A New Route for Protected Amino Alcohols from (*R*)-Glycidol. Copper(I) Mediated Alkylation of 4-Tosyloxymethyl-2-oxazolidinone[1)]

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Synopsis. The reaction of (*S*)-4-tosyloxymethyl-2-oxazolidinone, which was synthesized from (*R*)-glycidol through (*R*)-4-benzoyloxymethyl-2-oxazolidinone, with various lithium dialkylcuprate(I)s in THF proceeded smoothly to afford the corresponding protected amino alcohol derivatives in good yield.

Recently, efforts have been made to develop new synthetic methodologies for various amino acids including non-protenogenic amino acids which are found as constituents of biologically important peptides.[2)] γ-Alkylation of protected β-amino alcohols is one of the most efficient routes for the synthesis of these molecules, and some effective methods from amino acids have been reported.[2,3)]

Previously we have developed enantiomerically pure 4-hydroxymethyl-2-oxazolidinone derivatives as chiral serinol synthons from glycidol (**1**),[4)] and reported the diastereoselective synthesis of γ-hydroxy-β-amino alcohols from the developed chiral oxazolidinone building blocks.[5)] We now describe a new and concise route for the synthesis of various amino alcohols by a copper(I)-mediated alkylation of the tosylate **6**, which was prepared from the chiral building block **2**.

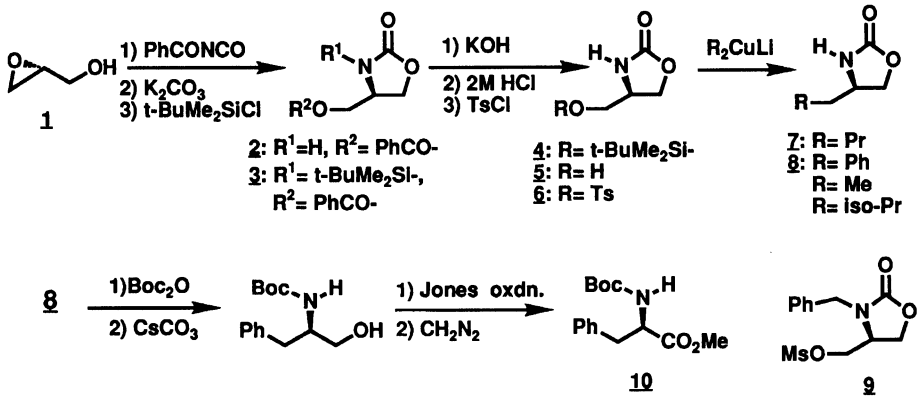
The tosylate **6** was synthesized as follows. Since serious racemization of **5** was admitted by a hydrolysis of **2** with various kinds of bases,[4)] **5** was prepared through **4** whose silyl group could be removed by treatment with acid. Thus, *R*-(+)-4-benzolyloxymethyl-2-oxazolidinone (**2**)[4)] was treated with *t*-butyldimethylsilyl chloride in the presence of 4-dimethylaminopyridine and triethylamine in DMF to give the *N*-silylated compound **3**. This was treated with potassium hydroxide in methanol to afford the *O*-silylated compound **4** in 88% yield for two steps. The silyl group migrated from nitrogen to oxygen without any racemization.[6)] Removing the silyl group with acid gave the alcohol **5**, which was reacted with tosyl chloride in pyridine without purification to afford the enantiomerically pure tosylate **6**.[7)] Thus, the electrophile for alkylation was prepared. Alkylation of the tosylate **6** with lithium dipropylcuprate(I) in THF proceeded smoothly to afford 4-butyl-2-oxazolidinone (**7**) in 88% yield. Replacement of **6** by methyl, phenyl, or isopropyl group was also successful in 98%, 80%, or 65% yield respectively in a 3.7 mmol scale. On the other hand, alkylation of 3-benzyl-4-mesyloxymethyl-2-oxazolidinone (**9**) gave less satisfactory results; the yield of the desired alkylation product was less than 50% on a 1 mmol scale. The solubility of the benzyl derivative **9** in THF might not be good enough for the smooth substitution reaction. Thus, a concise synthesis of protected amino alcohols was achieved.

4-Benzyl-2-oxazolidinone (**8**) was transformed to (*R*)-*N*-*t*-butoxycarbonylphenylalanine methyl ester (**10**) by the following sequences (Scheme 1). Thus, oxazolidinone **8** was reacted with di-*t*-butyl dicarbonate in the presence of 4-dimethylaminopyridine and triethylamine in THF to give the corresponding *N*-*t*-butoxycarbonyl derivative, whose oxazolidinone ring was hydrolyzed by treatment with cesium carbonate.[8)] The obtained alcohol was subjected to oxidation with Jones reagent followed by esterification with diazomethane to give **10**, which is a non-protenogenic amino acid ester. Physical data of **10** were identical with those of the authentic sample, including the absolute value of the optical rotation.[9)]

Experimental

The melting points were measured with a Yanagimoto micro melting-point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were taken on a JEOL A-400 spectrometer. Tetramethylsilane (δ=0.00) for ^{1}H and chloroform-*d* (δ=77.0) for ^{13}C were used as internal standards. IR spectra were recorded on a Hitachi 270-30 spectrometer. MS spectra were obtained on a JEOL SX-102 spectrometer. Elemental analyses were measured with a Perkin–Elmer Model 240.

(*R*)-4-Benzoyloxymethyl-2-oxazolidinone (2): To a solution of (*R*)-glycidol (33.2 ml, 0.500 mol) in CH_2Cl_2 (350 ml) was added benzoylisocyanate solution, prepared from benzoyl chloride (68.5 ml, 0.590 mol) and silver cyanate (90.3 g, 0.602 mol) in CCl_4 (413 ml); the mixture was stirred for 17 h at room temperature. After the solvent of the mixture was removed under reduced pressure, the residue dissolved in CH_2Cl_2 (300 ml) was added to a mixture of K_2CO_3 (31.2 g, 0.225 mol) and triethylbenzylammonium chloride (51.5 g, 0.226 mol) in CH_2Cl_2 (300 ml) and water (600 ml) at 0 °C. The resulting mixture was stirred for 6 h at room temperature, and then neutralized with 1 M HCl (1 M=1 mol dm^{-3}). The mixture was extracted with CH_2Cl_2, and the extract was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The obtained crude products were purified by column chromatography on silica gel to give (*R*)-4-benzoyloxymethyl-2-oxazolidinone (63.4 g, 57.2% for two steps) as colorless crystals: Mp 112—113 °C; $[\alpha]_D^{21}$ +29.6 (*c* 1.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=4.26 (2H, m), 4.42 (1H, m), 4.55 (1H, m), 7.44 (2H, m), 7.59 (1H, m), 8.03 (2H, m); ^{13}C NMR ($CDCl_3$) δ=51.2, 65.4, 66.9, 128.5, 129.1, 129.7, 130.0, 133.5, 159.7, 166.2; IR (Nujol) 3320, 1760, 1700 cm^{-1}. Found: C, 59.73; H, 5.00; N, 6.35%. Calcd for $C_{11}H_{11}O_4N$: C, 59.72; H, 5.01; N, 6.33%.



Scheme 1.

(*R*)-(−)-3-*t*-Butyldimethylsilyl-4-benzoyloxymethyl-2-oxazolidinone (3): To a solution of **2** (1.00 g, 4.52 mmol), triethylamine (1.89 ml, 13.5 mmol) and 4-dimethylaminopyridine (552 mg, 4.52 mmol) in DMF (6.8 ml) was added *t*-butyldimethylsilyl chloride (1.36 g, 9.04 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature, quenched with water, and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the residue, which was chromatographed over silica gel. The compound **3** was obtained in 94.8% yield as colorless crystals: Mp 78—79 °C; $[\alpha]_D^{21}$ −51.0 (*c* 1.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.37 (6H, s), 0.99 (9H, s), 4.07 (1H, m), 4.18 (1H, dd, *J*=4.6, 11.2 Hz), 4.40 (3H, m), 7.38 (2H, m), 7.59 (1H, m), 8.03 (2H, m); ^{13}C NMR ($CDCl_3$) δ=−5.0, 19.1, 26.8, 54.9, 65.6, 67.2, 128.6, 129.2, 129.7, 133.5, 161.5, 166.3; IR (Nujol) 1730, 1700 cm^{-1}. HRMS (FAB), Found: *m/z* 336.1649. Calcd for $C_{17}H_{26}O_4NSi$: M+H, 336.1624.

(*S*)-(+)-4-*t*-Butyldimethylsilyloxymethyl-2-oxazolidinone (4): To a solution of KOH (840 mg, 12.7 mmol) in methanol (20.0 ml) was added **3** (4.00 g, 11.9 mmol) in methanol (15.7 ml) at 0 °C and the mixture was stirred for 30 min at room temperature. The mixture was neutralized with 5% citric acid, concentrated in vacuo, diluted with ethyl acetate and water, and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$ and evaporated in vacuo. Chromatography of the residue gave **4** (2.44 g, 88.8%) as colorless crystals: Mp 59—60 °C; $[\alpha]_D^{21}$ +13.4 (*c* 1.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.06 (6H, s), 0.88 (9H, s), 3.61 (2H, d, *J*=5.6 Hz), 3.92 (1H, m), 4.17 (1H, q, *J*=4.9, 8.8 Hz), 4.44 (1H, t, *J*=8.8 Hz), 5.64 (1H, s); ^{13}C NMR ($CDCl_3$) δ=−5.5, 18.1, 25.7, 53.6, 64.7, 67.0, 159.8; IR ($CHCl_3$) 3320, 1740 cm^{-1}. HRMS (FAB), Found: *m/z* 232.1383. Calcd for $C_{10}H_{22}O_3NSi$: M+H, 232.1363.

(*S*)-4-*p*-Toluenesulfonyloxymethyl-2-oxazolidinone (6): A solution of **4** (5.00 g, 21.6 mmol) in THF (108 ml) was treated with 2 M HCl (21.6 ml) for 12 h at room temperature. After the solvent was removed under reduced pressure, the residue of crude **5** was dissolved in pyridine (43.2 ml) and was treated with *p*-toluenesulfonyl chloride (8.24 g, 43.2 mmol). The resulting solution was stirred for 24 h at room temperature, and then quenched with water. The mixture was concentrated in vacuo, and chromatographed over silica gel. The compound **6** was obtained in 88.5% yield as colorless crystals: Mp 125—126 °C; $[\alpha]_D^{24.0}$ +11.1 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=2.46 (3H, s), 4.08 (4H, m), 4.46 (1H, m), 6.02 (1H, s), 7.38 (2H, d, *J*=8 Hz), 7.79 (2H, m); ^{13}C NMR ($CDCl_3$) δ=21.7, 50.9, 66.3, 69.6, 128.0, 130.2, 132.0, 145.6, 158.8; IR (Nujol) 3300, 1770, 1730 cm^{-1}. HRMS (FAB), Found: *m/z* 272.0588. Calcd for $C_{11}H_{14}O_5NS$: M+H, 272.0621.

(*R*)-4-Butyl-2-oxazolidinone (7): To a solution of lithium dipropylcuprate(I) in THF, prepared by a reaction of copper(I) iodide (4.19 g, 22.0 mmol) in THF (44.0 ml) with propyllithium (27.5 ml of 1.6 M ethereal solution, 44.0 mmol) at −48 °C for 2 h, was added **6** (1.00 g, 3.68 mmol) in THF (17.6 ml). After stirring for 2 h at −23 °C, the mixture was quenched with saturated NH_4Cl, and extracted with ethylacetate. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Chromatography of the residue over silica gel gave 412 mg (78.1%) of the alkylated product: oil; $[\alpha]_D^{22.5}$ +10.1 (*c* 0.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.92 (3H, t, *J*=7.0 Hz), 1.31 (4H, m), 1.58 (2H, m), 3.86 (1H, m), 4.02 (1H, dd, *J*=6.2, 8.4 Hz), 4.48 (1H, t, *J*=8.5 Hz), 6.09 (1H, s); ^{13}C NMR ($CDCl_3$) δ=13.9, 22.4, 24.8, 31.4, 35.2, 52.6, 70.3, 160.0; IR (Nujol) 3310, 1770, 1730 cm^{-1}. HRMS (EI), Found: *m/z* 143.0950. Calcd for $C_7H_{13}O_2N$: M, 143.0943.

(*R*)-4-Benzyl-2-oxazolidinone: To a solution of lithium diphenylcuprate(I) in THF, prepared by a reaction of copper(I) iodide (2.15 g, 11.0 mmol) in THF (22.1 ml) with phenyllithium (12.2 ml of 1.8 M cyclohexane solution, 22.0 mmol) at 0 °C for 30 min, was added **6** (600 mg, 2.21 mmol) in THF (11.1 ml). After stirring for 6 h at room temperature, the mixture was quenched, worked up as usual, and chromatographed to give 315 mg (80.4%) of the alkylated product: Mp 88.0—89.0 °C; $[\alpha]_D^{22}$ +59.1 (*c* 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=2.88 (2H, m), 4.10 (2H, m), 4.43 (1H, t, *J*=7.8 Hz), 5.87 (1H, s), 7.27 (5H, m); ^{13}C NMR ($CDCl_3$) δ=41.1, 53.6, 69.3, 127.0, 128.8, 128.9, 135.8, 159.7; IR (KBr) 3290, 1760, 1712 cm^{-1}. HRMS (EI), Found: *m/z* 177.0775. Calcd for $C_{10}H_{11}O_2N$: M, 177.0787.

(*R*)-4-Ethyl-2-oxazolidinone: To a solution of lithium dimethylcuprate(I) in THF, prepared by a reaction of copper(I) iodide (1.75 g, 9.21 mmol) in THF (18.4 ml) with methyllithium (12.3 ml of 1.5 M etherial solution, 18.5 mmol) at −48 °C for 2 h, was added **6** (500 mg, 1.84 mmol) in THF (7.4 ml). After stirring for 4 h at room temperature, the mixture was quenched, worked up as usual, and chromatographed to give 207 mg (97.6%) of the alkylated

product: oil; $[\alpha]_D^{23}$ +5.8 (*c* 0.63, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=0.96 (3H, m), 1.61 (2H, m), 3.84 (1H, m), 4.02 (1H, m), 4.49 (1H, m), 6.87 (1H, s); ^{13}C NMR ($CDCl_3$) δ=9.2, 28.1, 53.9, 70.0, 160.4; IR (neat) 3300, 1740 cm^{-1}. HRMS (EI), Found: *m/z* 115.0637. Calcd for $C_5H_9O_2N$: M, 115.0631.

(*R*)-4-Isobutyl-2-oxazolidinone: To a solution of lithium diisopropylcuprate(I) in THF, prepared by a reaction of copper(I) iodide (1.97 g, 10.1 mmol) in THF (20.3 ml) with isopropyllithium (31.4 ml of 0.64 M hexane solution, 20.1 mmol) at −48 °C for 1 h, was added **6** (550 mg, 2.03 mmol) in THF (10.1 ml). After stirring for 3 h at −23 °C, the mixture was quenched, worked up as usual, and chromatographed to give 189 mg (65.0%) of the alkylated product: oil; $[\alpha]_D^{22}$ +11.9 (*c* 1.17, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=0.93 (6H, m), 1.39 (1H, m), 1.59 (2H, m), 3.99 (2H, m), 4.49 (1H, m), 6.44 (1H, s); ^{13}C NMR ($CDCl_3$) δ=22.0, 22.9, 24.9, 44.4, 51.0, 70.7, 160.6; IR (KBr) 3280, 1760 cm^{-1}. HRMS (EI), Found: *m/z* 143.0951. Calcd for $C_7H_{13}O_2N$: M, 143.0943.

(*R*)-4-Benzyl-3-*t*-butoxycarbonyl-2-oxazolidinone: To a stirred solution of **8** (150 mg, 0.846 mmol), triethylamine (0.141 ml, 1.02 mmol), and 4-dimethylaminopyridine (21.0 mg, 0.169 mmol) in THF (2.5 ml) was added di-*t*-butyldicarbonate (0.255 ml, 1.10 mmol) in THF (3.0 ml). The reaction mixture was stirred for 1 h at room temperature, and then treated with brine, and extracted with ethyl acetate. The extract was dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by column chromatography over silica gel to give (*R*)-3-*t*-butoxycarbonyl-4-benzyl-2-oxazolidinone (228 mg, 97.1%) as colorless crystals: Mp 100—101 °C; $[\alpha]_D^{22}$ −22.0 (*c* 0.500, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.59 (9H, s), 2.80 (1H, dd, *J*=9.8, 13.2 Hz), 3.29 (1H, dd, *J*=3.5, 13.5 Hz), 4.08 (1H, dd, *J*=2.7, 9.0 Hz), 4.15 (1H, m), 4.45 (1H, m), 7.30 (5H, m); ^{13}C NMR ($CDCl_3$) δ=28.0, 38.7, 56.1, 65.4, 84.0, 127.3, 129.0, 129.3, 135.3, 149.2, 152.0; IR (Nujol) 1810, 1720 cm^{-1}. HRMS (FAB), Found: *m/z* 278.1420. Calcd for $C_{15}H_{20}O_4N$: M+H, 278.1387.

(*R*)-*N*-*t*-Butoxycarbonyl-2-amino-3-phenyl-1-propanol: To a solution of (*R*)-3-*t*-butoxycarbonyl-4-benzyl-2-oxazolidinone (150 mg, 0.540 mmol) in MeOH (1.6 ml) was added solid cesium carbonate (35.1 mg, 0.108 mmol) at room temperature, and the mixture was stirred for 3 h. After neutralization of the reaction mixture with 5% citric acid, the solvent was concentrated in vacuo, and then the residue was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography over silica gel to give *N*-*t*-butoxycarbonyl-2-amino-3-phenyl-1-propanol (122 mg, 90.3%) as colorless crystals: Mp 94—95 °C; $[\alpha]_D^{22.0}$ +22.1 (*c* 0.425, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.38 (9H, s), 2.84 (2H, d, *J*=7 Hz), 3.55 (1H, m), 3.67 (1H, m), 3.87 (1H, m), 4.73 (1H, s), 7.28 (5H, m); ^{13}C NMR ($CDCl_3$) δ=28.4, 37.5, 53.8, 64.4, 79.8, 126.6, 128.6, 129.3, 137.8, 156.2; IR ($CHCl_3$) 3460, 1706 cm^{-1}. HRMS (FAB), Found: *m/z* 252.1603. Calcd for $C_{14}H_{22}O_3N$: M+H, 252.1594.

(*R*)-*N*-*t*-Butoxycarbonylphenylalanine Methyl Ester (10): To a solution of *N*-*t*-butoxycarbonyl-2-amino-3-phenyl-1-propanol (100 mg, 0.397 mmol) in acetone (2.0 ml) was added 2.7 M Jones reagent (0.420 ml) at 0 °C. The mixture was stirred for 2 h at 0 °C, then treated with brine, and extracted with ethyl acetate. To organic layer was washed with 10% sodium sulfite solution, brine, dried over $MgSO_4$ and evapolated in vacuo. The residue was treated with excess diazomethane in ether. The reaction mixture was quenched with saturated NH_4Cl, and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo. Chromatography of the residue gave **10** as colorless oil (86.0 mg, 78.9% for two steps): $[\alpha]_D^{27.5}$ +2.94 (*c* 2.44, CH_3OH) {lit, (*S*)-isomer: $[\alpha]_D$ −2.2 (*c* 10, CH_3OH)};[9] ^1H NMR ($CDCl_3$) δ=1.41 (9H, s), 3.08 (2H, m), 3.71 (3H, s), 4.59 (1H, dd, *J*=7.1, 13.6 Hz), 4.97 (1H, d, *J*=6.9 Hz), 7.24 (5H, m); ^{13}C NMR ($CDCl_3$) δ=28.3, 38.4, 52.2, 54.4, 79.9, 127.0, 128.5, 129.3, 136.0, 155.1, 172.3; IR (neat) 3400, 1760, 1720 cm^{-1}. HRMS (FAB), Found: *m/z* 280.1532. Calcd for $C_{15}H_{22}O_4N$: M+H, 280.1543.

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