lett.*, **25**, 1159 (1984).