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Stereoselective Synthesis of (*E*)-α,β-Dehydroamino Acid Esters

Yoko Yasuno,[a] Makoto Hamada,[a] Takeshi Yamada,[a] Tetsuro Shinada,*[a] and Yasufumi Ohfune*[a]

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Dehydroamino acid (Dhaa) is recognized as a useful tool or substrate for amino acid and peptide research. Although the stereoselective synthesis of the thermodynamically more stable *Z*-Dhaa has been well examined and established, the stereoselective synthesis of *E*-Dhaa has still remained to be a challenging synthetic task. In this paper, a stereoselective synthesis of *E*-Dhaa esters using a new (α-diphenylphosphono)glycine is described. The characteristic aspects of the new method are summarized as follows: (i) metal additives play an important role in the promotion of *E*-stereoselectivities. (ii) the use of NaI was effected for the synthesis of *E*-Dhaas bearing an aryl substituent and an amino functionality, (iii) $MgBr_2{\cdot}OEt_2$ and $ZnCl_2$ contributed to improve the *E*-stereoselective synthesis of *E*-Dhaas bearing an alkyl substituent and an oxygen functionality, (iv) various protecting and functional groups were compatible under the reaction conditions, and (v) *N*-Cbz, Boc, and acyl-α-(diphenylphosphono)glycines were served for the stereoselective olefination reaction to provide the corresponding *E*-Dhaas.

Introduction

α,β-Dehydro amino acids (Dhaas) are often recognized as constituents of biologically active natural peptides[1] and are widely used as starting materials for the synthesis of natural and non-natural α-amino acids by catalytic asymmetric hydrogenation reactions[2,3] and C–C bond-forming reactions involving 1,4-addition reactions, cyclopropanation reactions, [3+2] cycloaddition reactions, and the Diels–Alder reaction.[1–4] It has been reported that the introduction of Dhaas into peptides contributes to an enhancement in biological activity and chemical stability towards enzymes such as peptidases.[5]

Dhaas are conformationally restricted non-proteinogenic amino acid analogues in which the sp^3 carbon atoms at the α- and β-positions of the α-amino acids are replaced with sp^2 carbon atoms. Two geometrical isomers, (*E*)-**1** and (*Z*)-**2**, are available when a substituent is present at the β-position of α,β-dehydroalanine (Figure 1). The presence of these stereoisomers offers opportunities for comparative biological and chemical studies by using these stereoisomers in the research of amino acids and peptides. However, the potency has not fully tested because of the lack of practically useful synthetic methods for (*E*)-**1**.

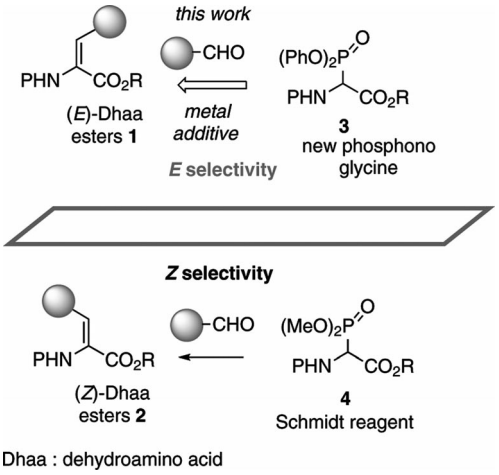

Figure 1. Stereoselective synthesis of (*E*)- and (*Z*)-Dhaa esters **1** and **2** by using **3** and **4**.

Much synthetic effort has been devoted to the synthesis of Dhaas as a result of their potential utilities. The Erlenmeyer reaction[5] and the Schmidt method, both of which involve the use of (dialkylphosphono)glycinate,[1g,6] are known to be representative methods to access various Dhaas. However, these established methods provide thermodynamically more stable (*Z*)-**2** as the major stereoisomer. In contrast, example of the stereoselective synthesis of (*E*)-**1** are relatively limited. Previously, the syntheses of (*E*)-**1** have been achieved by stereospecific β-elimination reactions of β-hydroxy-, thio-, and seleno-α-amino acid derivatives and by cross-coupling reactions involving β-halo Dhaas.[1,7] These methods require one of the stereoisomers of the synthetic precursors that are usually prepared in a

[a] Graduate School of Science Osaka City University,
3-3-138 Sugimoto, Sumiyoshi, Osaka 558-8585, Japan
Fax: +81-6-6605-3153
E-mail: shinada@sci.osaka-cu.ac.jp
ohfune@sci.osaka-cu.ac.jp
Homepage: http://www.sci.osaka-cu.ac.jp/chem/henkan/index_e.html

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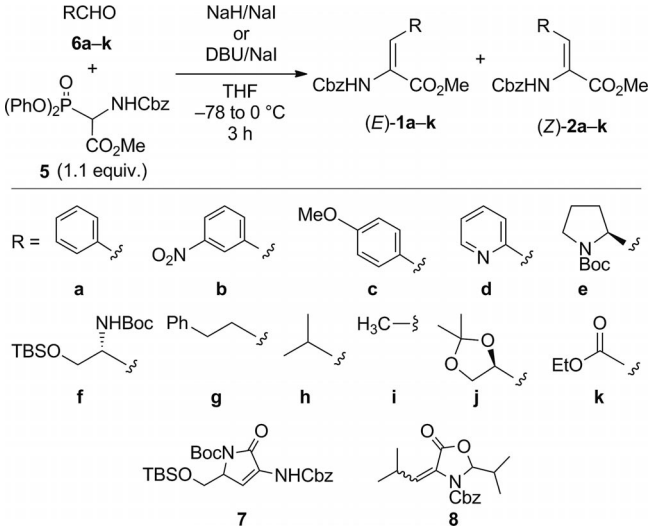
multistep sequence. In this context, the straightforward and efficient synthesis of a variety of (*E*)-**1** still remains an important synthetic subject in this research field.

Ando et al. developed an efficient Horner–Wadsworth–Emmons (HWE) reagent [$(PhO)_2P(=O)CH_2CO_2R$, R = alkyl] for the stereoselective synthesis of (*Z*)-α,β-unsaturated esters.[8] Inspired by the elegant synthetic results, we became intrigued by the idea of using (diphenylphosphono)glycinate (**3**), in which the $–P(=O)(OMe)_2$ moiety of Schmidt reagent **4**[1a] is replaced with a $–P(=O)(OPh)_2$ group. It was anticipated that preferential *Z* selectivity could be promoted by the introduction of Ando's reagent. Along this line, we prepared **3** for the first time and explored its synthetic utility in the total synthesis of a structurally complex unnatural amino acid natural product, kaitocephalin.[9] New reagent **3** allowed the stereoselective formation of the (*E*)-Dhaa (*E*/*Z* = >95:5) from the highly functionalized aldehyde having the right half moiety of kaitocephalin. We believed that the use of **3** could be extended to the synthesis of a variety of Dhaa esters of type (*E*)-**1** as a result of its synthetic advantages, including its high *E* selectivity, its simplistic utilization, and its compatibility with several functional groups. In this communication, we describe the potential utility of **3**, which holds promise for the synthesis of a variety of Dhaa esters of type (*E*)-**1**, as well as intriguing metal additive effects that play a key role in the promotion of the *E* stereoselectivity.

Results and Discussion

We reported that benzaldehyde (**6a**) underwent the (*E*)-stereoselective Dhaa synthesis with **5**[9] under Ando's olefination conditions [NaH/NaI[10] or 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU)/NaI;[8c] Table 1, entry 1]. We initially examined the scope of the reaction conditions by using aldehydes **6a**–**k**. Aromatic aldehydes **6b** and **6c** bearing a *m*-nitro and *p*-methoxy group, respectively, as well as 2-pyridinecarbaldehyde (**6d**) were converted into (*E*)-**1b**, (*E*)-**1c**, and (*E*)-**1d**, respectively, in a stereoselective manner (Table 1, entries 2–4).[11] *N*-Boc-prolinal (**6e**) was transformed in to (*E*)-**1e** with high *E* selectivity in 82% yield (Table 1, entry 5). Aldehyde **6f** derived from serine gave (*E*)-**1f** in low yield (29%; Table 1, entry 6). Instead, lactam **7** was obtained as the major product in 66% yield. These results indicate that an intramolecular cyclization between the ester and the carbamate groups, which are in close proximity, occurred after the *E* selective olefination. To circumvent the competitive cyclization reaction, milder reaction conditions (DBU/NaI) were attempted. Under these conditions, (*E*)-**1f** was selectively obtained in 74% (*E*/*Z* = 92:8; Table 1, entry 7). In contrast to the results described above, aliphatic aldehydes **6g**–**i** resulted in poor to moderate *E* selectivities (up to 72:28; Table 1, entries 8–11). 3-Phenylpropanal (**6g**) gave a 72:28 mixture of (*E*)-**1g**/(*Z*)-**2g** in 93% yield (Table 1, entry 8). Olefination of **6h** gave a 69:31 mixture of (*E*)-**1h**/(*Z*)-**2h** (15%), in addition to acetal **8** (26%; Table 1, entry 9). Although the formation of undesired acetal **8** was suppressed under the DBU/NaI conditions, the *E*/*Z* ratio was moderate (*E*/*Z* = 50:50; Table 1, entry 10). Similarly, the olefination reaction of acetoaldehyde (**6i**) gave a 1:1 mixture of (*E*)-**1i**/(*Z*)-**2i** (Table 1, entry 11). Aldehydes **6j** and **6k** bearing oxygen functionalities at the adjacent position underwent smooth olefination to give (*E*)-**1j** and (*E*)-**1k**, respectively, in high yield. However, these selectivities were moderate to good (up to 81:19; Table 1, entries 12 and 13). To improve the moderate *E* selectivities, we re-examined the reaction conditions by using **6g** as a model substrate (Table 2). After extensive experimentation, we found that the *E* stereoselectivity was dramatically influenced by metal additives. Among them, the use of DBU/$MgBr_2$·OEt_2/THF resulted in a significant improvement in the *E* stereoselectivity [(*E*)-**1g**/(*Z*)-**2g** = 87:13; Table 2, entry 5]. In sharp contrast, (*Z*)-**2g** was formed without any metal additive [(*E*)-**1g**/(*Z*)-**2g** = 4:96; Table 2, entry 1]. The use of KI or LiCl in the olefination reaction gave (*Z*)-**2g** as the major product (Table 2, entries 3 and 4). Although the use of $ZnCl_2$ contributed to improve the *E* selectivity (80:20; Table 2, entry 6), the product yield and *E* selectivity were not reproducible in this model substrate.

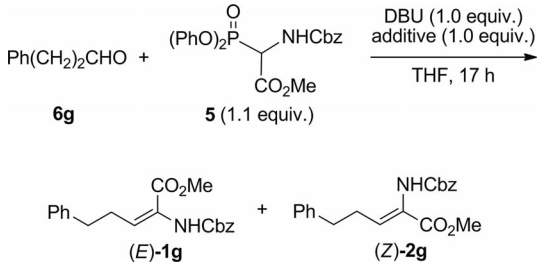
Table 1. Stereoselective synthesis of (*E*)-Dhaa esters **1a**–**j** by using **5**.



Entry	Substrate	Conditions	Yield [%]	(*E*)-**1**/(*Z*)-**2**[d]
1	**6a**	NaH, NaI	93	97:3
2	**6b**	NaH, NaI	100	97:3
3	**6c**	NaH, NaI	70	96:4
4	**6d**	NaH, NaI	75	90:10
5	**6e**	NaH, NaI	82	92:8
6	**6f**	NaH, NaI	29[a]	92:8
7	**6f**	DBU, NaI	74[b]	92:8
8	**6g**	NaH, NaI	93	72:28
9	**6h**	NaH, NaI	15[c]	69:31
10	**6h**	DBU, NaI	77	50:50
11	**6i**	NaH, NaI	100	52:48
12	**6j**	NaH, NaI	81	67:33
13	**6k**	NaH, NaI	82	81:19

[a] Byproduct **7** formed in 66% yield. [b] Byproduct **7** formed in 21% yield. [c] Byproduct **8** formed in 26% yield. [d] Determined by ^{1}H NMR spectroscopy (300 MHz, $CDCl_3$ or C_6D_6).[11]

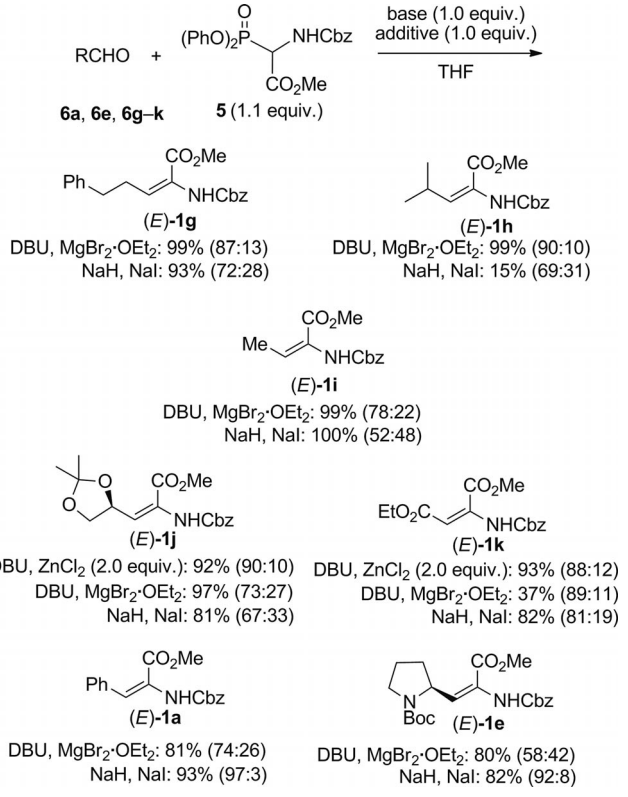
Table 2. Additive effects for the olefination of **6g**.



Entry	Additive	Temp. [°C]	Yield [%]	(*E*)-**1g**/(*Z*)-**2g**[a]
1	none	r.t.	97	4:96
2	NaI	–78 to 0	93	72:28
3	KI	–78	84	<5:>95
4	LiCl	–78	59	16:84
5	$MgBr_2{\cdot}OEt_2$	r.t.	99	87:13
6	$ZnCl_2$ (2.0 equiv.)	r.t.	27–62[b]	66:34 to 80:20[b]

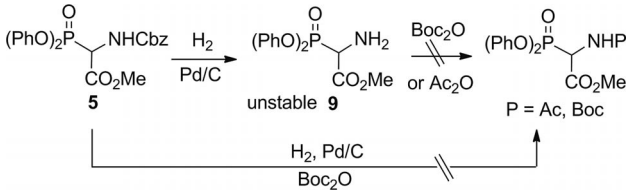
[a] Determined by ^{1}H NMR spectroscopy. [b] Not reproducible.

The $MgBr_2{\cdot}OEt_2$/DBU and $ZnCl_2$/DBU conditions were successfully applied to aliphatic aldehydes **6h**–**k** (Scheme 1). These results are summarized as follows: (1) The moderate to low *E* selectivity for **1h**–**k** in Table 1 was improved under the $MgBr_2{\cdot}OEt_2$/DBU conditions. (2) The DBU/$ZnCl_2$ conditions are more effective than the DBU/$MgBr_2{\cdot}OEt_2$ conditions for the syntheses of (*E*)-**1j** and (*E*)-**1k** [(*E*)-**1j**/$ZnCl_2$, 90:10 (92%) vs. $MgBr_2{\cdot}OEt_2$, 73:27 (97%); (*E*)-**1k**/$ZnCl_2$, 88:12 (93%) vs. $MgBr_2{\cdot}OEt_2$, 89:11 (37%)]. (3) Benzaldehyde (**6a**) and prolinal (**6e**) smoothly underwent the olefination reaction under the DBU/$MgBr_2{\cdot}OEt_2$ conditions. However, these *E* selectivities were moderate in comparison to those of the NaH/NaI conditions [**1a**: DBU/$MgBr_2{\cdot}OEt_2$, 74:26 vs. NaH/NaI, 97:3; **1e**: DBU/$MgBr_2{\cdot}OEt_2$, 58:42 vs. NaH/NaI, 92:8]. (4) Functional groups such as acetonide, Boc, and unsaturated ester are compatible under the reaction conditions. These results, coupled with our previous observations in the total synthesis of kaitocephalin by using **5**, proved the potential functional group compatibility of this reaction.



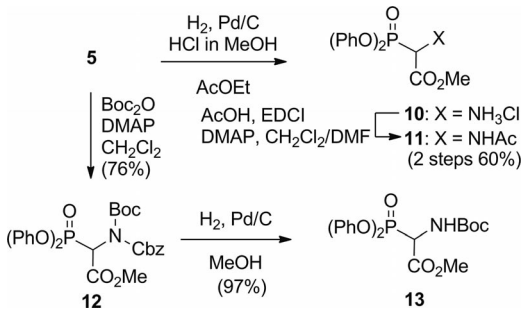
Scheme 1. Stereoselective synthesis of (*E*)-**1**.

We next turned our attention to *N*-acetyl **11** and *N*-Boc **13** for direct access to (*E*)-*N*-Boc and *N*-acyl Dhaas (Scheme 2). We thought that **11** and **13** could be prepared in a manner similar to the conversion of *N*-Cbz Schmidt reagent **4** to the corresponding Boc or *N*-acyl reagents.[6a] However, removal of the Cbz group of **5** gave a complex mixture in the absence or presence of an acylating reagent. The unexpected decomposition may have arisen from the elimination of $-P(=O)(OPh)_2$ from **9** as a result of the electronically more stable nature of $-P(=O)(OPh)_2$ than $-P(=O)(OMe)_2$.



Scheme 2. Hydrogenation of **5** without HCl.

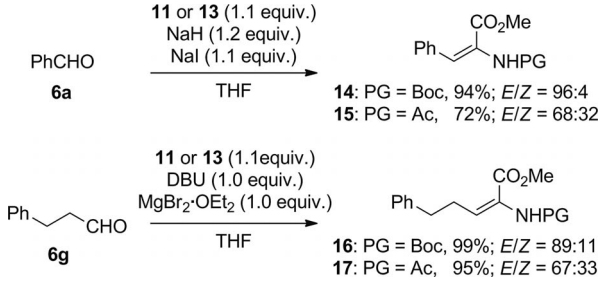
To circumvent the above obstacle, we attempted to trap the resulting free amine as an ammonium salt in situ to suppress the undesired elimination reaction (Scheme 3). As expected, the hydrogenation reaction of **5** in the presence of HCl gave stable HCl salt **10**. Although treatment of **10** with Et_3N gave a complex mixture, we found reaction conditions enabling the synthesis of *N*-acetyl derivative **11**. Treatment of **10** with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) in the presence of 4-(dimethylamino)pyridine (DMAP, 0.5 equiv.) furnished *N*-acetyl derivative **11** (60% from **5**).[12] In contrast, the installation of the Boc group to **5** under the same reaction conditions was unsuccessful. Alternatively, we developed a new method by the initial introduction of the Boc group to **5** by using Boc_2O in the



Scheme 3. Synthesis of *N*-Ac **11** and *N*-Boc **13**.

presence of DMAP (76%) followed by the removal of the Cbz group under the hydrogenation conditions to give **13** in 97% yield.

The olefination reaction of benzaldehyde (**6a**) with *N*-Boc **13** under the NaH/NaI conditions gave (*E*)-**14** in a highly stereoselective manner (Scheme 4). The reaction with **6g** in the presence of $MgBr_2{\cdot}OEt_2$ afforded (*E*)-**16** as the major stereoisomer (89:11). Switching to *N*-Ac derivatives **11** provided (*E*)-**15** and **17** in good yields. However, these selectivities were lower than those of *N*-Cbz **5** and *N*-Boc **13**. These results indicate that the carbamate moiety is superior to the acyl group in promoting *E* selectivity.

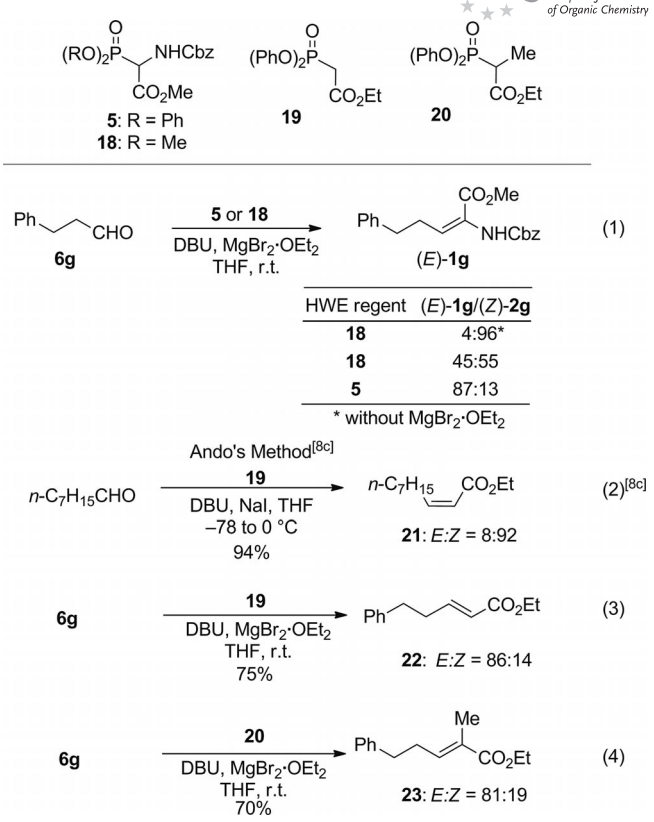


Scheme 4. HWE olefination with *N*-Ac **11** and *N*-Boc **13**.

To gain some insight into the reaction mechanism, olefination of **6g** with HWE reagents **18**, **19**, and **20** was attempted in the absence and in the presence of $MgBr_2{\cdot}OEt_2$ (Scheme 5). In the absence of $MgBr_2{\cdot}OEt_2$, **6g** was treated with Schmidt reagent **18** to give (*Z*)-**2g** in a highly stereoselective manner [*E*/*Z* = 4:96; Scheme 5, Eq. (1)]. Although the selectivity was moderate, treatment of **6g** with **18** under the DBU/$MgBr_2{\cdot}OEt_2$ conditions gave a 45:55 mixture of (*E*)-**1g**/(*Z*)-**2g**. These results corroborate the promoting effects of $MgBr_2{\cdot}OEt_2$ in the olefination reaction of not only new phosphonate **5** but also Schmidt reagent **18**. Ando reported that the reaction of **19** and *n*-$C_7H_{15}CHO$ with DBU/NaI preferentially produced (*Z*)-olefin **21** [*E*/*Z* = 8:92; Scheme 5, Eq. (2)].[8c] Interestingly, switching to $MgBr_2{\cdot}OEt_2$ provided (*E*)-**22** as the major isomer [*E*/*Z* = 86:14; Scheme 5, Eq. (3)]. Olefination with **20**[8f] in which the –NHCbz group of **5** is substituted with a methyl group resulted in the predominant formation of (*E*)-**22** [*E*/*Z* = 81:19; Scheme 5, Eq. (4)]. These results suggest that synergistic effects of the *N*-Ac, *N*-Boc, or *N*-Cbz group, $MgBr_2{\cdot}OEt_2$ or NaI, or –P(=O)(OPh)$_2$ play an important role in the stereoselective formation of (*E*)-**1** by using new phosphonates **5**, **11**, and **13**.

Conclusions

In summary, we have established a stereoselective synthetic method to access a wide variety of Dhaa esters of type (*E*)-**1** by olefination of phosphonates **5**, **11**, and **13** with commercially available and easily prepared aldehydes by choosing three reaction conditions that are currently used as standard protocols. The NaH/NaI and DBU/NaI systems are effective for aromatic aldehydes and aldehydes derived from amino acids. Aldehydes bearing an alkyl side



Scheme 5. Olefination reaction under the $MgBr_2{\cdot}OEt_2$/DBU conditions.

chain can be converted into the desired products under $MgBr_2{\cdot}OEt_2$/DBU conditions. $ZnCl_2$/DBU efficiently promotes the olefination of the aldehydes bearing an oxygen functionality. Although the full mechanistic details of the present HWE olefination remain unclear, synergistic effects of –NHP, –P(=O)(OPh)$_2$, and the metal additive play an important role in the *E*-stereoselective olefination. The use of **5**, **11**, and related acylating reagents permits access to a wide variety of (*E*)-**1** and offers the opportunity for biological and chemical studies that have, up to this point, remained unexplored in the realm of amino acids and peptides.

Experimental Section

Typical Procedure for the Preparation of (*E*)-1 under DBU/$MgBr_2{\cdot}OEt_2$ Conditions: To a solution of **5** (100 mg, 0.2 mmol) and $MgBr_2{\cdot}OEt_2$ (52 mg, 0.2 mmol) in THF (2 mL) was added DBU (30 μL, 0.2 mmol) at 0 °C under an atmosphere of argon. The mixture was stirred for 30 min at 0 °C. Aldehyde **6** (0.2 mmol) in THF (2 mL) was added to the mixture. The mixture was stirred for 17 h at room temperature, and then quenched with satd. NH_4Cl (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford (*E*)-**1**.

Supporting Information (see footnote on the first page of this article): General procedures, experimental data, and ^1H NMR and ^{13}C NMR spectral data.

Acknowledgments

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[11] The *E*/*Z* ratio was determined by comparison of the NMR spectroscopic data (olefinic proton, –NH, ester methyl group). This data is summarized in the Supporting Information. In most of the cases, the olefinic protons of (*E*)-**1** were observed at lower magnetic field than those of (*Z*)-**2**. The tendency is consistent with the data reported by Mazurkiewicz et al., see: R. Mazurkiewicz, A. Kuźnik, M. Grymel, N. Kuźnik, *Magn. Reson. Chem.* **2005**, *43*, 36–40.

[12] This method has been successfully extended to the synthesis of phosphonoglycinate derivatives possessing an amino acid residue in the amino group. Full details and synthetic applications will be reported in due course.

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