SYNTHESIS OF 3-ALLYL- AND 3-BENZYL-Δ^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

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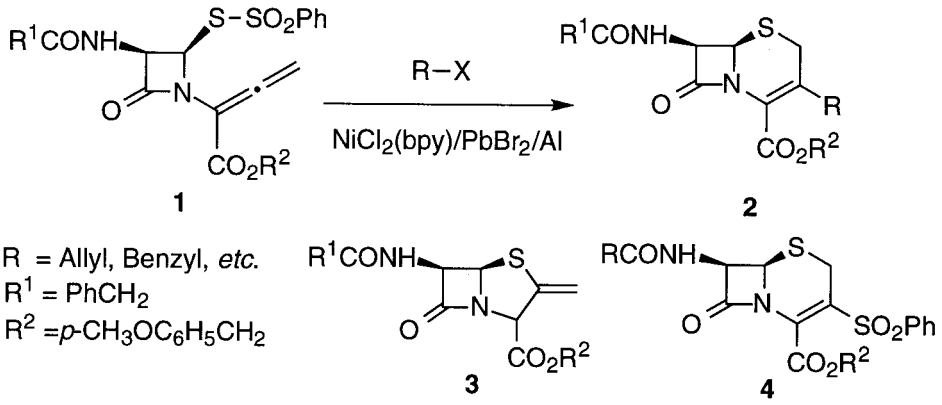
Abstract - One-pot synthesis of 3-allyl- and 3-benzyl-Δ^3-cephems through a sequential reductive 1,2-elimination/addition/cyclization of 3, 4-disubstituted 2-[2-oxo-3-phenylacetamido-4-(phenylsulfonylthio)azetidin-1-yl]-2-butenoates was successfully performed by treatment with allyl and benzyl halides 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-Δ^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]

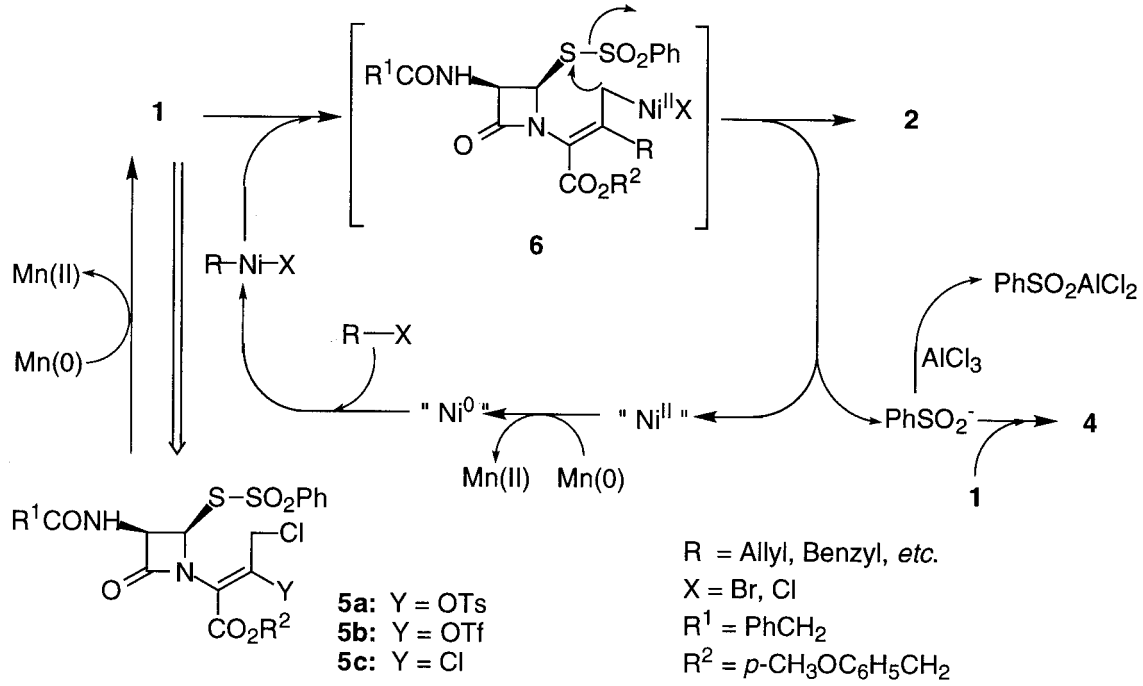
In the recent study, we have found that the 3,4-disubstituted 2-[2-oxo-3-phenylacetamido-4-(phenylsulfonylthio)azetidin-1-yl]-2-butenoates (**5**) (X = OTs, OTf, and Cl) could be utilized as a stable synthetic equivalent of the allenecarboxylates (**1**) to offer straightforward accesses to 2-*exo*-methylenepenams (**3**),[6,7] 3-chloro-Δ^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-Δ^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-Δ^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-Δ^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-Δ^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-Δ^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-Δ^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-Δ^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**)

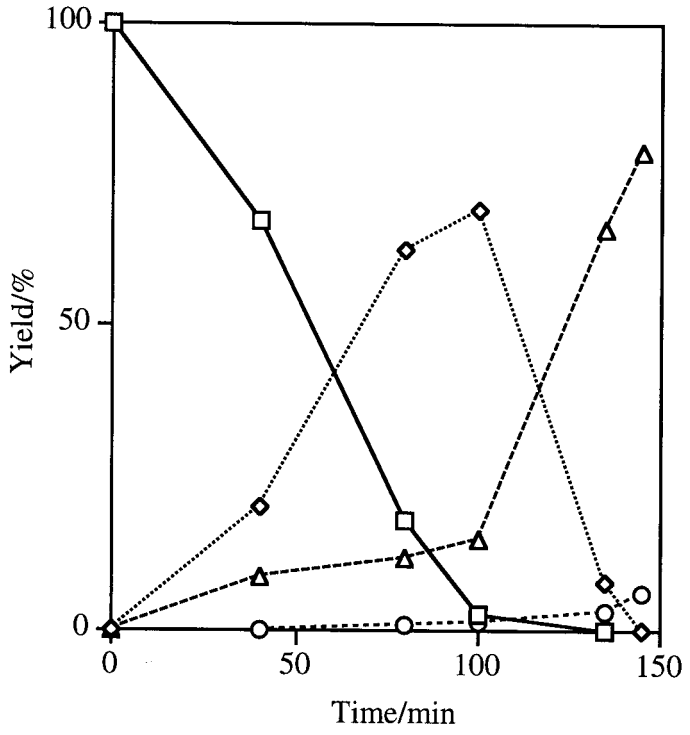


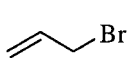
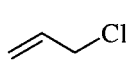
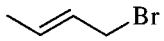
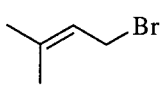
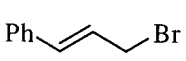
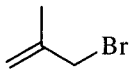
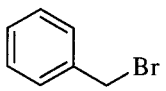
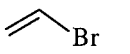
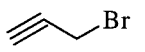
Fig. 1 Time course of the reaction of tosylate (**5a**) with Mn/$NiCl_2$(bpy)/$AlCl_3$ in NMP; (□) = tosylate (**5a**), (◇) = allenecarboxylate (**1**), (△) = 3-allyl-Δ^3-caphem (**2a**), (○) = 2-*exo*-methylenpenam (**3**).

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-Δ^3-cephem (**2a**) (Scheme 2).[4]

The Mn/$NiCl_2$(bpy)/$AlCl_3$/NMP system was successfully applied to the synthesis of the Δ^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 Δ^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-Δ^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 Δ^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-Δ^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-Δ^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-Δ^3-cephem (**2a**) (48 mg, 80%) and 2-*exo*-methylenepenam (**4**) (5 mg, 9%).

***p*-Methoxybenzyl 3-Allyl-7-phenylacetamido-Δ^3-cephem-4-carboxylate (2a)**[7]: IR (Nujol) 3263, 1782, 1704, 1652, 1615, 1587, 1537, 1517, and 1497 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 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-Δ^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-Δ^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-Δ^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-Δ^3-cephem (**2a**) (35 mg, 47%) together with 2-*exo*-methylenepenam (**3**) (4 mg, 6%).

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