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RING OPENING OF HOMOCHIRAL BICYCLIC OXAZOLIDINONES: SYNTHESIS OF ALLYLGLYCINOL DERIVATIVES

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Abstract: (4*R*,6a*S*)-2-Oxo-4-phenyl-2,4,5,6a,7-hexahydrooxazolo[3,2-c]oxazole and its 4-methyl analog were synthesized using (*R*)-phenylglycinol and (*S*)-alaninol as the chiral source, respectively. The ring opening reaction of the bicyclic oxazolidinones by an allyltrimethylsilane–titanium tetrachloride mixture afforded the corresponding substitution products with diastereoselectivity of up to ~3:1. The major substitution product was readily converted to allylglycinol derivatives.

INTRODUCTION

Bicyclic lactams **1** and **2** have been extensively utilized by Meyers and co-workers for the asymmetric syntheses of a variety of valuable compounds.[1] For example, nucleophilic additions to the aminal functionality in the bicyclic lactams provided 3-substituted pyrrolidines with high stereoselectivities, from which important inhibitory neurotransmitters (γ-aminobutyric acid analogs) were synthesized via **3**and **4**.[2] The stereochemical course of the nucleophilic addition to the aminal and **4**.[2] The stereochemical course of the nucleophilic addition to the aminal center is known to be dependent on several factors: the steric bulkiness of the substituent R,

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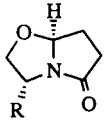
the presence or absence of the angular alkyl substituent, and nucleophiles used. Thus, a hydride (AlH_3) cleavage of **1** proceeds with the retention of stereochemistry at the aminal center while an allyl addition reaction (allyltrimethylsilane–$TiCl_4$) proceeds with inversion.[3] The allyl addition to **2** (R = *t*-Bu) resulted in inversion of the stereochemistry while the same reaction to **2** (R = Me) occurred with retention.[2] We were interested in bicyclic oxazolidinones **5** since analogous aminal opening reactions by nucleophiles would give valuable α-amino alcohols. It is also of interest to know how the presence of oxygen atom affects the stereochemical outcome, compared to the carbon counterpart **1**. Here, we report an efficient synthesis of **5** (R = Ph, Me) and the stereochemical results of the allyl addition to its aminal center, which led to a new synthesis of allylglycine derivative **6**.[4]



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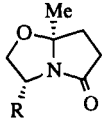

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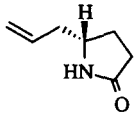

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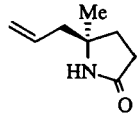

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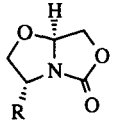
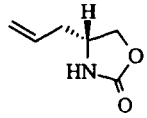


5a, R = Ph
5b, R = Me



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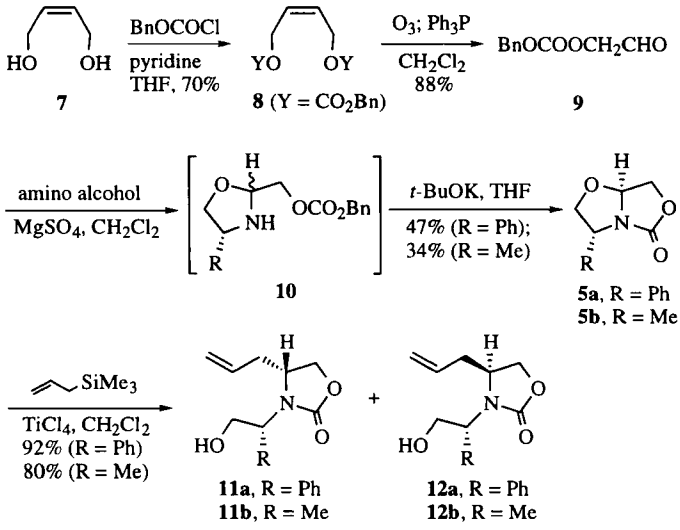
RESULTS AND DISCUSSION

Bicyclic oxazolidinone **5a** was synthesized from aldehyde **9**, which was readily prepared from commercially available 2-butene-1,4-diol by protection and subsequent ozonolysis. Treatment of aldehyde **9** with (*R*)-(-)-2-phenylglycinol in

the presence of magnesium sulfate gave the corresponding oxazolidine **10**, which without isolation was cyclized to **5a** in 47% yield by treatment with potassium *tert*-butoxide. Similarly, the methyl analog **5b** was synthesized using (*S*)-alaninol in 34% yield. Both were obtained as single diastereomers, judging from the ^{1}H NMR spectra of the products. The stereochemistry at the aminal center can preferably be depicted as shown in the structure because the other isomer would have unfavorable steric strain. The allyl addition to the aminal center in **5a** was then made with allyltrimethylsilane in the presence of titanium tetrachloride, affording a diastereomeric mixture of **11a** and **12a** with a 92% yield and a diastereoselectivity of 74:26. The diastereoselectivity was determined by ^{1}H NMR analysis of the crude product. Each diastereomer can be separated by SiO_2 column chromatography.



7 **8** (Y = CO_2Bn) **9**

10

5a, R = Ph
5b, R = Me

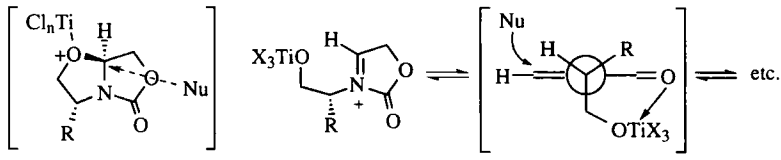
11a, R = Ph
11b, R = Me

12a, R = Ph
12b, R = Me

Scheme 1

Similarly, the allyl addition to **5b** produced a mixture of **11b** and **12b** with a 80% yield and a ratio of 63:37. In this case, both diastereomerswere hardly separable by SiO_2 column chromatography.

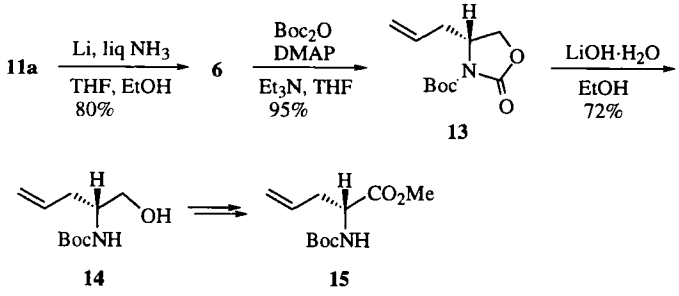
The decreased stereoselectivities observed with oxazolidinones **5** in the allylation reaction compared to the structurally similar lactams **1** raise a mechanistic argument. In the case of **1**, a diastereoselectivity of >9:1 was observed when R = Ph and lactam **3** was derived as the major product.[3] Meyers and co-workers observed an inversion of stereochemistry at the aminal center in the allyl addition to **1** (R = Ph, Me) while the stereochemistry was retained in the case of **2** (R = Ph, Me).[2] For the former case they suggested an S_N2-like delivery of the nucleophile from the less hindered α-face to the partially broken aminal center. In our case, this mechanistic picture depicted as **A** will lead to **11**, the major products obtained. They explained the anomalous stereochemical outcome observed in the case of **2** (R = Ph, Me) by open transition structures, involving a combination of the Felkin-Anh model for nucleophilic addition, allylic 1,3-strain, and chelation effects.[2] The added oxygen atom in oxazolidinones **5** can assist an iminium ion formation through the so-called electron-donating resonance effect; hence **5** may be more prone to form the iminium ion intermediate compared to **1**, which has no such effect. From the favorable open transition structure shown as **C** (R = Me or Ph), the products **12** will be produced, as suggested by Meyers and co-workers. Thus, the lowered diastereoselectivity in the allyl addition to oxazolidinones **5** compared to **1** may be explained by the participation of the open transition structure caused by the resonance stabilizing effect of the oxygen atom in the formation of the acyl iminium intermediates. Besides this electronic effect, a steric argument could also be considered: the oxygen atom in **5** would cause a diminished steric strain during



the nucleophilic attack compared to the carbon atom in **1**. However, further scrutiny of the mechanistic aspects is necessary to deduce more probable explanation for the different stereoselectivity.

The major isomer **11a** was readily converted to versatile allylglycine derivatives, as shown in Scheme 2. Thus, treatment of **11a** with lithium metal in liquid ammonia afforded oxazolidinone **6** in 80% yield. *N*-Protection with a *tert*-butoxycarbonyl (Boc) group and subsequent hydrolysis with lithium hydroxide gave *N*-Boc-allylglycinol **14** in 68% overall yield. The absolute stereochemistry at the newly generated carbon center was determined after converting **14** to the known compound (*R*)-(-)-**15**.[5]

In summary, we synthesized homochiral oxazolidinones **5** using chiral amino alcohols as chiral sources. When the bicyclic oxazolidinones are exposed to



Scheme 2

allyltrimethylsilane–titanium tetrachloride, allyl substitution products are obtained with diastereoselectivity of up to about 3:1. The lower selectivity than those observed with Meyers' oxazolidinones **1** was explained by a possible participation of open transition structures in the case of **5**, which is caused by the presence of the oxygen atom. The major substitution product was converted to allylglycinol derivatives.

EXPERIMENTAL

NMR spectral data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the delta scale, multiplicity (s: singlet, d: doublet, t: triplet, m: multiplet, dd: doublet of doublet, br s: broad singlet), integration, and coupling constant (in Hertz). Melting points were determined on a melting point apparatus and are uncorrected. Infrared spectra were recorded on an FT-IR spectrophotometer using NaCl plates. Mass spectra were recorded at 70 eV. Elemental analyses were performed by Seoul Branch Analytical Laboratory of Korea Basic Science Institute. Optical rotations were recorded on a digital polarimeter at wavelength of 589 nm. Flash column chromatography (CC) was carried out on Merck silica gel 60 (230-400 mesh). Analytical thin layer chromatography was carried out on Merck silica gel 60 F_{254} plates. Dichloromethane was distilled from calcium hydride prior to use. Tetrahydrofuran was distilled from sodium-benzophenone ketyl prior to use.

1,4-Bis{[(benzyloxy)carbonyl]oxy}-2-butene (8). A solution of benzyl chloroformate (21.7 mL, 148 mmol) in THF (50 mL) was added dropwise to a cold (0 °C) solution of 2-buten-1,4-diol (5.00 g, 56.8 mmol) and pyridine (11.93 mL, 148 mmol) in THF (113 mL) with stirring. The mixture was warmed to room temperature and stirred for 20 h. Most of the pyridinium salt was removed by

filtration and the filtered solution was evaporated, and the residue was dissolved in CH_2Cl_2 and washed sequentially with 1*N* HCl and brine. The organic layer was dried and evaporated. CC (eluent: 20% ethyl acetate in hexanes) of the residue gave **8** as a white solid (14.1 g, 70%): R_f 0.65 (40% ethyl acetate in hexanes); mp 45-46 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3042, 2984, 2902, 1742, 1454, 1391 and 1267; δ_H (300 MHz, $CDCl_3$) 4.75 (4 H, d, *J* 3.7), 5.15 (4 H, s), 5.80 (1 H, t, *J* 3.7) and 7.25 -7.38 (10 H, m); δ_C (75 MHz, $CDCl_3$) 63.9, 70.4, 128.6, 128.9, 129.2, 129.3, 135.8 and 155.6.

{[(Benzyloxy)carbonyl]oxy}ethanal (9). Ozonolysis of **8** (14.1 g, 39.5 mmol) in CH_2Cl_2 (78 mL) for 3 h at -78 °C and subsequent treatment with triphenylphosphine (12.4 g) afforded crude **9**. Purification by CC (eluent : 20% ethyl acetate in hexanes) gave **9** as a colorless oil (13.5 g, 88%); R_f 0.43 (40% ethyl acetate in hexanes); ν_{max} ($CHCl_3$)/cm^{-1} 3461, 3066, 3035, 2966, 2898, 1743, 1453, 1390, 1269 and 1048; δ_H (300 MHz, $CDCl_3$) 4.66 (2 H, s), 5.20 (1 H, s), 7.24-7.38 (5 H, m) and 9.64 (1 H, s); δ_C (75 MHz, $CDCl_3$) 71.0, 71.7, 128.9, 129.1, 129.2, 129.3, 155.3 and 196.0.

(4*R*, 6a*S*)-2-Oxo-4-phenyl-2,4,5,6a,7-hexahydrooxazolo[3,2-c] oxazole (5a). A solution of **9** (2.00 g, 10.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of magnesium sulfate (1.24 g, 10.3 mmol) and (*R*)-(-)-2-phenylglycinol (1.41 g, 10.3 mmol) in CH_2Cl_2 (15 mL) at 25 °C via a cannula and the resulting mixture was stirred for 2 h. The solid was filtered off and the filtrate was evaporated. The residue was dissolved in THF (25 mL) and it was treated with potassium *tert*-butoxide (122 mg, 1.03 mmol). The mixture was heated to reflux for two days. The resulting mixture was cooled to room temperature and diluted with water (25 mL) then extracted with ethyl acetate. The extract was dried and evaporated. CC (eluent : 20% ethyl acetate in hexanes) of the residue gave **5a**

as a white solid (987 mg, 47%); *Rf* 0.48 (40% ethyl acetate in hexanes); mp 70-71 °C; $[\alpha]^{24}_D$ -104.2 (*c* 1.00 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3029, 2981, 2935, 2876, 1758, 1461, 1392, 1219, 1157, 1091, 1023 and 993; δ_H (300 MHz, $CDCl_3$) 3.82 (1 H, dd, *J* 6.2 and 8.7), 4.43-4.57 (3 H, m), 5.14-5.25 (2 H, m) and 7.29 -7.40 (5 H, m); δ_C (75 MHz, $CDCl_3$) 62.3, 68.6, 74.0, 90.3, 126.4, 128.6, 129.6, 139.6 and 162.6; *m/z* (EI) 205 (M^+). $C_{11}H_{11}NO_3$ requires C, 64.37; H, 5.40; N, 6.83%. Found: C, 63.97; H, 5.34; N, 6.77%.

(4*R*, 6a*S*)-2-Oxo-4-methyl-2,4,5,6a,7-hexahydrooxazolo[3,2-c] oxazole (5b). This compound was prepared as a colorless oil in 34% yield (364 mg) from **9** (1.50 g, 7.72 mmol) and (*S*)-(+)-2-amino-1-propanol (580 mg, 7.72 mmol). *Rf* 0.46 (40% ethyl acetate in hexanes); $[\alpha]^{24}_D$ +34.8 (*c* 1.24 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2924, 1764, 1460, 1389, 1214, 1097 and 987; δ_H (300 MHz, $CDCl_3$) 1.31 (3 H, d, *J* 6.8), 3.42-3.48 (1 H, m), 4.14-4.24 (2 H, m), 4.36 (1 H, dd, *J* 1.2 and 10.0), 4.44 (1 H, dd, *J* 4.4 and 10.0) and 5.13 (1 H, dd, *J* 1.2 and 4.4); δ_C (75 MHz, $CDCl_3$) 19.3, 54.8, 68.4, 73.1, 88.7 and 162.3; *m/z* (EI) 143 (M^+).

***N*-[(2*R*)-1-hydroxy-2-phenylethan-2-yl]-(4*R*)-allyl-2-oxazolidinone (11a) and its (4*S*)-isomer (11b).** To a solution of **5a** (200 mg, 0.975 mmol) in CH_2Cl_2 (3 mL) at -78 °C under an argon atmosphere was added titanium(IV) chloride (118 μL, 1.07 mmol). After being stirred for 3 min, the mixture was treated with allyltrimethylsilane (186 μL, 1.17 mmol) and it was further stirred at -78 °C for 30 min. The reaction mixture was carefully treated with water (3 mL) and it was allowed to warm to room temperature then extracted with CH_2Cl_2. The extract was dried and evaporated. The ^1H NMR spectrum of the crude products exhibited a diastereomeric mixture of **11a** and **12b** in a ratio of 74:26. CC of the crude products (eluent: 30% ethyl acetate in hexanes) gave **11a** (158 mg) and **12a**

(60 mg) in a combined yield of 92%. **11a**: *Rf* 0.60 (80% ethyl acetate in hexanes); $[\alpha]^{29}_{D}$ -39.5 (*c* 1.00 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3411, 3073, 2921, 1730, 1641, 1429, 1244, 1066 and 1035; δ_H (300 MHz, $CDCl_3$) 2.23-2.40 (2 H, m), 3.60-3.69 (1 H, m), 3.77 (1 H, br s), 3.94 (1 H, dd, *J* 3.7 and 5.6), 4.07 (1 H, dd, *J* 5.6 and 8.7), 4.27-4.42 (2 H, m), 4.48 (1 H, dd, *J* 3.7 and 8.7), 5.12-5.20 (2 H, m), 5.57-5.71 (1 H, m) and 7.28-7.41 (5 H, m); δ_C (75 MHz, $CDCl_3$) 36.2, 55.1, 61.6, 64.0, 67.2, 120.6, 127.6, 128.8, 129.4, 131.3, 137.3 and 159.1; *m/z* (EI) 247 (M^+). **12a**: *Rf* 0.58 (80% ethyl acetate in hexanes); $[\alpha]^{24}_{D}$ +80.3 (*c* 1.00 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 2.10–2.17 (1 H, m), 2.27-2.34 (1 H, m), 3.13 (1 H, br s), 3.76-3.83 (1 H, m), 3.96-4.05 (2 H, m), 4.29-4.42 (2 H, m), 4.65 (1 H, dd, *J* 5.2 and 9.0), 5.00-5.09 (2 H, m), 5.43-5.54 (1 H, m) and 7.30-7.39 (5 H, m); *m/z* (EI) 247 (M^+).

***N*-[(2*R*)-1-hydroxypropan-2-yl)]-(4*R*)-allyl-2-oxazolidinone (12a) and its (4*S*)-isomer (12b).** Using a similar route to that for **11**, a diastereomeric mixture of **12a** and **12b** was obtained in a combined yield of 80% (104 mg), starting from **5b** (100 mg, 0.699 mmol). Both diastereomers were hardly separable by CC. The ^1H NMR spectrum of the mixture exhibited inseparable peaks except for the methyl groups [major: δ 1.29 (3 H, d, *J* 6.8); minor: δ 1.33 (3 H, *J* 6.8)], from which the diastereomeric ratio (**12a**: **12b** = 63 : 37) could be determined. The assignment of (4 *R*)-stereochemistry for **12a** was based on the assumption that the allyl addition to **5b** would follow the same stereochemical course as that in the case of **5a**. The mixture of **12a** and **12b**: *Rf* 0.25 (60% ethyl acetate in hexanes); δ_H (300 MHz, $CDCl_3$) 1.29 and 1.33 (3 H, d, *J* 6.8), 1.78 (1 H, br s), 2.28-2.38 (1 H, m), 2.47-2.54 (1 H, m), 3.55-3.72 (2 H, m), 3.82-3.98 (3 H, m), 4.02-4.08 (1 H, m), 4.31-4.37 (1 H, m), 5.15-5.22 (2 H, m) and 5.64-5.78 (1 H, m).

(*R*)-4-Allyl-2-oxazolidinone (6). Ammonia (~50 mL) was condensed into a stirred solution of compound **11a** (260 mg, 1.05 mmol) in dry THF (7 mL) and anhydrous ethyl alcohol (0.62 mL, 10.5 mmol) via a cold finger (with dry ice-acetone) under a static argon atmosphere. To the resulting cold solution was added enough lithium to produce a dark blue color that persisted for 3 min. The blue reaction mixture was then quenched by the careful addition of a small amount of ammonium chloride. The cold finger was then removed and the resulting solution was allowed to warm to room temperature over 4 h. The residual milky solution was concentrated, diluted with water (15 mL), and extracted with CH_2Cl_2. The extract was dried and evaporated. CC (eluent: 40% ethyl acetate in hexanes) of the residue gave **6** as a colorless oil (104 mg, 80%): *Rf* 0.37 (60% ethyl acetate in hexanes); $[\alpha]^{24}_D$ +9.7 (*c* 0.95 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3300, 2921, 2857, 1742, 1641, 1410, 1236, 1059 and 1019; δ_H (300 MHz, $CDCl_3$) 2.31-2.40 (2 H, m), 3.93 (1 H, dd, *J* 5.6 and 13.9), 4.05 (1 H, dd, *J* 5.6 and 8.6), 4.10-4.50 (1 H, m), 5.14-5.19 (2 H, m), 5.66-5.80 (1 H, m) and 6.60 (1 H, br s); δ_C (75 MHz, $CDCl_3$) 30.8, 52.2, 69.9, 119.8, 132.4 and 160.6; *m/z* (EI) 127 (M^+).

(*R*)-*N*-*tert*-butoxycarbonyl-4-allyl-2-oxazolidinone (13). Treatment of oxazolidinone **6** (80 mg, 0.629 mmol) with di-*tert*-butyl dicarbonate (200 mg, 1.01 mmol), triethylamine (105 μL, 0.755 mmol) and 4-dimethylaminopyridine (7.7 mg, 0.063 mmol) in CH_2Cl_2 (3 mL) at room temperature for 4 h gave the protected compound. An extractive workup with ethyl acetate and CC (eluent: 30% ethyl acetate in hexanes) gave **13** as a white solid (136 mg, 95%): *Rf* 0.72 (40% ethyl acetate in hexanes); mp 50-51 °C; $[\alpha]^{24}_D$ -58.8 (*c* 1.00 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2980, 2930, 1808, 1722, 1642, 1363, 1324, 1290, 1161 and 1062; δ_H (300 MHz, $CDCl_3$) 1.54 (9 H, s), 2.43-2.61 (2 H, m), 4.07-4.33 (3 H, m), 5.15-5.21 (2 H, m) and 5.64-5.78 (1 H, m).

(*R*)-2-(*N*-*tert*-Butoxycarbonyl)amino-4-penten-1-ol (14). Treatment of **13** (110 mg, 0.484 mmol) with $LiOH{\cdot}H_2O$ (102 mg, 2.42 mmol) in ethanol (5 mL)–water (1 mL) at room temperature for 3 h gave crude **14**. An extractive workup with Et_2O and CC (eluent: 20% ethyl acetate in hexanes) gave **14** as a white solid (70 mg, 72%): *Rf* 0.45 (40% ethyl acetate in hexanes); mp 45-46 °C; $[\alpha]^{24}_D$ -5.2 (*c* 1.00 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3373, 2978, 1691, 1644, 1520, 1392, 1367, 1251, 1171 and 1054; δ_H (300 MHz, $CDCl_3$) 1.38 (1 H, s), 1.43 (9 H, s), 2.20-2.31 (2 H, m), 3.26 (1 H, br s), 3.53-3.65 (3 H, m), 4.90 (1 H, br s), 5.07-5.14 (2 H, m) and 5.73-5.82 (1 H., m); δ_C (75 MHz, $CDCl_3$) 28.3, 36.3, 52.4, 55.1, 80.0, 118.3, 134.7 and 156.0; *m/z* (EI) 201 (M^+). $C_{10}H_{19}NO_3$ requires C, 59.68; H, 9.52; N, 6.96%. Found: C, 59.59; H, 9.66; N, 6.90%.

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