Facile access to 3-allyl- and 3-benzyl-Δ^3-cephems through reductive addition/cyclization of allenecarboxylate with allylic and benzylic halides in an [$NiCl_2$(bipy)]/$PbBr_2$/Al redox system

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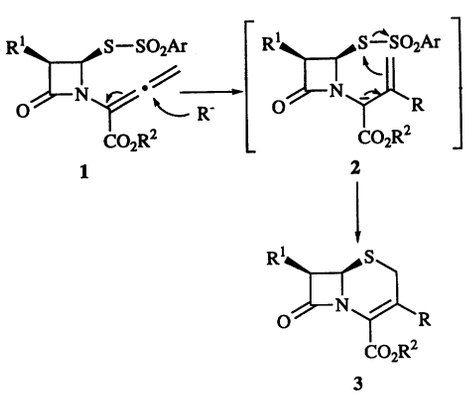
Sequential reductive addition/cyclization of the allenecarboxylate 1, derived from penicillin G, with allylic and benzylic halides is successfully achieved by the aid of a three-metal redox system consisting of aluminium metal (2.5 molar equiv.) and catalytic amounts of [$NiCl_2$(bipy)] (0.1 molar equiv.) and $PbBr_2$ (0.05 molar equiv.) in *N*-methyl-2-pyrrolidone (NMP) to afford the corresponding 3-allyl- and 3-benzyl-Δ^3-cephems 3a–i in 20–85% yields. The reactions of 1 with vinyl, prop-2-ynyl and phenyl halides in the same three-metal redox system result in the recovery of 1 and/or partial formation of 2-*exo*-methylenepenam 4. A similar electroreductive addition/cyclization of 1 with allyl bromide is performed by passage of an electrical current (3.2 F mol^{-1}) in an [$NiCl_2$(bipy)]/$PbBr_2$/NMP/(Pt cathode)–(Al anode) system.

Introduction

Since Morin's pioneering work in 1963 on penicillin→cephalosporin conversion,[1] penicillins have been widely used as a starting material for the synthesis of various β-lactam antibiotics.[2] This is because penicillins are readily available as a fermentation product, the skeletal characteristics and stereochemistry of which around the β-lactam ring may satisfy all requirements for the construction of a wide variety of β-lactams. Recently, we disclosed a conceptually new strategy[3] for the transformation of penicillins into 3-substituted Δ^3-cephems **3** involving sequential addition/cyclization of the allenecarboxylate **1** with heteroatom nucleophiles, *e.g.* amines, azide and thiols, which were introduced at the 3-position of the cephem framework (Scheme 1). We and Farina independently succeeded in the extension of the addition/cyclization methodology for the synthesis of 3-alkenyl-Δ^3-cephems, in which organotins/$Cu^{I}Cl$ combinations[4] and organocuprates[5] were employed as carbon nucleophiles. These methods, however, involve laborious operations since the former always produced troublesome tin residues and the latter was carried out at −100 °C.



Scheme 1

Although aluminium metal is an ideal reducing reagent because it is cheap, easy to handle and able to release 3 e^-/atom, its use in the modern organic chemistry is limited owing to lack of efficient electron transfer between aluminium metal and organic substrates. Recently, various combinations of aluminium metal and catalytic amounts of the metal salts have been developed and received much attention as a powerful reductant for various synthetic purposes,[6–10] wherein aluminium metal acts as an electron pool (or source) and metal salts work as an electron transfer catalyst. The chemical behaviour of the bimetal redox systems is highly dependent on the nature of the metal salts employed. For instance, Barbier-type allylation of carbonyl compounds ($SnCl_2$/Al, $PbBr_2$/Al and $BiCl_3$/Al),[6] imines ($TiCl_4$/Al)[7] and acetals ($PbBr_2$/Al),[8] reductive dimerization of imines ($PbBr_2$/Al),[9] reductive elimination/cyclization of 1-[2,3-dichloro- or 3-chloro-2-(trifluoromethylsulfonyloxy)-1-(*p*-methoxybenzyloxycarbonyl)prop-1-enyl]-3-(phenylacetamido)-4-phenylsulfonylthioazetidin-2-one ($PbBr_2$/Al)[10] have been successfully performed by the proper choice of metal salts (electron transfer catalyst). In this connection, we developed an [$NiCl_2$(bipy)]/$PbBr_2$/Al three-metal redox system which could promote homo coupling of alkenyl[11] and aryl halides[12] presumably through a disproportionation of the corresponding alkenyl Ni^{II} complexes. The mechanistic rationale encouraged us to investigate further applications of the three-metal redox system and we found that facile access to 3-allyl- and 3-benzyl-Δ^3-cephems **3** could be achieved by reductive addition/cyclization of the allenecarboxylate **1** with allylic and benzylic halides in NMP in the [$NiCl_2$(bipy)]/$PbBr_2$/Al redox system.[13] It is of interest to note that the role of aluminium in the three-metal redox is similar to that of a cathode in an electrolysis system. We, therefore, investigated the electroreductive cross coupling reaction of **1** with allyl bromide in an [$NiCl_2$(bipy)]/$PbBr_2$ combination as the electron-transfer catalyst (mediator).

Herein we describe the reductive addition/cyclization of the allenecarboxylate **1** with allylic and benzylic halides in the [$NiCl_2$(bipy)]/$PbBr_2$/Al redox system, leading to the 3-allyl- and 3-benzyl-Δ^3-cephems **3** together with the electrochemical version in an [$NiCl_2$(bipy)]/$PbBr_2$ redox system.

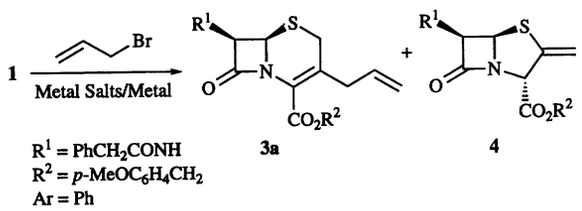
Results and discussion

At first, the reductive addition/cyclization of the allenecarboxylate **1** with allyl bromide, leading to 3-allyl-Δ^3-cephem **3a** (Scheme 2), was investigated in various metal salts/metal redox

Table 1 Reductive addition/cyclization of the allenecarboxylate **1** with allyl bromide in a metal salts/metal redox system[a]

Entry	Metal salts	Metal (molar equiv.)	Isolated yield (%)		
			3a	**4**	**1**
1	$[NiCl_2(bipy)]/PbBr_2$	Al (2.5)	47	16	—
2	$PbBr_2$	Al (2.5)	—	18	2
3	$[NiCl_2(bipy)]$	Al (2.5)	—	—	67
4	$[NiCl_2(bipy)]/PbBr_2$	—	—	—	62
5[b]	$[NiCl_2(bipy)]/PbBr_2$	Zn (5)	12	—	—
6	$[NiCl_2(bipy)]/PbBr_2$	Sn (5)	—	—	79
7	$[NiCl_2(bipy)]/PbBr_2$	$SnCl_2$ (5)	—	—	—
8	$NiCl_2/PbBr_2$	Al (2.5)	11	13	12
9	$PdCl_2/PbBr_2$	Al (2.5)	—	13	—
10[c]	$[PdCl_2(PhCN)_2]$	$SnCl_2$ (5)	—		—

[a] Carried out with metal salts (0.1 molar equiv. each) and allyl bromide (2 molar equiv.) at room temperature. [b] See ref. 15. [c] See ref. 16.



Scheme 2

systems. The reaction of **1** with allyl bromide (2 molar equiv.) in *N*,*N*-dimethylformamide (DMF) in the presence of aluminium metal (2.5 molar equiv.) and catalytic amounts of $[NiCl_2(bipy)]$ (0.1 molar equiv.) and $PbBr_2$ (0.1 molar equiv.) at room temperature afforded the 3-allyl-Δ^3-cephem **3a** (47%) together with 2-*exo*-methylenepenam **4** (16%) (Table 1, entry 1). Notably, any detectable amount of the undesired Δ^2-isomer (3-allyl-Δ^2-cephem) could not be observed in the crude products. The formation of the minor product **4** can be reasonably understood by assuming reductive cleavage of the S–S bond of **1** followed by intramolecular attack of the thus formed thiolate ion to the centre carbon of the allene moiety.[14] The presence of $[NiCl_2(bipy)]$, $PbBr_2$ and aluminium is indispensable for the formation of the 3-allyl-Δ^3-cephem **3a** (entries 2–4). In a $PbBr_2$/Al system, the 2-*exo*-methylenepenam **4** was formed without any other isolable products, indicating that reductive S–S bond fission of the thiosulfonate moiety mainly occurred (entry 2). On the other hand, no appreciable reaction occurred in the absence of $PbBr_2$ or aluminium, resulting in the recovery of **1** in 67 and 62% yields, respectively (entries 3 and 4). In entries 5–7, zinc, tin and tin(II) chloride were used in place of aluminium. Only zinc[15] could effect the desired reaction but the yield of the desired product **3a** was significantly reduced (12%) owing to the formation of a complex mixture (entry 5). Tin resulted in the recovery of most of **1** (79%) (entry 6) while tin(II) chloride brought about the formation of a complex mixture (entry 7). The reactions with other metal salts/metal combinations were also attempted (entries 8–10). An $NiCl_2/PbBr_2$/Al combination was less efficient, affording only 11% of **3a** along with **4** (13%) (entry 8). Both $PdCl_2/PbBr_2$/Al and $[PdCl_2(PhCN)_2]/SnCl_2$[16] combinations failed to provide any detectable amount of the desired product **3a** (entries 9 and 10).

Although it was found that the $[NiCl_2(bipy)]/PbBr_2$/Al redox system was, of those tested, the most effective for reductive addition/cyclization of the allenecarboxylate **1** with allyl bromide to give the 3-allyl-Δ^3-cephem **3a**, it was not of practical use because of the low product yield. In view of this we examined the reaction conditions and, particularly, the solvent effect.[17] Thus, the reductive addition/cyclization of **1** with allyl bromide was carried out in a variety of solvents (Table 2). NMP was the most efficient solvent; indeed, the desired reaction proceeded

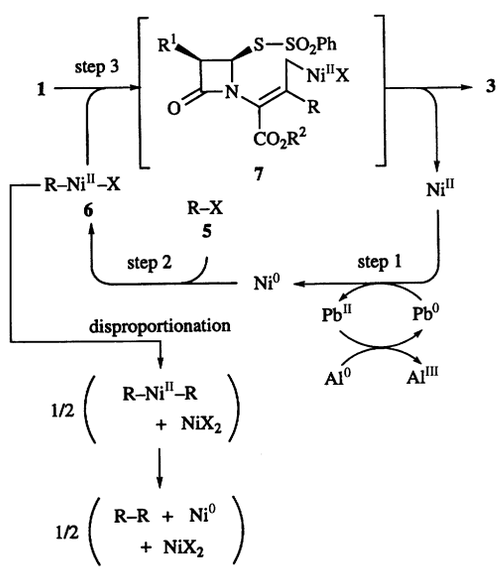
Table 2 Effect of solvent[a]

Entry	Solvent	Time (h)	Isolated yield (%)		
			3a	**4**	**1**
1	DMF	0.5	47	16	—
2	NMP	0.75	56	Trace	—
3	THF	0.75	—	—	59
4	MeCN	2.0	—	—	90
5[b]	MeOH	2.0	—	—	—
6[c]	NMP	0.75	85	Trace	—

[a] Carried out with $[NiCl_2(bipy)]$ (0.1 molar equiv.), $PbBr_2$ (0.1 molar equiv.), aluminium (2.5 molar equiv.) and allyl bromide (2 molar equiv.) at room temperature, unless otherwise noted. [b] *p*-Methoxybenzyl alcohol was obtained in 54% yield. [c] Carried out with $PbBr_2$ (0.05 molar equiv.) and allyl bromide (5 molar equiv.) at 35–40 °C.

smoothly in NMP to give **3a** in 56% yield together with a small amount of the 2-*exo*-methylenepenam **4** (entry 2). In contrast, when tetrahydrofuran (THF), acetonitrile and methanol were used, no reaction occurred and either **1** was recovered (59 and 90%; entries 3 and 4) or a mixture of **1** and *p*-methoxybenzyl alcohol (54%) was obtained (entry 5), the latter arising from decomposition of the ester moiety of **1**. When the amount of allyl bromide was increased from 2 to 5 molar equiv., the yield of **2** increased to 85% (entry 6). In the reaction in NMP, the amount of $PbBr_2$ could be reduced to 0.05 molar equiv. without a significant change in the product yield.

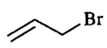
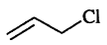
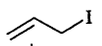
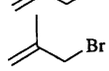
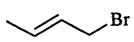
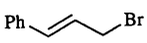
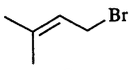
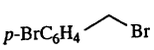
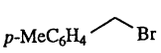
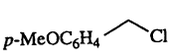
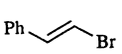
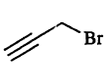
Although the reaction mechanism is unclear at present, it is likely that an Ni^0/Ni^{II}, Pb^0/Pb^{II} and Al^0/Al^{III} three-metal redox system promotes the reductive addition/cyclization of the allenecarboxylate **1** as illustrated in Scheme 3. The Ni^0 complex



Scheme 3

would be formed initially and then regenerated in the $[NiCl_2(bipy)]/PbBr_2$/Al redox system, in which aluminium releases the required electrons through a Pb^0/Pb^{II} redox mediatory system (step 1). The direct electron transfer from aluminium to Ni^{II} complex would not be effectively achieved (Table 1, entry 3). The oxidative addition of the Ni^0 complex with allyl bromide **5** (R = allyl, X = Br) would afford an Ni^{II} complex **6** (step 2).[18] The subsequent reaction of the Ni^{II} complex **6** with the allenecarboxylate **1** would produce an intermediate **7** (step 3) which would, in turn, undergo ring closure, leading to the 3-allyl-Δ^3-cephems **3a** (R = allyl) and Ni^{II} complex. To complete the reaction, we needed a 2–5 fold excess of allyl bromide (Table 2, entries 2 and 6). The facts can be explained by assuming that the disproportionation of the Ni^{II}

Table 3 Reductive addition/cyclization of the allenecarboxylate **1** with various halides in an $[NiCl_2(bipy)]/PbBr_2$/Al redox system[a]

Entry	R–X	Time (h)	Isolated yield (product) (%)	
			3	**4**
1		0.75	85 (**3a**)	Trace
2		0.75	61 (**3a**)	—
3		0.75	26 (**3a**)	5
4		1	73 (**3b**)	—
5		0.75	82 (**3c**)	—
6		0.75	60 (**3d**)	—
7		1.5	35 (**3e**)	10
8		1	83 (**3f**)	—
9		4	62 (**3g**)	—
10		2	32 (**3h**)	—
11		2	20 (**3i**)	14
12[b,c]		10	— (**3j**)	12
13[b,d]		10	— (**3k**)	30
14[b,e]		6	— (**3l**)	—

[a] Carried out in a similar manner to that described in the Experimental section unless otherwise noted. [b] Determined by HPLC: column: YMC Pack® AM-312 ODS 6 mm id × 150 mm, mobile phase: CH_3CN/H_2O = 55/45, flow rate: 2.0 ml/min. [c] The allenecarboxylate **1** and 3-phenylsulfonyl-Δ^3-cephem were obtained in 15 and 2% yields, respectively. 1,4-Diphenylbuta-1,3-diene was obtained in 90% yield (based on β-bromostyrene). [d] The allenecarboxylate **1** and 3-phenylsulfonyl-Δ^3-cephem were obtained in 1 and 2% yield, respectively. Iodobenzene was recovered in 86% yield. [e] Most of the allenecarboxylate **1** and prop-2-ynyl bromide were recovered.

complex **6** occurs competitively to give the corresponding dimer (R–R = hexa-1,5-diene).[19]

The reductive addition/cyclization of the allenecarboxylate **1** in the $[NiCl_2(bipy)]/PbBr_2$/Al/NMP system was successfully applied to the synthesis of various 3-substituted Δ^3-cephems **3** (Table 3). The reaction of **1** with allyl chloride and iodide proceeded in a similar manner although the yields of the 3-allyl-Δ^3-cephem **3a** decreased to 61 and 26% yields, respectively (entries 2 and 3). The reaction of **1** with crotyl, cinnamyl and prenyl bromides proceeded in a regioselective manner to afford the corresponding α-substituted products **3c**–**e**, exclusively (entries 5–7). When benzylic halides were used in place of the allylic halides, the corresponding 3-benzyl-Δ^3-cephem derivatives **3f**–**i** were obtained in 20–83% yields (entries 8–11).

A similar reaction of **1** with β-bromostyrene in the $[NiCl_2(bipy)]/PbBr_2$/Al/NMP system failed to produce any detectable amounts of the corresponding cephem **3j** (entry 12). This failure can be ascribed to the fact that the disproportionation[11] of the vinyl nickel(II) complex, [PhCH=CH–Ni^{II}–Br] **6j**, smoothly occurred to give 1,4-diphenylbuta-1,3-diene; indeed, 90% yield (based on β-bromostyrene) of the diene was obtained from the reaction mixture. The reaction of **1** with iodobenzene in the same three-metal redox system afforded the 2-*exo*-methylenepenam **4** (30%) without any detectable amount of the 3-phenyl-Δ^3-cephem **3k** (entry 13). Under these conditions, phenyl nickel(II) complex, [Ph–Ni^{II}–I] **6k**, seems not to be formed. The result is well in accordance with the fact that the reductive homo coupling of aryl iodides in the $[NiCl_2(bipy)]/PbBr_2$/Al effectively took place only in methanol but not in DMF or NMP.[12] When the reaction of **1** with prop-2-ynyl bromide was carried out in a similar manner, most of the allenecarboxylate **1** and prop-2-ynyl bromide were recovered intact (entry 14).

As mentioned above, the reductive addition/cyclization of the allenecarboxylate **1** with allylic and benzylic halides **5** into the 3-substituted Δ^3-cephems **3** was performed in the $[NiCl_2(bipy)]/PbBr_2$/Al redox system, wherein the aluminium would act as an electron pool and $[NiCl_2(bipy)]$ and $PbBr_2$ would work as an electron transfer catalyst. The role of aluminium, *i.e.* releasing the required electrons, is quite similar to that of a cathode in an electroreductive system. This consideration, in turn, enabled us to investigate the electrochemical version. Thus, the electrolysis of **1** in NMP containing $[NiCl_2(bipy)]$ (0.1 molar equiv.), $PbBr_2$ (0.05 molar equiv.) and allyl bromide (5 molar equiv.) was carried out in an undivided cell fitted with a platinum cathode and an aluminium anode. Regulated DC power at 6.7 mA cm^{-2} was supplied at room temperature until most of **1** was consumed (3.2 F mol^{-1}), affording the 3-allyl-Δ^3-cephem **3a** (53%) together with the 2-*exo*-methylenepenam **4** (11%) (Table 4, entry 1). The presence of catalytic amounts of $[NiCl_2(bipy)]$ and $PbBr_2$ is indispensable, since in the absence of $[NiCl_2(bipy)]$ or $PbBr_2$ no appreciable amount of **3a** was formed (entries 2 and 3). The yield of **3a** was highly dependent on the choice of the anode materials, decreasing in the following order: Al (53%) > Zn (20%) > Sn (not isolated), Pt (not isolated) (entries 1, 4–6). In fact, the 3-allyl-Δ^3-cephem **3a** could be produced in 34% yield without passage of a current, although a long reaction time was required to complete the reaction (entry 7). This fact suggests that the electroreductive addition/cyclization of **1** with allyl bromide would be achieved not only by cathodic reduction but also by chemical reduction with an aluminium anode.

In conclusion, we have developed a new methodology for the construction of the cephem framework which also allows the introduction of allyl or benzyl substituents at the 3-position. This is based on the reductive addition/cyclization of the allenecarboxylate **1** with allylic and benzylic halides in an $[NiCl_2(bipy)]/PbBr_2$/Al redox system. Similar addition/cyclization was achieved by electrolysis of a mixture of **1** and allyl bromide in the $[NiCl_2(bipy)]/PbBr_2$/NMP–(Al anode) system.

Experimental

IR spectra were obtained on a Japan Spectroscopic Co., Ltd. JASCO FT/IR-5000 spectrometer. ^1H and ^{13}C NMR spectra were recorded with a Varian VXR-200 (200 MHz for ^1H and 50 MHz for ^{13}C) spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 Series II CHNS/O analyser. High-performance liquid chromatography (HPLC) was executed with a Waters HPLC instrument equipped with a 600E system controller, a 486 tunable absorbance detector and a Hitachi D-2500 chromato-integrator. DMF and NMP were distilled over calcium hydride under reduced pressure and stored over 4 Å molecular sieves. THF was distilled over sodium and benzophenone before use. Acetonitrile was distilled over phosphorus pentoxide. Methanol was distilled over magnesium. The allenecarboxylate **1** was prepared according to the reported procedures in the literature.[3] All other reagents were available from commercial sources and used without further purification, unless otherwise noted.

General procedure for reductive addition/cyclization of allenecarboxylate with allylic or benzylic halides in an $[NiCl_2(bipy)]/PbBr_2$/Al redox system (Table 3, entries 1–11)

To a mixture of the allenecarboxylate **1** (100 mg, 0.17 mmol), $[NiCl_2(bipy)]$ (5 mg, 0.017 mmol), $PbBr_2$ (3 mg, 0.01 mmol) and

Table 4 Electroreductive addition/cyclization of the allenecarboxylate **1** with allyl bromide[a]

Entry	$[NiCl_2(bipy)]/PbBr_2$ (equiv.)	Electrode (anode)–(cathode)	Time (h)	Electrical current passed (F mol^{-1})	Isolated yield (%)		
					3a	**4**	**1**
1	0.1/0.05	(Al)–(Pt)	1.5	3.2	53	11	—
2	0/0.05	(Al)–(Pt)	1.5	3.2	—	—	72
3	0.1/0	(Al)–(Pt)	1.5	3.2	—	—	70
4	0.1/0.05	(Zn)–(Pt)	1.5	3.2	20	7	51
5	0.1/0.05	(Pt)–(Pt)	1.5	3.2	—	—	70
6	0.1/0.05	(Sn)–(Pt)	1.5	3.2	—	—	36
7	0.1/0.05	(Al)–(Pt)	12	0	34	Trace	—

[a] Carried out in a similar manner to that described in the Experimental section unless otherwise noted.

finely cut aluminium foil (11 mg, 0.43 mmol) in NMP (3 ml) was added the appropriate halide compound (0.85 mmol) under an argon atmosphere. After being stirred at 35–40 °C for 0.75–4 h, the reaction mixture was poured into ice-cold 5% aqueous HCl and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed (SiO_2, benzene–ethyl acetate = 8 : 1) to afford the 3-substituted Δ^3-cephems **3a**–**i** in 20–85% yields.

***p*-Methoxybenzyl 3-allyl-7-phenylacetamido-Δ^3-cephem-4-carboxylate 3a (entry 1).** According to the general procedure, the reaction of **1** (100 mg, 0.17 mmol) with allyl bromide (74 μl, 0.85 mmol) was carried out at 35–40 °C for 0.75 h to give **3a** (70 mg, 85%) (Found: C, 64.95; H, 5.44; N, 5.66. Calc. for $C_{26}H_{26}N_2O_5S$: C, 65.25; H, 5.48; N, 5.85%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3412 (NH), 1783 (C=O), 1721 (C=O) and 1682 (C=O); δ_H(200 MHz; $CDCl_3$) 2.88 (1 H, dd, *J* 7.7 and 14.3, CH_2C=C), 3.25 (1 H, d, *J* 18.3, SCH_2), 3.36 (1 H, d, *J* 18.3, SCH_2), 3.36 (1 H, d, *J* 18.3, SCH_2), 3.36 (1 H, dd, *J* 7.7 and 14.3, CH_2C=C), 3.61 (1 H, d, *J* 16.2, $PhCH_2$), 3.64 (1 H, d, *J* 16.2, $PhCH_2$), 3.79 (3 H, s, CH_3O), 4.90 (1 H, d, *J* 4.8, CHS), 5.08 (1 H, d, *J* 16.0, CC=CH_2), 5.09 (1 H, d, *J* 10.7, CC=CH_2), 5.17 (2 H, s, CO_2CH_2), 5.75 (1 H, m, CCH=C), 5.76 (1 H, dd, *J* 4.8 and 9.0, CHN), 6.16 (1 H, d, *J* 9.0, NH), 6.87 (2 H, d, *J* 8.7, Ar) and 7.21–7.42 (7 H, m, Ar); δ_C(50 MHz; $CDCl_3$) 27.9, 37.6, 43.3, 55.2, 57.3, 59.0, 67.6, 113.9, 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.

***p*-Methoxybenzyl 3-(2-methylprop-2-enyl)-7-phenylacetamido-Δ^3-cephem-4-carboxylate 3b (entry 4).** According to the general procedure, the reaction of **1** (100 mg, 0.17 mmol) with 3-bromo-2-methylpropene (86 μl, 0.85 mmol) was carried out at 35–40 °C for 1 h to give **3b** (62 mg, 73%) (Found: C, 65.83; H, 5.75; N, 5.63. Calc. for $C_{27}H_{28}N_2O_5S$: C, 65.83; H, 5.73; N, 5.69%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3410 (NH), 1779 (C=O), 1723 (C=O) and 1676 (C=O); δ_H(200 MHz; $CDCl_3$) 1.64 (3 H, s, CCH_3), 2.99 (1 H, d, *J* 13.9, CH_2C=C), 3.23 (1 H, d, *J* 18.2, SCH_2), 3.30 (1 H, d, *J* 18.2, SCH_2), 3.31 (1 H, d, *J* 13.9, CH_2C=C), 3.62 (1 H, d, *J* 15.5, $PhCH_2$), 3.64 (1 H, d, *J* 15.5, $PhCH_2$), 3.79 (3 H, s, CH_3O), 4.69 (1 H, s, CH_2=C), 4.84 (1 H, s, CH_2=C), 4.92 (1 H, d, *J* 4.7, CHS), 5.17 (2 H, s, CO_2CH_2), 5.75 (1 H, dd, *J* 4.7 and 9.0, CHN), 6.33 (1 H, d, *J* 9.0, NH), 6.87 (2 H, d, *J* 8.7, Ar) and 7.22–7.41 (7 H, m, Ar); δ_C(50 MHz; $CDCl_3$) 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.

***p*-Methoxybenzyl 3-but-2-enyl-7-phenylacetamido-Δ^3-cephem-4-carboxylate 3c (entry 5).** According to the general procedure, the reaction of **1** (100 mg, 0.17 mmol) with but-2-enyl bromide (87 μl, 0.85 mmol) was carried out at 35–40 °C for 0.75 h to give **3c** (70 mg, 82%) (Found: C, 65.56; H, 5.75; N, 5.98. Calc. for $C_{27}H_{28}N_2O_5S$: C, 65.83; H, 5.73; N, 5.69%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3390 (NH), 1779 (C=O), 1721 (C=O) and 1682 (C=O); δ_H(200 MHz; $CDCl_3$) 1.64 (3 H, d, *J* 7.1, CCH_3), 2.81 (1 H, dd, *J* 7.1 and 12.9, CH_2C=C), 3.06–3.31 (1 H, m, CH_2C=C), 3.17 (1 H, d, *J* 18.3, SCH_2), 3.38 (1 H, d, *J* 18.3, SCH_2), 3.62 (1 H, d, *J* 16.2, $PhCH_2$), 3.63 (1 H, d, *J* 16.2, $PhCH_2$), 3.78 (3 H, s, CH_3O), 4.89 (1 H, d, *J* 4.7, CHS), 5.17 (2 H, s, CO_2CH_2), 5.21–5.68 (2 H, m, CH=CH), 5.75 (1 H, dd, *J* 4.7 and 8.9, CHN), 6.21 (1 H, d, *J* 8.9, NH), 6.87 (2 H, d, *J* 8.7, Ar) and 7.21–7.41 (7 H, m, Ar); δ_C(50 MHz; $CDCl_3$) 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.

***p*-Methoxybenzyl 3-cinnamyl-7-phenylacetamido-Δ^3-cephem-4-carboxylate 3d (entry 6).** According to the general procedure, the reaction of **1** (100 mg, 0.17 mmol) with cinnamyl bromide (126 μl, 0.85 mmol) was carried out at 35–40 °C for 0.75 h to give **3d** (58 mg, 60%) (Found: C, 69.01; H, 5.28; N, 5.27. Calc. for $C_{32}H_{30}N_2O_5S$: C, 69.29; H, 5.45; N, 5.05%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3410 (NH), 1779 (C=O), 1723 (C=O) and 1680 (C=O); δ_H(200 MHz; $CDCl_3$) 2.97 (1 H, dd, *J* 8.2 and 14.4, CH_2C=C), 3.29 (1 H, d, *J* 18.1, SCH_2), 3.40 (1 H, d, *J* 18.1, SCH_2), 3.50 (1 H, dd, *J* 5.1 and 14.4, CH_2C=C), 3.61 (1 H, d, *J* 16.2, $PhCH_2$), 3.63 (1 H, d, *J* 16.2, $PhCH_2$), 3.78 (3 H, s, CH_3O), 4.91 (1 H, d, *J* 4.8, CHS), 5.20 (2 H, s, CO_2CH_2), 5.77 (1 H, dd, *J* 4.8, 9.0, CHN), 6.16 (1 H, d, *J* 9.0, NH), 6.01–6.32 (1 H, m, C*H*=CHPh), 6.40 (1 H, d, *J* 15.8, CH=C*H*Ph), 6.86 (2 H, d, *J* 8.6, Ar) and 7.18–7.40 (12 H, m, Ar); δ_C(50 MHz; $CDCl_3$) 28.0, 36.9, 43.3, 55.2, 57.3, 59.0, 67.7, 113.9, 123.3, 125.4, 126.2, 127.0, 127.6, 127.7, 128.5, 129.1, 129.4, 130.6, 131.1, 133.0, 133.6, 136.7, 159.8, 161.8, 164.5 and 171.1.

***p*-Methoxybenzyl 7-phenylacetamido-3-(3-methylbut-2-enyl)-Δ^3-cephem-4-carboxylate 3e (entry 7).** According to the general procedure, the reaction of **1** (100 mg, 0.17 mmol) with 3-methylbut-2-enyl bromide (98 μl, 0.85 mmol) was carried out at 35–40 °C for 1.5 h to give **3e** (31 mg, 35%) and the 2-*exo*-methylenepenam **4** (8 mg, 10%).

Compound **3e** (Found: C, 66.34; H, 5.87; N, 5.51. Calc. for $C_{28}H_{30}N_2O_5S$: C, 66.38; H, 5.97; N, 5.53%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3412 (NH), 1785 (C=O), 1717 (C=O) and 1680 (C=O); δ_H(200 MHz; $CDCl_3$) 1.62 (3 H, s, C=CCH_3), 1.69 (3 H, s, C=CCH_3), 2.92–3.26 (2 H, m, CH_2C=C), 3.17 (1 H, d, *J* 18.4, SCH_2), 3.38 (1 H, d, *J* 18.4, SCH_2), 3.63 (1 H, d, *J* 16.4, $PhCH_2$), 3.65 (1 H, d, *J* 16.4, $PhCH_2$), 3.80 (3 H, s, CH_3O), 4.90 (1 H, d, *J* 4.6, CHS), 5.06 (1 H, t, *J* 7.0, C=CH), 5.18 (2 H, s, CO_2CH_2), 5.76 (1 H, dd, *J* 4.6 and 8.8, CHN), 6.04 (1 H, d, *J* 8.8, NH), 6.88 (2 H, d, *J* 8.5, Ar) and 7.18–7.44 (7 H, m, Ar); δ_C(50 MHz; $CDCl_3$) 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.

Compound **4** (Found: C, 63.08; H, 4.94; N, 6.32. Calc. for $C_{23}H_{22}N_2O_5S$: C, 63.00; H, 5.06; N, 6.39%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3309 (NH), 1801 (C=O), 1743 (C=O) and 1666 (C=O); δ_H(200 MHz; $CDCl_3$) 3.62 (2 H, s, $PhCH_2$), 3.82 (3 H, s, CH_3O), 5.11 (2 H, s, CO_2CH_2), 5.18 (1 H, dd, *J* 1.5, 1.7, $CHCO_2$), 5.24 (1 H, dd, *J* 1.5, 2.2, C=CH), 5.35 (1 H, dd, *J* 1.7, 2.2, C=CH), 5.59 (1 H, d, *J* 4.0, CHS), 5.75 (1 H, dd, *J* 4.0 and 9.3, CHN), 6.13 (1 H, d, *J* 9.3, NH), 6.88 (2 H, d, *J* 8.5, Ar) and 7.18–7.44 (7 H, m, Ar); δ_C(50 MHz; $CDCl_3$) 43.3, 55.3, 60.0, 64.5, 67.8, 69.5, 108.0, 114.1, 126.8, 127.7, 129.1, 129.4, 130.2, 133.6, 146.1, 159.9, 166.9, 170.4 and 172.4.

***p*-Methoxybenzyl 3-benzyl-7-phenylacetamido-Δ³-cephem-4-carboxylate 3f (entry 8).** According to the general procedure, the reaction of **1** (100 mg, 0.17 mmol) with benzyl bromide (101 μl, 0.85 mmol) was carried out at 35–40 °C for 1 h to give **3f** (76 mg, 83%) (Found: C, 68.14; H, 5.35; N, 5.34. Calc. for $C_{30}H_{28}N_2O_5S$: C, 68.16; H, 5.34; N, 5.30%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3414 (NH), 1783 (C=O), 1723 (C=O) and 1680 (C=O); δ_H(200 MHz; $CDCl_3$) 3.11 (1 H, d, *J* 18.3, SCH_2), 3.30 (1 H, d, *J* 18.3, SCH_2), 3.49 (1 H, d, *J* 14.7, $PhCH_2$), 3.61 (1 H, d, *J* 15.9, $PhCH_2$), 3.63 (1 H, d, *J* 15.9, $PhCH_2$), 3.80 (3 H, s, CH_3O), 4.02 (1 H, d, *J* 14.7, $PhCH_2$), 4.92 (1 H, d, *J* 4.7, SCH), 5.21 (2 H, s, CO_2CH_2), 5.78 (1 H, dd, *J* 4.7 and 9.0, NCH), 6.07 (1 H, d, *J* 9.0, NH), 6.86 (2 H, d, *J* 8.7, Ar) and 7.14–7.39 (12 H, m, Ar); δ_C(50 MHz; $CDCl_3$) 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.

***p*-Methoxybenzyl 3-(*p*-bromobenzyl)-7-phenylacetamido-Δ³-cephem-4-carboxylate 3g (entry 9).** According to the general procedure, the reaction of **1** (100 mg, 0.17 mmol) with *p*-bromobenzyl bromide (212 mg, 0.85 mmol) was carried out at 35–40 °C for 4 h to give **3g** (65 mg, 62%) (Found: C, 59.05; H, 4.57; N, 4.57. Calc. for $C_{30}H_{27}N_2O_5SBr$: C, 59.31; H, 4.48; N, 4.61%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3410 (NH), 1783 (C=O), 1721 (C=O) and 1682 (C=O); δ_H(200 MHz; $CDCl_3$) 3.06 (1 H, d, *J* 18.4, SCH_2), 3.30 (1 H, d, *J* 18.4, SCH_2), 3.35 (1 H, d, *J* 14.8, $CH_2C_6H_4Br$), 3.61 (1 H, d, *J* 16.3, $PhCH_2$), 3.64 (1 H, d, *J* 16.3, $PhCH_2$), 3.80 (3 H, s, CH_3O), 4.00 (1 H, d, *J* 14.8, $CH_2C_6H_4Br$), 4.92 (1 H, d, *J* 4.8, SCH), 5.20 (2 H, s, CO_2CH_2), 5.79 (1 H, dd, *J* 4.8 and 9.1, NCH), 6.06 (1 H, d, *J* 9.1, NH), 6.86 (2 H, d, *J* 8.7, Ar), 7.07 (2 H, d, *J* 8.4, Ar) and 7.21–7.43 (9 H, m, Ar); δ_C(50 MHz; $CDCl_3$) 27.8, 37.9, 43.3, 55.2, 57.5, 59.1, 67.8, 113.9, 120.8, 123.9, 126.8, 127.7, 129.2, 129.4, 130.4, 130.6, 131.8, 133.6, 136.2, 159.9, 161.8, 164.5 and 171.1.

***p*-Methoxybenzyl 3-(*p*-methylbenzyl)-7-phenylacetamido-Δ³-cephem-4-carboxylate 3h (entry 10).** According to the general procedure, the reaction of **1** (100 mg, 0.17 mmol) with *p*-methylbenzyl bromide (115 μl, 0.85 mmol) was carried out at 35–40 °C for 2 h to give **3h** (30 mg, 32%) (Found: C, 68.50; H, 5.64; N, 5.15. Calc. for $C_{31}H_{30}N_2O_5S$: C, 68.61; H, 5.57; N, 5.16%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3350 (NH), 1775 (C=O), 1719 (C=O) and 1665 (C=O); δ_H(200 MHz; $CDCl_3$) 2.32 (3 H, s, CH_3), 3.11 (1 H, d, *J* 18.2, SCH_2), 3.30 (1 H, d, *J* 18.2, SCH_2), 3.45 (1 H, d, *J* 14.7, $CH_2C_6H_4CH_3$), 3.60 (1 H, d, *J* 16.4, $PhCH_2$), 3.65 (1 H, d, *J* 16.4, $PhCH_2$), 3.80 (3 H, s, CH_3O), 3.97 (1 H, d, *J* 14.7, $CH_2C_6H_4CH_3$), 4.91 (1 H, d, *J* 4.8, SCH), 5.21 (2 H, s, CO_2CH_2), 5.78 (1 H, dd, *J* 4.8 and 9.2, NCH), 6.00 (1 H, d, *J* 9.2, NH), 6.86 (2 H, d, *J* 8.7, Ar), 7.08 (3 H, s, Ar) and 7.21–7.36 (8 H, m, Ar); δ_C(50 MHz; $CDCl_3$) 21.0, 27.8, 38.2, 43.4, 55.3, 57.4, 59.0, 67.7, 113.9, 127.0, 127.7, 128.8, 129.2, 129.4, 129.4, 130.6, 131.6, 134.1, 136.5, 159.8, 162.0, 164.6 and 171.1.

***p*-Methoxybenzyl 3-(*p*-methoxybenzyl)-7-phenylacetamido-Δ³-cephem-4-carboxylate 3i (entry 11).** According to the general procedure, the reaction of **1** (100 mg, 0.17 mmol) with *p*-methoxybenzyl chloride (115 μl, 0.85 mmol) was carried out at 35–40 °C for 2 h to give **3i** (19 mg, 20%) and the 2-*exo*-methylenepenam **4** (11 mg, 14%) (Found: C, 66.57; H, 5.45; N, 4.99. Calc. for $C_{31}H_{30}N_2O_6S$: C, 66.65; H, 5.41; N, 5.01%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3360 (NH), 1783 (C=O), 1723 (C=O) and 1686 (C=O); δ_H(200 MHz; $CDCl_3$) 3.11 (1 H, d, *J* 18.4, SCH_2), 3.29 (1 H, d, *J* 18.4, SCH_2), 3.40 (1 H, d, *J* 14.7, $CH_2C_6H_4OCH_3$), 3.61 (1 H, d, *J* 16.2, $PhCH_2$), 3.63 (1 H, d, *J* 16.2, $PhCH_2$), 3.79 (3 H, s, CH_3O), 3.80 (3 H, s, CH_3O), 3.95 (1 H, d, *J* 14.7, $CH_2C_6H_4OCH_3$), 4.91 (1 H, d, *J* 4.7, SCH), 5.21 (1 H, d, *J* 12.1, CO_2CH_2), 5.22 (1 H, d, *J* 12.1, CO_2CH_2), 5.78 (1 H, dd, *J* 4.7 and 9.2, NCH), 6.03 (1 H, d, *J* 9.2, NH), 6.81 (2 H, d, *J* 8.7, Ar), 6.87 (2 H, d, *J* 8.7, Ar), 7.11 (2 H, d, *J* 8.7, Ar) and 7.21–7.39 (7 H, m, Ar); δ_C(50 MHz; $CDCl_3$) 27.7, 37.6, 43.2, 55.2, 57.4, 59.0, 67.6, 113.9, 114.0, 123.2, 127.0, 127.5, 129.0, 129.1, 129.3, 129.9, 130.5, 132.1, 133.7, 158.5, 159.8, 161.9, 164.6 and 171.1.

Reductive addition/cyclization of an allenecarboxylate with β-bromostyrene in an $[NiCl_2(bipy)]/PbBr_2$/Al redox system (Table 3, entry 12)

To a mixture of the allenecarboxylate **1** (100 mg, 0.17 mmol), $[NiCl_2(bipy)]$ (5 mg, 0.017 mmol), $PbBr_2$ (3 mg, 0.01 mmol) and finely cut aluminium foil (11 mg, 0.43 mmol) in NMP (3 ml) was added β-bromostyrene (109 μl, 0.85 mmol) under argon atmosphere. After being stirred at 35–40 °C for 10 h, an aliquot of the reaction mixture was analysed by HPLC, showing the presence of **1** (15%), 2-*exo*-methylenepenam **4** (12%), 3-phenylsulfonyl-Δ³-cephem (2%) and 1,4-diphenylbuta-1,3-diene (90% based on β-bromostyrene).

Reductive addition/cyclization of an allenecarboxylate with iodobenzene in an $[NiCl_2(bipy)]/PbBr_2$/Al redox system (Table 3, entry 13)

To a mixture of the allenecarboxylate **1** (100 mg, 0.17 mmol), $[NiCl_2(bipy)]$ (5 mg, 0.017 mmol), $PbBr_2$ (3 mg, 0.01 mmol) and finely cut aluminium foil (11 mg, 0.43 mmol) in NMP (3 ml) was added iodobenzene (95 μl, 0.85 mmol) under an argon atmosphere. After being stirred at 35–40 °C for 10 h, an aliquot of the reaction mixture was analysed by HPLC, showing the presence of **1** (1%), 2-*exo*-methylenepenam **4** (30%), 3-phenylsulfonyl-Δ³-cephem (2%) and iodobenzene (86%).

Reductive addition/cyclization of an allenecarboxylate with prop-2-ynyl bromide in an $[NiCl_2(bipy)]/PbBr_2$/Al redox system (Table 3, entry 14)

To a mixture of the allenecarboxylate **1** (100 mg, 0.17 mmol), $[NiCl_2(bipy)]$ (5 mg, 0.017 mmol), $PbBr_2$ (3 mg, 0.01 mmol) and finely cut aluminium foil (11 mg, 0.43 mmol) in NMP (3 ml) was added prop-2-ynyl bromide (76 μl, 0.85 mmol) under an argon atmosphere. After being stirred at 35–40 °C for 6 h, an aliquot of the reaction mixture was analysed by HPLC, showing the presence of **1** (>99%) and prop-2-ynyl bromide (>99%).

Electroreductive addition/cyclization of an allenecarboxylate with allyl bromide in an $[NiCl_2(bipy)]/PbBr_2$ system (Table 4, entry 1)

Electrolysis was carried out in an undivided cell fitted with aluminium anode and platinum cathode (1 × 1.5 cm^2 each). Into the cell was charged a mixture of the allenecarboxylate **1** (100 mg, 0.17 mmol), allyl bromide (103 mg, 0.85 mmol), $[NiCl_2(bipy)]$ (5 mg, 0.017 mmol), $PbBr_2$ (3 mg, 0.01 mmol) and Et_4NBF_4 (150 mg) in NMP (3 ml). The mixture was electrolysed at a constant current density (6.7 mA cm^{-2}) whilst being stirred at room temperature until most of the allenecarboxylate **1** had been consumed (1.5 h, 3.2 F mol^{-1}). The reaction mixture was poured into ice-cold 5% aqueous HCl and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed (SiO_2, benzene–ethyl acetate = 8:1) to afford the 3-allyl-Δ³-cephem **2a** (44 mg, 53%) together with the 2-*exo*-methylenepenam **4** (8 mg, 11%).

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