# Synthesis and Transformations of 3-Vinylcephalosporins. Part 6.[1] Reactions of Cephalosporin Phosphoranes with Bifunctional Carbonyl Compounds

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Cephalosporin C-3-phosphoranes have been converted into the corresponding 3-alkenylcephems and novel tricyclic derivatives on treatment with different bifunctional carbonyl compounds. The effect of substituents on the product ratio has been examined. The stereoselectivity of the ring-closure is explained on the basis of theoretical considerations.

3-Vinylcephalosporins, an important group of antibiotics first achieving prominence in the late 1980s,[2] are potent and orally active and we and others have examined their synthesis[2-4] and 1,3-dipolar cycloadditions.[5]

In studying the scope and limitations of the Wittig reactions of cephalosporin phosphorus ylides of type **1** (Scheme 1), we examined the reactions of **1** with bifunctional carbonyl compounds, such as glyoxal, methyl- and phenyl-glyoxal, biacetyl and butyl glyoxylate; our results are summarized in Table 1. Treatment of **1b** with methyl glyoxal (entry **d**), gave a fast reaction, the reaction mixture turning black in < 1 h. On completion of the reaction (*ca.* 3 h) the crude reaction mixture was partially purified by short column chromatography to give white crystals of **2d** (major) (m.p. 261–263 °C), the 200 MHz $^1$H NMR spectrum (Table 2) of which lacked the characteristic resonances of 3-vinylcephalosporins of type **3**. Although signals corresponding to the 1,2-disubstituted alkenyl group and to the C-2 methylene of the cephem dihydrothiazine moiety were absent, three methine resonances were observed. Thermospray mass spectrometric analysis revealed that **2d** possesses the same molecular weight as **3d**, although a hydroxy group was clearly detected. $^{13}$C NMR (Table 3), $^1$H-$^1$H and $^1$H-$^{13}$C COSY and LR INEPT analysis provided unambiguous evidence that **2d**(major) has a tricyclic structure and is a single diastereoisomer at C-2 and C-11. The C-11 epimer of **2d** [**2d**(minor)] (major : minor = *ca.* 1.5 : 1) and a *cis*/*trans* isomeric mixture of **3d** (3 : 1 ratio) were isolated by column chromatography of the mother liquor: the **2d** : **3d** ratio was *ca.* 2.5 : 1. On treatment with Jones reagent, the single isomer of **2d** and its C-11 isomeric mixture were converted into the same ketone **4d** in 90% yield.

Formation of **2d** can be explained by the mechanism outlined in Scheme 2. The cephem phosphorus ylide, generated from **1** by sodium hydrogen carbonate can be described as a mixture of the resonance-stabilized tautomers **8**, **9**, **10** and **11**, respectively. Aldol addition of the carbanion **11** to the aldehyde function of methylglyoxal gives the C-2 substituted intermediate **13** which then undergoes an intramolecular Wittig reaction to provide **2**. It was reported earlier[2,3] that the tautomer **9** reacts with acrylaldehyde to yield a 3,4-disubstituted tricyclic cephem **12**.

We also examined the effects of variations in $R^2$ and $R^3$ on the **2** : **3** ratio (Table 1). Treatment of glyoxal with **1a** and **1b** (entries a and b), gave only traces of the open-chain vinylcephems **3** whereas **2a** (amorphous solid) and **2b** (m.p. 207–209 °C) were obtained in good yields. The crystalline compounds were found to be single C-2,C-11 diastereoisomers.

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**Table 1** Reactions of cephalosporin phosphoranes with bifunctional carbonyl compounds

| | Substituent | | | Yield (%) | |
|---|---|---|---|---|---|
| Entry | $R^1$ | $R^2$ | $R^3$ | **2** | **3** |
| a | Ph | H | H | 60[a] | N.I. |
| b | PhO | H | H | 54[a,b] | N.I. |
| c | Ph | Me | H | 43[a,b] | 18[c] |
| d | PhO | Me | H | 55[a] | 21[c] |
| e | Ph | Ph | H | N.I. | 58[d] |
| f | PhO | Ph | H | N.I. | 61[d] |
| g | PhO | Me | Me | 35[e] | N.I. |
| h | Ph | $CO_2Bu$ | H | N.I. | 43[c] |

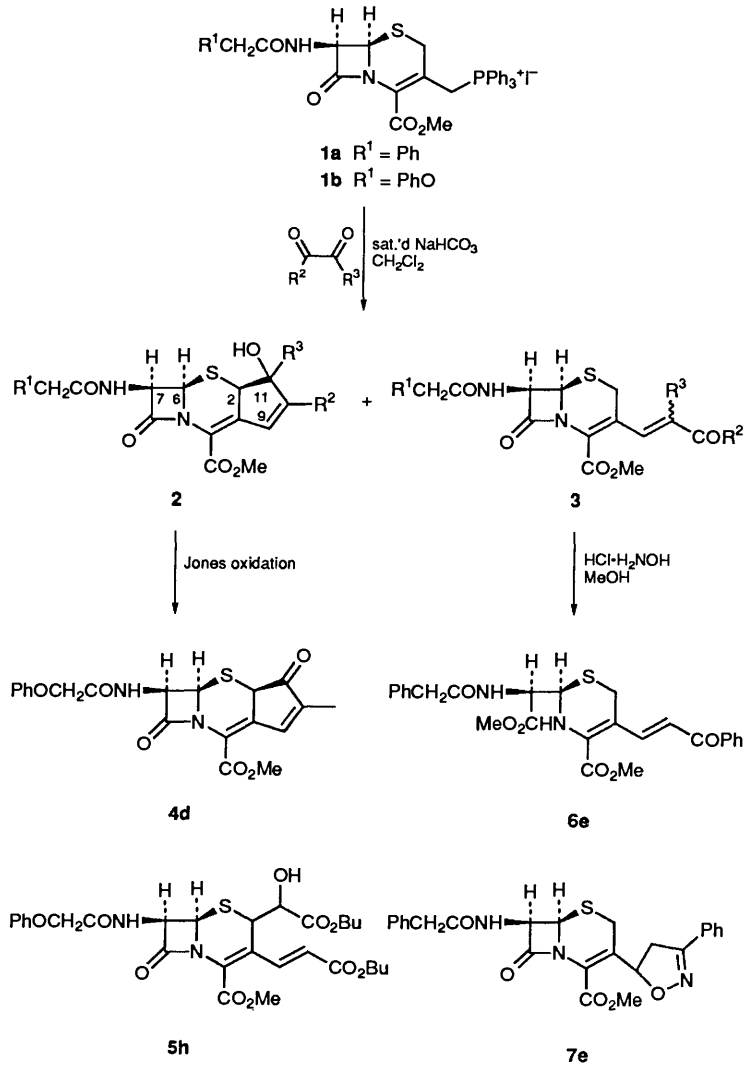
N.I. = not isolated. [a] Mixture of C-11 diastereoisomers. [b] The major epimer crystallized from the product mixture. [c] Mixture of *cis* and *trans* isomers. [d] Crystalline single *trans* isomers. [e] The two C-11 epimers were separated by chromatography.

In contrast, when the reaction of phenylglyoxal was examined (entries e and f), *trans*-**3e** (pale yellow crystals, m.p. 163–166 °C) and *trans*-**3f** (amorphous solid) were isolated from the reaction mixture. Treatment of **1b** with biacetyl (entry g) gave the tricyclic derivative **2g** as the only isolable product. In the reaction of **1a** and butyl glyoxylate (entry h), the open-chain vinylcephem **3h** was formed as the major product. The presence of a minor derivative was also detected. The $^1$H NMR spectrum of the crude product showed resonances characteristic of a double adduct, tentatively assigned as **5h**; however, it could not be purified to provide an homogeneous sample.

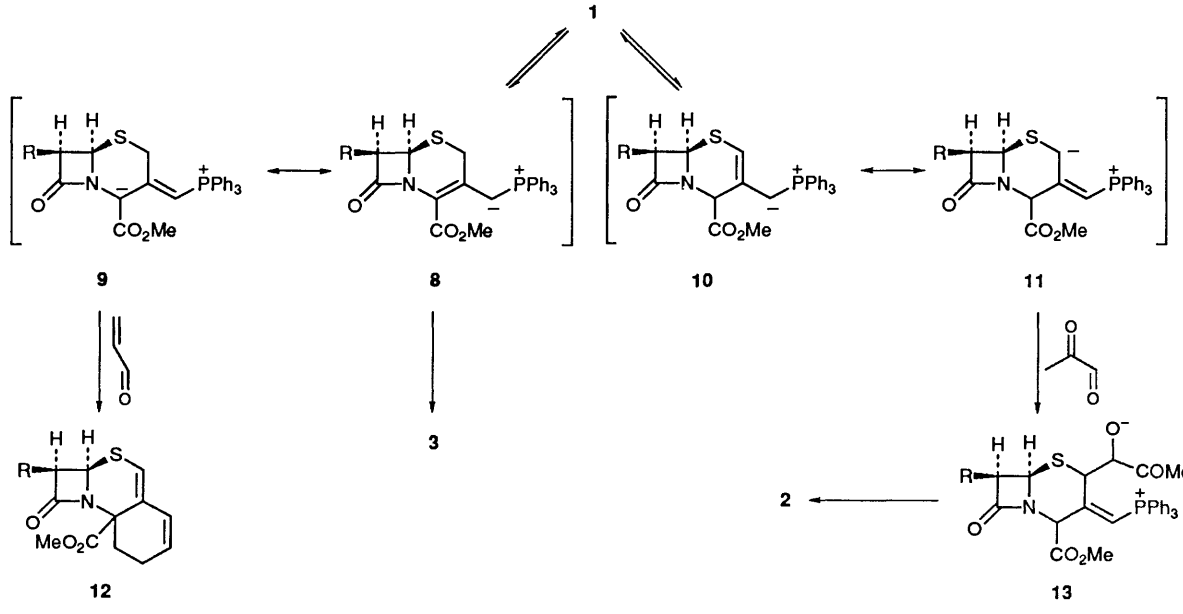
To provide further evidence for the unsaturated ketone structure of **3**, **3e** was treated with hydroxylamine hydrochloride.[6] This reaction caused cleavage of the β-lactam moiety and resulted in formation of the dimethyl ester **6e** in > 60% yield; none of the desired isoxazoline **7e** was observed.

These findings led us to conclude that: (i) the **2** : **3** ratio is a function of the substituent $R^2$ of the bifunctional carbonyl compound. (ii) Aldol products of type **5h** and **12** cannot be isolated.[7] (iii) The $S_N$ reaction of the ketone is not preferred (except in the case of **2g**). When the Wittig reaction of the aldehyde takes place, further reaction of the C-2 anion is blocked. (v) The aldol addition is always a completely stereoselective process at C-2.

Configurations at C-2 and C-11 in **2** were determined by means of $^1$H NMR, $^1$H-{$^1$H} NOE experiments and molecular modelling. The α-orientation of 2-H was unambiguously determined, since *ca.* 19% enhancement of 6-H(α) was observed when 2-H was irradiated (Fig. 1). Furthermore, the magnitude of coupling between 2-H(α) and 11-H (*J* 5 Hz) and the 6.8%




**Scheme 1** Reaction of cephalosporin phosphoranes with bifunctional carbonyl compounds




**Scheme 2** Proposed mechanism for formation of tricyclic cephems **2**

NOE revealed that the hydrogens are in a gauche orientation. Hence **2d**(major) possesses the 2*R*,11*S* configuration. Similar NOE values and coupling constants were observed for each of the major components of the products **2**, *i.e.* each possesses the

**Table 2** Selected $^1$H NMR spectral data for the major isomers of **2a–g**, **3c–h**, **4d** and **6e**

| Compd. | 2-H | 6-H[b] | 7-H[c] | 7-$CH_2$ | OMe | 9-H | 10-H | 11-H |
|---|---|---|---|---|---|---|---|---|
| **2a** | 4.05 | 5.11 | 5.78 | 3.63 | 3.85 | 6.35 | 6.95 | 4.91 |
| **2b** | 4.09 | 5.20 | 5.89 | 4.58 | 3.88 | 6.34 | *f* | 5.01 |
| **2c** | 4.13 | 5.28 | 5.65 | 3.50, 3.58[d] | 3.73 | 6.60[e] | | 4.55[g] |
| **2d** | 3.67 | 5.06 | 5.38 | 4.59 | 3.80 | *f* | | *f* |
| **2g** | 3.77 | 5.13 | 5.44 | 4.60 | 3.82 | *f* | | |
| **3c** | 3.34, 3.60[a] | 5.02 | 5.83 | 3.78 | 3.62 | 6.22[d] | 6.76[d] | |
| **3d** | 3.40, 3.65[a] | 5.10 | 5.93 | 4.58 | 3.81 | 6.25[d] | *f* | |
| **3e** | 3.60, 3.78[a] | 5.02 | 5.89 | 3.66 | 3.89 | 7.09[d] | *f* | |
| **3f** | 3.69, 3.90[a] | 5.11 | 5.92 | 4.60 | 3.94 | 6.84[d] | 7.71[d] | |
| **3h** | 3.50, 3.75[a] | 5.10 | 5.90 | 4.57 | 3.82 | 5.90[d] | *f* | |
| **4d** | 4.42 | 5.23 | 6.00 | 4.57 | 3.94 | 8.22 | | |
| **6e** | 3.55, 3.65[a] | 4.64[i] | 4.98 | 3.69 | 3.78, 3.90 | 6.80[d] | 8.46[d] | |

[a] d, *J* 17–18 Hz. [b] d, *J* 4.0–5.1 Hz. [c] dd, $J_1$ 4.0–5.1 Hz, $J_2$ = 7.9–9.4 Hz. [d] d, *J* 14.0 Hz. [e] t, *J* 1.4 Hz. [f] The signal is obscured by the aromatic hydrogen atoms. [g] dt, $J_1$ 5.0 Hz, $J_2$ 1.5 Hz, $J_3$ 1.4 Hz. [h] d, *J* 15–16.5 Hz. [i] m.

**Table 3** Selected $^{13}$C NMR data for the major isomers of **2b**, **2c**, **2d**, **2g**, **3e** and **3h**

| | Compound | | | | | |
|---|---|---|---|---|---|---|
| | **2b** | **2c** | **2d** | **2g** | **3e** | **3h** |
| C-2 | 51.83 | 51.10 | 51.95 | 60.63 | 24.14 | 27.79 |
| C-6 | 59.95 | 60.02 | 60.10 | 59.83 | 59.69 | 58.49 |
| C-7 | 57.33 | 57.95 | 59.64 | 54.66 | 58.04 | 57.29 |
| C-9 | 127.91 | 126.47 | 125.16 | 124.18 | 126.60 | 121.88 |
| C-10 | 144.22 | 156.75 | 156.30 | 155.29 | 128.20 | 141.18 |
| C-11 | 78.07 | 78.77 | 81.05 | 83.01 | 161.44 | 168.65 |
| 7-$CH_2$ | 66.88 | 41.46 | 67.24 | 67.33 | 42.23 | 67.09 |
| OMe | 52.14 | 51.88 | 50.51 | 52.19 | 52.82 | 52.50 |

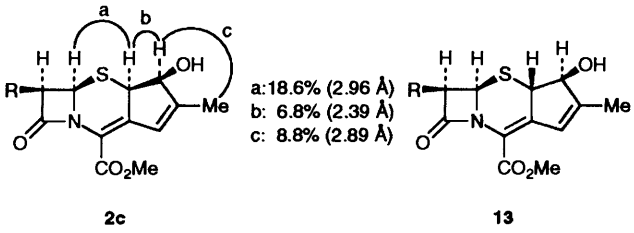
**Table 4** Dihedral angles (°) and pyramidality values for compounds **2d**(major) and **13**

| | **2d** | **13** |
|---|---|---|
| $\theta_1$ < 4-3-9-10 | −166.5 | 172.2 |
| $\theta_2$ < 9-3-2-11 | −23.3 | 16.6 |
| Pyramidality of C-2 | 0.73 | 0.72 |

same stereochemical arrangement. The minor components which retain the configuration at C-2 show, however, opposite orientation at C-11.

In order to elucidate the marked stereospecificity at C-2 during the formation of the new ring, we performed a molecular mechanics analysis of the isolated product **2d**(major) and its C-2 diastereoisomer **13**. MM + † and MMX calculations predicted that **2d** is energetically more favourable by −1.7 and −4.6 kcal $mol^{-1}$, respectively. These energy-difference values are sufficient to explain the stereoselectivity of the reaction. However, they also show that there is little difference in steric strain between the two fused ring structures. For instance, the dihedral angle $\theta_1$ of the two double bonds is near to 180° (Table 4) in both compounds, showing that the four atoms are nearly coplanar. The $\theta_2$ values are also similar but opposite in direction. The pyramidality ‡ at C-2 is also near to the ideal $sp^3$ hybridized

† The standard MM + force field of the HyperChem software package (AutoCad Inc.) was used. This method with its standard parameter sets reproduced the slightly pyramidal β-lactam nitrogen more satisfactorily than the MMX method (PCMODEL, Serena Software). This latter needs reparametrization to reproduce β-lactam compounds accurately. ‡ The generalized pyramidality index *P* is used. The magnitude of *P* varies between 0 and 1, and is independent of the bond lengths (it is 0.77 for the methane molecule): T. P. Radhakrishnan and I. Agranat *Struct. Chem.*, 1991, **2**, 107.




**2c** **13**

**Fig. 1** Model structures of **2c**(major) and its C-2 isomer. The observed $^1$H-{$^1$H} NOE values are indicated by curves. The atomic distances between the hydrogens, determined by molecular modelling, are given in parentheses.

carbon. Therefore, we have also analysed the transition states leading to **2d** and **13**.

Carbanions adjacent to sulfur tend to retain their chirality[8,9] and are capable of highly stereospecific reactions. Theoretical calculations[9,10] interpret this effect in terms of a stabilizing sulfur d-orbital interaction with the HOMO of the carbanion and with the occupied σ* of the opposite C–S bond. On the other hand, if the carbanion were orientated to the α-side, a repulsive interaction between the $C^-$ and sulfur lone pairs should result. These orbital interactions tend to promote formation of the new C-2,C-11 bond antiperiplanar to the C(6)–S bond, i.e. on the β-side. In conclusion, both molecular mechanics calculations and transition-state analysis predicts that the tricyclic cephalosporins possess a 2*R* configuration.

In contrast, a recent study[11] revealed that α-substitution was preferred in the aldol reaction of a 7α-OMe cephalosporin 1,1-dioxide with benzyl glyoxylate under basic conditions. Nevertheless, we assume that in our case an H-bond between the 7β-NH and the carbonyl compound also could have a directing effect. Therefore, the aldol addition of the C-2 carbanion **11** occurs on the β-face. The existence of such an influence was reported earlier.[12] This effect cannot be observed in the case of 7α-OMe, 7β-H substituted cephalosporin. Furthermore, a cephalosporin sulfone lacks the sulfur lone pairs and unoccupied d-orbitals, hence they cannot exert a repulsive effect on the C-2 carbanion lone pair.

Studies on the synthesis and transformations of tricyclic derivatives of type **2** having other C-4 and C-7 substituents are underway in our laboratory.

## Experimental

M.p.s were measured in a Kofler-type hot-plate apparatus and are uncorrected. IR spectra were recorded as potassium bromide discs on a Perkin–Elmer 283B instrument. NMR spectra were recorded on a Bruker VD 200SY spectrometer in

**Table 5** Physical data for cephalosporins **2a–6e**

| Compd. | $R_F$ | M.p. (°C) | $\nu_{max}$/cm $^{-1}$ | m/z (%) |
|---|---|---|---|---|
| **2a** | 0.18[a] | 230–233 | 1782, 1718, 1704, 1654, 1628 | 409(30)[f], 387(100)[e] |
| **2b** | 0.45[b] | 207–209 | 1776, 1718, 1684, 1600 | 403(100)[e] |
| **2c** | 0.6[a] | 261–263 | 1780, 1724, 1654 | 423(25)[f], 401(100)[e] |
| **2d** | 0.58[b] | | 1766, 1714, 1610 | 439(20)[f], 417(100)[e] |
| **2g**(major) | 0.19[c] | | 1770, 1716, 1682, 1614 | 430(100)[e] |
| **2g**(minor) | 0.28[c] | | 1764, 1734, 1712, 1684, 1600 | 430(100)[e] |
| **3c** | 0.59[b] | | 1782, 1720, 1658, 1608 | 401(100)[e] |
| **3d** | 0.57[b] | | 1784, 1722, 1688, 1598 | 417(100)[e] |
| **3e** | 0.38[c] | 163–166 | 1782, 1724, 1654, 1598 | 463(100)[e] |
| **3f** | 0.48[c] | | 1776, 1710, 1654, 1598 | 479(25)[e], 225(100) |
| **3h** | 0.44[a] | | 1784, 1716, 1600 | 475(100)[e] |
| **4d** | 0.57[d] | | 1792, 1710, 1654, 1600 | 432(100)[f], 415(42)[e] |
| **6c** | 0.47[g] | 144–146 | 1740, 1652, 1578, 1558 | 494(0.5)[h] |

[a] Hexane–ethyl acetate (1:1). [b] Ethyl acetate–hexane (7:3). [c] Toluene–ethyl acetate (7:3). [d] Ethyl acetate–hexane (3:2). [e] $MH^+$. [f] $MNH_4^+$. [g] Benzene–ethyl acetate (1:1). [h] $M^+$.

deuteriochloroform solution with tetramethylsilane as internal standard. Thermospray mass spectra were obtained on a VG Trio-2 quadropole spectrometer (methanol–0.1 mol $dm^{-3}$ ammonium acetate (1:1) eluent; 1 $cm^3$ $min^{-1}$ flow rate; 250 °C capillary temperature; 200 V). For TLC purposes Merck DC Alurolle Kieselgel 60 $F_{254}$ was used (UV light, ammonium molybdate/heat visualization). For column chromatography Merck Kieselgel 60 adsorbent was used (hexane–ethyl acetate or toluene–ethyl acetate solvent systems).

*General Procedure for the Preparation of Compounds* **2** *and* **3**.—The phosphorane **1** (2 mmol) was dissolved in dichloromethane (100 $cm^3$) and saturated aqueous sodium hydrogen carbonate (150 $cm^3$) and the carbonyl compound (2 equiv., 4 mmol) were added in one portion to the solution. The reaction mixture was stirred at room temperature for 3–14 h after which the organic layer was separated, washed with water (2 × 150 $cm^3$) and brine (150 $cm^3$), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The oily residue was partially purified by short column chromatography using a hexane–ethyl acetate (7:3) solvent system to give, in some cases, the pure products. The impure fractions were collected and subjected to column chromatography. The products were generally crystallized from dichloromethane–hexane, although some resisted crystallization. (For characteristic physical data see Tables 2, 3 and 5.) In most cases several minor products (> 5%) formed but we were not able to isolate them.

*Cephem* **4d**.—The hydroxy compound **2d** [**2d**(major) or its diastereoisomeric mixture] (1 mmol) was dissolved in acetone (50 $cm^3$) and Jones reagent (5 $cm^3$) was added to the solution. The resulting mixture was stirred at room temperature for 1 h after which it was evaporated under reduced pressure. The oily residue was dissolved in ethyl acetate (100 $cm^3$) and the solution washed with 10% aqueous sodium hydrogen carbonate (100 $cm^3$), water (2 × 100 $cm^3$) and brine (100 $cm^3$), dried ($MgSO_4$) and evaporated to provide a solid.

*Compound* **6e**.—Compound **3e** (100 mg) was dissolved in methanol (15 $cm^3$) and anhydrous sodium acetate (15 mg) and hydroxylamine hydrochloride (15 mg) were added in one portion to the solution. After the reaction mixture had been set aside overnight at room temperature it was diluted with water until the product crystallized out. The product was further purified by passage through a short silica column (toluene–ethyl acetate, 1:1) and then crystallization from aqueous methanol to give **6e**.

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