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Frequency of *C*-Allylations on Oligoglycinates via *N*-Ylides

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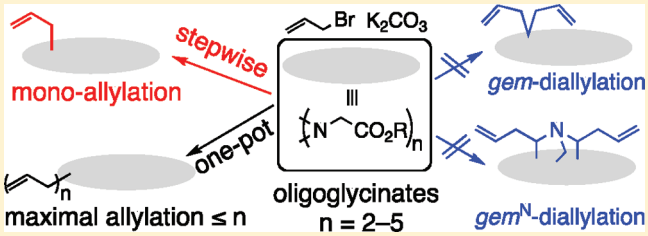
Supporting Information

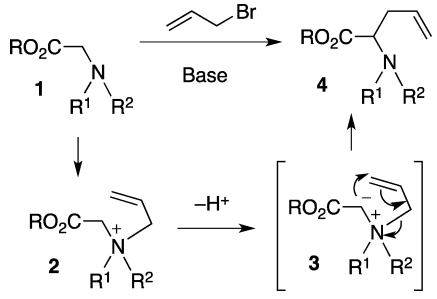
ABSTRACT: The highly selective mono-*C*-allylation of oligoglycinates such as a diethylenetriaminepentaacetate, an iminodiacetate, and an ethylenediaminetetraacetate via insertion of a vacuum operation between the *N*-allylation and C-migration steps is reported. It is contrastive that one-pot *N*-allylation−*C*-allylation procedure gave a mixture including multiallylated products. In the reaction with *N*-ylides, *gem*-*C*-diallylation and *α,α′*-*C*-diallylation of oligoglycinates are strongly inhibited even with the use of an excess of allyl bromide and base. A mechanism to explain this control of the frequency of *C*-allylation on oligoglycinates via *N*-ylides is also proposed.



INTRODUCTION

Base-promoted C-migration of one of four N-substituents of an ammonium cation, as well as *P*-, *S*-, or *Se*-analogues, has been classified as the Stevens rearrangement[1−4] in a broad sense. In a narrow sense, the Stevens rearrangement is often defined as reaction only via [1,2]-sigmatropy. In fact, the reaction from *N*-benzylic derivatives to *ortho*-substituted products via [2,3]-sigmatropy has been discriminated as the Sommett−Hauzer rearrangement.[5−7] As shown in Scheme 1, the rearrangement of

Scheme 1. *C*-Allylation of Glycinates 1 via [2,3]-Sigmatropic Rearrangement of *N*-Allyl Ylide 3



N-allylated ammonium salts such as **2** via [2,3]-sigmatropy to afford **4** via *N*-ylide **3** by Honda and Inoue et al.[8] can also be excluded from the narrowly defined Stevens rearrangement. The rearrangement via a thermal [1,2]-sigmatropic concerted pathway is theoretically prohibited, and the [1,2]-sigmatropic products can often be produced via a higher energetic biradical pathway.[5−7,9] The Sommett−Hauzer rearrangement accompanies the collapse of stable aromatic conjugation. Therefore, the [2,3]-sigmatropic rearrangement of the *N*-allylic ylide probably has the lowest transition state energy level among the three rearrangements.

It is considered that the transient concentration of *N*-ylide **3** in each moment is low, since **3** can be instantaneously converted to produce **4**. Accordingly, mild bases such as anhydrous potassium carbonate (K_2CO_3) can be strong enough to induce the rearrangement. In contrast, ordinary carbanion chemistry often requires the generation of stoichiometric equivalents of an unstable (highly reactive) carbanion using strong bases such as organolithiums or lithium amides. Furthermore, the molar ratio of each reagent must often be delicately controlled, and the exhaustive elimination of moisture or air must be achieved. In spite of such laborious efforts, *gem*-dialkylation can sometimes occur because of proton-transfer processes between a starting enolate and a produced monoalkylated carbonyl compound. In contrast, the *gem*-diallylation of a glycinate via an *N*-allylated ylide has not been reported even without rigorous control of the molar ratio between **1** and an electrophlie such as allyl bromide.[1−9] Accordingly, we concluded that rearrangement of **3** via [2,3]-sigmatropy might be a more efficient and facile carbon−carbon bond formation reaction of glycinates than ordinary carbanion chemistry and the other two rearrangements.

The carbon−carbon bond formation reaction of diethylenetriaminepentaacetic acid (DTPA) pentaester **5** with organic halide (R^3X) to afford **6** as reported by us[10] and two independent groups[11,12] is a typical example depicting the laboriousness and difficulty of the unstable cabanion chemistry (Scheme 2). By using an in situ generated ordinary unsatable carbanion species, **6** was obtained in low to moderate yields. Since the DTPA framework has five deprotonative methylenes, use of excess base and electrophile, prolonging the reaction period, or raising the reaction temperature increased the formation of multiallylated byproducts.[10] On the other hand,

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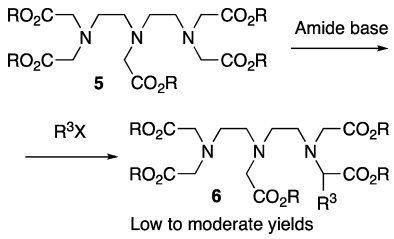
Scheme 2. Previously Reported Carbon−Carbon Bond Formation Reactions of DTPA Pentaesters 5



suppression of the molar ratio of reagents versus **5**, shortening the reaction period, or lowering the reaction temperature increased the recovery yield of **5**. Furthermore, our reported reaction[10] was often irreproducible on a large scale in spite of the laborious efforts taken, such as the exhaustive elimination of moisture and air and careful control of the molar ratio of substrate and reagents.

RESULTS AND DISCUSSION

Representative Result Using the Reaction of DTPA Pentaethyl Ester and Allyl Bromide with Potassium Carbonate Mixed in One Portion (Typical One-Pot Procedure). After reviewing the published unsatisfactory DTPA chemistry shown in Scheme 2,[10] we were looking for an alternative method for carbon−carbon bond formation at the framework of **5**. The potential for rearrangement chemistry as a viable approach was an attractive option. We therefore examined the reaction of **7** and various equivalents of allyl bromide with various bases and solvents, at different temperatures, and reaction periods (Scheme 3).[13,14] For convenience, the nitrogen atoms at right side, center, and left side are symbolized as N^R, N^C, and N^L, respectively. Because of the symmetric structure of **7**, N^L and N^R are often merged in the following discussion. The superscripted letter(s) on **8** indicates the *N*-allylated position(s) of the intermediates **9** in Schemes 4 and 5.

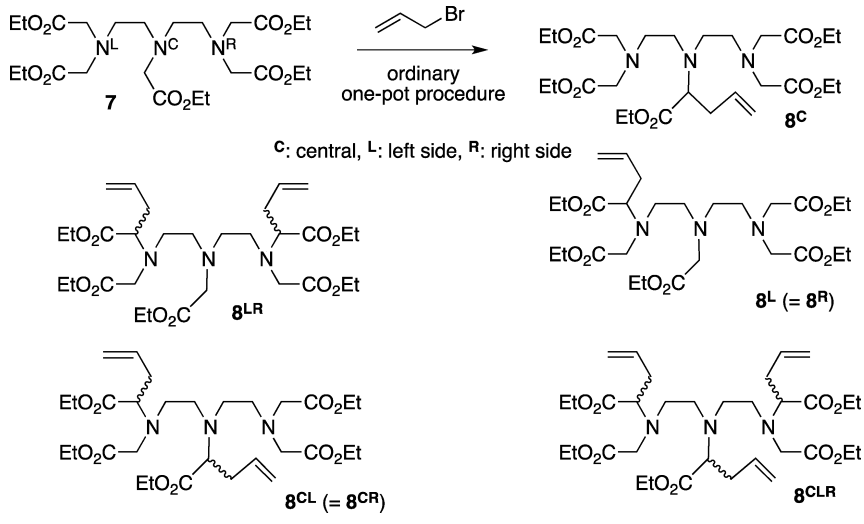
As we anticipated, carrying out the rearrangement was much simpler and more facile than ordinary anhydrous carbanion chemistry.[10−12] The results, however, were unfortunately not simple.[15] Purification of the crude products afforded mono- (8^C and 8^L), probably a diastereomeric mixture of di- (8^{CL} and 8^{LR}), and a diastereomeric mixture of tri-*C*-allylated products 8^{CLR}, along with the recovery of a non-negligible amount of starting material **7**. Furthermore, the molar ratio of **7** and **8** in the crude mixture was irreproducible and extremely sensitive to the molar ratio of each reagent, temperature, the reaction period, solvent, and so on. At this point, we realized that, for the same reasons affecting the carbanion chemistry in Scheme 2, it is difficult to control conflicting reactivity issues (prevention of multi-allylations and consumption of a satisfactory amount of starting material) at the same time using a complicated oligoglycinate such as **7**. In fact, no papers or patents on the application of the Stevens, Sommelet−Hauser, or Honda−Inoue rearrangements to complicated oligoglycinates were found during a broad search of the literature.[1−9] Accordingly, the first problem with carbanion chemistry (delicate control of various conditions) was unsolved, although the second problem (exhaustive elimination of moisture and air) was addressed.

Newly Developed Procedure for Selective Mono-*C*-Allylation of DTPA Pentaethyl Ester (Newly Devised Procedure). We have successfully demonstrated highly selective mono-*C*-allyation of **7** to afford 8^C in 63% isolated yield via a newly devised procedure that involves mixing **7** and allyl bromide without base (step A) followed by application of a vacuum to remove excess allyl bromide (step B) and irreversible C-migration (step C) (Scheme 4).[13,14]

This newly devised procedure for the highly selective formation of 8^C from **7** was successful for the following three reasons: (i) the volatility of allyl bromide plus the nonvolatility of 9^C, (ii) the acceptable stability of 9^C at low temperature during the vacuum operation, and (iii) the thermodynamic stability of 9^C compared with the other ammonium halides including 9^L, 9^{CL}, 9^{LR}, and 9^{LCR} (Scheme 5).

To examine the stability of 9^C, the crude mixture was left for 2 days at room temperature after step B and then heated with K_2CO_3. The yield of 8^C and consumption of **7** were dramatically decreased, and a non-negligible amount of 8^L, 8^{LR}, 8^{CL}, and 8^{CLR} was observed. That is to say, the result was very similar to the ordinary one-pot procedure with 1 equiv of allyl bromide. It is believed that 9^C was converted back to **7** and allyl bromide via equilibrium during the 2 days, and then step D occurred. In contrast, when step C was started immediately

Scheme 3. Allylation of 7 Using the Typical One-Pot Procedure



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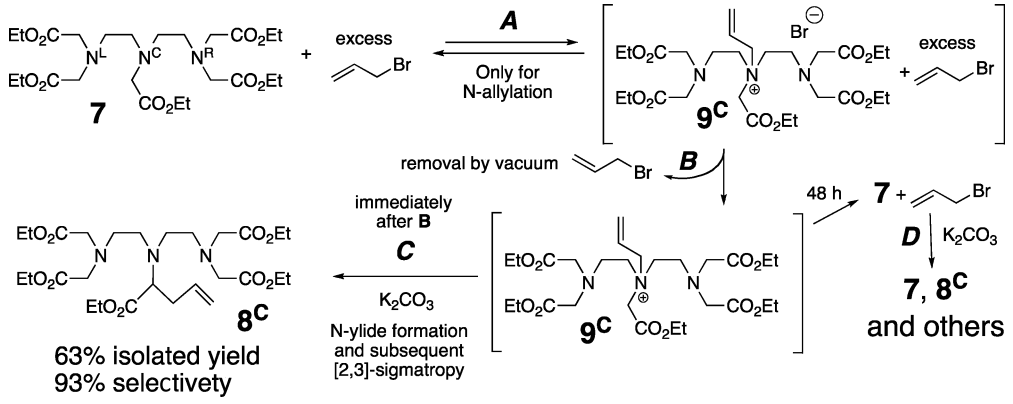
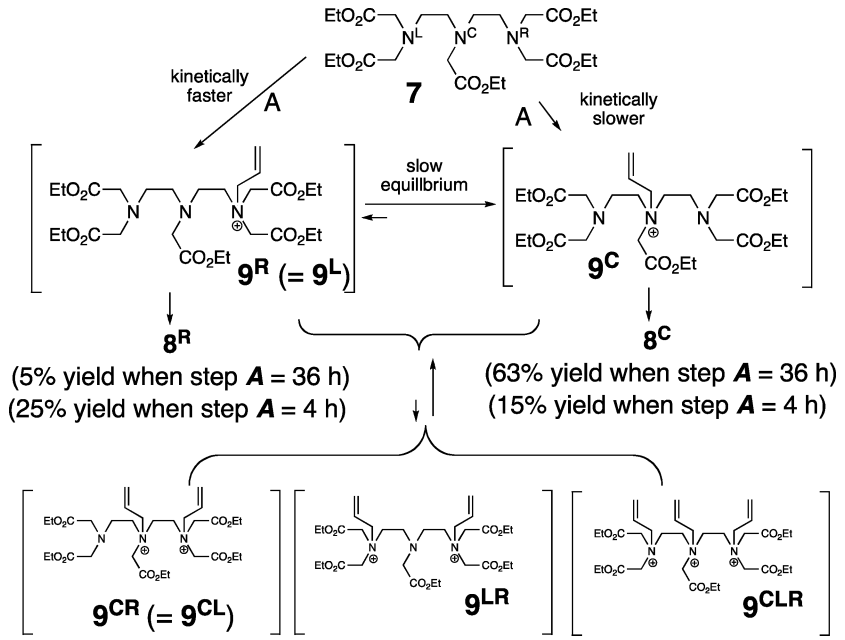
Scheme 4. Newly-Devised Procedure Involving a Vacuum Operation to Remove Excess Allyl Bromide



Scheme 5. Proposed Explanation for the Greater Thermodynamic Stability of 9^C versus Other Salts



after step B, chemical yield and selectivity for 8^C were excellent, as we mentioned in the first sentence of this subsection.

It was expected that the ammonium cation 9^C would be more stable than the cation 9^L since the quaternary ammonium salt on N^C is more stable than that on N^L because of the stronger basicity and nucleophilicity of N^C, which bears one electronegative neighboring group ($-CO_2Et$) compared to two $-CO_2Et$ neighboring groups on N^L. In fact, when step A was continued for a long enough period (36 h), 8^C and 8^L were obtained in 63 and <5% yield, respectively. In contrast, when step A was continued only for a short period (4 h), 8^C and 8^L were produced in 15 and 25% yield, respectively. Thus, formation of 9^L (= 9^R) could be kinetically faster than that of 9^C. It is likely that the concentration of 9^L was decreased hour by hour during step A as it underwent thermodynamic convertion to 9^C via either intramolecular allylic transformation among the three nitrogens or deallylation−reallylation via 7.

Next, we considered why 9^C is thermodynamically more stable than the other salts such as 9^L, 9^{CL}, 9^{LR}, and 9^{CLR}. We assumed that the di- and trication species 9^{CL}, 9^{LR}, and 9^{CLR} are less stable than the monocations 9^L and 9^C, mainly because of the electronic repulsion of cationic nitrogens and the steric repulsion of the allyl groups. Accordingly, we initially compared the stability of 9^C and 9^L.

Discovery of the Frequency of *C*-Allylations. With these results in hand, attention was again paid to the results shown in Scheme 3. Using an unsophisticated mathematical calculation, it was determined that the possible number of zero to fully allylalted derivatives of 7 is 1024 (= 2^{10}) because of the presence of 10 deprotonatable hydrogens in 7.[16] After diastereomeric and enantiomeric duplicates were merged, the possible number of compounds was reduced to 108 (= 3 × 6 × 6).[16] Up to this point, however, the symmetry of 7 was ignored. Next, *gem*-diallylated compounds were excluded on the basis of the result of our ^{13}C NMR analysis[17] and the results reported by various researchers,[1−9,15] giving 18 (= 2 × 3 × 3) compounds.[16] Finally, six compounds were merged because of the symmetry of 7 to leave 12 compounds,[16] which are listed in Table 1 (in fact, 11 compounds are listed because 7 itself is excluded).

According to the mechanism shown in Scheme 1, all of the generated intermediate(s) for the *N*-allylated ammonium cations of the 11 compounds listed in Table 1 can be easily illustrated. For example, 8^{LLR} can be obtained via zero N^C-, two

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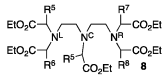
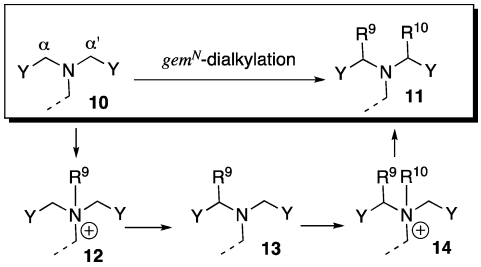
Table 1. Detected Products and Undetectable Compounds of Multi-Allylated Pentaethyl Diethylenetriaminepentaacetate 8 from 7 via the One-Pot Procedure

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8
	R^4 via N^C-allyl	R^5 via N^L-allyl	R^6 via N^L-allyl	R^7 via N^R-allyl	R^8 via N^R-allyl	experimental results	Frequency of considerable N-allylations at N^C–N^L–N^R
$\mathbf{8}^{C}$	allyl	H	H	H	H	detected	1–0–0
$\mathbf{8}^{L}$	H	allyl	H	H	H		0–1-0
$\mathbf{8}^{CL}$	allyl	allyl	H	H	H		1–1–0
$\mathbf{8}^{LR}$	H	allyl	H	allyl	H		0–1–1
$\mathbf{8}^{CLR}$	allyl	allyl	H	allyl	H		1–1–1
$\mathbf{8}^{LL}$	H	allyl	allyl	H	H	undetected	0–2–0
$\mathbf{8}^{CLL}$	allyl	allyl	allyl	H	H		1–2–0
$\mathbf{8}^{LLR}$	H	allyl	allyl	allyl	H		0–2–1
$\mathbf{8}^{CLLR}$	allyl	allyl	allyl	allyl	H		1–2–1
$\mathbf{8}^{LLRR}$	H	allyl	allyl	allyl	allyl		0–2–2
$\mathbf{8}^{CLLRR}$	allyl	allyl	allyl	allyl	allyl		1–2–2

N^L-, and one N^R-allylated cationic intermediates. In this case, the value is "0−2−1" in the column at the right-hand side of Table 1.

The exclusion of *gem*-diallylation is consistent with the results. The value for N^C is either 0 or 1, and the value for N^L (also N^R) is less than 3. It is obvious that all of the values for the detected five products $\mathbf{8}^{C}$, $\mathbf{8}^{L}$, $\mathbf{8}^{CL}$, $\mathbf{8}^{LR}$, and $\mathbf{8}^{CLR}$ are either 0 or 1. In contrast, in the case of the undetected compounds $\mathbf{8}^{LL}$, $\mathbf{8}^{CLL}$, $\mathbf{8}^{LLR}$, $\mathbf{8}^{CLLR}$, $\mathbf{8}^{LLRR}$, and $\mathbf{8}^{CLLRR}$, the values always contain the number 2 for at least one of the nitrogens. As a short summary, it can be concluded that diallylation at N^{α} and $N^{\alpha'}$ as shown in Scheme 6 did not occur. For convenience, such a

Scheme 6. Hardly Observable Dialkylation at N^{α} and $N^{\alpha'}$ (*gem*^{N}-Alkylation)

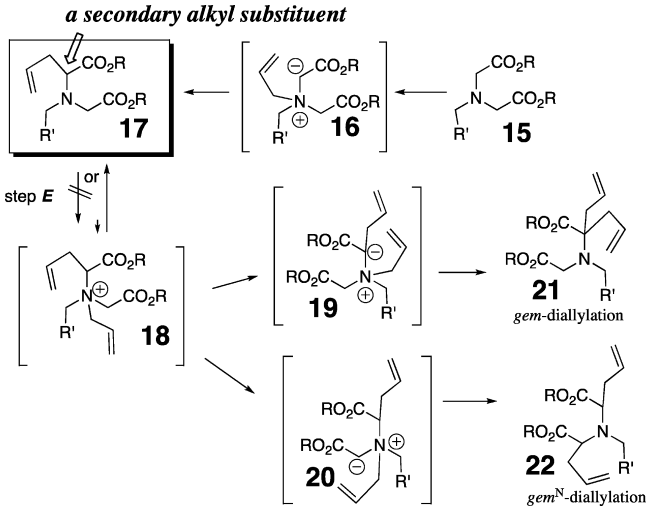


diallylation at N^{α} and $N^{\alpha'}$ is called a "*gem*^{N}-diallylation" in this manuscript. As far as we can determine, the *gem*^{N}-diallylation can occur via dual *N*-allylation (from **10** to **12**, and from **13** to **14**) and corresponding subsequent C-migrations (from **12** to **13**, and from **14** to **11**).

The above discussion led to us to understand the following simple principle for this reaction: one amino functionality manages only one *C*-allylation. As a result, neither the *gem*-diallylated nor *gem*^{N}-diallylated products were detected under the conditions of the ordinary one-pot procedure even in the presence of an excess amount of allyl bromide and K_2CO_3.

Next, we considered the reasons why only one allylation can occur on one nitrogen. Singly allylated product **17** can be, in fact, smoothly produced from **15** via *N*-ylide **16** (Scheme 7).

Scheme 7. Hypothesis for Undetected *gem*-Diallylation and *gem*^{N}-Diallylation



However, *N*-allylation of **17** (step E = second allylation) cannot occur since one of the three N-substituents has been changed to a secondary alkyl group after the first *C*-allylation.[18]

We believe that such a delicate increase in the steric hindrance can inhibit the further *N*-allylation. In contrast, the steps from **18** to either **21** or **22** via **19** or **20** cannot be interfered with since either simple deprotonation or intra-

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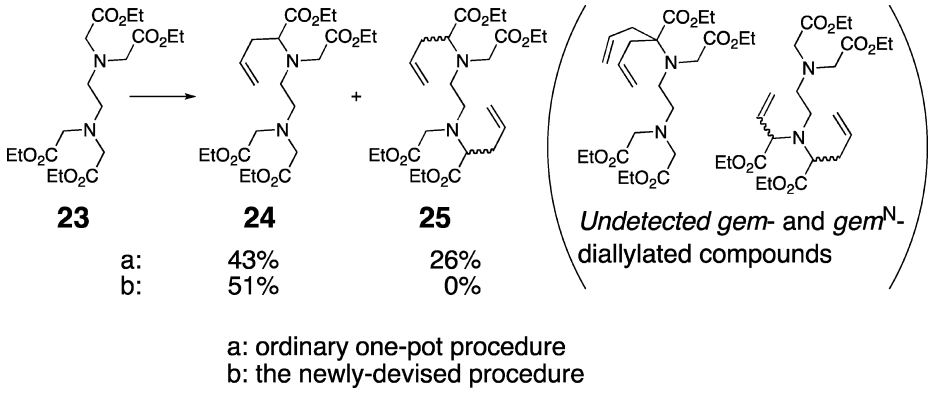
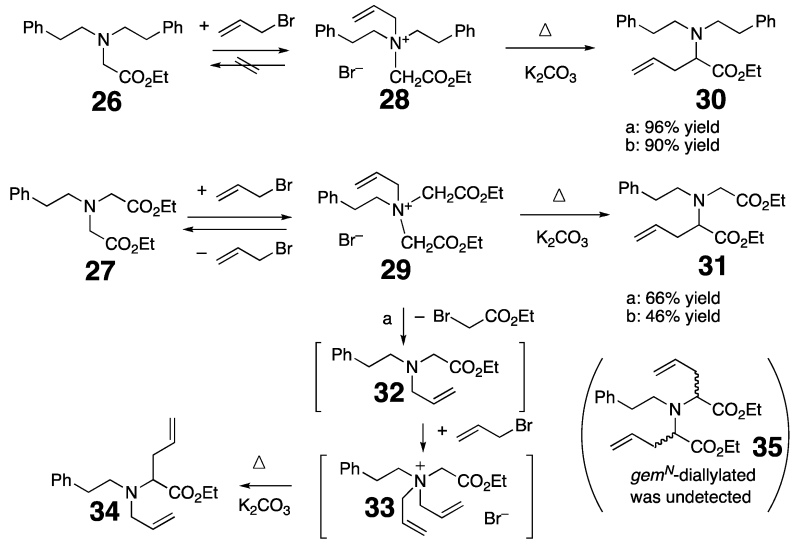
Scheme 8. *C*-Allylation of EDTA Derivative 23



Scheme 9. Allylation of Glycinates 26 and 27



molecular sigmatropy is not affected by such steric hindrance. It is concluded, therefore, that extreme minimization of the presence of **18** is the determinant for undetectable *gem*-diallylated and *gem*^{N}-diallylated compounds, although it is difficult to decide whether *N*-allylation of **17** (step E) is inhibited, or unstable salt **18** is immediately converted back to **17** and allyl bromide. The step from **17** to **18** corresponds to the step from **13** to **14** in Scheme 6.

***C*-Allylation of Other Glycinate Derivatives.** To explore the scope of the reaction, we next focused our attention on the *C*-allylation of other glycinates. The reaction of ethylenediaminetetraacetic acid (EDTA) tetraethyl ester (**23**)[19] afforded **24** and **25** in 43 and 26% yield, respectively using the ordinary one-pot procedure illustrated in Scheme 3 (Scheme 8). In the case of the newly devised procedure illustrated in Scheme 4, **25** was not detected at all, but **24** was produced in 51% yield. Neither *gem*-diallylation nor *gem*^{N}-diallylation were observed at all. Accordingly, highly selective mono-*C*-allylation on the EDTA framework was also successful using the newly devised procedure.

In contrast, at first glance, it was not apparent that the novel procedure provided any advantages for mono-*C*-allylation of ethyl glycinate **26** and iminodiacetic acid (IMDA) diethyl ester (**27**)[20] (Scheme 9). In the case of **26**, allylated product **30** was obtained in more than 90% yield using both procedures, while **27** was also afforded the monoallylated product **31** in satisfactory yield using both procedures. Accordingly, even the ordinary one-pot procedure was synthetically acceptable in the case of these simple glycinates. After careful observation and comparisons, however, we discovered several significant aspects in the case of **27**. Although **26** was smoothly consumed to afford **30** in excellent yield within a few hours in the one-pot procedure, **27** hardly disappeared even after 48 h. Instead, a very small amount of byproduct **34** was detected. It is believed that an equilibrium between **29** and "**32** + ethyl bromoacetate" could lead to formation of **34**[21] via **33**.[22] In contrast, the reaction of **27** via the newly devised procedure simply afforded a mixture of **31** and recovered **27**. Therefore, the suppression of byproducts such as **34** is an advantage provided by the newly devised procedure. Additionally, *gem*^{N}-diallylating compound **35** was not detected at all in either the ordinary one-pot or the newly devised procedure.

Finally, we isolated compound **28** as a model of the central ammonium salt **9**^{C} and prepared **29** as a model of the edged salt **9**^{L} because neither **9**^{C} nor **9**^{L} were separated or isolated because of their instability. The salt **28** was prepared from **26**

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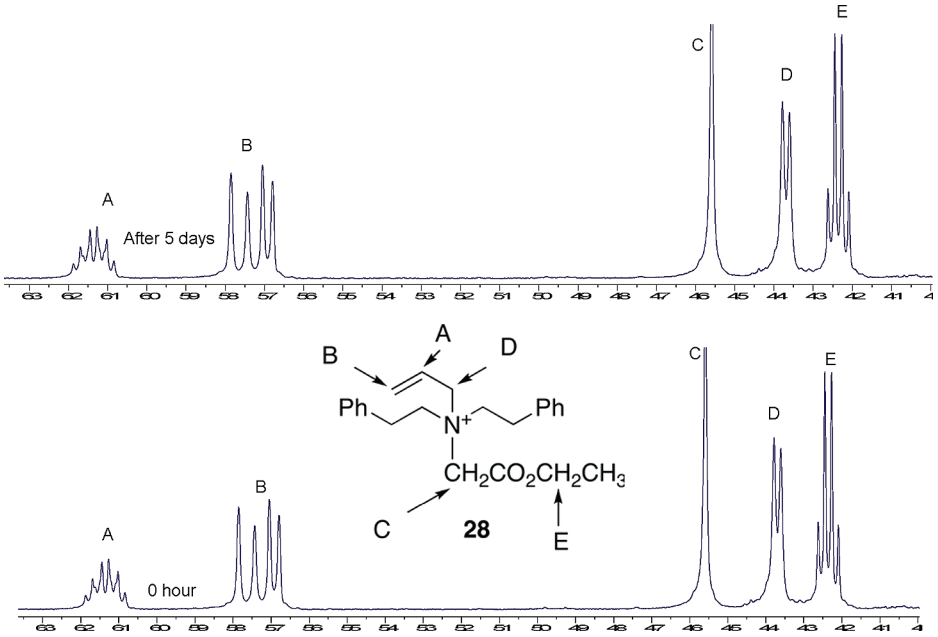

Figure 1. ^{1}H NMR spectra of the stable salt **28** at 60 °C.

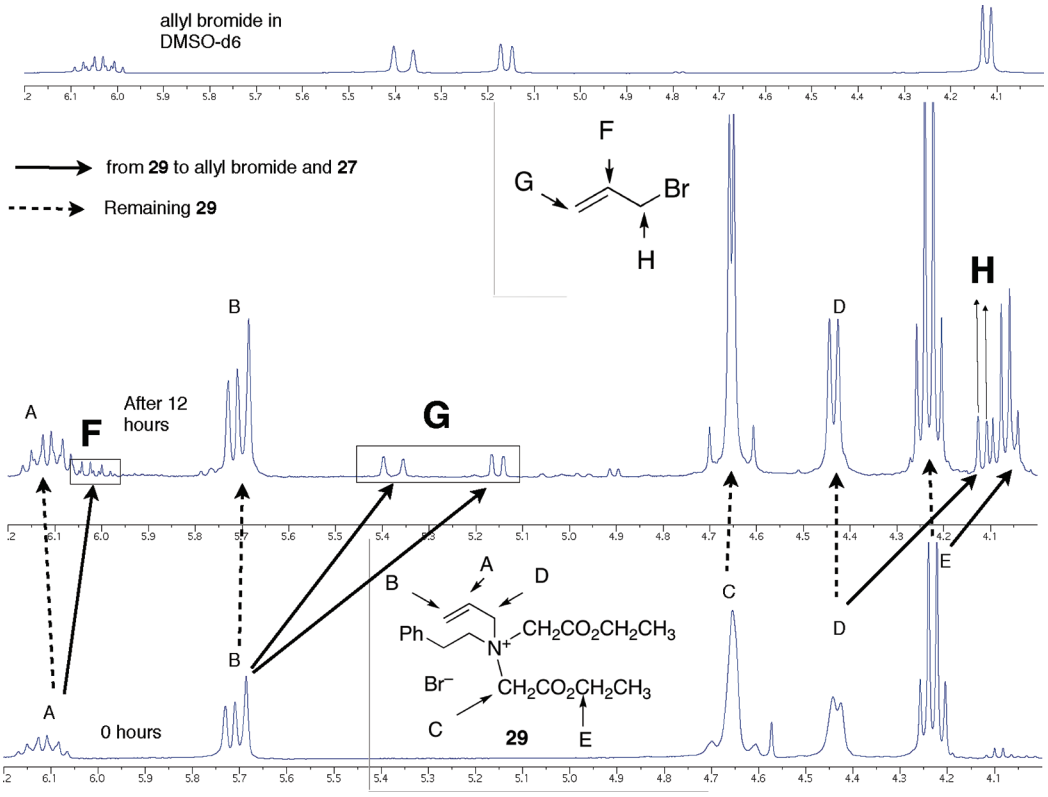

Figure 2. ^{1}H NMR spectra of the unstable salt **29** that generates allyl bromide.

and 10 equiv of allyl bromide in *tert*-butyl methyl ether for 48 h at 40 °C. In a similar procedure, however, **29** was not isolated as a precipitate from **27** and allyl bromide. Therefore, the salt **29** was briefly purified by preparative thin layer chromatography.

In a solution of DMSO-d_6 at 60 °C, the ^{1}H NMR spectrum of **28** did not change at all, even after 5 days (Figure 1). In contrast, extricated allyl bromide was observed in the ^{1}H NMR spectrum of **29** in DMSO-d_6 after 12 h (Figure 2), which indicates the presence of an equilibrium between **29** and "**27** + allyl bromide". This result supports the idea that $\mathbf{9}^{\mathbf{C}}$ is more stable than $\mathbf{9}^{\mathbf{L}}$ and confirms the highly selective formation of $\mathbf{8}^{\mathbf{C}}$ from **7**.

Finally, it is worth noting that in our NMR analysis, we observed the conversion of a quaternary ammonium halide (**QAX**) to a "tertiary amine (**TA**) + allyl bromide" such as in the case of **29** to **27** and **29** to **32**. The study of the reaction course from a **QAX** to a "**TA** + organic halide" has not been

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extensively investigated or reported, although the counter course (from **TA** to **QAX**) has been too trite to mention. Although the Hofmann elimination is very famous for a reaction course from a **QAX** to a **TA**, the side product is an olefin and not an organic halide.[23,24]

CONCLUSIONS

In the ordinary one-pot procedure for *C*-allylation of oligoglycinates via *N*-allyl ylides, we found that the maximal frequency of *C*-allylation is controlled by the inhibition of the formation of both *gem*-diallylation and *gem*^{N}-diallylation. Accordingly, the maximal frequency of *C*-allylation is equal to the number of amino groups and not the number of deprotonative protons. By inserting a vacuum operation between the *N*-allylation and C-migration steps, highly selective mono-*C*-allylation was accomplished, probably because of the prohibition of multication formation, and successfully applied to compounds possessing DTPA, EDTA, and IMDA frameworks. Synthetic applications using a mono-*C*-allylated oligoglycinate are now under investgation.[25]

EXPERIMENTAL SECTION

General Information. Reactions were carried out oven-dried or flame-dried glassware under argon atmosphere unless otherwise noted. *N*,*N*-Dimethylformamide (DMF) was distilled over calcium hydride under argon atmosphere at reduced pressure, and stocked in a screw-capped bottle. Sodium hydrogen carbonate was dissolved in demineralized water to prepare a saturated aqueous solution ($NaHCO_3$ aq). Column chromatography was performed using silica gel 60N (spherical, neutral, 63−210 μm). ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, or at 400 and 100 MHz, respectively, in the presence of tetramethylsilane as an internal standard unless otherwise noted. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants, *J*, are reported in Hz (Hertz).

Representative Ordinary One-Pot Procedure of 7. A mixture of **7** (100 mg, 0.187 mmol), allyl bromide (48.7 μL, 0.562 mmol), and K_2CO_3 (233.0 mg, 1.087 mmol) in DMF (0.937 mL) was heated for 6 days at 40 °C with stirring equipped with calcium chloride tube. After being cooled to room temperature, the reaction mixture was poured into $NaHCO_3$ aq (5 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over K_2CO_3 and concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/ethyl acetate (3/1−1/1) to afford **8**^{C} (21.2 mg, 0.0369 mmol, 20% yield), **8**^{L} (15.3 mg, 0.0266 mmol, 14% yield), and **7** (20.5 mg, 0.0383 mmol, 20% recovered yield), along with an unidentified mixture of several compounds (35−45 mg). The main components were purified by column chromatography to afford a mixture of compounds probably assigned as **8**^{LR} and **8**^{CL} (a mixture of diastereomeric and regioisomeric diallylated products, 30.55 mg, 0.0498 mmol, 27% yield) and a mixture of diastereomeric triallylated products of **8**^{CLR} (2.0 mg, 0.003 mmol, 2% yield). This result was merely one example, and each yield of all the isolated compounds was delicately influenced by the molar ratio of **7**, allyl bromide, and K_2CO_3, reaction period, or reaction temperature.

Newly Devised Procedure from 7 to Afford 8^{C}**.** A mixture of **7** (7.00 g, 13.1 mmol) and allyl bromide (10.2 mL, 118.1 mmol) in DMF (175 mL) was heated for 39 h at 40 °C with stirring equipped with calcium chloride tube. After being cooled to 0 °C, the reaction mixture was concentrated in vacuo to remove excess of allyl bromide at 0 °C. The residue was dissolved in DMF (175 mL), and K_2CO_3 (16.3 g, 118.1 mmol) was added. After being heated at 80 °C for 70 h with stirring equipped with calcium chloride tube, the resulting mixture was poured into $NaHCO_3$ aq (300 mL) and extracted with ethyl acetate (300 mL × 3). The combined organic layers were washed with brine (200 mL), dried over K_2CO_3, and concentrated in vacuo. The residue was purified by column chromatography eluted with hexane/ethyl acetate (1/1) to afford very trace amount of a mixture of di- and triallylated products (<0.5 mg), **8**^{L} (0.38 g, 0.66 mmol, 5% yield), **8**^{C} (4.80 g, 8.30 mmol, 63% yield), and **7** (0.70 g, 1.30 mmol, 10% recovered yield). This result was confirmed by six repeated examinations of the same scale and was highly reproducible even when 30.0 g (56.22 mmol) of **7** was used to afford **8**^{C} in 58% yield (18.7 g, 32.61 mmol). The major product **8**^{C} was easily discriminated from **8**^{L} because **8**^{C} is more symmetric than **8**^{L}, which was easily judged by NMR.

Characterization of Tetraethyl 2,2′,2″,2‴-(2,2′-(1-Ethoxy-1-oxopent-4-en-2-ylazanediyl)bis(ethane-2,1-diyl))bis-(azanetriyl)tetraacetate (8^{C}**).** A colorless oil: FT-IR (neat) 3628, 3448, 3077, 2981, 2366, 2055, 1732, 1642, 1446, 1370, 1343, 1188, 1029, 917, 856, 808, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80 (ddt, *J* = 16.8, 10.0, 6.8, 1H), 5.08 (d, *J* = 16.8, 1H), 5.03 (dt, *J* = 10.0, 0.4, 1H), 4.20−4.13 (m, 10H), 3.57 (s, 8H), 3.50 (t, *J* = 7.6, 1H), 2.88−2.77 (m, 6H), 2.71−2.66 (m, 2H, 2.51 (ddd, *J* = 14.0, 7.6, 6.8, 1H), 2.35 (ddd, *J* = 14.0, 7.6, 6.8, 1H), 1.285 (t, *J* = 6.8, 12H), 1.276 (t, *J* = 6.8, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2 (C), 170.9 (C × 4), 134.9 (CH), 116.5 (CH_2), 63.6 (CH), 60.2 (CH_2 × 4), 60.0 (CH_2), 55.1 (CH_2 × 4), 53.3 (CH_2 × 2), 50.2 (CH_2 × 2), 34.3 (CH_2), 14.3 (CH_3), 14.1 (CH_3 × 4); ESI-HRMS *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{48}O_{10}N_3$ 574.3340; found 574.3331.

Characterization of Diethyl 2,2′-(2-((2-((1-Ethoxy-1-oxopent-4-en-2-yl)(2-ethoxy-2-oxoethyl)amino)ethyl)(2-ethoxy-2-oxoethyl)amino)ethylazanediyl)diacetate (8^{L}**).** A colorless oil: FT-IR (neat) 3626, 3542, 3453, 3077, 2981, 2938, 2907, 2873, 2386, 2350, 2057, 1883, 1731, 1643, 1465, 1446, 1371, 1344, 1189, 1029, 919, 861, 807, 725, 574 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.83 (ddt, *J* = 16.8, 10.0, 6.8, 1H), 5.08 (d, *J* = 16.8, 1H), 5.03 (d, *J* = 10.0, 1H), 4.19−4.12 (m, 10H), 3.60−3.45 (m, 9H), 2.90−2.77 (m, 8H), 2.49 (ddd, *J* = 10.0, 6.8, 6.8 1H), 2.40 (ddd, *J* = 10.0, 6.8, 6.8), 1.29−1.26 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3 (C), 171.7 (C), 171.4 (C), 171.1 (C × 2), 134.5 (CH), 116.9 (CH_2), 64.3 (CH), 60.43 (CH_2 × 2), 60.40 (CH_2), 60.3 (CH_2), 60.2 (CH_2), 55.3 (CH_2 × 2), 55.1 (CH_2), 53.2 (CH_2), 52.8 (CH_2), 52.7 (CH_2), 52.3 (CH_2), 50.7 (CH_2), 34.9 (CH_2), 14.5 (CH_3), 14.34 (CH_3), 14.31 (CH_3 × 2), 14.28 (CH_3); ESI-HRMS *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{47}O_{10}N_3Na$ 596.3159; found 596.3152.

Ordinary One-Pot Procedure of 23 and Allyl Bromide. A solution of **23** (121 mg, 0.30 mmol) and allyl bromide (260 μL, 3.00 mmol) in DMF (1.0 mL) suspended with K_2CO_3 (373 mg, 2.70 mmol) was heated at 60 °C for 72 h. After being cooled to room temperature, the resulting mixture was poured into $NaHCO_3$ aq (4 mL) and extracted with ethyl acetate (25 mL × 3). The combined organic layers were washed with brine (30 mL), dried over K_2CO_3, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane/ethyl acetate (3:1) to afford **23** (19.0 mg, 0.047 mmol, 15% recovery yield), **24** (63.0 mg, 0.140 mmol, 43% yield), and **25** (34.0 mg, 0.070 mmol, 26% yield).

Newly Devised Procedure of 23 and Allyl Bromide. To a solution of **23** (61.0 mg, 0.150 mmol) in DMF (0.5 mL) was added allyl bromide (130 μL, 1.50 mmol) at room temperature, and the mixture was stirred for 52 h at 40 °C. After being cooled to room temperature, the resulting solution was concentrated in vacuo to remove DMF and the excess allyl bromide. The residue was dissolved in DMF (0.5 mL) and suspended with K_2CO_3 (187 mg, 1.35 mmol). The resulting suspension was stirred for 41 h at 60 °C, cooled to room temperature, poured into $NaHCO_3$ aq (2 mL), and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine (20 mL), dried over K_2CO_3, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane/ethyl acetate (3:1) to afford **23** (19.0 mg, 0.047 mmol, 31% recovery yield) and **24** (34.0 mg, 0.076 mmol, 51% yield).

Characterization of 24. A pale yellow oil: FT-IR (neat) 3445, 3078, 2981, 2937, 2907, 2873, 2360, 2342, 2064, 1889, 1732, 1643, 1541, 1521, 1447, 1371, 1343, 1191, 1030, 919, 858, 807, 752, 719 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.60 (ddt, *J* = 10.0, 17.2, 7.2, 1H), 5.01 (d, *J* =17.2, 1H), 4.95 (d, *J* = 10.0, 1H), 4.13−4.03 (m, 8H), 3.58−3.38 (m, 3H), 3.52 (s, 4H), 2.89−2.73 (m, 4H), 2.42 (dt, *J* =

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14.4, 7.2, 1H), 2.33 (dt, J = 14.4, 7.2, 1H), 1.20 (bt, J = 7.2, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.5 (C), 172.0 (C), 171.4 (C × 2), 134.7 (CH), 117.1 (CH_2), 64.1 (CH), 60.4 (CH_2 × 3), 60.3 (CH_2), 55.2 (CH_2 × 4), 52.8 (CH_2), 52.6 (CH_2), 50.8 (CH_2), 34.7 (CH_2), 14.3 (CH_3), 14.13 (CH_3 × 2), 14.09 (CH_3); ESI-HRMS m/z [M + Na]$^+$ calcd for $C_{21}H_{36}O_8N_2Na$ 467.2369; found 467.2364.

Characterization of 25. A pale yellow oil (a 1:1 mixture of diastereomers): FT-IR (neat) 3445, 3078, 2980, 2935, 2908, 2873, 2360, 2341, 2042, 1868, 1844, 1827, 1731, 1642, 1541, 1521, 1446, 1371, 1339, 1269, 1188, 1156, 1030, 980, 918, 857, 766, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.94−5.78 (m, 2H), 5.17−5.03 (m, 4H), 4.184 (q, J = 7.2, 4H), 4.176 (q, J = 7.2, 4H), 3.68−3.46 (m, 6H), 2.96−2.76 (m, 4H), 2.53 (dt, J = 14.1, 7.5, 2H), 2.33 (dt, J = 14.1, 7.5, 2H), 1.31 (t, J = 7.2, 6H), 1.30 (t, J = 7.2, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.54 and 172.51 (C × 2), 171.9 (C × 2), 134.8 and 134.7 (CH × 2), 117.11 and 117.07 (CH_2 × 2), 64.5 and 64.3 (CH × 2), 60.5 and 60.4 (CH_2 × 2), 53.02 and 52.99 (CH_2 × 2), 51.4 and 51.3 (CH_2 × 2), 14.5 (CH_3 × 2), 14.3 (CH_3 × 2); ESI-HRMS m/z [M + Na]$^+$ calcd for $C_{24}H_{40}O_8N_2Na$ 507.2682; found 507.2682.

Preparation of 26. A suspension of ethyl glycinate hydrochloride (1.00 g, 7.16 mmol), 2-bromoethylbenzene (5.87 mL, 42.3 mmol), K_2CO_3 (6.94 g, 50.2 mmol), and potassium iodide (1.43 g, 8.59 mmol) in acetonitrile (20 mL) was heated at reflux with stirring for 16 h. After being cooled to room temperature, the resulting mixture was poured into $NaHCO_3$ aq (10 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over K_2CO_3, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane/ethyl acetate (9:1) to afford **26** as a pale yellow oil (2.00 g, 6.44 mmol, 90% yield): FT-IR (neat) 3444, 3085, 3061, 3026, 2980, 2936, 2858, 2472, 1947, 1872, 1804, 1737, 1653, 1603, 1543, 1496, 1454, 1419, 1368, 1270, 1183, 1134, 1080, 1031, 977, 966, 909, 854, 747, 699, 571 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.23 (m, 4H), 7.22−7.14 (m, 6H), 4.16 (q, J = 7.2, 2H), 3.44 (s, 2H), 3.00−2.85 (m, 4H), 2.84−2.70 (m, 4H), 1.26 (t, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.8 (C), 141.5 (C × 2), 130.1 (CH × 4), 129.7 (CH × 4), 127.4 (CH × 2), 61.8 (CH_2), 57.7 (CH_2 × 2), 56.6 (CH_2), 35.7 (CH_2 × 2), 15.7 (CH_3); ESI-HRMS m/z [M + Na]$^+$ calcd for $C_{20}H_{25}O_2N_1Na$ 334.1783; found 334.1756.

Preparation of 28. A mixture of **26** (47.0 mg, 0.15 mmol) and allyl bromide (130 μL, 1.50 mmol) in TBME (200 μL) was stirred for 48 h at 40 °C. The resulting suspension was filtered at room temperature, and the residue was washed with TBME to afford **28** as a white precipitate (44.0 mg, 0.10 mmol, 68% yield): FT-IR (KBr) 3052, 3023, 3000, 2953, 2360, 2342, 1962, 1889, 1824, 1752, 1636, 1601, 1558, 1541, 1497, 1472, 1438, 1405, 1302, 1272, 1208, 1099, 1038, 941, 916, 876, 763, 704, 594, 540, 506, 428 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.41−7.26 (m, 10H), 6.17 (ddt, J = 10.4, 16.8, 7.2, 1H), 5.80 (d, J = 16.8), 5.71 (d, J = 10.4, 1H), 4.63 (s, 2H), 4.43 (d, J = 7.2, 2H), 4.26 (q, J = 7.2, 2H), 3.81−3.77 (m, 4H), 3.16−3.12 (m, 4H), 1.26 (t, J = 7.2, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.8 (C), 136.0 (C × 2), 129.1 (CH × 4), 128.8 (CH × 4), 128.1 (CH_2), 127.1 (CH × 2), 125.5 (CH), 62.5 (CH_2), 62.3 (CH_2), 60.5 (CH_2 × 2), 56.7 (CH_2), 27.9 (CH_2 × 2), 13.8 (CH_3); ESI-HRMS m/z [M]$^+$ calcd for $C_{23}H_{30}O_2N_1$ 352.2271; found 352.2268.

Preparation of 29. A mixture of **27** (88.0 mg, 0.30 mmol) and allyl bromide (260 μL, 3.00 mmol) in diethyl ether (100 μL) was stirred for 5 days at room temperature. The resulting mixture was directly purified by preparative thin layer chromatography eluted with hexane/ethyl acetate (1:1) to afford **29** (41.0 mg, 0.144 mmol, 48% yield) as a gummy solid.

Ordinary One-Pot Procedure of 26 and Allyl Bromide. A solution of **26** (47.0 mg, 0.15 mmol) and allyl bromide (130 μL, 1.50 mmol) in DMF (0.5 mL) suspended with K_2CO_3 (187 mg, 1.35 mmol) was heated at 60 °C for 72 h. After being cooled to room temperature, the resulting mixture was poured into $NaHCO_3$ aq (2 mL) and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine (20 mL), dried over K_2CO_3, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane/ethyl acetate (9:1) to afford **30** (49.0 mg, 0.14 mmol, 93% yield).

Newly Devised Procedure of 26 and Allyl Bromide. To a solution of **26** (47.0 mg, 0.150 mmol) in DMF (0.5 mL) was added allyl bromide (130 μL, 1.50 mmol) at room temperature, and the mixture was stirred for 39 h at 40 °C. After being cooled to room temperature, the resulting solution was concentrated in vacuo to remove DMF and the excess allyl bromide. The residue was dissolved in DMF (0.5 mL) and suspended with K_2CO_3 (187 mg, 1.35 mmol). The resulting suspension was stirred for 70 h at 80 °C, cooled to room temperature, poured into $NaHCO_3$ aq (2 mL), and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine (20 mL), dried over K_2CO_3, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane/ethyl acetate (9:1) to afford **30** (47.0 mg, 0.13 mmol, 90% yield).

Characterization of 30. A pale yellow oil: FT-IR (neat) 3439, 3062, 3026, 2979, 2935, 2858, 2738, 2366, 2335, 1944, 1869, 1802, 1729, 1641, 1604, 1541, 1496, 1454, 1369, 1339, 1271, 1225, 1178, 1136, 1098, 1030, 998, 915, 855, 746, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29−7.22 (m, 4H), 7.20−7.11 (m, 6H), 5.70 (ddt, J = 10.0, 17.2, 7.2, 1H), 5.04 (d, J = 17.2, 1H), 5.00 (d, J = 10.0, 1H), 4.12 (q, J = 7.2, 2H), 3.47 (t, J = 7.2, 1H), 2.99−2.89 (m, 2H), 2.86−2.71 (m, 4H) 2.70−2.60 (m, 2H), 2.45 (dt, J = 7.2, 14.4, 1H), 2.26 (dt, J = 7.2, 14.4, 1H), 1.24 (t, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.0 (C), 141.8 (C × 2), 136.6 (CH), 130.3 (CH × 4), 129.7 (CH × 4), 127.3 (CH × 2), 118.1 (CH_2), 65.0 (CH), 61.5 (CH_2), 54.9 (CH_2 × 2), 37.1 (CH_2), 35.9 (CH_2 × 2), 15.9 (CH_3); ESI-HRMS m/z [M + H]$^+$ calcd for $C_{23}H_{30}O_2N_1$ 352.2277; found 352.2278.

Ordinary One-Pot Procedure of 27 and Allyl Bromide. A solution of **27** (44.0 mg, 0.15 mmol) and allyl bromide (130 μL, 1.50 mmol) in DMF (0.5 mL) suspended with K_2CO_3 (187 mg, 1.35 mmol) was heated at 60 °C for 72 h. After being cooled to room temperature, the resulting mixture was poured into $NaHCO_3$ aq (2 mL) and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine (20 mL), dried over K_2CO_3, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane/ethyl acetate (6:1) to afford **27** (8.0 mg, 0.027 mmol, 18% recovery yield) and **31** (33.0 mg, 0.10 mmol, 66% yield), (80% yield based on conversion of **27**), along with a trace amount of **34**.

Newly Devised Procedure of 27 and Allyl Bromide. To a solution of **27** (44.0 mg, 0.15 mmol) in DMF (0.5 mL) was added allyl bromide (130 μL, 1.50 mmol) at room temperature, and the mixture was stirred for 39 h at 40 °C. After being cooled to room temperature, the resulting solution was concentrated in vacuo to remove DMF and the excess allyl bromide. The residue was dissolved in DMF (0.5 mL) and suspended with K_2CO_3 (187 mg, 1.35 mmol). The resulting suspension was stirred for 70 h at 80 °C, cooled to room temperature, poured into $NaHCO_3$ aq (2 mL), and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine (20 mL), dried over K_2CO_3, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane/ethyl acetate (6:1) to afford **27** (15.0 mg, 0.051 mmol, 34% recovery yield) and **31** (23.0 mg, 0.069 mmol, 46% yield), (70% yield based on conversion of **27**).

Characterization of 31. A pale yellow oil: FT-IR (neat) 3444, 3064, 3027, 2980, 2936, 2871, 2365, 2341, 1945, 1869, 1731, 1642, 1604, 1541, 1497, 1454, 1371, 1338, 1270, 1186, 1150, 1113, 1030, 978, 917, 856, 749, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.24 (m, 2H), 7.21−7.15 (m, 3H), 5.80 (ddt, J = 7.2, 10.1, 17.2, 1H), 5.08 (dd, J = 1.2, 17.2, 1H), 5.03 (bd, J = 10.0, 1H), 4.15 (q, J = 7.2, 2H), 4.14 (q, J = 7.2, 2H), 3.59 (d, J = 17.2, 1H), 3.52 (t, J = 7.2, 1H), 3.47 (d, J = 17.2, 1H), 3.03−2.87 (m, 2H), 2.86−2.67 (m, 2H), 2.48 (dt, J = 14.4, 7.2, 1H), 2.39 (dt, J = 14.4, 7.2, 1H), 1.27 (t, J = 7.2, 3H), 1.26 (t, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5 (C), 140.0 (C), 134.6 (CH), 128.9 (CH × 2), 128.4 (CH × 2), 126.2 (CH), 117.2 (CH_2), 64.5 (CH), 60.6 (CH_2), 60.4 (CH_2), 54.8 (CH_2), 52.6 (CH_2), 35.3 (CH_2), 35.0 (CH_2), 14.5 (CH_3), 14.3 (CH_3); ESI-HRMS m/z [M + Na]$^+$ calcd for $C_{19}H_{27}O_4N_1Na$ 356.1838; found 356.1834.

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Alternative Preparation of 34. A mixture of ethyl glycinate hydrochloride (279.0 mg, 2.00 mmol), 2-bromoethylbenzene (334 μL, 2.10 mmol), K_2CO_3 (415.0 mg, 3.00 mmol), and potassium iodide (33.0 mg, 0.40 mmol) in acetonitrile (4 mL) was heated at reflux for 24 h. After being cooled to room temperature, the resulting mixture was poured into $NaHCO_3$ aq (10 mL) and extracted with ethyl acetate (40 mL × 3). The combined organic layers were washed with brine (50 mL), dried over K_2CO_3, and concentrated in vacuo. The residue was briefly purified by silica gel column chromatography eluted with hexane/ethyl acetate (1:2) to afford ethyl *N*-(2-phenylethyl)glycinate (191.0 mg, 0.920 mmol, 46% yield), which was used in the next step without further purification.

The briefly purified ethyl *N*-(2-phenylethyl)glycinate (188.0 mg, 0.910 mmol) was treated with allyl bromide (942 μL, 10.9 mmol) and K_2CO_3 (1132 mg, 8.19 mmol) in DMF (3 mL) at 60 °C for 48 h. After being cooled to room temperature, the resulting mixture was poured into $NaHCO_3$ aq (10 mL) and extracted with ethyl acetate (40 mL × 3). The combined organic layers were washed with brine (50 mL), dried over K_2CO_3, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane/ethyl acetate (14:1) to afford a pale yellow oil (227 mg, 0.789 mmol, 87% yield from ethyl *N*-(2-phenylethyl)glycinate). The R_f value of thin layer chromatography and ^{1}H NMR of the product were completely identical with **34** obtained from **27**. The FT-IR, ^{13}C NMR, and HRMS of **34** as described below were the data of the product obtained from this alternative preparation procedure.

34, a pale yellow oil: FT-IR (neat) 3443, 3078, 3027, 2979, 2935, 2840, 2360, 2341, 1943, 1844, 1801, 1730, 1642, 1604, 1558, 1541, 1497, 1453, 1417, 1369, 1340, 1271, 1225, 1180, 1155, 1028, 996, 969, 917, 747, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27–7.21 (m, 2H), 7.18–7.12 (m, 3H), 5.83–5.65 (m, 2H), 5.18 (bd, J = 17.2, 1H), 5.08 (bd, J = 10.0, 1H), 5.04 (dd, J = 1.6, 17.2, 1H), 4.99 (bd, J = 10.0, 1H), 4.19–4.06 (m, 2H), 3.47 (t, J = 7.2, 1H), 3.44–3.35 (m, 1H), 3.16 (dd, J = 14.4, 7.2, 1H), 2.96–2.86 (m, 1H), 2.81–2.61 (m, 3H), 2.46 (dt, J = 14.4, 7.2, 1H), 2.31 (dt, J = 14.4, 7.2, 1H), 1.24 (t, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6 (C), 140.5 (C), 136.9 (CH), 135.1 (CH), 128.9 (CH × 2), 128.3 (CH × 2), 126.0 (CH), 116.9 (CH_2), 116.8 (CH_2), 63.1 (CH), 60.1 (CH_2), 54.5 (CH_2), 52.8 (CH_2), 35.5 (CH_2), 34.5 (CH_2), 14.6 (CH_3); ESI-HRMS m/z $[M + H]^+$ calcd for $C_{18}H_{26}O_2N_1$ 288.1964; found 288.1959.

■ ASSOCIATED CONTENT

Supporting Information

Charts of ^{1}H and ^{13}C NMR of $\mathbf{8}^{C}$, $\mathbf{8}^{L}$, **24**–**26**, **28**, **30**, **31**, and **34**; charts of ^{1}H NMR of **29** and two of the roughly purified compounds [nonseparable $\mathbf{8}^{LR}/\mathbf{8}^{CL}$ (also a diastereomeric mixture), and $\mathbf{8}^{CLR}$ (a diastereomeric mixture)]; details of the mathematical combinations for multiallylation of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Independent work on the mono-*C*-allylation of DTPA penta-*tert*-butyl ester was reported, although the selectivity was unclear because they did not mention any details about the byproducts: Giovenzana, G. B.; Imperio, D.; Lattuadab, L.; Uggerib, F. *Org. Biomol. Chem.* **2011**, *9*, 679–681.
(16) Details of the mathematical combination for multiallylation of **7** are available in the Supporting Information.
(17) The ^{13}C NMR spectrum of the crude mixture of this one-pot procedure did not show any significant peaks around 75 ppm. This value was estimated as the quaternary carbon of *gem*-diallylated glycinyl residues using the ^{13}C NMR predicting function of ChemDraw version 11.
(18) As an example of tertiary amine bearing a secondary alkyl group, **30** in DMF (0.3 M) was treated at 60 °C for 72 h with an extremely large excess of reagents (50 equiv of allyl bromide and 9 equiv of K_2CO_3). Even under such an aggressive condition, the recovered **30** (70–80% yield) was the main ingredient in the crude mixture. The low mass spectra (ESI) of the crude mixture showed several small peaks, one of which appeared at 391 (molecular weight of the *gem*-diallylated product). Isolation of the *gem*-diallylated product was, however, unsuccessful.
(19) Preparation of **23**: Wathier, M.; Grinstaff, M. W. *J. Am. Chem. Soc.* **2008**, *130*, 9648–9649.
(20) Preparation of **27**: We introduced a large alkyl group to prepare **27** according to the known method in order to prepare a starting material that would not be volatile and thus enable better calculation of recovery yield. The reason for the choice of the large group on **26** is the same. López-Cobeñas, A.; Cledera, P.; Sánchez, J. D.; López-Alvarado, P.; Ramos, M. T.; Avendaño, C.; Menéndez, J. C. *Synthesis* **2005**, 3412–3422.
(21) The byproduct **34** was also prepared via an alternative synthetic route because it was obtained in a very small amount. See the detail in the Experimental Section.
(22) Although the alternative route to afford **34** via *N*-allylation of **31**, followed by elimination of ethyl bromoacetate, can also be considered, the route via **32** and **33** is preferable. In fact, several attempts of the reaction of **31** in DMF with K_2CO_3 and allyl bromide (50 equiv to **31**) did not afford any *C*-allylated products. This result is consistent with the phenomenon shown in Scheme 7.
(23) Although the reaction from **QAX** to "**TA** + organic halides" is reversible (Hofmann elimination is irreversible), the reported reaction

herein may be classified as a subsidiary of the Hofmann elimination. Incidentally, we found a few old papers where the reaction from **QAX** to **TA** due to a nucleophilic attack by halide anion was described: Westaway, K. C.; Poirier, R. A. *Can. J. Chem.* **1975**, *53*, 3216−3226. Westaway, K. C.; Ali, S. F. *Can. J. Chem.* **1979**, *57*, 1354−1367.

(24) An example from quaternary ammonium perchlorates or tetrafluoroborates to **TA** due to an intermolecular nucleophilic attack by an amine, a thiol, or a carboxylate: Knier, B. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 6789−6798.

(25) We have demonstrated an example of the synthetic applications of this chemsitry.[13,14] In our previously reported patent[13] and paper,[14] the terminal olefinic moiety of $\mathbf{8}^{C}$ and *N*-Boc-2-(4-iodophenyl) ethanamine via Mizoroki−Heck reaction was described. We are planning to synthesize a conjugate molecule possessing high chelating ability for heavy metal cations and transporting ability to a specific organ, nidus, or cells by using the resulting DTPA derivative bearing primary amino group at the edge of the C-branched chain.

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