Bioorganic & Medicinal Chemistry Letters, Vol.3, No.11, pp. 2451-2456, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

STEREOSELECTIVE FORMATION OF TRICYCLIC CEPHALOSPORINS IN REACTIONS OF CEPHEM PHOSPHORUS YLIDES AND KETOALDEHYDES[1]

János Pitlik,[#*] Tamás E. Gunda[#], Gyula Batta[#] and József Jekő[+]

[#]*Research Group for Antibiotics of the Hungarian Academy of Sciences, Lajos Kossuth University, H-4010 Debrecen, P. O. Box 70, and* [+]*Alkaloida Chemical Company, Ltd., H-4440 Tiszavasvári, P.O. Box 1, Hungary*

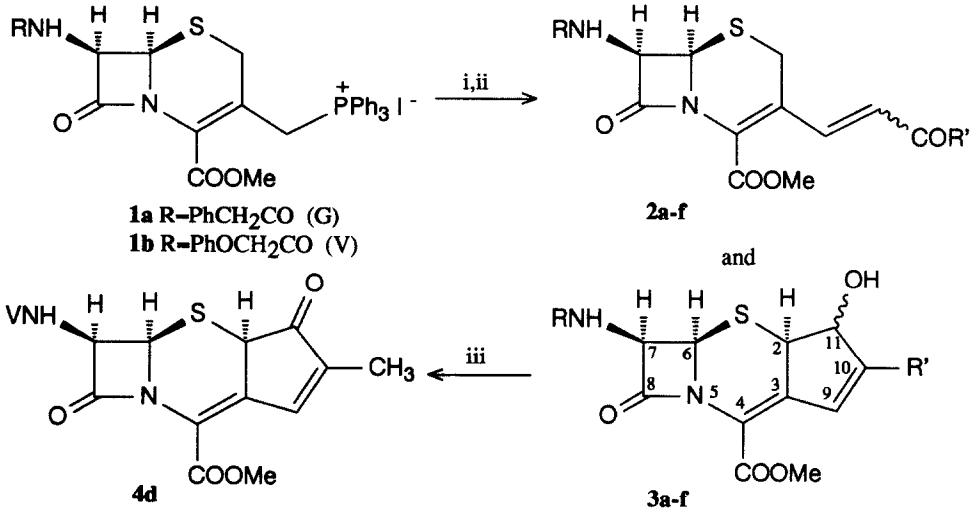
(*Received* 6 *July* 1993; *accepted* 30 *August* 1993)

Abstract: Novel tricyclic cephalosporins (**3a-d**) and cephem 3-α,β-unsaturated ketones (**2c-f**) were obtained in a Wittig-type approach with cephalosporin C-3 phosphorus ylides and keto-substituted aldehydes in completely stereoselective reactions. The product ratio was found to be a function of the substituent on the aldehyde. Structure elucidation of the products was carried out by means of NMR methods and molecular mechanics.

3-Vinylcephalosporins are one of the most important groups of antibiotics from the late eighties.[2] They are potent, orally active antibacterial agents. Some of them are commercially available drugs or are currently under clinical trial. We and others have examined their synthesis[2,3] and 1,3-dipolar cycloaddition reactions.[4-6]

In our studies on the scope and limitations of Wittig reactions of cephalosporin phosphorus ylides of type **1**, we examined the reactions of **1** with keto-substituted aldehydes, glyoxal, methylglyoxal and phenylglyoxal. When **1b** was reacted with methylglyoxal a very fast reaction was observed and the reaction mixture turned black in less than an hour. The crude reaction mixture was pre-purified by short column chromatography, when white crystals of **3d** (major)(mp. 261-3 °C) (Figure 1, Table 1) precipitated. The 200 MHz ^{1}H-NMR spectrum of the main product **3d** (major) lacked the characteristic resonances of 3-vinylcephems of type **2**.[7] Signals corresponding to the 1,2-disubstituted alkenyl group and to the C-2-CH_2 of the cephem dihydrothiazine moiety were missing and three CH resonances appeared. Thermospray MS analysis revealed that **3d** possesses the same molecular weight as **2d**. However, the presence of a hydroxy group was clearly detected. COSY, ^{1}H-^{13}C heterocorrelated NMR and LR INEPT analysis provided unambiguous evidence that **3d** (major) has a tricyclic structure and is a single diastereomer at C-2 and C-11. The other C-11 epimer of **3d** and a *cis/trans* isomeric mixture of **2d** were isolated by column chromatography from the mother liquor. The **3d:2d** ratio was ca. 2.5:1. Formation of **3d** can be explained by the following reaction mechanism: 1) The cephem phosphorus ylide **5** exists in equilibrium with its resonance-stabilized tautomers **6** and **7**. 2) Carbanion **7** undergoes aldol addition to the aldehyde function of methylglyoxal to give a C-2 substituted intermediate (**8**). 3) **8** undergoes an intramolecular Wittig reaction to provide **3**. It was reported earlier that tautomer **6** reacts with acrylaldehyde to yield a C-3, C-4-substituted tricyclic cephem **9**.[2,8]

On treatment with the Jones reagent, the single isomer of **3d** and its C-11 isomeric mixture (ca. 2:1 ratio) were converted to the same ketone **4d**.[7]



Reagents: i) sat. $NaHCO_3$, CH_2Cl_2; ii) OHC-COR' (R'=H, CH_3, Ph); iii) Jones oxidation.

Figure 1

Table 1. Reactions of cephalosporin phosphoranes with ketoaldehydes.

Entry	R	R'	yield (%)	
			2	3
a	G	H	traces	60
b	V	H	traces	54
c	G	Me	18[a]	43
d	V	Me	21[a]	55
e	G	Ph	58[b]	traces
f	V	Ph	61[b]	traces

[a] mixture of *cis* and *trans* isomers
[b] single *trans* isomers

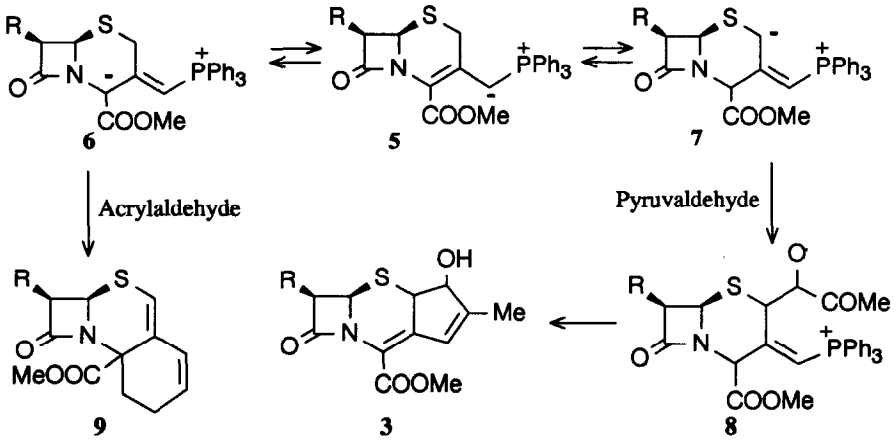


Figure 2. Proposed mechanism of formation of cyclopentenylcephems 3.

We also examined the effect of R' on the **2**:**3** ratio (Table 1). When glyoxal was reacted with **1a** and **1b**, the open-chain vinylcephems (**2**) were formed only in traces and **3a** and **3b** (mp. 207-9 °C) were obtained in good yields. They were found to be single diastereomers at C-2 and C-11. However, when the reaction of phenylglyoxal was examined, *trans* isomers of **2e** (mp. 163-6 °C) and **2f** were isolated as pale yellow crystals.

Our findings led us to conclude that: 1) The **2**:**3** ratio is a function of the substituent R' on the keto-aldehyde. 2) Aldol products[9] of type **8** cannot be isolated 3) The S_N reaction of the ketone is not preferred. 4) When the Wittig reaction of the aldehyde takes place, further reaction of the C-2 anion is blocked. 5) The aldol addition is always a completely *stereoselective* process.

The configurations at C-2 and C-11 in **3** were determined by means of ^{1}H-NMR, ^{1}H-{^{1}H} NOE experiments and molecular modelling (Figures 3 and 4).

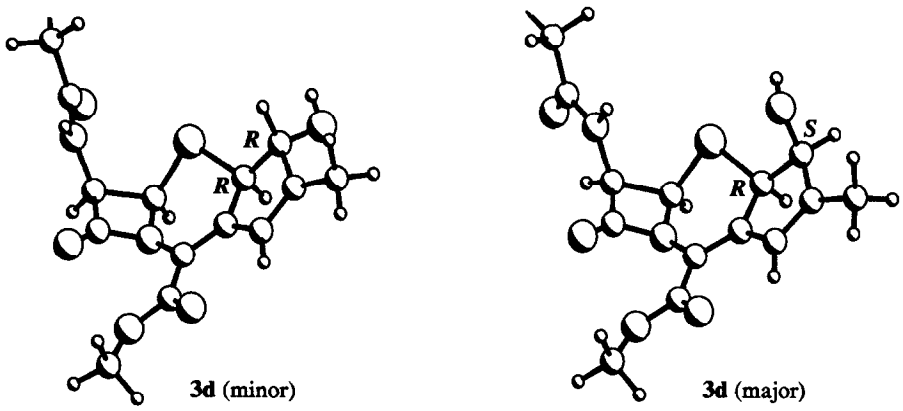
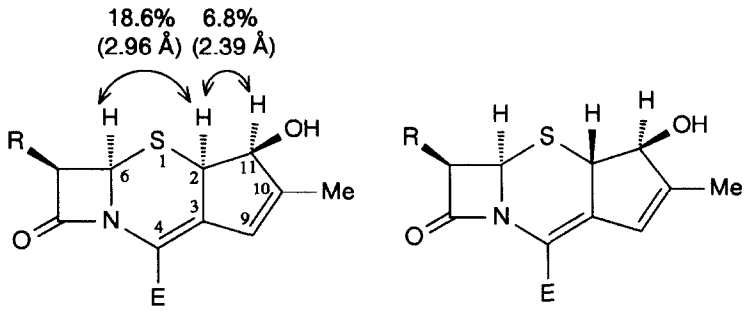


Figure 3. Pluto plot of **3d** *(major) and* **3d** *(minor) in their refined minimal conformation. The phenyl group on the C-7 side chain is omitted for compactness.*

The α-orientation of H-2 was unambiguously determined, since ca. 19 % enhancement was observed on H-6(α) when H-2 was irradiated. Furthermore, the magnitude of coupling between H-2(α) and H-11 (J=5 Hz) and the 6.8 % NOE value revealed that the hydrogens are in *gauche* orientation. Hence **3d** (major) possesses the ***2R,11S*** configuration.



3d (major) **10**

*Figure 4. Simplified structure of **3d** (major) and its diastereomer **10**. The observed most important NOE values are indicated by double-headed arrows. The distances between the hydrogens, determined by molecular modelling, are also given.*

In order to elucidate the marked stereospecificity at C-2 during formation of the new ring, we performed molecular mechanics analysis of the isolated product (**3d**) and its C-2,C-11 diastereomer (**10**). MM+[10] and MMX calculations predicted that **3d** is energetically more favourable by -1.7 and -4.6 kcal/mol, respectively. The AMBER force field exhibited an even smaller difference. This minimal difference in steric energy shows that there are no relevant steric strains in the joined rings of either isomer. For instance, the dihedral angle Θ_1 of the two double bonds is near to 180° (Table 2) in both compounds, showing that the four atoms are nearly co-planar. The Θ_2 values are also similar, but opposite in direction. The pyramidality[11] at C-2 is also near to the ideal sp^3 hybridized carbon. Thus, purely steric factors relating to the end-product are insufficient to explain the stereoselectivity of the reaction. The answer may lie in the preference of one transition state over the other.

*Table 2. Dihedral angles and pyramidality values for model compounds **3d** and **10**.*

	3d	**10**
Θ_1 < 4-3-9-10	-166.5°	172.2°
Θ_2 < 9-3-2-11	-23.3°	16.6°
pyramidality of C-2	0.73	0.72

Carbanions adjacent to sulphur tend to retain their chirality[12,13] and are capable of highly stereospecific reactions. Theoretical calculations[13,14] interpret this effect in terms of a stabilizing sulphur d-orbital interaction with the HOMO of the carbanion and with the unoccupied σ^* of the opposite C-S bond. On the other hand, if the carbanion were oriented to the α-side, a repulsive interaction between the C^- and sulphur lone pairs should result. There is no reason to suppose the formation of a distinct carbanion at C-2 during the simultaneous Wittig process and nucleophilic attack on the aldehyde group, but, the above orbital interactions tend to promote formation of the new C-2–C-11 bond anti-periplanar to the C-6–S bond, i.e. it takes place on the β-side (Figure 5).

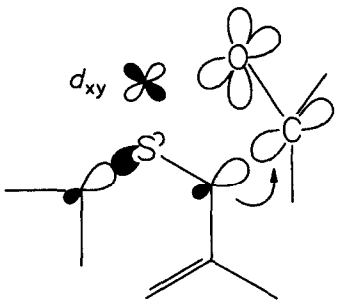


Figure 5. Anti-periplanar formation of the C-2-C-11 bond of cyclopentenylcephalosporins 3.

Acknowledgements: The authors wish to thank the Hungarian Academy of Sciences (OTKA T7460) and the Hungarian Scientific Foundation of the Hungarian Credit Bank (Magyar Tudományért Alapítvány, Magyar Hitelbank, Rt.) for financial support, and Professor F. Sztaricskai for valuable advice.

References and Notes:

1. Synthesis and Transformations of 3-Vinylcephalosporins, 5; for part 4, see Pitlik, J. *Synth. Commun.* **1993**, submitted.
2. Pitlik, J.; Batta, Gy.; Sztaricskai, F. *Liebigs Ann. Chem.* **1992**, 895. and references cited therein.
3. e.g. Farina, V.; Baker, S.R.; Beningi, D.A.; Hauck, S.I., Sapino, C., Jr. *J. Org. Chem.* **1990**, *55*, 5833. and references cited therein.
4. Pitlik, J.; Gunda, T.E.; Miskolczi, I. *J. Heterocycl. Chem.* **1990**, *27*, 1281.
5. Spry, D.O.; Snyder, N.J.; Kasher, J.S. *J. Antibiot., 1989*, 42, 1653.
6. Fell, S.C.M.; Pearson, M.J.; Burton, G.; Bateson, J.H. *J. Chem. Soc. Perkin Trans. 1.* **1991**, 1361.
7. All new compounds gave satisfactory spectral and analytical data consistent with the proposed structure. e.g. **3b**: mp. 207-9 °C; R_f= 0.45 (EtOAc:hexane=7:3); IR (KBr) cm^{-1} 3420, 1776, 1718, 1684, 1600, 1534, 1494, 1436, 1366, 1292, 1234, 1100, 1062, 754; ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H, OCH_3), 4.09 (d, H, J= 4.7 Hz, H-2), 4.58 (s, 2H, OCH_2), 5.01 (m, H, H-11), 5.20 (d, H, J= 4.9 Hz, H-6), 5.89 (dd, H, J_1= 4.9 Hz, J_2= 9.1 Hz, H-7), 6.34 (dd, H, J_1= 5.8 Hz, J_2= 2 Hz, H-10), 6.9 - 7.3 (m, 7H); ^{13}C NMR ($CDCl_3$, J-echo) δ 51.831 (C-2), 52.137 (OCH_3), 57.327 (C-6), 59.954 (C-7), 66.875 (OCH_2), 78.070 (C-11), 114.612 (CH), 117.358 (q), 122.059 (CH), 129.546 (CH), 129.907 (C-10), 138.301 (q), 144.219 (C-9), 156.810 (q), 161.729 (CO), 164.686 (CO), 168.657 (CO); MS (thermospray) m/z 403 (MH^+, 100%).
2d: R_f= 0.57 (EtOAc:hexane=7:3); IR (KBr) cm^{-1} 3404, 3330, 2954, 1784, 1722, 1688, 1596, 1524, 1492, 1438, 1370, 1326, 1232, 1176, 1100, 1064, 1022, 756, 736, 694; ^1H NMR ($CDCl_3$) δ (for the *cis* isomer) 2.24 (s, 3H, CH_3), 3.39 (d, H, J= 17.9 Hz, 2-CH_2-H_a), 3.65 (d, H, J= 17.9 Hz, 2-CH_2-H_b), 3.81 (s, 3H, OCH_3), 4.58 (s, 2H, OCH_2), 5.10 (d, H, J= 4.9 Hz, H-6), 5.93 (dd, H, J_1= 4.9 Hz, J_2= 9.37 Hz, H-7), 6.25 (d, H, J= 11.8 Hz, =CH), 6.9 - 7.4 (m, 7H); (for the *trans* isomer) 2.32 (s, 3H, CH_3), 3.71 (d, H, J= 18.1 Hz, 2-CH_2-H_a), 4.09 (d, H, J- 18.1 Hz, 2-CH_2-H_b), 3.93 (s, 3H, OCH_3), 4.59 (s, 2H, OCH_2), 5.16 (d, H, J= 4.8 Hz, H-6), 5.96 (dd, H, J_1= 4.8 Hz, J_2= 9 Hz, H-7), 6.30 (d, H, J= 16.3 Hz, =CH), 6.9 - 7.4 (m, 7H); MS (thermospray) m/z 417 (MH^+, 100 %).

3d: R_f= 0.58 (EtOAc:hexane = 7:3); IR (KBr) cm^{-1} 3418, 1766, 1714, 1610, 1494, 1436, 1382, 1330, 1236, 1082, 756; ^1H NMR ($CDCl_3$) δ **(major)** 2.06 (s, 3H, CH_3), 3.67 (d, H, J= 2.3 Hz, H-2), 3.80 (s, 3H, OCH_3), 4.39 (bs, H, OH), 4.59 (s, 2H, OCH_2), 5.06 (d, H, J= 4.0 Hz, H-6), 5.38 (dd, H, J_1= 4.0 Hz, J_2= 7.7 Hz, H-7), 6.9 - 7.4 (m, 7H), 7.73 (d, 1H, J= 7.7 Hz, NH); **(minor)** 2.00 (s, 3H, CH_3), 4.07 (d, H, J= 4.9 Hz, H-2), 3.86 (s, 3H, OCH_3), 4.74 (bs, H, OH), 4.56 (s, 2H, OCH_2), 5.17 (d, H, J= 4.8 Hz, H-6), 5.84 (dd, H, J_1= 4.8 Hz, J_2= 9 Hz, H-7), 6.9 - 7.4 (m, 8H); ^{13}C NMR ($CDCl_3$-DMSO-d_6) δ **(major)** 15.241 (CH_3), 50.505 (OCH_3), 51.946 (C-6), 59.637 (C-2), 60.100 (C-7), 81.047 (C-11), 114.835 (CH), 121.954 (CH), 129.567 (CH), 125.161 (C-9), 114.333 (q), 138.152 (q), 156.298 (q), 156.835 (CO), 157.181 (CO), 157.419 (CO); **(minor)** 14.537 (CH_3), 50.505 (OCH_3), 51.644 (C-6), 57.296 (C-2), 59.956 (C-7), 79.277 (C-11), 114.658 (CH), 122.122 (CH), 129.567 (CH), 125.321 (C-9), 161.372 (q), 162.922 (q), 164.618 (q), 166.274 (CO), 168.619 (CO), 168.747 (CO); MS (thermospray) m/z 439 (MNa^+, 20 %), 417 (MH^+, 100 %);
2f: R_f= 0.48 (toluene:EtOAc = 7:3); IR (KBr) cm^{-1} 3408, 3288, 2926, 1776, 1710, 1674, 1654, 1598, 1532, 1492, 1434, 1372, 1300, 1276, 1220, 1176, 1160, 1108; ^1H NMR ($CDCl_3$) δ 3.69 (d, 1H, J= 17.1 Hz, 2-CH_2-H_a), 3.90 (d, H, J= 17.1 Hz, 2-CH_2-H_b), 3.94 (s, 3H, OCH_3), 4.60 (s, 2H, OCH_2), 5.11 (d, H, J= 4.8 Hz, H-6), 5.92 (dd, H, J_1= 4.8 Hz, J_2= 9.1 Hz, H-7), 6.84 (d, H, J= 16.4 Hz, =CH), 6.93 - 7.49 (m, 11H), 7.71 (d, 1, J= 16.4 Hz, -CH); MS (thermospray) m/z 479 (MH^+, 100 %).
4d: R_f= 0.57 (EtOAc:hexane = 3:2); IR (KBr) cm^{-1} 3628, 3416, 1792, 1710, 1654, 1646, 1624, 1600, 1590, 1522, 1496, 1436, 1436, 1364, 1710, 1242, 1174, 1096, 1064, 756; ^1H-NMR ($CDCl_3$) δ 2.70 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 4.42 (s, H, H-2), 4.57 (s, 2H, OCH_2), 5.23 (d, H, J= 5.1, H-6), 6.00 (dd, H, J_1= 5.1 Hz, J_2= 9.2 Hz, H-7), 6.9-7.4 (m, 6H, arom.+NH), 8.22 (s, H, 3'-H); MS (thermospray) m/z 432 (MNa^+, 100%), 415 (MH^+, 42%).

8. Hatanaka, M.; Yamamoto, Y.; Ishimaru, T. *J. Chem. Soc. Chem. Commun.* **1984**, 1705.
9. Hatanaka, M.; Yamamoto, Y.; Ishimaru, T.; Takai, Y. *Chem. Lett.* **1985**, 183, and Schingler, H.; Weir, N.G. in *Recent Advances in the Field of* β-*Lactam Antibiotics* (Elks, J., Ed.), Chemical Society, Spec. Publ. No. 28., London, 1977, pp. 153-160.
10. 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 with the MMX method (PCMODEL, Serena software). This latter needs reparametrization to reproduce β-lactam compounds accurately.
11. The generalized pyramidality index **P** of Radhakrishnan, T. P. and Agranat, I. (*Struct. Chem.* **1991**, *2*, 107.) 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 with 109.4° bond angles).
12. Buncal, E. *Carbanions: mechanistic and isotopic aspects*; Elsevier, 1975, pp. 59-65
13. Okazaki, R.; O-oka, M.; Akiyama, T.; Inamoto, N.; Niwa, J.; Kato, S. *J. Am. Chem. Soc.* **1987**, *109*, 5413.
14. Wolfe, S.; LaJohn, L. A. *Tetrahedron Lett.* **1983**, *24*, 3789.