Efficient Asymmetric Synthesis of (*S*)-2-Methylasparagine

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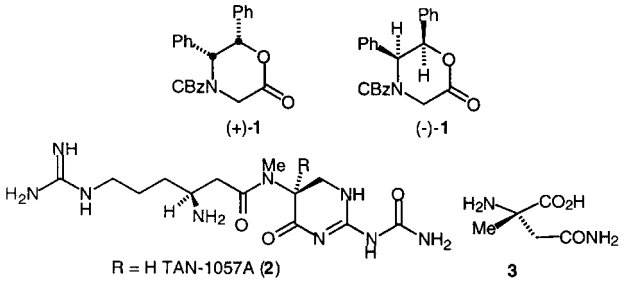
Abstract: (*S*)-2-methylasparagine was prepared from both (*5S, 6R*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one ((-)-**1**) and its antipode ((+)-**1**) *via* stereoselective glycine enolate alkylation as a key step.

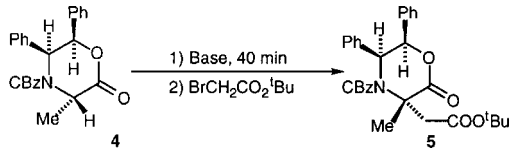
Synthesis of nonproteogenic unnatural α-amino acids has become of considerable interest, due to the impact such substances have made on the design and development of enzyme inhibitors and as tools for exploring enzymatic reaction mechanisms. As a consequence, the literature is replete with reports concerning asymmetric synthesis of optically pure amino acids.[1] In particular, α,α-dialkylated α-amino acids have attracted considerable attention since these substances have proven to be invaluable constituents of potent protease inhibitors such as dopa,[2,3] ornithine, glutamate, (*S*)-adenosylmethionine decarboxylase,[4] and aspartate aminotransferase.[5] In addition, the introduction of α,α-dialkylated amino acids into peptide chains results in restricting the available range of backbone conformations.[6] Recently, we reported the total syntheses of TAN-1057A (**2**)-D,[7] which are anti MRSA (methicillin-resistant *Staphylococcus aureus*) agents.[8,9] In connection with an ongoing synthetic study on the synthesis of TAN-1057A analogues, we required optically pure (*S*)-2-methylasparagine.



The synthesis of α-methylated asparagine has not been previously reported, and due to the potential use of such an amino acid in other applications in modifying bioactive asparagine-containing peptides, we report an efficient asymmetric synthesis of (*S*)-2-methylasparagine using (*5S,6R*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one ((-)-**1**) and its antipode ((+)-**1**). The approach described herein permits access to either the (*S*)- or (*R*)-enantiomer and should be applicable to the synthesis of a range of α-alkylated asparagine derivatives.

We have previously reported the asymmetric synthesis of monosubstituted and α,α-disubstituted α-amino acids using diphenyloxazinone derivatives (**1**) as templates.[10-13] First, we examined alkylation of **4,** which was derived from (-)-**1** in the reported manner,[11] under several reaction conditions (Scheme 1, Table 1).

The alkylation of compound **4**, which was prepared from (-)-lactone **1**, with potassium bis(trimethylsilyl)amide was, in contrast to what we have generally observed[11] for this type of reaction previously, found to be ineffective (entries 1-4 in table). On the other hand, a combination[14] of sodium bis(trimethylsilyl)amide and 15-crown-5 gave better results (entries 5-8 in table). Further, best results were obtained with low concentration of the substrate (**4**) (compare entries 7 *vs.* 8 in table). As a result, dialkylated lactone **5** was obtained in 71 % yield under the reaction conditions of entry 8 in Table 1.[15]



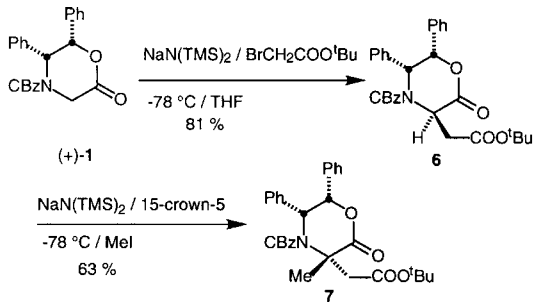
Scheme 1

Table 1. Enolate alkylation of compound **4**

Entry	Conc.Base (M)[a]	Additive	Temp. (°C)	Time (hr)	Yield (%)[b]
1	0.036KN(TMS)$_2$	none	-78	2	43
2	0.05 KN(TMS)$_2$	HMPA	-78 → 0	1.5	trace
3	0.01 KN(TMS)$_2$	18-crown-6	-78	0.5	-----[e]
4c	0.05 KN(TMS)$_2$	none	-78	1	-----[e]
5	0.05 NaN(TMS)$_2$	15-crown-5	-78	2	57
6	0.05 NaN(TMS)$_2$	15-crown-5	-78 → rt[d]	12	34
7	0.06 NaN(TMS)$_2$	15-crown-5	-78	7	40
8	0.03 NaN(TMS)$_2$	15-crown-5	-78	0.33	71

a) Concentration of the lactone **4**. b) Isolated yields of **5**. c) To a THF solution of *tert*-butyl α-bromoacetate and the lactone **4**, KN(TMS)$_2$ was added. d) Room temperature. e) Unidentified compound was obtained

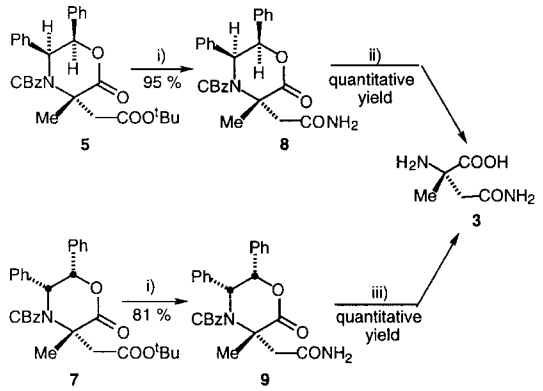
Next, we examined an alternative synthesis of the dialkylated lactone **7** from the (+)-lactone **1**. The primary distinction of this approach is that the order of alkylation reactions of the (+)-lactone **1** occurs in the reversed sequence relative to that employed with (-)-**1**. Thus, *tert*-butoxycarbonylmethylation of compound (+)-**1**, *via* enolate generation with sodium bis(trimethylsilyl)amide and quenching with *tert*-butyl α-bromoacetate furnished **6** in 81% yield as a single diastereomer.[16] Next, methylation of **6** was accomplished with sodium bis(trimethylsilyl)amide and 15-crown-5, followed by quenching the enolate with methyl iodide providing the dialkylated compound **7** in 51% overall yield from (+)-**1** as a single diastereomer (Scheme 2).[17]



Scheme 2

With the dialkylated compounds **5** and **7** in hand, transformation of these substances to (*S*)-2-methylasparagine (**10**) was examined and accomplished as shown in Scheme 3.

Removal of the *tert*-butyl group from **5** and **7** with TFA was accomplished, followed by amination with EEDQ and ammonium hydrogencarbonate[18] to give the corresponding amides **8** and **9** in good yields.[19] Finally, the hydrogenolysis of diphenyloxazines **8** and **9** with H_2 (60 psi) in the presence of $PdCl_2$ was accomplished furnishing (*S*)-2-methylasparagine (**3**) in essentially quantitative yields.[20]



Reagents and conditions: i) a) TFA/CH_2Cl_2, room temperature, 1hr; b) EEDQ/NH_4HCO_3/$CHCl_3$; iii) H_2 (60 psi)/$PdCl_2$, EtOH-THF (2:1)

Scheme 3

In summary, the asymmetric synthesis of (*S*)-2-methylasparagine **3** from both (*5S,6R*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one ((-)-**1**) and its antipode ((+)-**1**) has been acheived in 5 steps. Due to the commercial availability of both (+)-**1** and (-)-**1**, this approach can be directly utilized for preparing the enantiomer of **3** in an unambiguous fashion.

Acknowledgment. This work was supported by the National Science Foundation.

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13) The requisite diphenyloxazines **1** utilized to prepare compounds **4** and **6** are commercially available from Aldrich Chemical Co.; (-)-**1**: catalog #33187-2 (CAS Registry #100516-54-9); the antipode of (+)-**1**: Catalog #33185-6 (CAS Registry #105228-46-4).

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15) **Preparation of (*3S,5S,6R*)-4-(benzyloxycarbonyl)-3-*tert*-butoxycarbonylmethyl-5,6-diphenyl-3-methyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (5).** To a THF solution (180 mL) of compound **4**[11] (1.89 g, 4.71 mmol) and 15-crown-5 (9.34 g, 47.4 mmol), 1.0 M $NaN(TMS)_2$ in THF (7.1 mL, 7.1 mmol) was added dropwise at -78 °C under an Ar atmosphere. After the resulting solution was stirred at the same temperature for 30 min, *tert*-butyl α-bromoacetate (2.1 mL, 2.76 g, 14.1 mmol) was added dropwise to the reaction mixture. After the reaction mixture was stirred at -78 °C for 20 min. To a reaction mixture, sat. NH_4Cl (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with AcOEt (50 mL x 2). The combined organic layer was washed with sat. NaCl (150 mL x 3), dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by silica gel flash chromatography (eluted with Hexanes : EtOAc = 7 : 1) to give compound **5** (colorless solid, 1.72 g, 71 % yield from compound **4**). Colorless prisms ($^iPr_2O$), mp 152-153 °C. $[\alpha]_D^{25}$ = +96.0° (CH_2Cl_2, *c* = 0.68). ^1H NMR (300 MHz) (393 K, DMSO-d_6) δ TMS: 1.41 (9H, s), 1.66 (3H, s), 3.08 (1H, d, J = 14.8 Hz), 3.62 (1H, d, J = 15.0 Hz), 5.16 (2H, s), 5.66 (1H, d, J = 3.3 Hz), 6.28 (1H, d, J = 3.6 Hz), 7.00-7.04 (2H, m), 7.08-7.31 (13H, m). IR (KBr): 1746, 1712 (C=O) cm^{-1}. MS(FAB+): 516 (M^++H). Anal. Calcd for $C_{31}H_{33}NO_6$: C, 72.21; H, 6.45; N, 2.72. Found: C, 72.40; H, 6.43; N, 2.75.

16) **Preparation of (*3R,5R,6S*)-4-(benzyloxycarbonyl)-3-*tert*-butoxycarbonylmethyl-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (6).** To a THF solution (110 mL) of compound (+)-**1** (2.00 g, 5.17 mmol), 1.0 M $NaN(TMS)_2$ in THF (5.17 mL, 5.17 mmol) was added dropwise at -78 °C under an Ar atmosphere. After the resulting solution was stirred at the same temperature for 40 min, *tert*-butyl α-bromoacetate (0.92 mL, 1.21 g, 6.2 mmol) in THF (10 mL) was added dropwise to the reaction mixture. After the reaction mixture was stirred at -78 °C for 2 hr, and poured into EtOAc (200 mL). The organic layer was washed with water (150 mL x 2) and sat. NaCl (150 mL x 1), dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by silica gel flash chromatography (eluted with CH_2Cl_2 : EtOAc = 20 : 1) to give compound **6** (colorless solid, 2.09 g, 81 % yield from compound (+)-**1**). Colorless prisms ($^iPr_2O$), mp 191-192 °C. $[\alpha]_D^{25}$ = +12.1° (CH_2Cl_2, *c* = 1.07). ^1H NMR (300 MHz) (393 K, DMSO-d_6) δ TMS: 1.44 (9H, s), 3.07 (1H, dd, J = 14.3 Hz, 5.4 Hz), 3.14 (1H, dd, J = 14.3 Hz, 7.5 Hz), 4.97 (1H, d, J = 12.9 Hz), 5.02 (1H, d, J = 12.6 Hz), 5.23 (1H, dd, J = 7.5 Hz, 4.5 Hz), 5.25 (1H, d, J = 3.0 Hz), 6.25 (1H, d, J = 3.0 Hz), 6.57-6.60 (2H, m), 7.01-7.26 (13H, m). IR (KBr): 1741, 1726, 1696 (C=O) cm^{-1}. MS(FAB+): 502 (M^++H), 446 (M^+-*tert*-Bu). Anal. Calcd for $C_{30}H_{31}NO_6$: C, 71.84; H, 6.23; N, 2.79. Found: C, 71.70; H, 6.00; N, 2.79.

17) **Preparation of (*3S,5R,6S*)-4-(benzyloxycarbonyl)-3-*tert*-butoxycarbonylmethyl-5,6-diphenyl-3-methyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (7).** To a THF solution (30 mL) of compound **6** (0.378 g, 0.75 mmol) and MeI (0.47 mL, 1.06 g, 7.5 mmol), 1.0 M $NaN(TMS)_2$ in THF (0.83 mL, 0.83 mmol) was

added dropwise at -78 °C under an Ar atmosphere, followed by addition of 15-crown-5 (0.99 g, 4.5 mmol). After the resulting solution was stirred at the same temperature for 1 hr, poured into EtOAc (60 mL). The organic layer was washed with water (30 mL x 2) and sat. NaCl (30 mL x 1), successively, and dried over anhydrous $MgSO_4$, filtered, concentrated, and purified by silica gel radial chromatography (eluted with Hexanes : CH_2Cl_2 : Et_2O = 8 : 2 : 1) to give compound **7** (colorless semi-solid, 0.245 g, 63 % yield from compound **6**). Colorless semi-solid, mp 48-50 °C . $[\alpha]_D^{25}$ = +18.2° (CH_2Cl_2, *c* = 0.62). ^{1}H NMR (300 MHz) (393 K, DMSO-d_6) δ TMS: 1.30 (9H, s), 2.00 (3H, s), 3.23 (1H, d, J = 15.3 Hz), 3.34 (1H, d, J = 15.3 Hz), 5.05 (1H, d, J = 12.3 Hz), 5.14 (1H, d, J = 12.6 Hz), 5.49 (1H, d, J = 3.3 Hz), 6.27 (1H, d, J = 3.6 Hz), 7.01-7.28 (15H, m). IR (KBr): 1758, 1735, 1701 (C=O) cm^{-1}). MS(FAB+): 516 (M^++H). HRMS Calcd for $C_{31}H_{34}NO_6$ for 516.2386. Found: 516.2402.

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(19) **General Procedure for transformation of *tert*-butyl esters 5 and 7 to amides 8 and 9.** A CH_2Cl_2 solution (1.0 mL) of *tert*-butyl ester (0.213 g, 0.413 mmol) and TFA (1.0 mL) was stirred at 0 °C for 10 min and then at room temperature for 1 h. After evaporation of the solvent and excess TFA, EEDQ (0.157 g, 0.62 mmol), NH_4HCO_3 (0.196 g, 2.48 mmol), $CHCl_3$ (5 mL) were added to the residue, successively. The resulting mixture was stirred at room temperature for 12 hrs and diluted with CH_2Cl_2 (20 mL). The organic phase was washed with H_2O (15 mL x 2), dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure to give an oily residue, which was purified by using radial TLC (Hexanes: AcOEt = 2 : 5).

(*3S,5S,6R*)-4-(benzyloxycarbonyl)-3-carbamoylmethyl-5,6-diphenyl-3-methyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (8). 95 % yield from compound **5**. Colorless amorphous solid, Mp 92-94 °C. $[\alpha]_D^{25}$ = +116° (CH_2Cl_2, *c* = 0.27). ^{1}H NMR (300 MHz) (393 K, DMSO-d_6) δ TMS: 1.67 (3H, s), 2.96 (1H, d, J = 15.0 Hz), 3.77 (1H, d, J = 15.6 Hz), 5.18 (2H, s), 5.64 (1H, d, J = 3.6 Hz), 6.50 (1H, d, J = 3.3 Hz), 6.81 (2H, brs), 7.06-7.34 (15H, m). IR (KBr): 3455, 3353 (NH), 1741, 1697 (C=O) cm^{-1}. MS (FAB+): 459 (M^++H), 415 (M^+-$CONH_2$). Anal. Calcd for $C_{27}H_{26}N_2O_5$: C, 70.73; H, 5.72; N, 6.11. Found: C, 70.74; H, 6.01; N, 5.89.

(*3S,5R,6S*)-4-(benzyloxycarbonyl)-3-carbamoylmethyl-5,6-diphenyl-3-methyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (9). 81% yield from compound **7**. Colorless amorphous solid, mp 69-70 °C . $[\alpha]_D^{25}$ = +15.2° (CH_2Cl_2, *c* = 1.08). ^{1}H NMR (300 MHz) (348 K, DMSO-d_6) δ TMS 1.99 (3H, s), 3.28 (1H, d, J = 15.0 Hz), 3.56 (1H, d, J = 15.0 Hz), 5.05 (1H, d, J = 12.9 Hz), 5.12 (1H, d, J = 12.3 Hz), 5.40 (1H, d, J = 3.9 Hz), 6.31 (1H, d, J = 3.6 Hz), 6.67 (2H, brs), 7.00-7.32 (15H, m). IR (KBr): 3468, 3358 (NH, OH), 1752, 1702 (C=O) cm^{-1}. MS(FAB+): 459 (M^++H). HRMS Calcd for $C_{27}H_{27}N_2O_5$ (M^++H): 459.1920. Found: 459.1937.

(20) **General Procedure for hydrogenation of amides 8 and 9.** A mixture of the amide (2.73 g, 5.96 mmol), $PdCl_2$ (0.32 g), THF-EtOH (1 : 2) (20 mL) was stirred vigorously under H_2 (60 psi) for 3 days. After filtration through ®Celite 545, the ®Celite 545 was washed with EtOH, and the solvent was evaporated under reduced pressure to give a residue, which was dissolved in H_2O (30 mL). The aqueous phase was washed with Et_2O (10 mL x 3) and H_2O was evaporated at room temperature to give a pure amino acid (**3**) (0.74 g, 94% yield) as a colorless solid.

(*S*)-2-Methylasparagine (3). 98:2 er (on the basis of ^{19}F-NMR of the Mosher amide of compound **3**) Colorless amorphous solid, mp 85-87 °C. $[\alpha]_D^{25}$ = +17.7 ° (EtOH, *c* = 0.43). ^{1}H NMR (300 MHz) (300 K, D_2O) δ TMS: 1.60 (3H, s), 2.86 (1H, d, J = 17.4 Hz), 3.12 (1H, d, J = 17.4 Hz). IR (KBr): 3405, 3176 (NH, OH), 1728, 1671 (C=O) cm^{-1}. MS(FAB+): 147 (M^++H). HRMS Calcd for $C_5H_{11}N_2O_3$ (M^++H): 147.0770. Found: 147.0774.