# SYNTHESIS OF 3-ALLYL- AND 3-BENZYL-$\Delta^3$-CEPHEMS THROUGH SEQUENTIAL REDUCTIVE 1,2-ELIMINATION/ ADDITION/CYCLIZATION OF 3,4-DISUBSTITUTED 2-BUTENOATES IN ALLYL AND BENZYL HALIDES/Mn/$NiCl_2$ /$AlCl_3$/NMP SYSTEMS

Hideo Tanaka,* Yoshihisa Tokumaru, and Sigeru Torii

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Okayama 700-8530, Japan

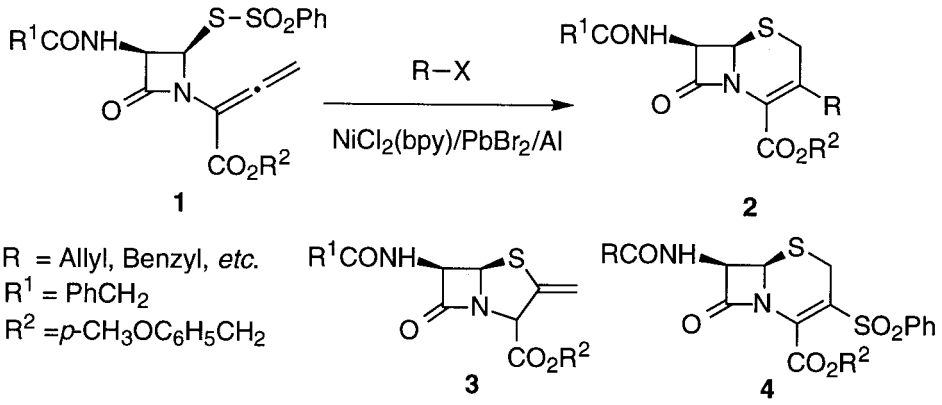
**Abstract** - One-pot synthesis of 3-allyl- and 3-benzyl-$\Delta^3$-cephems through a sequential reductive 1,2-elimination/addition/cyclization of 3, 4-disubstituted 2-[2-oxo-3-phenylacetamido-4-(phenylsulfonylthio)azetidin-1-yl]-2-butenoates was successfully performed by treatment with allyl and benzyl halides in an Mn/$NiCl_2$(bpy)/$AlCl_3$/*N*-methyl-2-pyrroridinone (NMP) system.

β-Lactam antibiotics represent the most widely prescribed drugs used in medicine because of their high antibacterial activity and exceptionally low toxicity toward host. A wide variety of potent β-lactam antibiotics have been produced by chemical modifications of naturally occurring penicillins and cephalosporins.[1] Recently, we and Kant's group have independently developed a new methodology for the formation of cephalosporin framework bearing various heteroatom and carbon substituents at the C(3)-position, which relies on a sequential addition/cyclization of allenecarboxylate (**1**) with various heteroatom and carbon nucleophiles.[2,3] In this connection, we disclosed a straightforward syntheses of 3-allyl- and 3-benzyl-$\Delta^3$-cephems (**2**) through reductive addition/cyclization of the allenecarboxylate (**1**) with allyl and benzyl halides in an Al/$PbBr_2$/$NiCl_2$(bpy) system.[4] The method is, however, not necessarily satisfactory for practical use because the key intermediate (**1**) is hard to handle owing to its liability.[5]

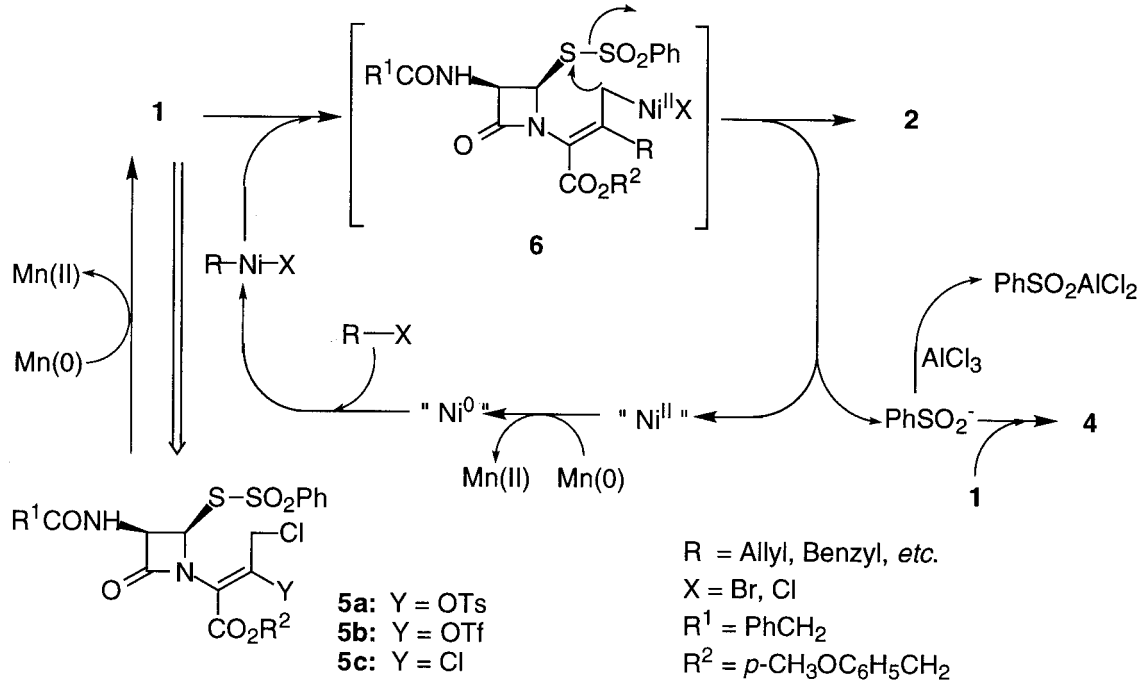
In the recent study, we have found that the 3,4-disubstituted 2-[2-oxo-3-phenylacetamido-4-(phenylsulfonylthio)azetidin-1-yl]-2-butenoates (**5**) (X = OTs, OTf, and Cl) could be utilized as a stable synthetic equivalent of the allenecarboxylates (**1**) to offer straightforward accesses to 2-*exo*-methylenepenams (**3**),[6,7] 3-chloro-$\Delta^3$-cephems,[7] and 3-norcephems.[8] In the initial stage of the transformations, reductive 1,2-elimination of **5** took place preferentially, leading to the allenecarboxylate (**1**).

Our attention was, in turn, focused on one-pot transformation of the 3,4-disubstituted 2-butenoates (**5**) into the 3-alkenyl- and 3-benzyl-$\Delta^3$-cephems (**2**) through the allenecarboxylate (**1**). Herein, we describe that

both reductive 1,2-elimination of 3,4-disubstituted 2-butenoates (**5**)[7] and subsequent reductive addition of allyl and benzyl halides proceeded smoothly in a newly devised Mn/$NiCl_2$(bpy)/$AlCl_3$/*N*-methyl-2-pyrroridinone (NMP) system to afford the 3-allyl- and 3-benzyl-$\Delta^3$-cephems (**2**), respectively.




**Scheme 1**




**Scheme 2**

The 3,4-disubstituted 2-butenoates (**5**) were easily prepared starting from readily available penicillin G[7] and stable enough to survive for several days under ambient conditions. The one pot transformation of the 3,4-disubstituted 2-butenoate (**5a**) (Y = OTs) into the 3-allyl-$\Delta^3$-cephems (**2a**) (R = allyl) was carried out by treatment with allyl bromide as follows (Table 1). A mixture of **5a**, allyl bromide (2.2 molar amounts), Mn (10 molar amounts), $NiCl_2$(bpy) (0.1 molar amount), and $AlCl_3$(1.0 molar amount) in NMP was stirred at ambient temperature for 2 h under argon atmosphere to afford 3-allyl-$\Delta^3$-cephem (**2a**) in 80% yield together with a small amount of 2-*exo*-methylenepenam (**3**) (9%) (entry 1). The formation of the minor product (**3**) can be understood by assuming reductive S-S bond cleavage of the intermediary

allenecarboxylate (**1**) followed by an intramolecular addition/cyclization.[7]

A similar reaction was performed either in an Al (7 molar amounts)/$PbBr_2$ (0.01 molar amounts)/$NiCl_2$(bpy) (0.1 molar amount)/NMP system or in a Zn (10 molar amounts)/$NiCl_2$(bpy) (0.1 molar amounts)/NMP system though the yields of the desired product (**2a**) were lower than that in the Mn/$NiCl_2$(bpy)/$AlCl_3$/NMP system (entries 2 and 3). The presence of a catalytic amount of $NiCl_2$(bpy) is indispensable for the formation of **2a** since in the absence of $NiCl_2$(bpy), only reductive 1,2-elimiation of **5a** occurred; thus, reaction of **5a** with Mn (10 molar amounts) and $AlCl_3$ (1.0 molar amount) in NMP afforded **1** in 80% yield (entry 4). The presence of $AlCl_3$ seems indispensable for 1,2-elimination of **5a** to **1**, since without $AlCl_3$ no appreciable reaction occurred, recovering most of **5a** (entry 5). Notably, $AlCl_3$ would also play a significant role as a trapping reagent of phenylsulfinate ion,[7] which would be formed in the final cyclization stage and work as a nucleophile for sequential addition/cyclization of the intermediary allenecarboxylate (**1**), leading to 3-phenylsulfonyl-$\Delta^3$-cephem (**4**). Actually, when a mixture of **5a** and allyl bromide was stirred with Mn and $NiCl_2$(bpy) in NMP for 2.5 h at ambient temperature, the undesired product (**4**) was formed as a major product (26%) (entry 6). Reaction temperature was also important, since the reaction was carried

**Table 1**. Reaction of 3,4-Disubstituted Butenoate (**5a**) (Y = OTs) with Allyl Bromide

| entry | Metal | Additives | | Temp. /°C | Time /h | Yield/% [b] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | **1** | **2** | **3** | **4** |
| 1 | Mn | $NiCl_2$(bpy) | $AlCl_3$ | rt | 2 | - | 80 | 9 [c] | trace |
| 2 | Al | $NiCl_2$(bpy) | $PbBr_2$ | rt | 2 | - | 52 | 22 [c] | - |
| 3 | Zn | $NiCl_2$(bpy) | - | rt | 2 | - | 50 | - | - |
| 4 | Mn | - | $AlCl_3$ | rt | 2 | 80 [c] | - | - | - |
| 5 [d] | Mn | - | - | rt | 3 | - | - | - | - |
| 6 | Mn | $NiCl_2$(bpy) | - | rt | 2.5 | - | 7 | trace | 26 |
| 7 | Mn | $NiCl_2$(bpy) | $AlCl_3$ | 40-45 | 1 | trace | trace | 54 [c] | 13 [c] |
| 8 [d] | Mn | $PbCl_2$ | $Me_3SiCl$ | rt | 2 | - | - | - | - |
| 9 [d] | Mn | - | $CrCl_2$ | rt | 2 | - | - | - | - |

[a]All reactions were carried out under argon atmosphere. [b]Isolated yields. [c]Determind by HPLC. HPLC conditions: column, YMC-Pack AM-312ODS (6.0ø x 150 mm); mobile phase, $CH_3CN/H_2O$ = 65/35; flow rate, 1.0 mL/min, detection UV at 254 nm. [d]Most of the butenoate (**5a**) was recovered intact.

out at 40 °C to afford 2-*exo*-methylenpenam (**3**) (54%) together with a small amount of 3-sulfonyl-$\Delta^3$-

cephem (**4**) (13%) (entry 7). Recently, combinations of manganese metal with metal salts, such as Mn with a catalytic amount of $PbCl_2$[9] and with a catalytic amount of $CrCl_2$,[10] were reported as a potent reagent for several reductive transformation. These combinations were, however, not effective for the reductive 1,2-elimination of the 3,4-disubstituted 2-butenoate (**5a**) and subsequent reductive addition of allyl bromide, resulting in the recovery of most of **5a** (entries 8 and 9).

The time course of the transformation of **5a** into 3-allyl-$\Delta^3$-cephem (**2a**) in the Mn/$NiCl_2$(bpy)/$AlCl_3$/NMP system was monitored by HPLC (Figure 1). In the initial stage of the reaction, the allenecarboxylate (**1**)

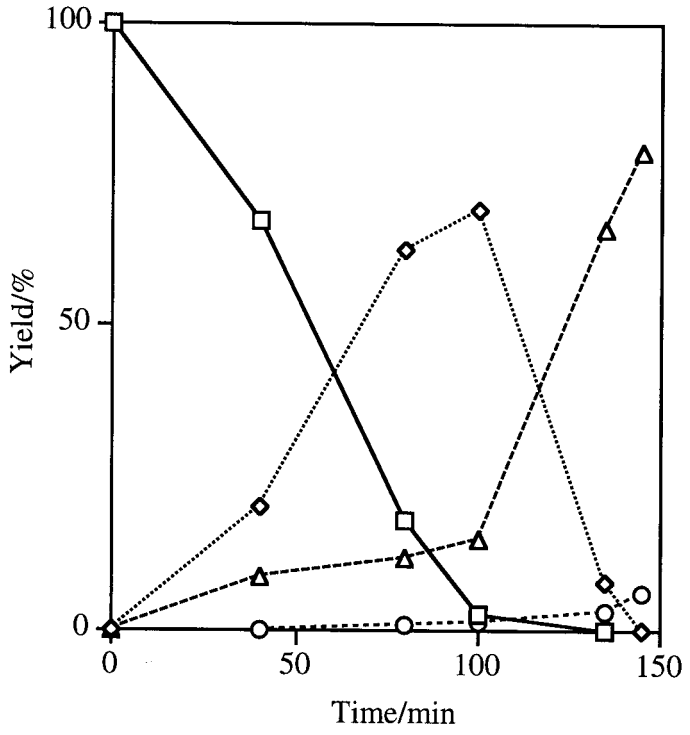


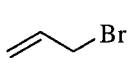
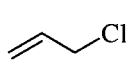
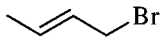
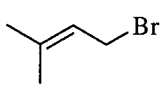
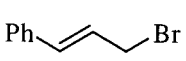
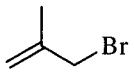
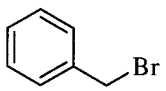
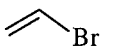
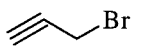

**Fig. 1** Time course of the reaction of tosylate (**5a**) with Mn/$NiCl_2$(bpy)/$AlCl_3$ in NMP; ( □ ) = tosylate (**5a**), ( ◇ ) = allenecarboxylate (**1**), ( △ ) = 3-allyl-$\Delta^3$-caphem (**2a**), ( ○ ) = 2-*exo*-methylenpenam (**3**).

was mainly formed and accumulated until most of the starting material (**5a**) was consumed. In the course of the reaction, formation of a small amount of **2a** was also observed but after then, conversion of **1** to **2a** smoothly occurred, indicating that the reductive 1,2-elimination[7] of **5a** leading to **1** and subsequent reductive addition of allyl bromide followed by cyclization of the adduct **6** affords the 3-allyl-$\Delta^3$-cephem (**2a**) (Scheme 2).[4]

The Mn/$NiCl_2$(bpy)/$AlCl_3$/NMP system was successfully applied to the synthesis of the $\Delta^3$-cephems (**2**) bearing allylic and benzylic C(3)-substituents (Tabel 2). The reaction of **5a** with allyl chloride also took place but proceeded slowly to afford **2a** in only 36% yield even after prolonged reaction time (5.3 h) (entry 2). The reaction of **5a** with 2-butenyl, 3-methyl-2-butenyl, 3-phenyl-2-propenyl, and 2-methyl-2-propenyl bromides afforded the corresponding C(3)-substituted $\Delta^3$-cephems (**2b~e**) in good to moderate yields (entries 3~6). Each of the reactions (entries 3~5) proceeded in a regioselective manner, resulting in the

exclusive substitution at α-position of the allylic bromides. A similar reaction with benzyl bromide afforded 3-benzyl-$\Delta^3$-cephem (**2f**) (20%) together with **3** (21%) (entry 7). In contrast, the reaction of **5a** with vinyl and propargylic bromides in the Mn/$NiCl_2$(bpy)/$AlCl_3$/NMP system did not afford appreciable amounts of the corresponding C(3)-substituted $\Delta^3$-cephems (**2**) but 2-*exo*-methylenepenam (**3**) (53%) and allenecarboxylate (**1**) (80%) were mainly formed, respectively. Probably, organonickel spieces (R-Ni-Br) generated *in situ* in halide/Mn/$NiCl_2$(bpy) system would not be stable enough to survive until the formation of an appreciable amount of allenecarboxylate (**1**).[11]

**Table 2.** 3,4-Disubstituted 2-butenoates (**5a**) (Y = OTs) with Allyl, Benzyl, and Propargyl Halides.[a]

| entry | Halides | Time /h | Yield/% | |
|---|---|---|---|---|
| | | | **2** [b] | **3** [g] |
| 1 |  [c] | 2 | 80 (**2a**) | 9 |
| 2 |  [d] | 5.3 | 36 (**2a**) | 17 |
| 3 |  [c] | 1.7 | 67 (**2b**) | 9 |
| 4 |  [e] | 1.0 | 72 (**2c**) | 21 |
| 5 |  [e] | 1.6 | 60 (**2d**) | 20 |
| 6 |  [c] | 2.0 | 52 (**2e**) | 17 |
| 7 |  [c] | 1.0 | 20 (**2f**) | 21 |
| 8 |  [f] | 1.0 | - | 53 |
| 9 |  [f] | 1.0 | - [h] | - |

[a]All reactions were carried out with Mn (10 molar amounts), $NiCl_2$(bpy) (0.1 molar amount), and $ACl_3$ (1.0 molar amount) at 20-25 °C under argon atmospher. [b]Isolated yield. [c]2.2 molar amounts. [d]3.0 molar amounts. [e]2.5 molar amounts. [f]2.8 molar amounts. [g]Determind by HPLC. HPLC conditions: see footnote c of Table 1. [h]Allenecarboxylate (**1**) was obtained in 80% yield.

The reactions of triflate (**5b**) (Y = OTf)[7] and dichloride (**5c**) (Y = Cl)[7] with allyl bromide were also attempted as an alternative access to the 3-allyl-$\Delta^3$-cephem (**2a**). A mixture of the triflate (**5b**), allyl bromide (2.1 molar amounts), Mn (10 molar amounts), $NiCl_2$(bpy) (0.1 molar amount), and $AlCl_3$ (1.0 molar amount) in NMP was stirred at ambient temperature for 3 h to afford **2a** (45%) together with **3** (17%). Similarly, the dichloride (**5c**) was converted to **2a** in 47% yield.

In conclusion, the one-pot synthesis of 3-allyl- and 3-benzyl-$\Delta^3$-cephems (**2**) through the sequential reductive 1,2-elimination/addition/cyclization of 3,4-disubstituted 2-butenoates (**5**) (Y = OTs, OTf, and Cl) was performed by treatment with allyl and benzyl halides in an Mn/$NiCl_2$(bpy)/$AlCl_3$/NMP system. The presence of both a catalytic amount of $NiCl_2$(bpy) and $AlCl_3$ was indispensable; the combination of Mn/$AlCl_3$ would work as a potent reductant for the 1,2-elimination of **3** and *in situ* generated organonickel spices (R-Ni-X) would act as a nucleophile for the subsequent addition-cyclization stage (Scheme 2).

## EXPERIMENTAL

IR spectra were obtained on a Japan Spectroscopic Co., Ltd. JASCO FT/IR-VALOR-III spectrophotometer. MS spectra were obtained on a Hitachi M-80 mass spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded with Varian Gemini-200 (200 and 50 MHz) spectrometer. High performance liquid chromatography (HPLC) was executed with a Shimadzu HPLC instrument equipped with an LC-10AT LC pump, an LC-10AV UV-VIS detector, and a C-R6A integrator. Elemental analyses were performed on a Perkin Elmer CHNS 2400 microanalyzer. NMP was distilled over calcium hydride under reduced pressure and stored over 4A molecular sieves. 3,4-Disubstituted 2-butenoates (**5**) (R = OTs, OTf, and Cl) were prepared according to the procedures reported in a previous paper.[7] All other reagents were available from commercial sources and used without further purification.

**Reaction of 3-Chloro-4-(*p*-toluenesulfonyloxy)-2-butenoate (5a) with Allyl Bromide in an Mn/$AlCl_3$/$NiCl_2$(bpy) System.** A mixture of Mn powder (77 mg, 1.3 mmol), $AlCl_3$ (17.5 mg, 0.13 mmol), and $NiCl_2$ (bpy) (3.7 mg, 0.013 mmol) in NMP (0.5 mL) was stirred at ambient temperature for 20 min under argon. To the mixture was added a solution of **5a** (100 mg, 0.13 mmol) and allyl bromide (31 mg, 0.28 mmol) in NMP (1.5 mL). After being stirred for additional 2 h at ambient temperature, the reaction mixture was poured into ice-cold 5% HCl, and extracted with ethyl acetate. The combined extracts were washed with water and with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed ($SiO_2$, toluene/ethyl acetate: 5/1) to give 3-allyl-$\Delta^3$-cephem (**2a**) (48 mg, 80%) and 2-*exo*-methylenepenam (**4**) (5 mg, 9%).

***p*-Methoxybenzyl 3-Allyl-7-phenylacetamido-$\Delta^3$-cephem-4-carboxylate (2a)**[7]: IR (Nujol) 3263, 1782, 1704, 1652, 1615, 1587, 1537, 1517, and 1497 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.87 (dd, $J$ = 7.6, 14 Hz, 1H), 3.21 (d, $J$ = 18.4 Hz, 1H), 3.37 (dd, $J$ = 7.6, 14 Hz, 1H), 3.38 (d, $J$ = 18.4 Hz, 1H), 3.62 (d, $J$ = 16 Hz, 1H), 3.65 (d, $J$ = 16 Hz, 1H), 3.80 (s, 3H), 4.91 (d, $J$ = 4.7 Hz, 1H), 5.08 (d, $J$ = 16 Hz, 1H), 5.09 (d, $J$ = 9.8 Hz, 1H), 5.18 (s, 2H), 5.75 (m, 1H), 5.77 (dd, $J$ = 4.7, 9.0 Hz, 1H),

6.01 (d, $J$ = 9.0 Hz, 1H), 6.90 (d, $J$ = 8.8 Hz, 2H), and 7.20-7.45 (m, 7H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 27.9, 37.6, 43.3, 55.2, 57.3, 59.0, 67.6, 113.6, 117.9, 123.3, 127.1, 127.6, 129.1, 129.4, 130.5, 131.3, 133.7, 133.9, 159.8, 161.7, 164.5 and 171.1.

**2-*exo*-Methylenepenam (3)**[6,7]: IR ( KBr ) 3309, 1801, 1743, 1666, 1627, and 1531 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) δ 3.62 (s, 2H), 3.82 (s, 3H), 5.11 (s, 2H), 5.18 (dd, $J$ = 1.5, 1.6 Hz, 1H), 5.24 (dd, $J$ = 1.7, 1.9 Hz, 1H), 5.35 (dd, $J$ = 1.7, 1.9 Hz, 1H), 5.57 (d, $J$ = 4.0 Hz, 1H), 5.75 (dd, $J$ = 4.0, 8.9 Hz, 1H), 6.08 (d, $J$ = 8.9 Hz, 1H), and 6.85-7.40 (m, 9H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 43.25, 55.26, 59.97, 64.53, 67.80, 69.53, 107.97, 114.05, 126.75, 127.65, 129.10, 129.36, 130.17, 133.62, 146.07, 159.92, 166.93, 170.39, and 172.35.

**Reaction of 3-Chloro-4-(*p*-toluenesulfonyloxy)-2-butenoate (5a) with Allyl Chloride in an Mn/$AlCl_3$/$NiCl_2$(bpy) System.** In a similar manner, the reaction of **5a** (100 mg, 0.13 mmol) with allyl chloride (28 mg, 0.37 mmol) was carried out at rt for 5.3 h to give **2a** (20 mg, 36%).

***p*-Methoxybenzyl 3-(2-Butenyl)-7-phenylacetamido-Δ$^3$-cephem-4-carboxylate (2b).** In a similar manner, the reaction of **5a** (100 mg, 0.13 mmol) with crotyl bromide (37 mg, 0.28 mmol) was carried out at rt for 1.7 h to give **2b** (41 mg, 67%): IR (Nujol) 3266, 1773, 1712, 1706, 1652, 1615, 1586, 1534, 1518, and 1495 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) δ 1.65 (d, $J$ = 6.0 Hz, 3H), 2.87 (dd, $J$ = 8, 14 Hz, 1H), 3.1-3.3 (m, 1H), 3.25 (d, $J$ = 18 Hz, 1H), 3.35 (d, $J$ = 18 Hz, 1H), 3.62 (d, $J$ = 16 Hz, 1H), 3.63 (d, $J$ = 16 Hz, 1H), 3.79 (s, 3H), 4.89 (d, $J$ = 4 Hz, 1H), 5.18 (s, 2H), 5.2-5.6 (m, 2H), 5.76 (dd, $J$ = 4, 8 Hz, 1H), 6.08 (d, $J$ = 8 Hz, 1H), 6.87 (d, $J$ = 8 Hz, 2H), and 7.1-7.5 (m, 7H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 12.9, 17.8, 27.9, 30.7, 43.1, 55.1, 57.3, 59.0, 67.4, 113.8, 122.6, 125.5, 126.3, 127.0, 127.1, 127.4, 128.7, 128.8, 128.9, 129.3, 130.4, 133.1, 133.8, 159.7, 161.8, 164.5, and 171.3. Anal. Calcd for $C_{27}H_{28}N_2O_5S$: C,65.83; H,5.73; N, 5.69. Found: C, 65.83; H, 5.75; N,5.63.

***p*-Methoxybenzyl 3-(2-Methyl-2-butenyl)-7-phenylacetamido-Δ$^3$-cephem-4-carboxylate (2c).** In a similar manner, the reaction of **5a** (100 mg, 0.13 mmol) with 4-bromo-2-methyl-2-butene (49 mg, 0.32 mmol) was carried out at rt for 1 h to give **2c** (46 mg, 72%): IR (Nujol) 3278, 1766, 1713, 1653, 1614, 1586, 1530, 1518, and 1498 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$) δ 1.62 (s, 3H), 1.69 (s, 3H), 3.0-3.3 (m, 2H), 3.14 (d, $J$ = 18.2 Hz, 1H), 3.38 (d, $J$ = 18.2 Hz, 1H), 3.62 (d, $J$ = 16.3 Hz, 1H), 3.65 (d, $J$ = 16.3 Hz, 1H), 3.80 (s, 3H), 4.90 (d, $J$ = 4.8 Hz, 1H), 5.0-5.1 (m, 1H), 5.17 (d, $J$ = 13 Hz, 1H), 5.18 (d, $J$ = 13 Hz, 1H), 5.75 (dd, $J$ = 4.8, 9.4 Hz, 1H), 5.99 (d, $J$ = 9.4 Hz, 1H), 6.87 (d, $J$ = 8.6 Hz, 2H), and 7.2-7.4 (m, 7H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 18.0, 25.8, 28.0, 32.0, 43.4, 55.3, 57.2, 58.9, 67.5, 113.9, 119.8, 122.4, 127.1, 127.7, 129.2, 129.5, 130.6, 133.2, 133.6, 135.1, 159.7, 161.9, 164.4 and 171.1. Anal. Calcd for $C_{28}H_{30}N_2O_5S$: C, 66.38; H, 5.97; N, 5.53. Found: C, 66.34 H, 5.87; N, 5.51.

***p*-Methoxybenzyl 3-Cinnamyl-7-phenylacetamido-Δ$^3$-cephem-4-carboxylate (2d).** In a similar manner, the reaction of **5a** (100 mg, 0.13 mmol) with cinnnamyl bromide (63 mg, 0.32 mmol) was carried out at rt for 1.6 h to give **2d** (43 mg, 60%): IR (Nujol) 3291, 1757, 1715, 1663, 1611, 1533, 1513,

and 1497 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 2.97 (dd, *J* = 8.4, 14 Hz, 1H), 3.30 (d, *J* = 18 Hz, 1H), 3.42 (d, *J* = 18 Hz, 1H), 3.56 (dd, *J* = 10, 14 Hz, 1H), 3.62 (d, *J* = 16 Hz, 1H), 3.65 (d, *J* = 16 Hz, 1H), 3.79 (s, 3H), 4.92 (d, J = 4.8 Hz, 1H), 5.21 (s, 2H), 5.79 (dd, *J* = 4.8, 9 Hz, 1H), 6.02 ( d, *J* = 9 Hz, 1H), 6.1-6.2 (m, 1 H), 6.42 (d, *J* = 16 Hz, 1H), 6.87 (d, *J* = 8 Hz, 2H), and 7.2-7.4 (m, 12H); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 28.0, 36.9, 43.3, 55.2, 57.3, 59.0, 67.7, 113.9, 123.3, 125.4, 126.2, 127.7, 128.5, 129.1, 129.4, 130.6, 131.1, 133.0, 133.6, 136.7, 159.8, 161.8, 164.4 and 171.1. Anal. Calcd for $C_{32}H_{30}N_2O_5S$: C, 69.29; H, 5.45; N, 5.05. Found: C, 69.01; H, 5.28; N, 5.27.

***p*-Methoxybenzyl 3-(2-Methyl-2-propenyl)-7-phenylacetamido-$\Delta^3$-cephem-4-carboxylate (2e).** In a similar manner, the reaction of **5a** (100 mg, 0.13 mmol) with 3-bromo-2-methylpropene (40 mg, 0.28 mmol) was carried out at rt for 1 h to give **2e** (33 mg, 54%): IR (Nujol) 3290, 3030, 1781, 1715, 1652, 1612, 1590, 1531, 1513, and 1497 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 1.65 (s, 3H), 2.96 (d, *J* = 15 Hz, 1H), 3.24 (d, *J* = 18 Hz, 1H), 3.32 (d, *J* = 18 Hz, 1H), 3.33 (d, *J* = 15 Hz, 1H), 3.63 (d, *J* = 16 Hz, 1H), 3.65 (d, *J* = 16 Hz, 1H), 3.80 (s, 3H), 4.69 (s, 1H), 4.84 (s, 1H), 4.93 (d, *J* = 4.6 Hz, 1H), 5.17 (s, 2H), 5.77 (dd, *J* = 4.6, 9.2 Hz, 1H), 6.02 (d, *J* = 9.2 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), and 7.2-7.5 (m, 7H); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 22.2, 28.0, 40.9, 43.3, 55.2, 57.7, 59.0, 67.5, 113.3, 113.9, 123.9, 127.0, 127.6, 129.1, 129.4, 130.5, 131.5, 133.7, 141.7, 159.8, 161.7, 164.5, and 171.1. Anal. Calcd for $C_{27}H_{28}N_2O_5S$: C, 65.83, H, 5.73, N, 5.69. Found: C, 65.83, H, 5.75, N, 5.63.

***p*-Methoxybenzyl 3-Benzyl-7-phenylacetamido-$\Delta^3$-cephem-4-carboxylate (2f).** In a similar manner, the reaction of **5a** (100 mg, 0.13 mmol) with benzyl bromide (47 mg, 0.28 mmol) was carried out at rt for 1 h to give **2f** (14 mg, 20%): IR (Nujol) 3279, 1767, 1720, 1713, 1657, 1612, 1585, 1517, and 1495 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 3.04 (d, *J* = 18.0 Hz, 1H), 3.24 (d, *J* = 18.0 Hz, 1H), 3.42 (d, *J* = 15.0 Hz, 1H), 3.55 (s, 2H), 3.73 (s, 3H), 3.96 (d, *J* = 15.0 Hz, 1H), 4.85 (d, *J* = 4.0 Hz, 1H), 5.15 (s, 2H), 5.73 (dd, *J* = 4.0, 10.0 Hz, 1H), 5.93 (d, *J* = 10.0 Hz, 1H), and 6.7-7.4 (m, 14H); $^{13}C$ NMR (50 MHz, $CDCl_3$) δ 27.9, 38.5, 43.3, 55.2, 57.4, 59.0, 67.7, 113.9, 123.6, 126.9, 127.0, 127.6, 128.7, 128.9, 129.1, 129.4, 130.6, 131.5, 133.6, 137.2, 159.8, 161.9, 164.5 and 171.1. Anal. Calcd for $C_{30}H_{28}N_2O_5S$: C, 68.16; H, 5.34; N, 5.30. Found: C, 68.14; H, 5.35; N, 5.37.

**Reaction of 3-Chloro-4-(*p*-toluenesulfonyloxy)-2-butenoate (5a) with Vinyl Bromide in an Mn/$AlCl_3$/$NiCl_2$(bpy) System.** A mixture of Mn powder (77 mg, 1.3 mmol), $AlCl_3$(18 mg, 0.13 mmol), and $NiCl_2$(bpy) (3.7 mg, 0.013 mmol), in NMP (0.5 mL) was stirred at ambient temperature under argon for 20 min. To the mixture was added a solution of **5a** (100 mg, 0.13 mmol) in NMP (1.5 mL) and vinyl bromide (46 mg, 0.35 mmol). After being stirred for additional 2 h at ambient temperature, an aliquot of the reaction mixture was analyzed by HPLC, showing the presence of 2-*exo*-methylenepenam (**3**) (53%).

**Reaction of 3-Chloro-4-(*p*-toluenesulfonyloxy)-2-butenoate (5a) with Propargyl Bromide**

**in an $Mn/AlCl_3/NiCl_2(bpy)$ System.** A mixture of Mn powder (77 mg, 1.3 mmol), $AlCl_3$ (18 mg, 0.13 mmol), and $NiCl_2(bpy)$ (3.7 mg, 0.013 mmol) in NMP (0.5 mL) was stirred at ambient temperature under argon for 20 min. To the mixture was added a solution of **2a** (100 mg, 0.13 mmol) and propargyl bromide (49 mg, 0.35 mmol) in NMP (1.5 mL). After being stirred for additional 2 h at ambient temperature, an aliquot of the reaction mixture was analyzed by HPLC, showing the presence of allenecarboxylate (**1**) (80%).

**Reaction of 3-Chloro-4-trifluoromethanesulfonyloxy-2-butenoate 5b with Allyl Bromide in an $Mn/AlCl_3/NiCl_2(bpy)$ System.** A mixture of Mn powder (77 mg, 1.3 mmol), $AlCl_3$ (18 mg, 0.13 mmol), and $NiCl_2(bpy)$ (3.7 mg, 0.013 mmol) in NMP (0.5 mL) was stirred at ambient temperature under argon for 20 min. To the mixture was added a solution of **5b** (100 mg, 0.13 mmol) and allyl bromide (31 mg, 0.28 mmol) in NMP (1.5 mL) was added. After being stirred for additional 2 h at ambient temperature, the reaction mixture was poured into ice-cold 5% HCl, and extracted with ethyl acetate. The combined extracts were washed with water and with brine, dried($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed ($SiO_2$, toluene/ethyl acetate: 5/1) to give 3-allyl-$\Delta^3$-cephem (**2a**) (29 mg, 45%) and 2-*exo*-methylenepenam (**3**) (10 mg, 17%).

**Reaction of 3,4-Dichloro-2-butenoate (5c) with Allyl Bromide in an $Mn/AlCl_3/NiCl_2(bpy)$ System.** A mixture of Mn powder (84 mg, 1.5 mmol), $AlCl_3$ (21 mg, 0.15 mmol), and $NiCl_2(bpy)$ (4.5 mg, 0.016 mmol) in NMP (0.5 mL) was stirred at ambient temperature under argon for 20 min. To the mixture was added a solution of **5c** (100 mg, 0.15 mmol) and allyl bromide (42 mg, 0.35 mmol) in NMP (1.5 mL). After being stirred for additional 2 h at ambient temperature, the reaction mixture was poured into ice-cold 5% HCl and extracted with ethyl acetate. The combined extracts were washed with water and with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed ($SiO_2$, toluene/ethyl acetate: 5/1) to give 3-allyl-$\Delta^3$-cephem (**2a**) (35 mg, 47%) together with 2-*exo*-methylenepenam (**3**) (4 mg, 6%).

## ACKNOWLEDGMENTS

This work was partly supported by Grants-in-Aid for Scientific Research on Priority Areas (No. 283, "Innovative Synthetic Reaction") from the Ministry of Education, Science, Sports, and Culture, Government of Japan. The NMR Laboratory of Faculty of Engineering, Okayama University is thanked for obtaining $^1H$ and $^{13}C$ NMR spectra.

## REFERENCES AND NOTES

1. 'Recent Advances in the Chemistry of β-Lactam Antibiotics', ed. by G. I. Gregory, The Royal Society of Chemistry, Burlington House, London, 1980; 'Recent Advances in the Chemistry of β-Lactam Antibiotics', ed. by J. Elks, The Chemical Society , Burlington House, London, 1977.
2. J. Kant and V. Farina, *Tetrahedron Lett.*, 1992, **33**, 3563; J. Kant, J. A. Roth, C. E. Fuller, D. G. Walker, D. A. Benigni, and V. Farina, *J. Org. Chem.*, 1994, **59**, 4956.

3. H. Tanaka, Y. Kameyama, S. Sumida, T. Yamada, Y. Tokumaru, T. Shiroi, M. Sasaoka, M. Taniguchi, and S. Torii, *Synlett*, 1991, 888; S. Torii and H. Tanaka, *J. Synth. Org. Chem. Jpn*, 1996, **54**, 941 and references are cited therein.
4. H. Tanaka, S. Sumida, K. Sorajo, and S. Torii, *J. Chem. Soc., Chem. Commun.*, 1994, 1461; H. Tanaka, S. Sumida, K. Sorajo, Y. Kameyama, and S. Torii, *J. Chem. Soc., Perkin Trans. 1*, 1996, 637.
5. The allenecarboxylate **1** can be stored in a refrigerator for several days without appreciable change but gradually decomposed under ambient conditions, particularly in the presence of a trace amount of acid or base.
6. J. E. Baldwin, A. K. Forrest, S. Ko, and L. N. Sheppard, *J. Chem. Soc., Chem. Commun.*, 1987, 81; H. Tanaka, Y. Kameyama, A. Kosaka, T. Yamauchi, and S. Torii, *Tetrahedron Lett.*, 1991, **32**, 7445, and references cited therein.
7. H. Tanaka, S. Sumida, Y. Nishioka, N. Kobayashi, Y. Tokumaru, Y. Kameyama, and S. Torii, *J. Org. Chem.*, 1997, **62**, 3610.
8. H. Tanaka, Y. Yamaguchi, S. Sumida, and S. Torii, *Chem. Commun.*, 1996, 2705.
9. K. Takai, T. Ueda, T. Hayashi, and T. Moriwake, *Tetrahedronn Lett.*, 1996, **37**, 7049; K. Takai, T. Ueda, N. Ikeda, and T. Moriwake,*J, Org. Chem.*, 1996, **61**, 7990; K. Takai, T. Ueda, H.Kaihara, Y. Sunami, and T. Moriwake, *J, Org. Chem.*, 1996, **61**, 8728.
10. A. Fuerstner and N. Shi, *J. Am. Chem. Soc.*, 1996, **118**, 2533; A. Fuerstner and N. Shi, *J. Am. Chem. Soc.*, 1996, **118**, 12349.
11. H. Tanaka, A. Kosaka, S. Yamashita, K. Morisaki, and S. Torii, *Tetrahedron Lett.*, 1989, **30**, 1261.

Received, 28th April, 1999