Diastereoselective Solid-Phase Radical Addition to Oxime Ether Anchored to Polymer Support

Hideto MIYABE,[1] Chihiro KONISHI, and Takeaki NAITO*

Kobe Pharmaceutical University; Motoyamakita, Higashinada-ku, Kobe 658–8558, Japan.
Received December 27, 2002; accepted February 8, 2003; published online February 10, 2003

Stereocontrol in radical reactions of oxime ether anchored to polymer support was studied. Highly diastereoselective solid-phase radical reaction was achieved by using triethylborane and diethylzinc as a radical initiator at low reaction temperature, providing a novel method for the synthesis of the α-amino acid derivatives with excellent diastereoselectivities.

Key words solid-phase; radical reaction; oxime ether; diastereoselective

Combinatorial chemistry has became a core technology for the rapid development of novel lead compounds in the pharmaceutical industry and for the optimization of therapeutic efficacy.[2—9] Therefore, the development of solid-phase radical reactions is a new subject of considerable interest as a carbon–carbon bond-forming method on solid support.[10—19] Some recent reports have shown that radical reactions could be performed on solid supports by using AIBN or SmI_2 as a radical initiator. We have also demonstrated that triethylborane or diethylzinc have the potential to induce intermolecular radical reactions on solid support.[20—22]

Stereocontrol in free radical-mediated reactions has been of great importance in organic synthesis. In recent years, a high degree of stereocontrol in solution-phase radical reactions has been achieved at low reaction temperature mainly by using triethylborane as a radical initiator. We have recently demonstrated that the employment of triethylborane or diethylzinc, particularly at low reaction temperature, facilitated the control of stereochemistry in solid-phase radical reaction.[20—23] We report here in detail the triethylborane- or diethylzinc-induced diastereoselective radical reaction of Oppolzer's camphorsultam derivatives of oxime ether anchored to polymer support.[23]

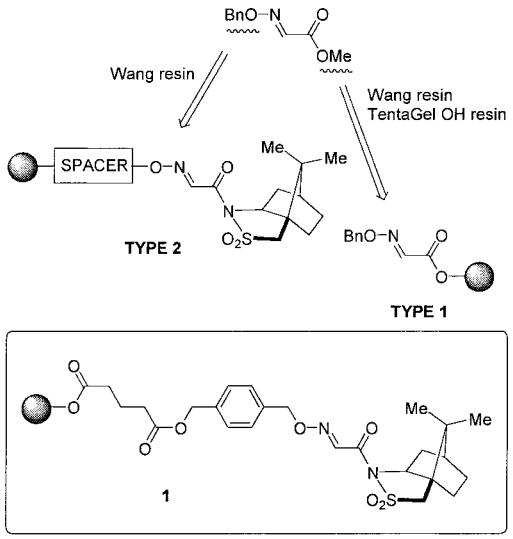

Chart 1

Results and Discussion

Our recent studies showed that triethylborane has the potential to induce solid-phase radical reaction of oxime ether (TYPE 1) on solid support even at −78 °C and acts multiply as a radical initiator, a Lewis acid, and a radical terminator (Chart 1).[20] Based on these results, we next investigated the control of stereochemistry in solid-phase reactions of oxime ether (TYPE 2) by using triethylborane and diethylzinc at low reaction temperature.[23] The auxiliary of choice was Oppolzer's camphorsultam since it had shown good characteristics in our previous work on solution-phase radical reactions.[24,25]

Preparation of chiral oxime ether **1** anchored to a polymer support is shown in Chart 2. Treatment of *p*-xylylene glycol **2** with TBSCl and imidazole gave the *t*-butyldimethylsilylated *p*-xylylene glycol derivative **3** in 62% yield. Mesylation of **3** in the presence of triethylamine in CH_2Cl_2 followed by treatment with *N*-hydroxyphthalimide in one-pot afforded the desired imide **5** in 79% yield.[26] One-pot preparation of oxime ether **7** was achieved by treatment of imide **5** with hydrazine monohydrate in MeOH and subsequent condensation with 2-hydroxy-2-methoxyacetic acid methyl ester.[27] Treatment of oxime ether **7** with (1*R*)-(+)-2,10-camphorsultam in the presence of trimethyl aluminum in boiling dichloroethane gave oxime ether **8** having sultam in quantitative yield as a single *E* isomer. Treatment of **8** with pyridinium *p*-toluenesulfonate in EtOH at 60 °C gave deprotected alcohol **9** in 89% yield. Treatment of alcohol **9** with glutaric anhydride gave carboxylic acid **10** in 99% yield. The carboxylic acid **10** could be attached to Wang resin by the treatment with DCC in the presence of DMAP in CH_2Cl_2 at 20 °C for 12 h to give the resin-bound oxime ether **1**.[28] The loading level of the resin-bound glyoxylic oxime ether **1** was determined to be 0.83 mmol/g by quantification of nitrogen by elemental analysis.

Expecting that the direct comparison of the solid-phase radical reactions with the solution-phase radical reactions would lead to informative and instructive suggestions regarding reactivity and stereoselection in solid-phase reaction, we also investigated the solution-phase radical addition to oxime ether **10** (Chart 3). We first investigated the simple addition of an ethyl radical, generated from triethylborane and O_2, to the oxime ether **10** in CH_2Cl_2 at −78 °C (Table 1, entry 1). As expected, the reaction proceeded smoothly to give the eth-

* To whom correspondence should be addressed. e-mail: taknaito@kobepharma-u.ac.jp

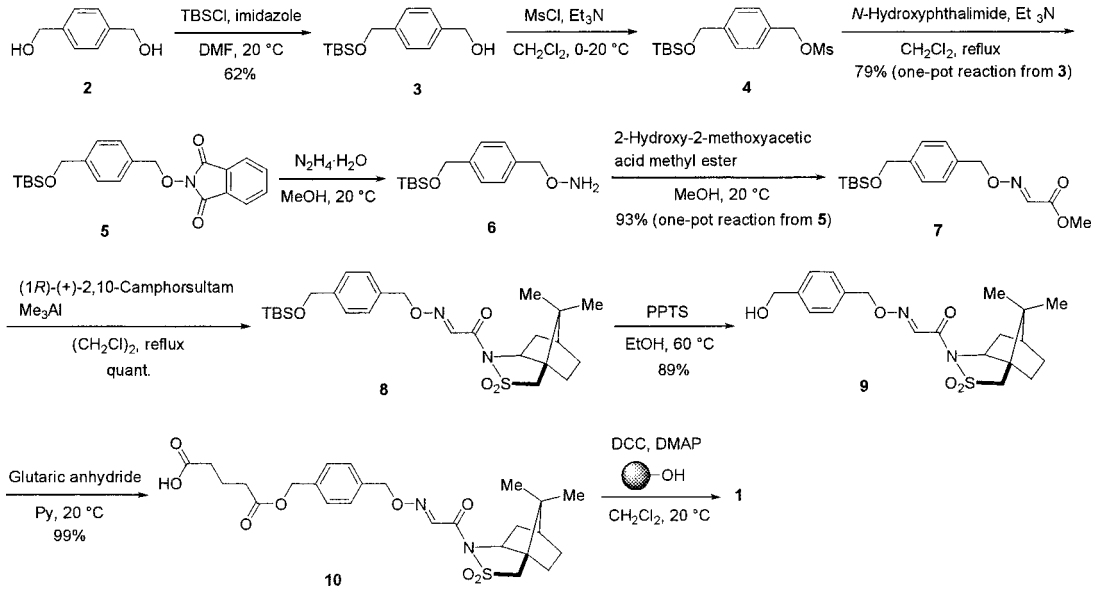

Chart 2

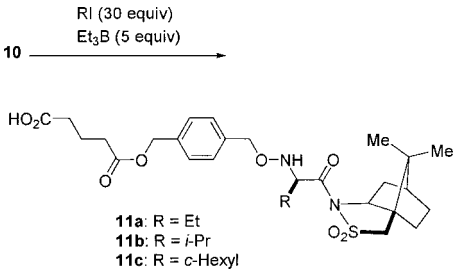

Chart 3

Table 1. Solution-Phase Radical Addition to **10**

Entry	RI	Solvent	T (°C)	Product	Yield (%)[c]	Selectivity[d]
1[a]	None	CH_2Cl_2	−78	**11a**	91	>95% de
2[a]	None	Toluene	−78	**11a**	82	>95% de
3[b]	*i*-PrI	CH_2Cl_2	0	**11b**	86	90% de
4[b]	*c*-Hexyl I	CH_2Cl_2	0	**11c**	79	91% de

a) Reactions were carried out with Et_3B (5 eq) in CH_2Cl_2 or toluene at −78 °C. *b*) Reactions were carried out with RI (30 eq) and Et_3B (5 eq) in CH_2Cl_2 at 0 °C. *c*) Isolated yields. *d*) Diastereoselectivities were determined by ^{1}H-NMR analysis.

ylated product **11a** in 91% yield. The diastereomeric purity was found to be not less than 95% de. The absolute configuration of major product was assigned to be *R* since their ^{1}H-NMR data showed similarity with that of major product in solution-phase radical reaction showed in our recent report.[24,25] The replacement of CH_2Cl_2 with toluene as a solvent were also effective for the reaction (entry 2). The development of tin-free radical reactions has generated considerable interest from both economical and environmental points of view. We recently reported the solution-phase radical addition to oxime ethers in the absence of Bu_3SnH and by using Et_3B or Et_2Zn,[29,30] which acts multiply as a Lewis acid, a radical initiator, and a terminator. Thus, we next investigated the isopropyl radical addition to oxime ether **10** in the absence of tributyltin hydride under the iodine atom-transfer reaction conditions (entry 3). The isopropyl radical addition to **10** was carried out with isopropyl iodide (30 equiv) and triethylborane (5 eq) in the absence of tributyltin hydride in CH_2Cl_2 at 0 °C for 30 min. After purification, the desired isopropylated amino acid **11b** was obtained in 86% combined yield and in 90% de. The addition of a cyclohexyl radical also proceeded smoothly under the same reaction conditions to give the cyclohexylated product **11c** in 79% yield with good diastereoselectivity (entry 4).

We next investigated the ethyl radical addition to the Wang resin-bound oxime ether **1** (Chart 4). To a flask containing oxime ether **9** and undegassed CH_2Cl_2 was added a commercially available 1.0 M solution of triethylborane in hexane, and then the reaction mixture was stirred at −78 °C for 30 min (Table 2, entry 1). The resin **12a** was then filtered and washed successively with CH_2Cl_2 and AcOEt, and the subsequent cleavage of the resin with trifluoroacetic acid (TFA)/CH_2Cl_2 (1 : 5, v/v) gave the crude ethylated α-amino acid derivative which was purified by the preparative TLC (hexane/AcOEt 2 : 3, v/v) to afford the amino acid derivative **11a** in 74% isolated yield. The absolute configuration of major product was R and the diastereomeric purity was not less than 95% de. The solid-phase reaction of **1** in toluene also proceeded smoothly under similar reaction conditions (entry 2). Recently, Ryu and Komatsu reported that diethylzinc-air system can serve as an initiator of tin hydride-mediated radical reaction as well as triethylborane.[31] In order to test the viability of diethylzinc, we next investigated the ethyl radical addition to oxime ether **1** using a commercially available 1.0 M solution of diethylzinc at −78 °C (entries 3, 4). Diethylzinc could also be utilized to achieve a high degree of stereocontrol in solid-phase radical reaction of **1** to afford the ethylated product **11a** in good isolated yields with excellent diastereoselectivities. It is noteworthy that diethylzinc works well as an effective radical initiator for the solid-phase radical reaction without interference of polystyrene skeleton of the resin, and good chemical yield was observed even at low reaction temperature.

To test the generality of the solid-phase radical reaction of **1**, we next investigated the reaction using different radical

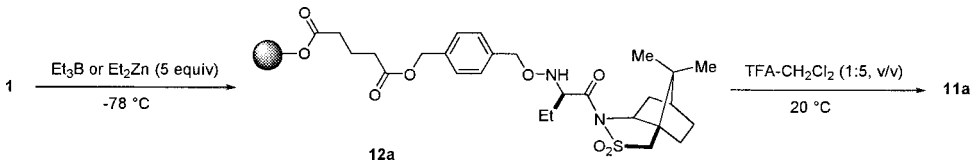

Chart 4

Table 2. Solid-Phase Ethyl Radical Addition to **1**[a]

Entry	Initiator	Solvent	Yield (%)[b]	Selectivity[c]
1	Et_3B	CH_2Cl_2	74	>95% de
2	Et_3B	Toluene	67	>95% de
3	Et_2Zn	CH_2Cl_2	67	>95% de
4	Et_2Zn	Toluene	59	>95% de

a) Reactions were carried out with Et_3B or Et_2Zn (5.0 eq) in CH_2Cl_2 at −78 °C. *b*) Isolated yields. *c*) Diastereoselectivities were determined by ^{1}H-NMR analysis.

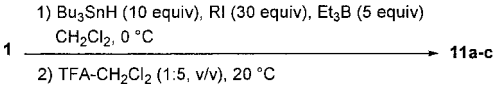

Chart 5

Table 3. Solid-Phase Alkyl Radical Addition to **1**

Entry	RI	Additive	T (°C)	Yield (%)[c]	Product
1[a]	*i*-PrI	Bu_3SnH	−78	43	**11b** : **11a** = 1 : 4
2[a]	*i*-PrI	Bu_3SnH	0	41	**11b** : **11a** = 1 : 1
3[a]	*c*-Hexyl I	Bu_3SnH	0	45	**11c** : **11a** = 1 : 5
4[b]	*i*-PrI	none	0	78	**11b** : **11a** = 1 : 4

a) Reactions were carried out with RI (30 eq), Bu_3SnH (10 eq), and Et_3B (5 eq) in CH_2Cl_2. *b*) Reactions were carried out with RI (30 eq) and Et_3B (5 eq) in CH_2Cl_2. *c*) Combined yields.

precursors under the stannyl radical-mediated reaction conditions (Chart 5). However, the reactivity of oxime ether **1** anchored to polymer support was quite different from that of oxime ether **10** in solution-phase reactions. In the case of the isopropyl radical addition to **1** in the presence of Bu_3SnH (10 eq) at −78 °C, the addition of ethyl radical, generated from triethylborane, competed with the stannyl radical-mediated isopropyl radical addition to give a small amount of the isopropylated product **11b** and a large amount of the undesired ethylated product **11a** in 43% combined yield (Table 3, entry 1). The formation of **11b** was found to be dependent on the reaction temperature, thus changing the temperature from −78 °C to 0 °C led to an effective increase in the ratio **11b**/**11a** to 1 : 1 (entry 2). The addition of a bulky cyclohexyl radical proceeded in low chemical efficiency under the same reaction conditions to give a large amount of the undesired ethylated product **11a** (entry 3). As comparison with the stannyl radical-mediated reaction, we also investigated the isopropyl radical addition to **1** in the absence of Bu_3SnH (10 eq) at −78 °C (entry 4). However, the addition of ethyl radical, generated from triethylborane, competed with iodine atom-transfer process to give a large amount of the ethylated product **11a**. Although the precise reason for the preferential ethylation is unclear, triethylborane presumably concentrated on solid-support as Lewis acid and gave a large amount of ethyl radical around the surface of resin.

Selective formation of the desired alkylated products **11** was achieved in the reaction using triethylborane in RI/toluene (4 : 1, v/v) at 0 °C (Chart 6). The isopropyl radical addition to **1** in *i*-PrI/toluene (4 : 1, v/v) proceeded smoothly to give the isopropylated product **11b** in 69% isolated yield with good diastereoselectivity after purification by the preparative TLC (Table 4, entry 1). The addition of a bulky cyclohexyl radical proceeded in slightly low chemical efficiency under the same reaction conditions to give the cyclohexylated product **11c** in 58% isolated yield (entry 2). Diethylzinc worked well under similar reaction conditions to give the alkylated products with good selectivity (entries 3, 4). In the solid-phase reactions, the often tedious workup to remove excess reagents from reaction mixture was eliminated by washing of the resin with solvents. Additionally, the carbon–carbon bond-forming solid-phase radical reactions are run without any special precautions such as dry, degassing and purification of solvents and reagents. Thus, employment of a neutral species such as an uncharged free radical would overcome the tedious operations with organometallic reagents on solid-phase reactions.

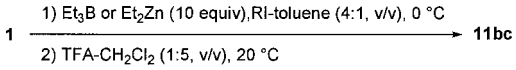

Chart 6

Table 4. Solid-Phase Alkyl Radical Addition to **1** in RI-Toluene[a]

Entry	Initiator	RI	Product	Yield (%)[b]	Selectivity[c]
1	Et_3B	*i*-PrI	**11b**	69	92% de
2	Et_3B	*c*-Hexyl I	**11c**	58	92% de
3	Et_2Zn	*i*-PrI	**11b**	53	90% de
4	Et_2Zn	*c*-Hexyl I	**11c**	41	90% de

a) Reactions were carried out with Et_3B or Et_2Zn (10 eq) in *i*-PrI/toluene (4 : 1, v/v) at 0 °C. *b*) Isolated yields of major diastereomers **11b** and **11c**. *c*) Diastereoselectivities were determined by ^{1}H-NMR analysis.

In conclusion, we have demonstrated the utility of triethylborane and diethylzinc in stereoselective solid-phase radical reactions. The radical addition to the chiral oxime ethers anchored to a polymer support proceeded smoothly even at low reaction temperature to give α-amino acid derivatives with excellent diastereoselectivities.

Experimental

General Melting points are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded at 200 or 300 MHz and at 50 or 125 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by electron ionization (EI), chemical ionization (CI), or secondary ion (SI)-MS methods. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$). Flash column chromatography was performed using E. Merck Kieselgel 60 (230—400 mesh).

4-(*t*-Butyldimethylsiloxymethyl)phenylmethanol (3) To a solution of *p*-xylyene glycol (1.0 g, 7.2 mmol) and imidazole (1.2 g, 18 mmol) in *N*,*N*-dimethylformamide (DMF) (3 ml) was added dropwise a solution of *t*-butyldimethylsilyl chloride (1.1 g, 7.3 mmol) in DMF (5 ml) under a nitrogen at-

mosphere at 20 °C. After the reaction mixture was stirred at the same temperature for 3 h, the reaction mixture was diluted with Et_2O. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 5 : 1) afforded **3** (1.1 g, 62%) as a colorless oil and 1,4-di(*t*-butyldimethylsiloxymethyl)benzene (0.26 g, 10%) as a white solid. **3**: IR ($CHCl_3$) cm^{-1}: 3608, 3447, 2930, 1514, 1471. ^{1}H-NMR ($CDCl_3$) δ: 7.29 (4H, m), 4.73 (2H, s), 4.62 (2H, br s), 0.94 (9H, s), 0.09 (6H, s). ^{13}C-NMR ($CDCl_3$) δ: 140.7, 139.4, 126.8, 126.1, 65.0, 64.6, 25.8, 18.2, −5.4. high resolution (HR)-MS *m/z*: 252.1554 (Calcd for $C_{14}H_{24}O_2Si$: 252.1544).

1,4-Di(*t*-butyldimethylsiloxymethyl)benzene: IR ($CHCl_3$) cm^{-1}: 2956, 1472. ^{1}H-NMR ($CDCl_3$) δ: 7.28 (4H, m), 4.73 (4H, s), 0.94 (18H, s), 0.09 (12H, s). ^{13}C-NMR ($CDCl_3$) δ: 140.0, 125.9, 64.8, 25.8, 18.3, −5.4. HR-MS *m/z*: 366.2419 (Calcd for $C_{20}H_{38}O_2Si_2$: 366.2408).

***N*-[4-(*t*-Butyldimethylsiloxymethyl)benzyloxy]phthalimide (5)** To a solution of **3** (7.3 g, 29 mmol) and Et_3N (4.4 ml, 32 mmol) in CH_2Cl_2 (40 ml) was added dropwise mesyl chloride (2.5 ml, 32 mmol) under a nitrogen atmosphere at 0 °C. After the reaction mixture was stirred at the same temperature for 1 h, Et_3N (4.4 ml, 32 mmol) and *N*-hydroxyphthalimide (5.9 g, 58 mmol) were added at 20 °C. After being heated at reflux for 8 h, the solvent was evaporated at reduced pressure. After the resulting residue was dissolved in AcOEt, the organic phase was washed with 1 N NaOH, saturated aqueous $NaHCO_3$, and water, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by recrystallization (hexane/AcOEt) afforded **5** (9.0 g, 79%) as colorless crystals: mp 82—84 °C (hexane/AcOEt); IR ($CHCl_3$) cm^{-1}: 2956, 1733, 1469. ^{1}H-NMR ($CDCl_3$) δ: 7.68—7.81 (4H, m), 7.50, 7.33 (each 2H, d, J=8.0 Hz), 5.20, 4.74 (each 2H, s), 0.93 (9H, s), 0.08 (6H, s). ^{13}C-NMR ($CDCl_3$) δ: 163.3, 142.6, 134.2, 132.1, 129.7, 128.7, 125.9, 123.3, 79.5, 64.5, 25.7, 18.2, −5.5. HR-MS *m/z*: 397.1711 (Calcd for $C_{22}H_{27}NO_4Si$: 397.1708). *Anal*. Calcd for $C_{22}H_{27}NO_4Si$: C, 66.47; H, 6.85; N, 3.52. Found: C, 66.30; H, 6.82; N, 3.38.

Methyl (*E*)-2-[4-(*t*-Butyldimethylsiloxymethyl)benzyloxyimino]ethanate (7) To a solution of **5** (12 g, 30 mmol) in MeOH (200 ml) was added a solution of hydrazine monohydrate (1.7 g, 33 mmol) in MeOH (10 ml) under a nitrogen atmosphere at 20 °C. After the reaction mixture was stirred at the same temperature for 1 h, a solution of 2-hydroxy-2-methoxyacetic acid methyl ester (7.2 g, 60 mmol) in MeOH (10 ml) was added to the reaction mixture at 20 °C. After being stirred at the same temperature for 8 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 10 : 1) afforded **7** (9.4 g, 93%) as a colorless oil: IR ($CHCl_3$) cm^{-1}: 2956, 1737, 1600, 1467. ^{1}H-NMR ($CDCl_3$) δ: 7.54 (1H, s), 7.33 (4H, m), 5.28, 4.74 (each 2H, s), 3.85 (3H, s), 0.94 (9H, s), 0.10 (6H, s). ^{13}C-NMR ($CDCl_3$) δ: 162.3, 141.8, 140.7, 134.3, 128.4, 126.1, 77.9, 64.5, 52.3, 25.8, 18.2, −5.4. HR-MS *m/z*: 337.1698 (Calcd for $C_{17}H_{27}NO_4Si$: 337.1708).

***N*-[(*E*)-2-[4-(*t*-Butyldimethylsiloxymethyl)benzyloxyimino]ethanonyl]-bornane-10,2-sultam (8)** To a solution of (1*R*)-(+)-2,10-camphorsultam (2.0 g, 9.3 mmol) and glyoxylic oxime ether **7** (3.8 g, 11 mmol) in CH_2ClCH_2Cl (40 ml) was added Me_3Al (1.0 M in hexane, 11 ml, 11 mmol) under a nitrogen atmosphere at 20 °C. After being heated at reflux for 24 h, the reaction mixture was diluted with 1 N HCl and then extracted with CH_2Cl_2. The organic phase was washed with water, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 4 : 1) afforded **8** (4.8 g, quantitative) as a colorless oil: $[\alpha]_D^{22}$ +61.9 (c=2.3, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 2959, 1693, 1585, 1463. ^{1}H-NMR ($CDCl_3$) δ: 8.19 (1H, s), 7.33 (4H, m), 5.29, 4.74 (each 2H, s), 3.98 (1H, dd, J=7.1, 5.3 Hz), 3.51, 3.45 (each 1H, d, J=13.7 Hz), 2.20—2.00 (2H, m), 1.95—1.82 (3H, m), 1.48—1.28 (2H, m), 1.15, 0.97 (each 3H, s), 0.94 (9H, s), 0.10 (6H, s). ^{13}C-NMR ($CDCl_3$) δ: 158.9, 141.6, 140.7, 134.2, 128.5, 126.0, 78.0, 65.0, 64.5, 52.8, 48.7, 47.6, 44.5, 38.1, 32.7, 26.1, 25.7, 20.7, 19.6, 18.2, −5.5. HR-MS *m/z*: 520.2421 (Calcd for $C_{26}H_{40}N_2O_5SSi$: 520.2425).

***N*-[(*E*)-2-(4-(Hydroxymethyl)benzyloxyimino)ethanonyl]bornane-10,2-sultam (9)** To a solution of the silylated sultam derivative **8** (4.8 g, 9.2 mmol) in EtOH (60 ml) was added pyridinium *p*-toluenesulfonate (4.6 g, 18 mmol) under a nitrogen atmosphere at 20 °C. After being heated at 60 °C for 2 h, the solvent was evaporated at reduced pressure. After the resulting residue was dissolved in CH_2Cl_2, the organic phase was washed with saturated aqueous $NaHCO_3$, and water, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 1 : 1) afforded **9** (3.3 g, 89%) as colorless crystals: mp 139—142 °C (hexane/AcOEt); $[\alpha]_D^{21}$ +80.0 (c=1.09, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3606, 2964, 1693, 1586, 1458. ^{1}H-NMR ($CDCl_3$) δ: 8.20 (1H, s), 7.37 (4H, m), 5.30, 4.69 (each 2H, s), 3.98 (1H, dd, J=7.2, 5.8 Hz), 3.51, 3.46 (each 1H, d, J=13.8 Hz), 2.12—2.05 (2H, m), 1.96—1.87 (3H, m), 1.47—1.26 (2H, m), 1.15, 0.97 (each 3H, s). ^{13}C-NMR ($CDCl_3$) δ: 158.9, 141.1, 140.8, 135.0, 128.7, 126.9, 77.9, 65.0, 64.7, 52.9, 48.7, 47.7, 44.5, 38.1, 32.7, 26.2, 20.7, 19.7. HR-MS *m/z*: 406.1560 (Calcd for $C_{20}H_{26}N_2O_5S$: 406.1561). *Anal*. Calcd for $C_{20}H_{26}N_2O_5S$: C, 59.09; H, 6.45; N, 6.89; S, 7.89. Found: C, 59.04; H, 6.69; N, 6.90; S, 7.96.

Glutaric Acid Monoester of *N*-[(*E*)-2-(4-(Hydroxymethyl)benzyloxyimino)ethanonyl]bornane-10,2-sultam (10) To a solution of **9** (7.2 g, 18 mmol) in pyridine (15 ml) was added glutaric anhydride (2.0 g, 18 mmol) under a nitrogen atmosphere at 20 °C and the reaction mixture was then heated at 80 °C for 1 h. After glutaric anhydride (2.0 g, 18 mmol) was added to the reaction mixture and then the reaction mixture was heated at 80 °C for 1 h, glutaric anhydride (2.0 g, 18 mmol) was added to the reaction mixture. After being heated at 80 °C for 2 h, the reaction mixture was diluted with AcOEt and then was washed with 5% HCl, water, brine, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by flash chromatography (hexane/AcOEt 3 : 2) afforded **10** (9.1 g, 99%) as a colorless oil: $[\alpha]_D^{21}$ +67.1 (c=0.92, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3684, 2969, 1732, 1586, 1519. ^{1}H-NMR ($CDCl_3$) δ: 8.20 (1H, s), 7.40—7.31 (4H, m), 5.31, 5.11 (each 2H, s), 3.98 (1H, dd, J=6.8, 5.6 Hz), 3.52, 3.46 (each 1H, d, J=14.0 Hz), 2.45—2.36 (4H, m), 2.13—1.90 (7H, m), 1.48—1.36 (2H, m), 1.16, 0.98 (each 3H, s). ^{13}C-NMR ($CDCl_3$) δ: 178.1, 172.5, 159.0, 140.9, 135.9, 128.7, 128.3, 77.7, 65.8, 65.1, 52.9, 48.8, 47.7, 44.6, 38.1, 33.0, 32.8, 26.2, 20.7, 19.73, 19.67. HR-MS *m/z*: 520.1903 (Calcd for $C_{25}H_{32}N_2O_8S$: 520.1877).

Attachment of the Sultam Derivative to Wang Resin To a suspension of Wang resin (0.83 mmol/g, 6.0 g, 5.0 mmol) in CH_2Cl_2 (100 ml) were added **10** (5.2 g, 10 mmol), DCC (5.1 g, 25 mmol) and DMAP (0.3 g, 2.5 mmol) under a nitrogen atmosphere at 20 °C. After the reaction mixture was stirred at the same temperature for 1 h and then staid for 11 h, the resin **1** was filtered, washed well with CH_2Cl_2, AcOEt followed by MeOH and then dried *in vacuo*.

Ethyl Radical Addition to Oxime Ether 10 (Table 1, entries 1, 2). To a solution of oxime ether **10** (234 mg, 0.45 mmol) in CH_2Cl_2 or toluene (10 ml) was added Et_3B (1.0 M in hexane, 2.25 ml, 2.25 mmol) under a nitrogen atmosphere at −78 °C. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 2 : 3, 2-fold development) afforded **11a**. $[\alpha]_D^{19}$ +70.0 (c=0.97, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 2965, 1731, 1457. ^{1}H-NMR ($CDCl_3$) δ: 7.36, 7.30 (each 2H, br d, J=7.5 Hz), 5.10 (2H, s), 4.72, 4.66 (each 1H, d, J=11.7 Hz), 4.28 (1H, dd, J=7.8, 4.8 Hz), 3.96 (1H, br t, J=6.3 Hz), 3.51, 3.48 (each 1H, d, J=14.1 Hz), 2.48—2.36 (4H, m), 2.13—1.80 (7H, m), 1.75—1.23 (4H, m), 1.12, 0.97 (each 3H, s), 0.95 (3H, t, J=7.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 178.2, 173.7, 172.5, 137.8, 135.0, 128.6, 127.9, 75.1, 66.0, 64.8, 64.1, 52.8, 48.4, 47.6, 44.4, 38.1, 33.0, 32.7, 32.5, 26.2, 23.7, 20.5, 19.7, 19.6, 10.3. SI-MS *m/z*: 549.3320 (Calcd for $C_{27}H_{38}N_2O_8S$–H (negative, M^+–H): 549.3332).

Alkyl Radical Addition to Oxime Ether 10 (Table 1, entries 3, 4). To a solution of oxime ether **10** (292 mg, 0.562 mmol) and RI (16.8 mmol) in CH_2Cl_2 (15 ml) was added Et_3B (1.0 M in hexane, 2.81 ml, 2.81 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 2 : 3, 2-fold development) afforded **11b** and **11c**. **11b**, $[\alpha]_D^{19}$ +59.1 (c=1.0, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 2966, 1732, 1456. ^{1}H-NMR ($CDCl_3$) δ: 7.36, 7.30 (each 2H, br d, J=7.8 Hz), 5.10 (2H, s), 4.69, 4.62 (each 1H, d, J=12.0 Hz), 4.14 (1H, br d, J=5.1 Hz), 3.97 (1H, br t, J=6.3 Hz), 3.51, 3.47 (each 1H, d, J=13.5 Hz), 2.48—2.37 (4H, m), 2.14—1.82 (8H, m), 1.48—1.28 (2H, m), 1.12, 0.97 (each 3H, s), 1.00, 0.86 (each 3H, d, J=6.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 178.4, 174.0, 172.5, 137.9, 134.9, 128.7, 127.9, 75.0, 67.9, 66.0, 64.9, 52.9, 48.2, 47.5, 44.4, 38.3, 33.0, 32.7, 32.6, 30.0, 26.2, 20.5, 19.7, 19.6, 17.6. HR-MS *m/z*: 565.2572 (Calcd for $C_{28}H_{40}N_2O_8S$+H (M^++H): 565.2582). **11c**, $[\alpha]_D^{19}$ +50.0 (c=0.98, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 2933, 1731, 1451. ^{1}H-NMR ($CDCl_3$) δ: 7.35, 7.29 (each 2H, br d, J=8.1 Hz), 5.10 (2H, s), 4.68, 4.61 (each 1H, d, J=12.0 Hz), 4.14 (1H, m), 3.97 (1H, br t, J=6.3 Hz), 3.51, 3.46 (each 1H, d, J=14.4 Hz), 2.48—2.37 (4H, m), 2.17—1.79 (7H, m), 1.78—0.95 (13H, m), 1.13, 0.97 (each 3H, s). ^{13}C-NMR ($CDCl_3$) δ: 178.2, 173.9, 172.5, 138.0, 134.9, 128.7, 127.9, 74.9, 67.7, 66.0, 64.9, 52.9, 48.2, 47.5, 44.4, 39.7, 38.3, 33.0, 32.7, 32.6, 29.6, 28.6, 26.2, 26.1, 26.0, 25.8, 20.4, 19.8, 19.6. HR-MS *m/z*:

605.2900 (Calcd for $C_{31}H_{44}N_2O_8S+H$ ($M^+ +H$): 605.2894).

Ethyl Radical Addition to Oxime Ether 1 (Table 2). To a suspension of oxime ether **1** (0.83 mmol/g, 200 mg, 0.166 mmol) in CH_2Cl_2 (10 ml) was added Et_3B or Et_2Zn (1.0 M in hexane, 0.83 ml, 0.83 mmol) under a nitrogen atmosphere at −78 °C. After the reaction mixture was stirred at the same temperature for 30 min, the resin was filtered, washed well with CH_2Cl_2 and AcOEt, and then dried *in vacuo*. To a flask with the resulting resin was added TFA/CH_2Cl_2 (1 : 5, v/v, 5.0 ml) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 30 min, the reaction mixture was filtered and washed with CH_2Cl_2 (50 ml), and the filtrate was concentrated at reduced pressure. After the resulting residue was dissolved in CH_2Cl_2, the organic phase was washed with diluted aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 2 : 3, 2-fold development) afforded the α-amino acid derivative **11a** (68 mg, 74%) in the case of Et_3B or (61 mg, 67%) in the case of Et_2Zn.

Alkyl Radical Addition to Oxime Ether 10 (Table 3). To a suspension of oxime ether **1** (0.83 mmol/g, 200 mg, 0.166 mmol), Bu_3SnH (0.45 ml, 1.66 mmol) and RI (4.98 mmol) in CH_2Cl_2 (10 ml) was added Et_3B (1.0 M in hexane, 0.83 ml, 0.83 mmol) under a nitrogen atmosphere at −78 or 0 °C. After the reaction mixture was stirred at the same temperature for 30 min, the resin was filtered, washed well with CH_2Cl_2 and AcOEt, and then dried *in vacuo*. To a flask with the resulting resin was added TFA/CH_2Cl_2 (1 : 5, v/v, 5.0 ml) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 30 min, the reaction mixture was filtered and washed with CH_2Cl_2 (50 ml), and the filtrate was concentrated at reduced pressure. After the resulting residue was dissolved in CH_2Cl_2, the organic phase was washed with diluted aqueous $NaHCO_3$, and water, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 3 : 2, 3-fold development) afforded the α-amino acid derivatives **11b** and **11c**.

Alkyl Radical Addition to Oxime Ether 1 (Table 4) To a suspension of oxime ether **1** (0.83 mmol/g, 200 mg, 0.166 mmol) in RI/toluene (4 : 1, v/v, 5 ml) was added Et_3B or Et_2Zn (1.0 M in hexane, 0.83 ml, 0.83 mmol) under a nitrogen atmosphere at 0 °C. After the reaction mixture was stirred at the same temperature for 15 min, Et_3B or Et_2Zn (1.0 M in hexane, 0.83 ml, 0.83 mmol) was added to the reaction mixture. After the reaction mixture was stirred at the same temperature for 15 min, the resin was filtered, washed well with CH_2Cl_2 and AcOEt, and then dried *in vacuo*. To a flask with the resulting resin was added TFA/CH_2Cl_2 (1 : 5, v/v, 5.0 ml) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 30 min, the reaction mixture was filtered and washed with CH_2Cl_2 (50 ml), and the filtrate was concentrated at reduced pressure. After the resulting residue was dissolved in CH_2Cl_2, the organic phase was washed with diluted aqueous $NaHCO_3$, and water, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt 3 : 2, 3-fold development) afforded the α-amino acid derivatives **11b** and **11c**.

Acknowledgements We thank a Grant-in-Aid for Scientific Research (B) from the Japan Society for the Promotion of Science (JSPS) and the Science Research Promotion Fund of the Japan Private School Promotion Foundation for research grants.

References and Notes

1) Present address: *Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606–8501, Japan*.
2) Brown R. C. D., *J. Chem. Soc., Perkin Trans. 1*, **1998**, 3293—3320 (1998).
3) *Chem. Rev.*, **97** (1997), whole issue of No. 2, pp. 347—510.
4) Hermkens P. H. H., Ottenheijm H. C. J., Rees D. C., *Tetrahedron*, **53**, 5643—5678 (1997).
5) Balkenhohl F., von dem Bussche-Hünnefeld C., Lansky A., Zechel C., *Angew. Chem., Int. Ed. Engl.*, **35**, 2288—2337 (1996).
6) Früchtel J. S., Jung G., *Angew. Chem., Int. Ed. Engl.*, **35**, 17—42 (1996).
7) Thompson L. A., Ellman J. A., *Chem. Rev.*, **96**, 555—600 (1996).
8) *Acc. Chem. Res*., **29** (1996), whole issue of No. 3, pp. 112—170.
9) Hermkens P. H. H., Ottenheijm H. C. J., Rees D., *Tetrahedron*, **52**, 4527—4554 (1996).
10) Routledge A., Abell C., Balasubramanian S., *Synlett*, **1997**, 61—62 (1997).
11) Du X., Armstrong R. W., *J. Org. Chem.*, **62**, 5678—5679 (1997).
12) Du X., Armstrong R. W., *Tetrahedron Lett.*, **39**, 2281—2284 (1998).
13) Berteina S., De Mesmaeker A., *Tetrahedron Lett.*, **39**, 5759—5762 (1998).
14) Berteina S., Wendeborn S., De Mesmaeker A., *Synlett*, **1998**, 1231—1233 (1998).
15) Watanabe Y., Ishikawa S., Takao G., Toru T., *Tetrahedron Lett.*, **40**, 4535—4538 (1999).
16) Caddick S., Hamza D., Wadman S. N., *Tetrahedron Lett.*, **40**, 7285—7288 (1999).
17) Zhu X., Ganesan A., *J. Comb. Chem.*, **1**, 157—162 (1999).
18) Enholm E. J., Gallagher M. E., Jiang S., Batson W. A., *Org. Lett.*, **2**, 3355—3357 (2000).
19) Sibi M. P., Chandramouli S. V., *Tetrahedron Lett.*, **38**, 8929—8932 (1997).
20) Miyabe H., Fujishima Y., Naito T., *J. Org. Chem.*, **64**, 2174—2175 (1999).
21) Miyabe H., Tanaka H., Naito T., *Tetrahedron Lett.*, **40**, 8387—8390 (1999).
22) Miyabe H., Fujii K., Tanaka H., Naito T., *Chem. Commun.*, **2001**, 831—832 (2001).
23) Miyabe H., Konishi C., Naito T., *Org. Lett.*, **2**, 1443—1445 (2000).
24) Miyabe H., Ushiro C., Naito T., *Chem. Commun.*, **1997**, 1789—1790 (1997).
25) Miyabe H., Ushiro C., Ueda M., Yamakawa K., Naito T., *J. Org. Chem.*, **65**, 176—185 (2000).
26) Diether R. K., Datar R., *Can. J. Chem.*, **71**, 814—823 (1993).
27) Moody C. J., Gallagher P. T., Lightfoot A. P., Slawin A. M. Z., *J. Org. Chem.*, **64**, 4419—4425 (1999).
28) Wang resins purchased from Novabiochem was used in all experiments.
29) Miyabe H., Ueda M., Yoshioka N., Naito T., *Synlett*, **1999**, 465—467 (1999).
30) Miyabe H., Fujii K., Naito T., *Org. Lett.*, **1**, 569—572 (1999).
31) Ryu I., Araki F., Minakata S., Komatsu M., *Tetrahedron Lett.*, **39**, 6335—6336 (1998).