Generation and reaction of copper(I) hydride in the copper(I) chloride–tributyltin hydride–NMP system: synthesis of 3-norcephalosporin

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Received (in Cambridge, UK) 31st August 1999, Accepted 23rd September 1999

Synthesis of 3-norcephalosporin **1** was performed successfully by reaction of either 3-trifluoromethylsulfonyloxy-Δ^3-cephem **2**, allenecarboxylate **3** or 3,4-disubstitued but-2-enoates **4** with copper(I) chloride and tributyltin hydride in *N*-methylpyrrolidin-2-one (NMP). Generation and reactions of a copper(I) hydride species in the copper(I) chloride–tributyltin hydride–NMP or *N*,*N*-dimethylformamide (DMF) system are discussed.

Introduction

Since the first report on the generation of copper(I) hydride by Würtz,[1] many efforts have been devoted to the preparation, characterization and reaction of various copper(I) hydrides. The copper(I) hydrides elaborated so far are classified into the following two categories. One is copper(I) hydrides stabilized by pyridine or phosphines,[2] *e.g.* $(Bu_3P)CuH$ [2b] and $(dppe)(CuH)_2$.[2c] Thermally stable copper(I) hydride hexamers, $[(R_3P)CuH]_6$ (R = phenyl, *p*-tolyl, *etc.*), were isolated and proved to be mild reducing agents for conjugate hydride reduction of α,β-unsaturated carbonyl compounds.[3] The other is copper(I) hydride "ate" complexes generated by reactions of lithium dimethylcuprate with lithium aluminium hydride,[4] copper(I) hydride–pyridine complex [2b] with organolithiums [5] and copper(I) salts with $LiAlH(OCH_3)_3$, $NaAlH_2(OCH_2CH_2OCH_3)_2$ and $KBH(Bu^s_3)$.[6] Recently, Lipshutz reported a convenient method for formation of halohydrocuprate, X(H)CuLi (X = Cl or I), by hydride transfer of tributyltin hydride to dihalocuprate, Cl(I)CuLi, in THF, which was successfully utilized for conjugate reduction of enones and enals.[7] The reactions of the copper(I) hydrides developed so far have, however, met only limited applications, *e.g.* conjugate reduction of α,β-unsaturated carbonyl compounds or reduction of alkyl halides and alkyl sulfonates to the corresponding hydrocarbons.[2–7]

Incidentally, Ghosal,[8] Piers,[9] Beddoes,[10] Takeda,[11] Allred,[12] Nicolaou [13] and Falck [14] performed Stille-type reactions with the aid of copper(I) salts and organotin compounds without palladium catalysts, in which transmetallation of organotins with copper(I) salts would produce the corresponding organocopper(I) species. Farina reported ^{119}Sn-NMR studies on the formation of a vinylcopper(I) species by the transmetallation of tributylvinyltin with copper(I) iodide in NMP as well as application of the *in situ* generated copper species to the synthesis of 3-alkenylcephems.[15] Independently, we developed new synthetic routes to 3-alkenylcephems from penicillin through alkenylation of either 3-trifluoromethylsulfonyloxy-Δ^3-cephem **2** or allenecarboxylate **3** with alkenylcoppers generated *in situ* by reaction of copper(I) chloride with alkenyltributyltins in a highly polar solvent, *e.g.* DMF or NMP.[16]

On the basis of the above results, we investigated the generation of copper(I) hydride in a copper(I) chloride–tributyltin hydride–highly polar solvent system as well as reactions of the *in situ* generated copper(I) hydride species with β-lactam derivatives **2** and **3** and 3,4-disubstituted but-2-enoates **4**, leading to 3-norcephalosporin **1** [17] which is a promising precursor of an important class of orally active drugs (Scheme 1).[18] Herein, we describe the generation and reactions of the copper(I) hydride in the copper(I) chloride–tributyltin hydride–NMP (or DMF) system.

Results and discussion

^{1}H NMR studies of copper(I) chloride–tributyltin hydride–DMF system

Our tactics for the generation of the copper(I) hydride rely on the transmetallation of tributyltin hydride with copper(I) salts. As a preliminary experiment, reaction of copper(I) chloride and tributyltin hydride in DMF-d_7 was investigated by ^{1}H NMR in order to obtain evidence to support the formation of the copper(I) hydride. Thus, a mixture of tributyltin hydride (0.04 mmol) and copper(I) chloride (0.05 mmol) in DMF-d_7 (0.7 ml) was placed in an NMR tube and the time course of the reaction was monitored by ^{1}H NMR (Fig. 1). Two characteristic resonance peaks ascribable to the hydride and α-methylene protons of tributyltin hydride were observed at 4.68 and 0.97 ppm, respectively, while a new triplet peak at 1.18 ppm appeared immediately after the reaction started and gradually increased, which was identical to that of α-methylene protons of tributyltin chloride. Indeed, an almost quantitative amount of tributyltin chloride was isolated after the reaction was completed (*ca.* 1 h). A small peak observed at 4.54 ppm can be assigned as hydrides of dibutyltin dihydride generated by redistribution of tributyltin hydride with copper(I) chloride.[19] The formation of tributyltin chloride suggests that the transmetallation shown in eqn. (1) takes place gradually in the

$$Bu_3SnH + CuCl \longrightarrow \text{“CuH”} + Bu_3SnCl \qquad (1)$$

copper(I) chloride–tributyltin hydride–DMF system. In this connection, it is of interest to note that evolution of gas (H_2) and precipitates of metallic copper in the NMR tube were observed in the course of the reaction. These observations can be explained by assuming decomposition of the *in situ* generated copper(I) hydride species, leading to hydrogen and metallic copper [eqn. (2)].[2b]

$$\text{“CuH”} \longrightarrow 1/2H_2\uparrow + Cu\downarrow \qquad (2)$$

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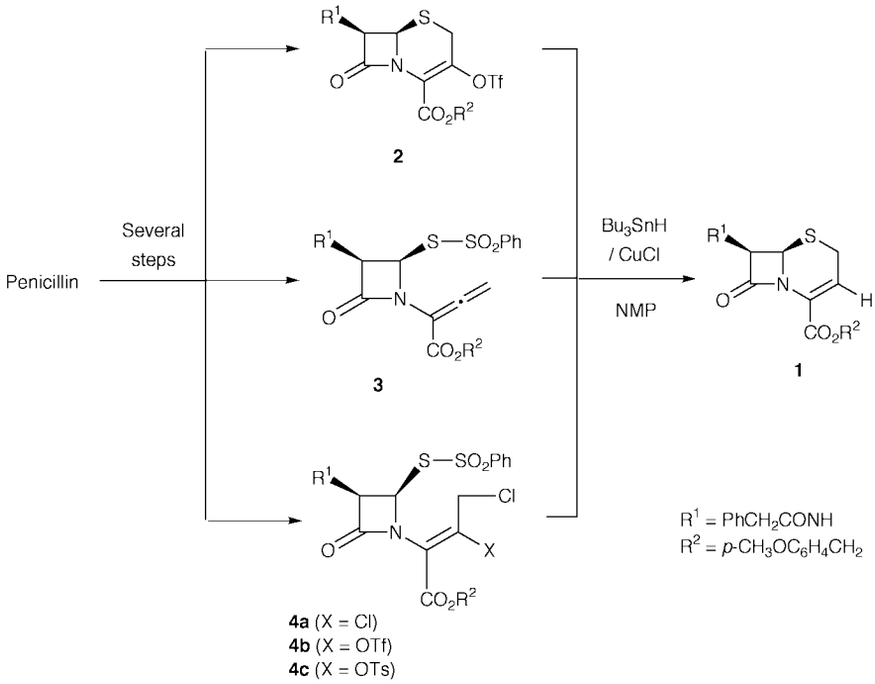


Scheme 1

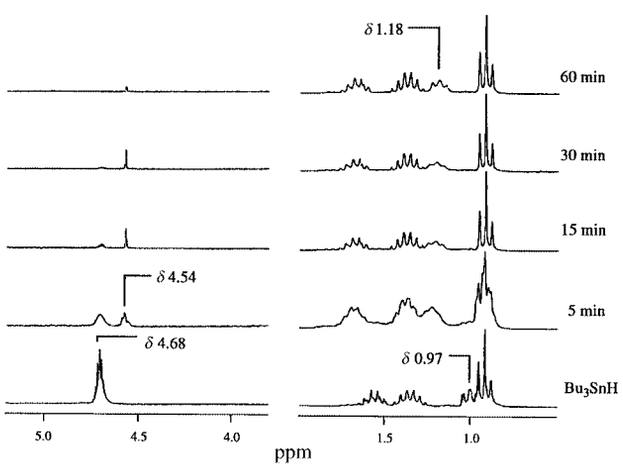
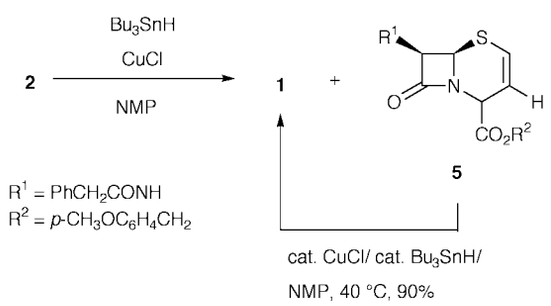


Fig. 1 ^{1}H NMR Spectra of CuCl/Bu_3SnH in DMF-d^7.

Although direct spectral evidence for the formation of the copper(I) hydride could not be obtained, it is likely that the transmetallation of tributyltin hydride with copper(I) chloride in DMF proceeds smoothly to produce the highly reactive copper(I) hydride together with tributyltin chloride. This consideration, in turn, encouraged us to investigate applications of the copper(I) hydride to synthesis of the 3-norcephalosporin **1** from the 3-trifluoromethylsulfonyloxy-Δ^3-cephem **2**, the allenecarboxylate **3** and the 3,4-disubstituted but-2-enoates **4**.

Synthesis of 3-norcephalosporin 1

The 3-trifluoromethylsulfonyloxy-Δ^3-cephems **2** have become intensively used as versatile intermediates for the syntheses of C(3)-substituted cephems. Introduction of various C(3) substituents has been performed by Stille cross-coupling reaction with organotins,[20] palladium-catalyzed alkoxycarbonylation in the presence of carbon monoxide and alcohols[21] and other substitution reactions with a copper(I) chloride–alkenyltributyltins combination,[16b] with organocuprates[22] and with metal halides.[23] In order to open a new access to the 3-norcephalosporin **1**, we investigated the reaction of **2** with the *in situ* generated copper(I) hydride (Scheme 2).



Scheme 2

Reaction of **2** with copper(I) chloride (1.0 molar equiv.) and tributyltin hydride (2.6 molar equiv.) in NMP was carried out at 25 °C for 1 h to afford a mixture of the 3-norcephalosporin **1** (30%) and its Δ^2-isomer **5** (49%) (Table 1, entry 1). The ratio of **1** to **5** was highly dependent on the reaction temperature. Thus, the Δ^2-isomer **5** (81%) was exclusively formed at 0 °C (entry 2), while the reaction at more than 30 °C afforded only the Δ^3-isomer **1** (82%) (entries 3 and 4). On the other hand, when the Δ^2-isomer **5** was treated with a catalytic amount of tributyltin hydride (0.2 molar equiv.) and copper(I) chloride (0.2 molar equiv.) in NMP at 40 °C for 1 h, the Δ^3-isomer **1** was obtained in 90% yield (Scheme 2). These results suggest that the Δ^2-isomer **5** is a kinetic product initially formed and the 3-norcephalosporin **1** is a thermodynamically stable isomer produced by isomerization of **5** in the reaction media.

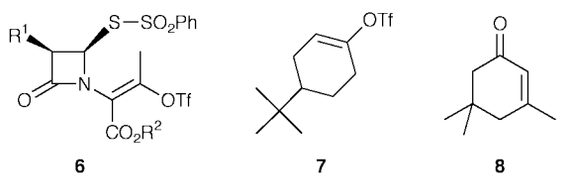
Reaction of the *in situ* generated copper(I) hydride species with triflates **6** and **7** and enone **8** was also investigated (Scheme 3). Upon treatment of **6**, **7** and **8** with copper(I) chloride and tributyltin hydride in NMP at room temperature, however, no appreciable reaction occurred, resulting in the recovery of **6** (84%), **7** (96%) and **8** (91%), respectively. These results suggest that the copper(I) hydride species generated in the copper(I) chloride–tributyltin hydride–NMP system is different in reactivity from the copper hydride species so far reported.[2–7]

The transformation of **2** to **1** *via* **5** cannot be reasonably explained by a simple addition–elimination reaction of **2** with the copper(I) hydride. A plausible mechanism including a

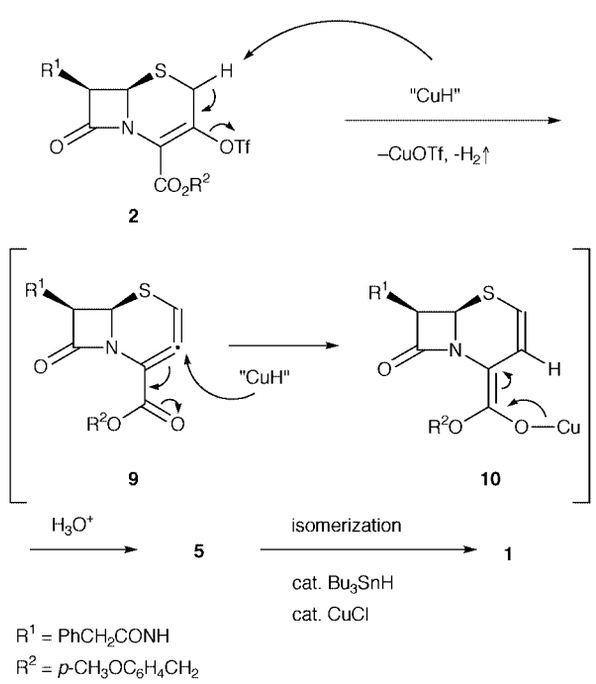
Table 1 Reaction of **2** with copper(I) chloride and tributyltin hydride[a]

Entry	Temp./°C	Time/h	Isolated yield (%)	
			1	**5**
1	25	1	30	49
2	0	2	—	81
3	30	0.5	82	—
4	40	0.5	82	—

[a] Carried out with **2** (0.17 mmol), copper(I) chloride (1.0 molar equiv.) and tributyltin hydride (2.6 molar equiv.) in NMP (2 ml).



Scheme 3



Scheme 4

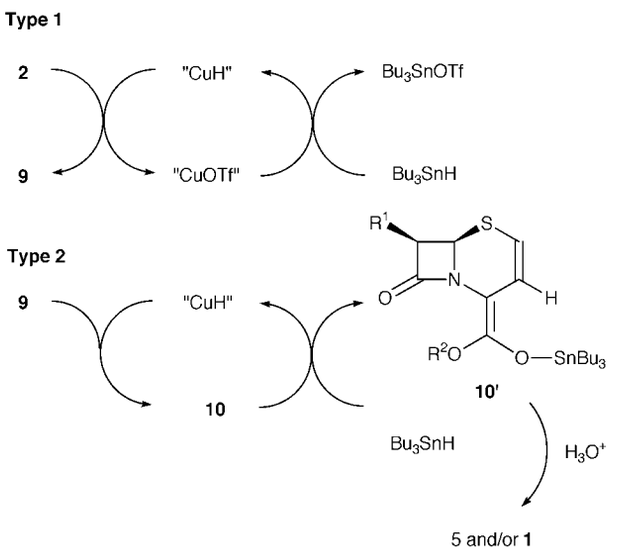
six-membered allenic compound **9**[16b,24,25] is illustrated in Scheme 4. In the initial stage of the reaction, 1,2-elimination of **2** with the *in situ* generated copper(I) hydride would produce the six-membered allenic intermediate **9** which would, in turn, react with the copper(I) hydride to give the Δ^2-isomer **5** through an adduct **10**. Finally, isomerization of **5** may afford the thermodynamically stable Δ^3-isomer **1**.

According to Scheme 4, altogether two molar equivalents of the copper hydride should be required; one for 1,2-elimination and one for the subsequent addition stage. However, as shown in Table 2, the amounts of copper(I) chloride could be reduced to 0.05–0.5 molar equivalents without significant change of the product yields (83–88%). These results can be explained by assuming a "CuH" recycling system involving two types of reactions for regeneration of the copper(I) hydride as illustrated in Scheme 5. The 1,2-elimination of **2** with the copper(I) hydride would give the six-membered allene **9** together with copper(I) triflate, which would subsequently undergo trans-

Table 2 Copper(I) chloride-catalyzed reaction of **2** with tributyltin hydride[a]

Entry	CuCl (molar equiv.)	Temp./°C	Time/h	Isolated yield (%)	
				1	**5**
1	0.3	40	1	83	—
2	0.1	40	1	83	—
3	0.05	40	1	85	—
4	0.5	−5	4	—	88

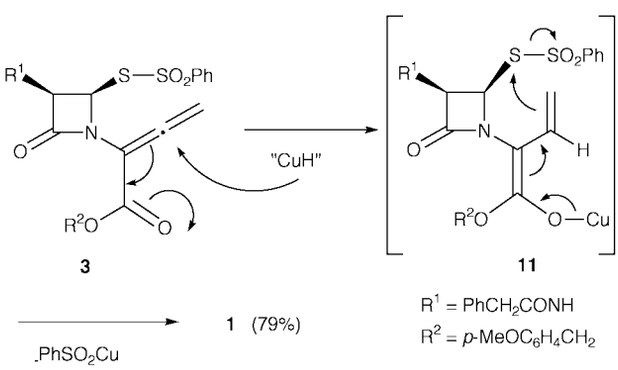
[a] Carried out with **2** (0.09 mmol) and tributyltin hydride (2.6 molar equiv.) in NMP (1 ml).



Scheme 5

metallation with tributyltin hydride to reproduce the copper(I) hydride (Type 1). On the other hand, regeneration of the copper(I) hydride would also be achieved by the reaction of tributyltin hydride with the adduct **10** (Type 2), leading to tributyltin enolate **10′** which would be hydrolyzed to give the Δ^2-isomer **5**. Thus far regenerated copper(I) hydride would repeatedly react with **2** and **9** to afford **9** and the adduct **10**, respectively.

Next, we investigated conversion of the allenecarboxylate **3** to **1** through Michael addition of the copper(I) hydride to the central carbon of the allene moiety of **3** and subsequent ring closure of an adduct **11** (Scheme 6).[16,26,27] The sequential



Scheme 6

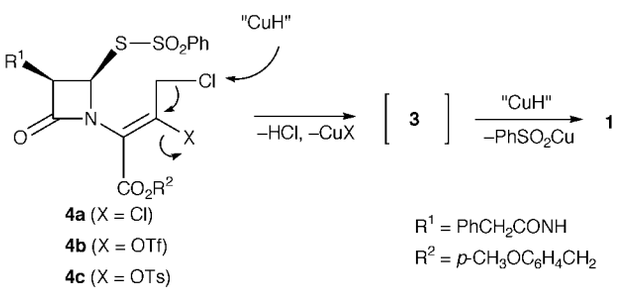
reaction could be performed successfully by treatment of **3** with copper(I) chloride and tributyltin hydride (1.5 molar equiv. each) in NMP at room temperature, affording **1** in 79% yield without any detectable amount of the Δ^2-isomer **5**.

Table 3 Transformation of 3,4-disubstituted but-2-enoates **4** to 3-norcephalosporin **1**[a]

Entry	Sub.	Bu_3SnH		CuCl/molar equiv.	Time/h	Isolated yield (%)	
		Total amount mol. equiv.	No. of portions			**1**	**4**
1	**4a**	2.2	1	2.0	4	36	34
2	**4a**	4.4	1	3.0	6	40	34
3	**4a**	4.0	4[b]	2.0	2	80	—
4	**4a**	4.0	4[b]	4.0	2	81	—
5	**4b**	5.0	5[b]	4.0	2.5	79	—
6	**4c**	4.0	4[b]	4.0	2	76	—

[a] Carried out with **4** (0.15 mmol) in NMP (3 ml) at room temperature. [b] Portions of tributyltin hydride added at intervals of 30 min.

The above procedure must be one of the most straightforward approaches to the 3-norcephalosporin **1**, but is not necessarily satisfactory for practical use because the allenecarboxylate **3** is not always easy to handle owing to its lability.[28] 3,4-Disubstituted but-2-enoates **4a**–**c** (X = Cl, OTf and OTs) were found to be potent synthetic equivalents of the allenecarboxylate **3** to offer a new methodology for the construction of the cephalosporin framework (Scheme 7).[17]



Scheme 7

Reaction of the 3,4-dichlorobut-2-enoate **4a** (X = Cl) with copper(I) chloride and tributyltin hydride in NMP was carried out in the following manner (Table 3). To a mixture of **4a** and copper(I) chloride (2.0 molar equiv.) in NMP was added tributyltin hydride (2.2 molar equiv.) in one portion and the mixture was stirred for 4 h to give the 3-norcephalosporin **1** (36%) together with recovered **4a** (34%) (Table 3, entry 1). Even with excess amounts (4.4 molar equiv.) of tributyltin hydride, a considerable amount of **4a** (34%) was recovered (entry 2). The completion of the reaction could be accomplished successfully by portionwise addition of tributyltin hydride (1 molar equiv. × 4) at 0.5 h intervals, giving the desired product **1** in 80 and 81% yields (entries 3 and 4). In a similar manner, the transformation of triflate **4b** (X = OTf) and tosylate **4c** (X = OTs) into the 3-norcephalosporin **1** was also performed in 79 and 76% yields, respectively (entries 5 and 6).

The time course of the cyclization of **4a** to **1** was monitored by HPLC, showing that during the course of the reaction, the allenecarboxylate **3** was formed and then gradually disappeared.[17] This fact indicates that the reductive 1,2-elimination of the vicinal dichloro group of **4a** leading to **3** and subsequent hydride addition–cyclization of **3** would proceed in a stepwise manner to afford the 3-norcephalosporin **1** (Scheme 7). The copper(I) hydride generated from the transmetallation of tributyltin hydride with copper(I) chloride would work both as the reducing agent for the 1,2-elimination and as a hydride source of the latter addition–cyclization stage.

In conclusion, three different synthetic routes to the 3-norcephalosporin **1** were developed by use of the copper(I) hydride generated in the copper(I) chloride–tributyltin hydride–NMP system. The reaction of 3-trifluoromethylsulfonyloxy-Δ^3-cephem **2** with copper(I) chloride and tributyltin hydride in NMP afforded either Δ^2-isomer **5** or Δ^3-isomer **1** depending on the temperature. The reaction of the allenecarboxylate **3**, derived from penicillin, in a similar reaction system gave **1** in good yields. The direct transformation of the 3,4-disubstituted but-2-enoates **4a**–**c** to the 3-norcephalosporin **1** *via* the allene-*carboxylate* **3** could be performed by portionwise addition of tributyltin hydride in NMP containing copper(I) chloride.

Experimental

IR spectra were recorded with a Japan Spectroscopic Co., Ltd. JASCO VALOR-III spectrometer. ^1H and ^{13}C NMR spectra were measured on a Varian Gemini 200 spectrometer (200 MHz for ^1H and 50 MHz for ^{13}C). Elemental analyses were carried out with Perkin-Elmer 2400 Series II CHNS/O analyzer. HPLC was executed with a Waters HPLC instrument equipped with a 600 E system controller, a Waters 486 tunable absorbance detector, and a Hitachi D-2500 chromato-integrator. The 3-trifluoromethylsulfonyloxy-Δ^3-cephem **2**,[23] the allenecarboxylate **3**[26c] and the 3,4-disubstituted but-2-enoates **4**[29] were prepared from penicillin according to the reported procedures. NMP was distilled from calcium hydride and stored over molecular sieves 4 Å. All other chemical reagents were used as supplied without further purification.

Reaction of 3-trifluoromethylsulfonyloxy-Δ^3-cephem 2 with CuCl and tributyltin hydride (Table 1, entry 1)

Into a mixture of **2** (100 mg, 0.17 mmol) and copper(I) chloride (17 mg, 0.17 mmol) in NMP (2 ml) was added tributyltin hydride (129 mg, 0.44 mmol) at 25 °C under nitrogen. After being stirred at 25 °C for 1 h, the reaction mixture was poured into ice-cooled 5% HCl aq. and extracted with ethyl acetate. The combined extracts were washed successively with water and brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was dispersed in diethyl ether (10 ml) and the insoluble materials were collected by filtration. The solids were chromatographed (SiO_2, toluene–ethyl acetate = 1 : 1) to afford 3-norcephalosporin **1** (22 mg, 30%) and Δ^2-isomer **5** (37 mg, 49%).

3-Norcephalosporin 1. (Found: C, 62.91; H, 5.07; N, 6.21; $C_{23}H_{22}N_2O_5S$ requires C, 63.00; H, 5.06; N, 6.39%); ν_{max} (KBr)/cm^{-1} 3226, 1756, 1731, 1657 and 1517; δ_H(200 MHz; $CDCl_3$) 3.33 (1 H, dd, *J* 6.1 and 19.2, SCH_2), 3.53 (1 H, dd, *J* 2.7 and 19.2, SCH_2), 3.63 (1 H, d, *J* 16.2, PhCH_2), 3.68 (1 H, d, *J* 16.2, PhCH_2), 3.80 (3 H, s, OCH_3), 4.90 (1 H, d, *J* 5.1, SC*H*), 5.17 (1 H, d, *J* 11.9, CO_2CH_2), 5.22 (1 H, d, *J* 11.9, CO_2CH_2), 5.86 (1 H, dd, *J* 5.1 and 9.2, NC*H*), 6.15 (1 H, d, *J* 9.2, N*H*), 6.50 (1 H, dd, *J* 2.7 and 6.1, C=C*H*), 6.86 (2 H, d, *J* 8.7, Ar) and 7.26–7.35 (7 H, m, Ar); δ_C(50 MHz; $CDCl_3$) 24.0, 43.3, 55.2, 56.9, 59.6, 67.5, 113.9, 119.8, 127.0, 127.6, 128.0, 129.1, 129.4, 130.4, 133.7, 159.8, 161.3, 164.4 and 171.2.

Δ^2-Isomer 5. (Found: C, 62.74; H, 5.32; N, 6.16; $C_{23}H_{22}N_2O_5S$ requires C, 63.00; H, 5.06; N, 6.39%); ν_{max}(KBr)/cm^{-1} 3286,

1756, 1731, 1657 and 1517; δ_H(200 MHz, $CDCl_3$) 3.65 (2 H, s, PhCH_2), 3.82 (3 H, s, CH_3O), 4.87 (1 H, dd, *J* 2.5 and 4.3, C*H*CO), 5.12 (1 H, d, *J* 7.7, CO_2CH_2), 5.16 (1 H, d, *J* 7.7, CO_2CH_2), 5.14 (1 H, d, *J* 3.9, C*H*S), 5.70 (1 H, dd, *J* 3.9 and 8.8, C*H*N), 5.79 (1 H, dd, *J* 4.3 and 10.3, C*H*), 6.09 (1 H, d, *J* 8.8, N*H*), 6.25 (1 H, dd, *J* 2.5 and 10.3, C*H*), 6.89 (2 H, d, *J* 8.7, Ar) and 7.26–7.34 (7 H, m, Ar); δ_C(50 MHz, $CDCl_3$) 43.9, 50.0, 54.2, 55.9, 61.3, 68.5, 113.8, 114.5, 114.7, 120.8, 127.3, 128.3, 129.8, 130.1, 130.9, 131.0, 134.2, 160.6, 165.4, 168.0 and 171.7.

Isomerization of Δ^2-isomer 5 to 3-norcephalosporin 1

Into a mixture of **5** (100 mg, 0.23 mmol) and copper(I) chloride (5 mg, 0.046 mmol) in NMP (2 ml) was added tributyltin hydride (13 mg, 0.046 mmol) under nitrogen. After being stirred at 40 °C for 1 h, the reaction mixture was poured into ice-cooled 5% HCl aq. and extracted with ethyl acetate. The combined extracts were washed successively with water and brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was dispersed in diethyl ether (10 ml) and the insoluble materials were collected by filtration. The solids were chromatographed (SiO_2, toluene–ethyl acetate = 1 : 1) to afford 3-norcephalosporin **1** (90 mg, 90%).

Reaction of allenecarboxylate 3 with CuCl and tributyltin hydride

Into a mixture of **3** (150 mg, 0.26 mmol) and copper(I) chloride (39 mg, 0.39 mmol) in NMP (1.5 ml), tributyltin hydride (114 mg, 0.39 mmol) was added under nitrogen. After being stirred at room temperature for 1 h, the reaction mixture was poured into ice-cooled 5% HCl aq. and extracted with ethyl acetate. The combined extracts were washed successively with water and brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed (SiO_2, toluene–ethyl acetate = 1 : 1) to afford **1** (90 mg, 79%).

Reaction of 3,4-dichlorobut-2-enoate 4a with CuCl and tributyltin hydride (Table 3, entry 3)

Into a mixture of **4a** (100 mg, 0.15 mmol) and copper(I) chloride (30 mg, 0.30 mmol) in NMP (3 ml), tributyltin hydride (44 mg, 0.15 mmol) was added portionwise (4 times) at intervals of 0.5 h at room temperature under nitrogen. After being stirred for an additional 0.5 h, the reaction mixture was poured into ice-cooled 5% HCl aq. and extracted with ethyl acetate. The combined extracts were washed successively with water and brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was suspended in hexane (10 ml) and the insoluble materials were collected by filtration. The solids were chromatographed (SiO_2, toluene–ethyl acetate = 1 : 1) to afford **1** (53 mg, 80%).

Reaction of triflate 4b (Table 3, entry 5)

Into a mixture of **4b** (107 mg, 0.15 mmol) and copper(I) chloride (59 mg, 0.6 mmol) in NMP (3 ml), tributyltin hydride (44 mg, 0.15 mmol) was added portionwise (5 times) at intervals of 0.5 h at room temperature under a nitrogen atmosphere. After being stirred for an additional 0.5 h, the reaction mixture was worked up in a similar manner to that described above to afford **1** (52 mg, 79%).

Reaction of tosylate 4c (Table 3, entry 6)

Into a mixture of **11c** (125 mg, 0.15 mmol) and copper(I) chloride (59 mg, 0.6 mmol) in NMP (3 ml), tributyltin hydride (44 mg, 0.15 mmol) was added portionwise (4 times) at intervals of 0.5 h at room temperature under a nitrogen atmosphere. After being stirred for an additional 0.5 h, the reaction mixture was worked up in a similar manner to that described above to afford **1** (50 mg, 76%).

Acknowledgements

We acknowledge financial support by a Grant-in-Aid for Scientific Research (06453140 partly and priority area No. 283) from the Ministry of Education, Science, Sports and Culture of Japan. SC-NMR Laboratory of Okayama University is appreciated for obtaining NMR spectra.

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Paper 9/07049D