Articles

Anti-Selective Dihydroxylation Reactions of Monosubstituted and (*E*)-Ester Conjugated Allylic Amines by Bulky Alkyl Groups

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Received January 31, 2009, Accepted March 11, 2009

The OsO_4-catalyzed dihydroxylations of a monosubstituted allylic amine and γ-amino-α,β-unsaturated (*E*)-esters with bulky alkyl groups showed a high *anti*-selectivity. Since the acyclic conformation of *N*-acyloxy protected allylic amines was efficiently controlled by a bulky *t*-Bu or OBO ester group, the *anti* diastereoselectivity of >12.5:1 was obtained without applying a chiral reagent. The synthetic utility of the present method was demonstrated by a stereoselective and efficient synthesis of an α-glucosidase inhibitor **15** from commercially available *N*-Cbz-L-serine **6** in 11 steps and 31% yield.

Key Words: Asymmetric synthesis, Amino alcohols, Dihydroxylations, OBO ester

Introduction

A dihydroxylation reaction of chiral allylic amines with OsO_4 is one of the convenient methods to produce an amino alcohol moiety that is a key motif present in numerous bioactive natural products and synthetic compounds.[1] In the case of cyclic allylic amines, the desired facial selectivity of the dihydroxylation reactions could be effectively produced by substrate- or chelation-controlled reactions.[2] However, the acyclic allylic amines with widely used *N*-acyl or *N*-acyloxy protecting groups resulted in low or often inconsistent selectivity due to their flexible acyclic conformation.[3] The well-established Sharpless asymmetric dihydroxylation gave mixed results in several cases.[4]

We have been interested in the diastereoselective dihydroxylation reactions of acyclic allylic amines by controlling acyclic conformation of the substrates. Enhanced stereochemical results have been achieved by using the *N*-diarylmethylene[5] or *N*,*N*-diBoc group[6] instead of the *N*-acyloxy protecting groups. Since these protecting groups efficiently controlled the acyclic conformation of the allylic amines, the high diastereoselectivity was obtained without the need of chiral reagents. In a few cases, the stereoselectivities obtained from the above methods were better than those of the Sharpless asymmetric dihydroxylation.

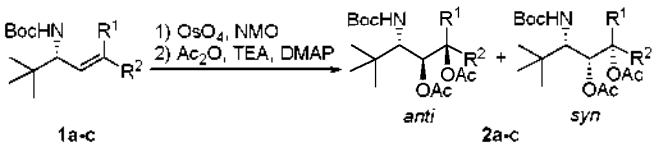
However, the above methods have a disadvantage that the readily available and versatile *N*-protecting groups such as an *N*-Boc or *N*-Cbz group cannot be used. Here, we would like to report that a bulky alkyl group of chiral allylic amines can be utilized to control effectively their acyclic conformation and a high and useful selectivity could be achieved even with the versatile and widely used *N*-Boc or *N*-Cbz group.

In our previous report, the OsO_4-catalyzed dihydroxylations of γ-amino-α,β-unsaturated (*E*)-esters with the *N*-diarylmethylene group gave consistent *anti*-selectivity (6.7:1 - 19:1).[5b] The selectivities increased as the alkyl group of the substrates became larger. The similar stereochemical trend was observed by Reetz and coworkers with the *N*-Boc derivatives of the γ-amino-α,β-unsaturated (*E*)-esters.[3c] They reported the highest *anti*-selectivity of *ca.* 4.3:1 when the alkyl group was an i-Pr group. The increased *anti*-selectivities (3.7:1 - 7:1) were also observed with the *N*-diarylmethylene derivatives of the monosubstituted allylic amines.[5a] Thus, we envisioned that a bulkier alkyl group such as a *tert*-alkyl group in both γ-amino-α,β-unsaturated (*E*)-esters and monosubstituted allylic amines would induce higher *anti*-selectivity even with the popular *N*-protecting groups and without any chiral reagents.

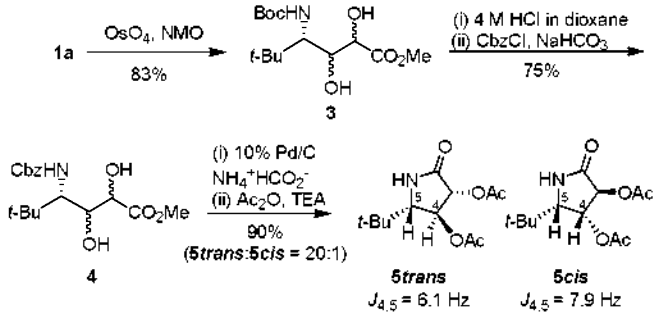
Results and Discussion

First, we have examined the OsO_4-catalyzed dihydroxylation of the *N*-Boc derivatives of a monosubstituted allylic amine and γ-amino-α,β-unsaturated esters that have a *tert*-Bu group in the alkyl chain (Table 1). The starting compounds **1a-c** were prepared from the Wittig olefination of the corresponding amino aldehyde that was derived from an oxidation of commercially available *N*-Boc-*tert*-leucinol. The dihydroxylations were conducted with catalytic amount of OsO_4

Table 1. Dihydroxylations of allylic amines with a *t*-Bu group



Substrate	Product	R^1	R^2	*anti*:*syn*	Yield (%)
1a	**2a**	H	CO_2Me	>20:1	83
1b	**2b**	CO_2Me	H	1:1	70
1c	**2c**	H	H	20:1	61



Scheme 1. Assignment of the relative stereochemistry of **2a**.

and more than 2 equivalents of NMO as a co-oxidant and then the crude diol products were acetylated to give diacetates **2a-c**. To our excitement, the dihydroxylation reaction of the γ-amino-α,β-unsaturated (*E*)-ester **1a** showed a ratio of more than 20 to 1 for its *anti*-isomer on its ^{1}H NMR spectrum. The monosubstituted olefin **1c** also resulted in the high *anti*-selectivity. These stereoselective results with a bulky *tert*-butyl group were quite high compared with those of previously reported results.[5a] Especially, the substrate-controlled or chiral agent-controlled dihydroxylations of monosubstituted allylic amines exhibited low and (or) mixed selectivity with a few exceptions.[3a,7] On the other hand, the same reaction of γ-amino-α,β-unsaturated (*Z*)-ester **1b** gave a 1:1 diastereomeric mixture.

The relative stereochemistry of a mixture of the diol products from **1a** was determined by transformation of the amino diol **3** into the corresponding γ-lactam derivatives **5** (Scheme 1). The *N*-Boc group of **3** was replaced with the *N*-Cbz group of **4** in two steps. Then, the *N*-Cbz protected diol **4** was treated under catalytic hydrogenation conditions to form a lactam ring after removal of the *N*-Cbz group, which was followed by acetylation to give a diastereomeric mixture of γ-lactams **5**. The coupling constant $J_{4,5}$ of a major isomer of **5**, ***5trans***, was 6.1 Hz, whereas that of a minor isomer, ***5cis***, showed larger value, 7.9 Hz. In general, the $J_{4,5}$ values of *cis*-γ-lactams are known to be larger than those of *trans*-γ-lactams.[5b,8] Therefore, the relative stereochemistry of the two hydroxyl groups in the major isomer of **2a** should be *anti* to the amino group. The *anti*-selectivity for the diacetates **2c** was also confirmed by measuring the $J_{4,5}$ value (7.3 Hz) of the corresponding oxazolidinone compound derived from the major isomer of **2c**.[9] Another evidence for the configurational assignment is given below.

The high *anti*-selectivity exhibited by conjugated (*E*)-ester **1a** and the monosubstituted olefin **1c** can be rationalized by employing the transition state models proposed by Houk, Kishi and Vedejs (Figure 1).[10] According to the Houk model, a deactivating substituent such as the *N*-Boc group would take preferentially the 'inside' conformation **A** to minimize its orbital overlap with the C-C double bond when the severe $A^{1,3}$ allylic strain is absent. Addition of OsO_4 from the bottom side of the '*N*-inside' conformer would give an *anti* diol as a major product. When the size of the alkyl group R is small, the '*N*-outside' conformer **B** would compete with the '*N*-inside' conformer of **A**, resulting in a reduced *anti*-selectivity. How-

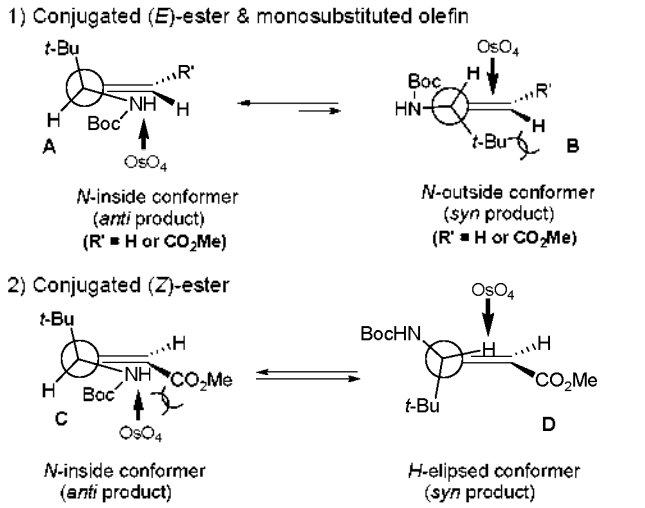
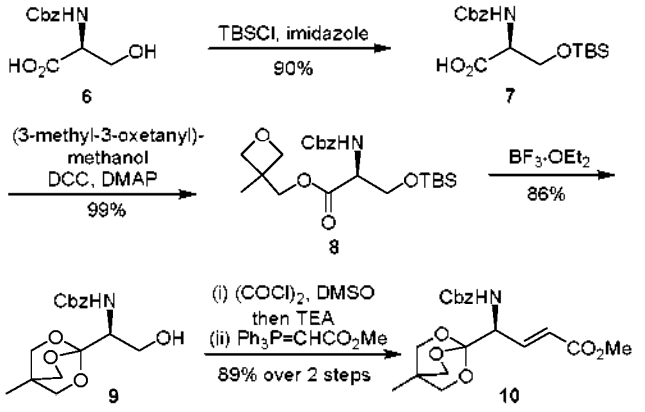


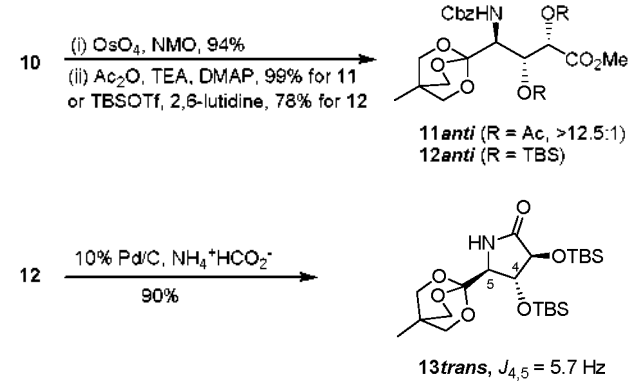
Figure 1. Probable transition state models.



Scheme 2. Preparation of the *N*-Cbz derivative of (*E*)-3,4-didehydroglutamate OBO ester **10**.

ever, when R is a bulky *t*-Bu group, the conformer **B** should be strongly disfavored because of the increased repulsive interaction between the *t*-Bu group and the double bond. In the case of conjugated (*Z*)-ester **1b**, the *N*-inside conformer **C** would be unfavorable owing to the severe steric hindrance between the methoxy carbonyl group and the *N*-Boc group. Therefore, the conjugated (*Z*)-ester **1b** in Table 1 resulted in poor selectivity. The *syn*-selectivity with some (*Z*)-olefins have been reported in literature.[5b,10d]

With the above results in hand, we wanted to apply the diastereoselective dihydroxylation reaction to the conjugated (*E*)-ester **10** with an OBO ester group in the alkyl chain. Since the OBO ester is a bulky group similar to the *t*-Bu group, a high diastereoselectivity of the dihydroxylation would be expected under the same reaction conditions. Moreover, the OBO ester group can be readily functionalized to a carboxylic acid or the acid derivatives such as an alcohol or an amine. If the desired high selectivity could be achieved, several interesting bioactive compounds with an amino diol unit would be efficiently prepared. Although the OBO ester group has been utilized for some diastereoselective reactions, it has not been utilized as a stereodirecting group in the OsO_4-catal-

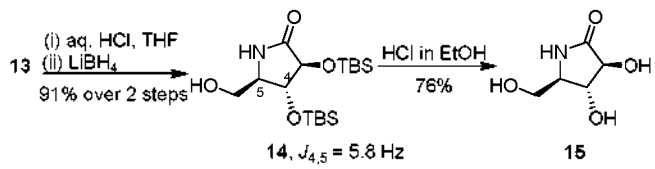


Scheme 3. Dihydroxylation of conjugated (*E*)-ester **10** and determination of the relative stereochemistry.

yzed dihydroxylation reactions to date.[11]

An *N*-Cbz derivative of (*E*)-3,4-didehydroglutamate OBO ester **10** was prepared from commercially available *N*-Cbz-L-serine **6** with a slight modification from the reported procedure (Scheme 2).[11] After a selective protection of the primary alcohol of **6** with a TBS group, a DCC-mediated coupling of the carboxylic acid of **7** with (3-methyl-3-oxetanyl) methanol produced oxetanylmethyl ester **8** in excellent yield. The esterification step required only a stoichiometric amount of (3-methyl-3-oxetanyl)methanol. Then, compound **8** was treated with $BF_3 \cdot OEt_2$ to give the OBO ester functionality of **9** with concomitant deprotection of the TBS group. The above modified procedure for the OBO ester formation did not require excessive amount of the rather expensive alcohol[11a] or conversion of the oxetanylalcohol into its tosylate before the esterfication step.[11b,c] Moreover, the desired oxetanylmethyl ester was prepared in higher yield and shorter reaction time. A Swern oxidation of OBO ester **9** followed by a Wittig olefination with the corresponding stabilized ylide provided the desired conjugated (*E*)-ester **10**.

The OsO_4-catalyzed dihydroxylation of **10** was conducted under the same conditions as shown in Scheme 1 (Scheme 3). The resulting amino diol was isolated in 94% yield but the diastereomeric ratio of the diol product was difficult to be determined because of the some broad peaks in its ^{1}H-NMR spectrum. After acetylation of the crude diol product, the diastereomeric ratio was shown to be more than 12.5:1 by ^{1}H NMR and GC/MS analyses of diacetate **11**. To confirm the relative configuration of the new stereogenic centers with the hydroxyl groups, we tried to convert diacetate **11** into the corresponding γ-lactam as shown in Scheme 1. However, some unknown side reactions occurred during the cyclization reaction of **11** to cause a low yield of the corresponding γ-lactam. Fortunately, a cyclization reaction of the TBS-protected amino diol **12** gave only the major isomer of the desired γ-lactam **13**, **13*trans***. The measured coupling constant $J_{4,5}$ of **13*trans*** was 5.7 Hz, which indicated that the major isomer was the *trans* isomer at C-4 and C-5 although the minor isomer of **13** could not be isolated. The *O*-Ac derivative of the major isomer of the γ-lactam, obtained from **11** as mentioned above, also had the similar $J_{4,5}$ value of 5.8 Hz. An unambiguous assignment of the relative stereochemistry was established after conversion of the major isomer of **13** into one of our target compounds **15**, a bioactive α-glucosidase inhibitor (see below Scheme 4).



Scheme 4. Synthesis of the target compound **15** from **13**.

It should be noted that the observed selectivity for the *anti* isomer (>12.5:1) in the present study is a much improved result. The reported diastereoselectivities from the γ-amino-α,β-unsaturated (*E*)-esters with an *N*-Boc or *N*-Cbz group were not consistent and useful.[3] Especially, the serine-derived γ-amino-α,β-unsaturated (*E*)-esters and ketones gave the mixed results ranging from 1:1.9 to 6:1 of an *anti*:*syn* ratio.[12] It is also interesting to note that the selectivity obtained from compound **10** is comparable to that of the γ-amino-α,β-unsaturated (*E*)-ester (*anti*:*syn* = 13:1) with a 2-aryloxazoline group in the alkyl chain, which was possible only with the chiral AD-mix-β reagent used.[12b]

The potential applications of the present method are an efficient and highly stereoselective synthesis of natural and unnatural compounds with an amino diol unit such as 3,4-dihydroxyglutamic acid,[8a] 3,4-di-*epi*-polyoxamic acid,[13] d-iminoarabinitol[14] and a key structural motif found in sphingosine analogs.[15] As an example, Scheme 4 shows a straightforward conversion of γ-lactam **13** into a chiral azasugar 2-pyrrolidinone **15**, an α-glucosidase inhibitor. Thus, the OBO ester group of **13** was hydrolyzed under acidic conditions and then, the resulting ester group was reduced by $LiBH_4$ to afford the primary alcohol of **14** in 91% yield. Finally, deprotection of the TBS groups gave (3*S*,4*R*,5*R*)-3,4-dihydroxy-5-hydroxymethyl-2-pyrrolidinone **15**. The NMR spectrum and optical rotation value well matched those reported in literature.[16] Thus, it established unequivocally the relative stereochemistry of **13*trans***.

In conclusion, we have found that the OsO_4-catalyzed dihydroxylation reactions of the monosubstituted allylic amine and the γ-amino-α,β-unsaturated-(*E*)-esters with a bulky group in the alkyl chain provide a high *anti*-selectivity even with versatile *N*-acyloxy protecting groups such as a *N*-Boc or *N*-Cbz group. The high selectivity was also possible even without addition of chiral agents. Therefore, the OBO ester group in the alkyl chain of the conjugated (*E*)-ester **10** was proved to be a functionalized stereodirecting group in the OsO_4-catalyzed dihydroxylations. The potential of the present method was demonstrated by an efficient conversion of the key *N*-Boc or *N*-Cbz intermediate **12** into one of the target compounds **15**, an α-glucosidase inhibitor. Its further synthetic applications to other bioactive target compounds are currently underway in our lab.

Experimental Section

Methyl (2*E*,4*R*)-4-(*tert*-butoxycarbonyl)amino-5,5-dime-

thylhex-2-enoate (1a). Mp 102-104 °C; $[\alpha]_D^{20}$ -2.4 (*c* 0.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.45 (s, 9H), 3.75 (s, 3H), 4.08-4.14 (m, 1H), 4.62 (br d, 1H, *J* = 9.6), 5.94 (d, 1H, *J* = 15.6), 6.97 (dd, 1H, *J* = 15.6, 6.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 28.2, 34.7, 51.4, 59.9, 79.4, 121.6, 146.2, 155.3, 166.5; HRMS (CI) calcd for $C_{14}H_{26}NO_4$ (M^++H) 272.1862, found 272.1861.

Methyl 4-(*tert*-butoxycarbonyl)amino-2,3-dihydroxy-5,5-dimethylhexanoate (3). To a solution of (*E*)-ester **1a** (271 mg, 1.0 mmole) and NMO (294 mg, 2.5 mmole) in dry THF (10 mL) was added OsO_4 (25 mg, 0.1 mmole). The resulting mixture was stirred for 8 h at room temperature and then, the reaction was quenched with a saturated aq. Na_2SO_3 solution (5 mL). The resulting mixture was extracted with Et_2O (20 × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by SiO_2 column chromatography (Hexane/EtOAc = 2:1) to give diol **3** (253 mg, 83%, > 20:1 diastereomeric mixture) as white solid. The major isomer of **3** (**3*anti*-(2*R*,3*S*,4*S*)**): mp 103-105 °C; $[\alpha]_D^{20}$ -1.0 (*c* 0.34, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 1.44 (s, 9H), 2.57 (d, 1H, *J* = 10.2), 3.53 (dd, 1H, *J* = 10.0, 8.3), 3.80 (d, 1H, *J* = 4.6), 3.83 (s, 3H), 4.00 (dd, 1H, *J* = 10.2, 8.3), 4.40 (d, 1H, *J* = 4.6), 4.93 (d, 1H, *J* = 10.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4, 28.3, 34.2, 52.7, 60.8, 72.2, 72.3, 80.2, 157.3, 173.0; HRMS (CI) calcd for $C_{14}H_{28}NO_6$ (M^++H) 306.1917, found 306.1917.

3,4-Diacetoxy-5-*tert*-butylpyrrolidin-2-one (5). Diol **4** (120 mg, 0.354 mmole) was dissolved in MeOH (10 mL), and both 10% Pd/C (60 mg) and HCO_2NH_4 (450 mg, 7.07 mmol) were sequentially added to the solution. The mixture was heated at 65 °C for 1 h. Then, the reaction mixture was cooled, filtered through a Celite pad followed by rinsing with Et_2O (10 mL × 2). The combined filtrate and washings were evaporated under reduced pressure. The crude product was dissolved in DCM (10 mL) and treated with Ac_2O (0.16 mL, 1.77 mmole), TEA (0.25 mL, 1.77 mmole) and DMAP (8 mg, 0.07 mmole). The reaction mixture was stirred for 3 h at room temperature. Then, the reaction was quenched with a 10% aq. $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with DCM (10 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by SiO_2 column chromatography (hexane/EtOAc = 1:1) to give diol **5** (82 mg, 90%, 20:1 diastereomeric mixture) as waxy solid. The major isomer of **5** (**5*trans*-(3*R*,4*S*,5*S*)**): $[\alpha]_D^{20}$ -20.1 (*c* 0.76, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H), 2.08 (s, 3H), 2.15 (s, 3H), 3.39 (dd, 1H, *J* = 6.1, 1.0), 5.37 (t, 1H, *J* = 6.1), 5.45 (d, 1H, *J* = 6.1), 6.93 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 20.7, 25.3, 32.9, 64.3, 73.6, 75.5, 169.7, 169.9, 170.1; HRMS (CI) calcd for $C_{12}H_{20}NO_5$ (M^++H) 258.1341, found 258.1342. The minor isomer of **5** (**5*cis*-(3*S*,4*R*,5*S*)**): ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 9H), 2.13 (s, 3H), 2.18 (s, 3H), 3.54 (d, 1H, *J* = 7.9), 5.58 (t, 1H, *J* = 7.9), 5.72 (d, 1H, *J* = 7.9), 6.38 (br s, 1H).

Methyl 4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-4-(benzyloxycarbonyl)amino-2,3-diacetoxybutanoate (11). To a solution of (*E*)-ester **10** (95 mg, 0.252 mmol) and NMO (74 mg, 0.629 mmol) in dry THF (5 mL) was added OsO_4 (7 mg, 0.025 mmol). The resulting mixture was stirred for 8 h at room temperature. The reaction was quenched with a saturated aqueous Na_2SO_3 solution (5 mL), and the aqueous layer was extracted by Et_2O (10 mL × 4). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude diol could be purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give a diastereomeric mixture of the diol product (97 mg, 94%) as waxy oil. For the in-situ acetylation, the crude diol product was dissolved in DCM (10 mL) followed by addition of Ac_2O (0.12 mL, 1.26 mmole), TEA (0.18 mL, 1.26 mmol) and DMAP (4 mg, 0.03 mmole). After 3 h at room temperature, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (10 mL). The resulting mixture was then extracted with Et_2O (10 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to give **11** (117 mg, 99%) as waxy solid (> 12.5:1 diastereomeric mixture). The major isomer of **11** (**11*anti*-(2*S*,3*R*,4*S*)**): ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (s, 3H), 1.97 (s, 3H), 2.19 (s, 3H), 3.72 (s, 3H), 3.88 (s, 6H), 4.41 (dd, 1H, *J* = 10.7, 6.6 Hz), 5.05 (d, 1H, *J* = 12.3 Hz), 5.13 (d, 1H, *J* = 12.3 Hz), 5.15 (d, 1H, *J* = 10.7 Hz), 5.56 (d, 1H, *J* = 2.2 Hz), 5.68 (dd, 1H, *J* = 6.6, 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 20.5, 20.6, 30.5, 52.5, 54.0, 66.9, 68.7, 71.8, 72.6, 107.3, 127.9, 128.0, 128.4, 136.3, 156.2, 167.8, 169.3, 169.8; HRMS (EI) calcd for $C_{23}H_{29}NO_{11}$ (M^+) 495.1741, found 495.1740.

Methyl 4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-4-(benzyloxycarbonyl)amino-2,3-di(*tert*-butyldimethylsilyloxy)butanoate (12). The crude amino diol (610 mg, 1.48 mmol) obtained from the OsO_4-catalyzed dihydroxylation reaction of (*E*)-ester **10** as mentioned above was dissolved in dry DCM (20 mL) followed by addition of TBSOTf (0.74 mL, 3.26 mmol) and 2,6-lutidine (0.69 mL, 5.93 mmol) at 0 °C under nitrogen atmosphere. After 30 min, the reaction mixture was warmed to room temperature and stirred for another 1 h. The reaction was quenched by a saturated aqueous $NaHCO_3$ solution (15 mL) and then, the resulting mixture was extracted with DCM (20 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified with silica gel column chromatography (hexane/EtOAc = 2:1) to give **12** (0.739 g, 78%) as white solid. The major isomer of **12** (**12*anti*-(2*S*,3*R*,4*S*)**): mp 138-140 °C; $[\alpha]_D^{20}$ +0.64 (*c* 0.62, EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ -0.09 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.10 (s, 3H), 0.80 (s, 12H), 0.93 (s, 9H), 3.68 (s, 3H), 3.91 (s, 6H), 4.11 (dd, 1H, *J* = 9.4, 4.6 Hz), 4.39 (dd, 1H, *J* = 4.6, 1.2 Hz), 4.79 (d, 1H, *J* = 1.2 Hz), 5.03 (d, 1H, *J* = 12.4 Hz), 5.09 (d, 1H, *J* = 12.4 Hz), 6.20 (d, 1H, *J* = 9.4), 7.28-7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.59, -4.90, -4.58, -4.47, 14.4, 17.7, 18.3, 25.4, 25.8, 30.5, 51.5, 59.0, 66.3, 68.9, 72.4, 75.0, 107.9, 127.4, 127.7, 128.1, 136.9, 156.9, 172.5; HRMS (CI) calcd for $C_{31}H_{53}NO_9Si_2$ (M^++H) 640.3339, found 640.3337.

(3*S*,4*R*,5*S*)-5-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-3,4-bis(*tert*-butyldimethylsilyloxy)pyrrolidin-2-one

(**13*trans***). To a solution of **12** (590 mg, 0.922 mmol) in EtOAc (25 mL) were added HCO_2NH_4 (1.18 g, 18.8 mmol) and 10 wt% Pd/C (300 mg). The resulting mixture was heated to reflux for 1 h. After the reaction was completed, the reaction mixture was filtered through a Celite pad and rinsed with EtOAc (20 mL × 2). Then the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (hexane/EtOAc = 2:1) to give only the major isomer of γ-lactam **13** (**13*trans***, 394 mg, 90%) as white solid. The minor isomer of **13** (**13*cis***) was scarcely detected and not isolable. Mp 135-137 °C; $[\alpha]_D^{20}$ -8.3 (*c* 0.68, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.14 (s, 3H), 0.19 (s, 3H), 0.82 (s, 3H), 0.89 (s, 9H), 0.92 (s, 9H), 3.38 (d, 1H, *J* = 5.7 Hz), 3.90 (s, 6H), 4.16 (dd, 1H, *J* = 5.7, 1.0 Hz), 4.35 (t, 1H, *J* = 5.7 Hz), 5.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.7, -4.5, -4.1, -3.8, 14.3, 17.9, 18.3, 25.8, 26.0, 30.7, 61.5, 72.5, 76.4, 78.5, 106.9, 172.8; HRMS (CI) calcd for $C_{22}H_{44}NO_6Si_2$ (M^-+H) 474.2707, found 474.2705.

(**3*S*,4*R*,5*R*)-5-Hydroxymethyl-3,4-bis(*tert*-butyldimethylsilyloxy)pyrrolidin-2-one (14).** To a solution of **13*trans*** (794 mg, 1.68 mmol) in THF (20 mL) was added an aqueous HCl solution (1 M, 0.2 mL) at room temperature. After stirring for 1 h, the reaction solvent was evaporated under reduced pressure. The crude product was dissolved in dry THF (20 mL) and then $LiBH_4$ (2.5 mL, 2.0 M in THF) was added to the reaction mixture at 0 °C. After 1.5 h, the reaction was quenched by a saturated aqueous NH_4Cl solution (10 mL). Then, the resulting mixture was extracted with Et_2O (25 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (hexane/EtOAc = 2:1) to give **14** (573 mg, 91%) as white solid. Mp 112-114 °C; $[\alpha]_D^{20}$ +0.82 (*c* 0.34, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.14 (s, 3H), 0.19 (s, 3H), 0.89 (s, 9H), 0.92 (s, 9H), 2.92 (t, 1H, *J* = 5.7 Hz), 3.39-3.44 (m, 1H), 3.54-3.60 (m, 1H), 3.78-3.84 (ddd, 1H, *J* = 11.9, 5.8, 3.2 Hz), 4.00 (t, 1H, *J* = 5.8 Hz), 4.15 (d, 1H, *J* = 5.8 Hz), 6.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.5, -4.4, -4.0, -3.9, 18.0, 18.4, 25.9, 26.0, 60.6, 62.7, 76.9, 78.0, 174.5; HRMS (CI) calcd for $C_{17}H_{38}NO_4Si_2$ (M^-+H) 376.2339, found 376.2341.

(**3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)pyrrolidin-2-one (15).** γ-Lactam **14** (100 mg, 0.266 mmole) was dissolved in EtOH (5 mL) and an aqueous HCl solution (6 M, 2 mL) was added to the solution at room temperature. The resulting mixture was stirred for 2 h. After the reaction was completed, the solvent was evaporated under reduced pressure. Then, the crude product was dissolved in Et_2O (10 mL) followed by addition of H_2O (10 mL), and the phases were separated. The aqueous layer was evaporated under reduced pressure to give the product **15** (30 mg, 76%) as white solid. Mp 135-137 °C; $[\alpha]_D^{20}$ +15.4 (*c* 0.72, H_2O); ^{1}H NMR (D_2O) δ 3.39-3.44 (m, 1H), 3.57 (dd, 1H, *J* = 12.3, 4.8 Hz), 3.75 (dd, 1H, *J* = 12.3, 3.0 Hz), 3.97 (t, 1H, *J* = 7.8 Hz), 4.27 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR (D_2O) δ 58.7, 60.7, 75.3, 76.3, 176.2; HRMS (CI) calcd for $C_5H_{10}NO_4$ (M^-+H) 148.0611, found 148.0610.

Acknowledgments. We thank the BK 21 Program and Agency for Defence Development of Korea for financial support. This work was also supported in part by Samsung Electronics Manufacturing Technology Team and KOSEF through Research Center for Energy Conversion and Storage.

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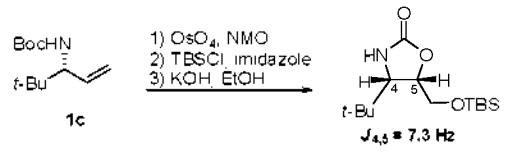

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