On the preparation of 2-substituted cephalosporin sulfoxides *via* anionic intermediates

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The LDA-generated anions of cephalosporin sulfoxides may give rise to a mixture of C-2- and/or C-4-substituted products owing to the delocalized nature of the negative charge. Under optimized conditions 2α-crotonoyl- and 2α-cinnamoylcephalosporin sulfoxides can be obtained in satisfactory yields, and are useful starting materials for cycloaddition reactions leading to novel analogues with β-lactamase or HLE enzyme-inhibiting properties.

Introduction

The chemistry of 2-substituted cephalosporins has never been a very intensively probed area of β-lactam antibiotics, nevertheless interesting findings can be found in the literature. The main reason is that according to the early investigations these compounds possess only moderate antimicrobial activities. This situation has profoundly changed since the emergence of the human leucocyte elastase (HLE)[1a] and β-lactamase[1b] enzyme inhibitors: both the higher oxidation state of the sulfur and the C-2 substitution of the cephem ring system led to new compounds with enhanced enzyme-inhibitory properties.[1c] The carbon atom at position 2 of cephalosporins is chemically only moderately active: oxidation of the sulfur ensures enhanced chemical reactivity; H-2 possesses a clearly acidic character, especially in the sulfones, but oxidized derivatives have greatly diminished antibacterial activity.

There are surprisingly few investigations dealing with substitution of the cephem C-2 atom *via in situ* generated atoms. Instead of submitting a long discussion of the outcome of electrophilic substitution under various conditions, we refer only to the literature survey presented in Scheme 1. It be seen that substitution of the dihydrothiazine ring in the presence of a strong base may lead to various mono- or disubstituted products at C-2 or C-4, depending strongly on the base and electrophilic reagents used, and on the oxidation state of the sulfur atom. Maiti *et al.*[8] suggested that with sp^2 partners the C-2 substitution is preferred to that at C-4. Indeed, this is the case with CO_2 or CS_2. Both C-2 and C-4 products form with different alkyl derivatives. Mention must be made of the C-7 substitution, although it is not shown in Scheme 1: this reaction may also easily occur when the C-7 atom is unsubstituted, or carries a strongly electron-withdrawing substituent, and formation of the carbanion on the dihydrothiazine ring is suppressed in some way. A similar distribution of products can be observed in the case of Michael acceptors, such as acrylonitrile or methyl vinyl ketone. In the case of cephem sulfones only one profound investigation can be found in the literature (Alpegiani *et al.*[7]), describing, again, the varied distribution of C-2 and C-4 products.

Results and discussion

The goal of our investigations was to find an acceptable method for the preparation, with an optimized yield, of cephem sulfoxides bearing an unsaturated substituent at position 2. These compounds may serve as starting materials for different cycloaddition reactions leading to cephalosporins with various heterocyclic C-2 side-chains with possible HLE and β-lactamase enzyme-inhibitory properties. To have a better understanding of the heterogeneity of the above-mentioned reactions, we performed different semiempirical QM/PM3 calculations on the anions of various cephem sulfoxides. Thus, for example, Fig. 1A shows the calculated Mullikan charges of the most relevant carbon atoms of the anion which was produced by the abstraction of one proton from C-2. This C-2 carbon next to the sulfur possesses the highest value of negative charge; however, C-4 exhibits a high value of electron density also, owing to charge delocalization over the unsaturated system. Fig. 1B depicts the highest occupied molecular orbital (HOMO) of the same system. This reveals that the HOMO is concentrated mainly on atoms C-2 and C-4 (and to a lesser extent on the β-lactam ring), both atoms sharing practically the same level of electron density on the HOMO orbital. In the first approximation this means that in the case of electrophilic reactions, C-2 and C-4 would exhibit about the same intrinsic activity. In fact, the ratio of products is influenced also by steric factors, as well as by secondary orbital interactions between the reagent and the anion, not to mention other reaction conditions – these factors explain the diversity of the literature findings.

Deprotonation of the side-chain NH may lead to a delocalized anion involving the β-lactam C-7 atom and the C=O group, especially at higher base concentration. Its extent is strongly dependent on the nature of the side-chain. This may cause the known epimerization of penicillins at C-6 with bases; on the other hand, in the presence of excess of base (~4 equiv.) alkylation and alkylthiolation reactions result in the formation of 7α-substituted and 7α,2α-substituted cephem compounds. This is discussed in ref. 4 in detail. In spite of the more pronounced acidity of the C-2 protons of the sulfoxides, in our work we also found that the outcome of the reaction is dependent very much on the compounds and reaction conditions used. Extensive degradation in the reaction mixture and very low isolable yields are commonplace. There are a few representative examples in Scheme 2, using benzhydryl 7-phenoxyacetamido-cephalosporanate- or -3-*c*-deacetoxycephalosporanate 1-oxide (**1a**, **b**; $R'' = CH_2OAc$ or CH_3) and different halogen compounds. The isolated yields of the new cephem derivatives **2**, **3** and **4** after work-up with column chromatography are very low. In the case of substrates **1a** and **1b** benzophenone was isolated (up to 30%) as proof of degradation. There were no appreciable differences regarding the cephem C-3 substituents methyl *vs.* acetoxymethyl.

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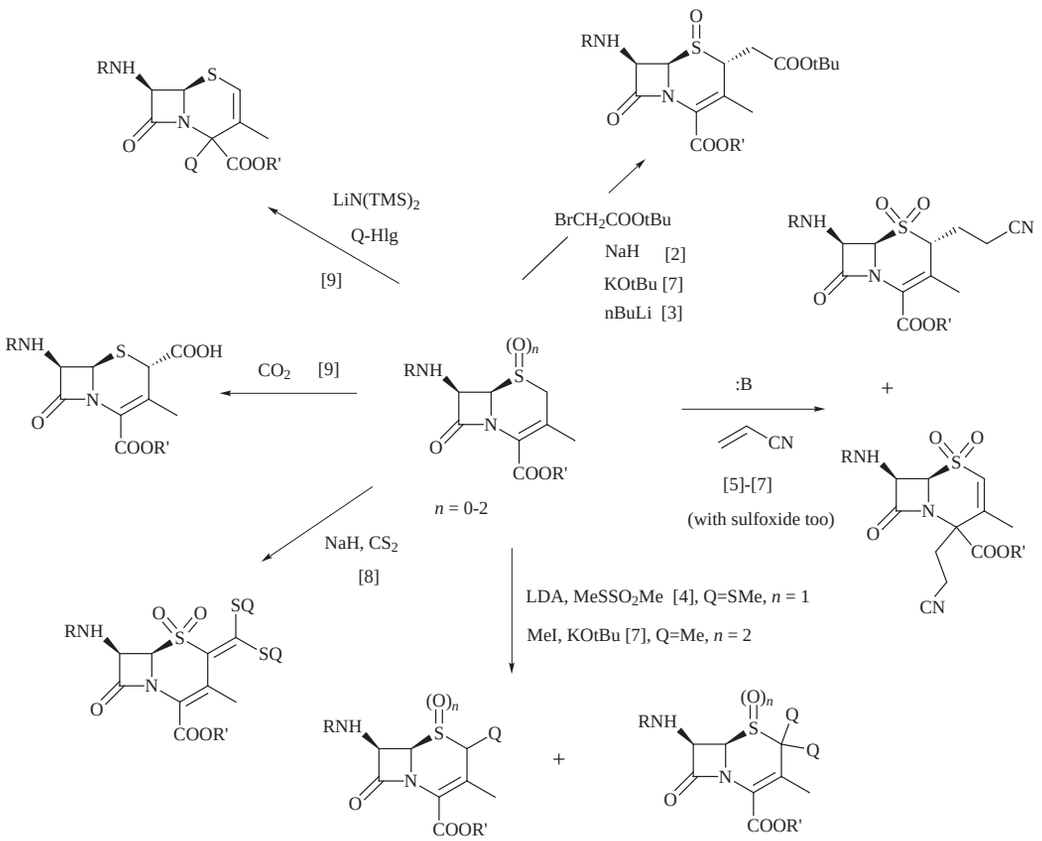


Scheme 1 Numbers in square brackets are references.

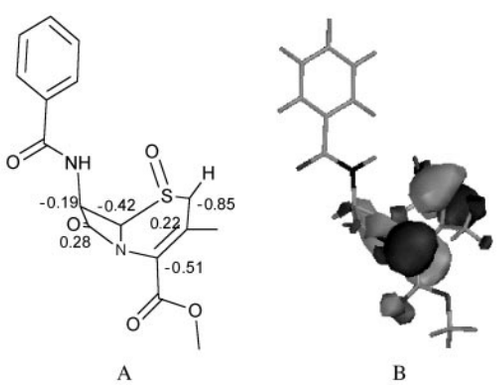
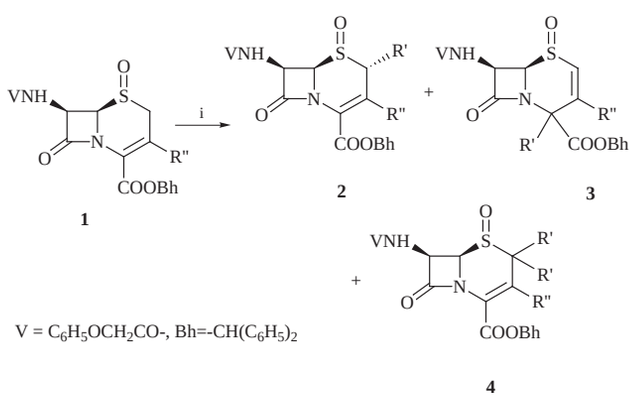


Fig. 1 MOPAC PM3 Mullikan point charges and contour plot of the HOMO of the 2-anion of the energy-minimized methyl 7β-benzamido-3-*c*-deacetoxycephalosporanate 1β-oxide **5**.



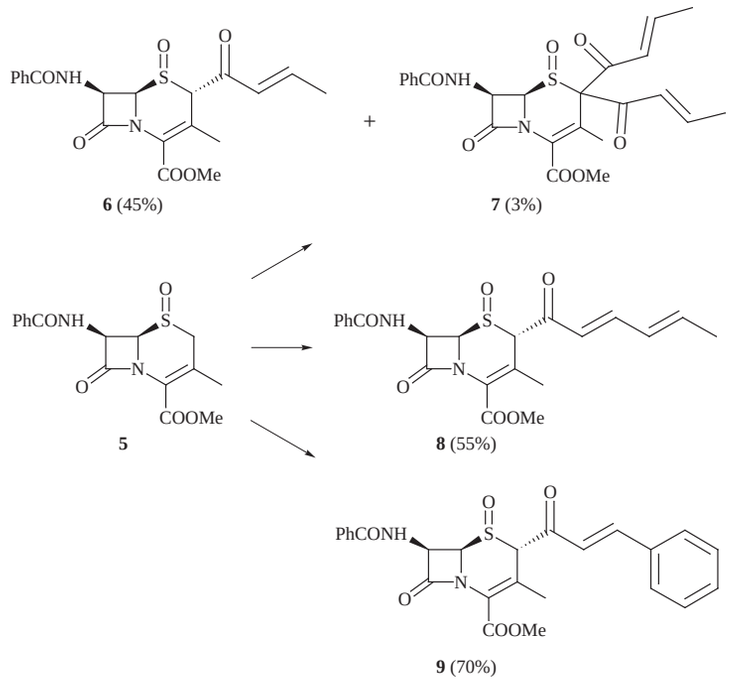
Entry	R′	R″	Yield (%) 2	3	4
a	$CH_2CH{=}CH_2$	CH_2OAc	3	1	8
b	$CH_2CH{=}CH_2$	CH_3	15	20	
c	CH_2CO_2Et	CH_2OAc	31		
d	sorbyl	CH_2OAc	20		
e	sorbyl	CH_3	15		7

Scheme 2 *Reagents and conditions*: i, (1) *n*-BuLi, Et_2NH, THF, −40 °C; (2) R′-Halogen, THF, HMPA, −40 °C.

On trying different 7β-amides ($C_6H_5OCH_2CONH$-, BocNH-, PhtN-, $C_6H_5CH_2CONH$-, C_6H_5CONH-) as well as ester protecting groups we found that the best results were obtained with the use of the simple benzamide. In fact, no products could be isolated when *tert*-butoxycarbonyl (*t*-Boc) or phthaloyl protection groups were applied. Methyl ester was chosen to protect the 4-carboxy group. Thus, with compound **5** three different reagents were used (Scheme 3). The deprotonation step was carried out in THF with 2.5–3 equiv. of *in situ* prepared LDA (*n*-BuLi + $HNPr^i)_2$, and the subsequent reactions with 1.5–2.5 equiv. of the electrophilic partners were conducted in the presence of HMPA. In the case of the 2-crotonoyl (but-2-enoyl) derivative we could isolate a minor amount of the 2,2-disubstituted product **7** as well as the monosubstitution product **6**. By careful optimization of the reaction conditions, it was possible to avoid column chromatography in each of these cases, and compounds **8** and **9** were obtained in 55 and 70% yield, respectively.

The configuration of the products was examined by ^{1}H-{^{1}H} nuclear Overhauser enhancement (NOE) experiments. It is quite characteristic of 2-substituted cephems that in the case of 2β-substituents the 2α-proton exhibits NOE interaction with the 6α-proton, but there is no such interaction in the opposite steric position. The measured NOE interactions of compound **9** are shown in Fig. 2, and the data are consistent with the substituent being in the α-position.

Of the reaction parameters we probed, the most important one was the influence of temperature. As the reaction is slightly exothermic, without adequate cooling the rise in the inner



Scheme 3 *Reagents and conditions*: i, LDA, THF; −40 °C; ii, R-Cl, THF, HMPA, −40 to −45 °C.

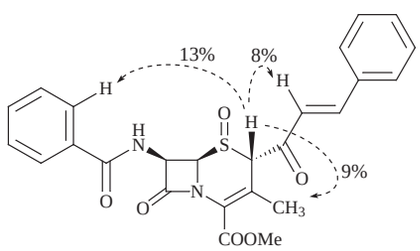


Fig. 2 Important ^{1}H-{^{1}H} NOE-values of compound **9**.

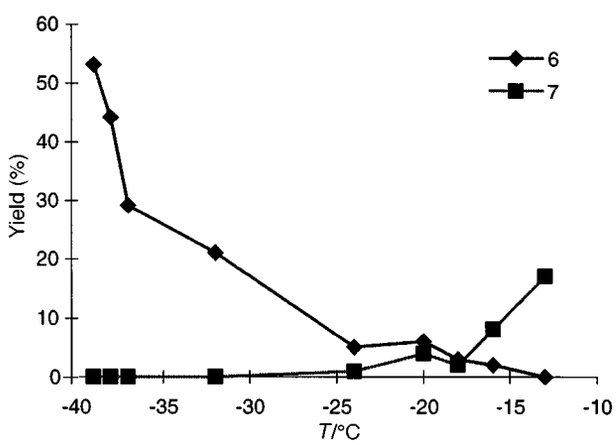


Fig. 3 The isolated yields of compounds **6** and **7** *vs* reaction temperature.

temperature immediately caused the appearance of unwanted 2,2-disubstituted products (**7**). In one experiment we performed several measurements at different inner temperatures to map the product distribution in the reaction **5** → **6** + **7**. It can be clearly seen from Fig. 3 that to achieve a good yield of the monosubstituted product, the inner temperature must be under −40 °C. Above −20 °C only the 2,2-disubstituted product could be isolated. It is also worthy of note that the optimum amount of the base is 2.5–3.0 equiv. With smaller quantities a considerable part of the cephem remains unchanged, which means that instead of a single deprotonation a complex acid–base system is present in the reaction mixture.

Experimental

General

Mps were determined on a Koffler-type hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 283B spectrophotometer in KBr pellets. The ^{1}H-NMR spectra were recorded on a Bruker WP-SY-200 instrument, with Me_4Si as internal standard. *J*-Values are given in Hz. Elemental analyses were done on a Carlo-Erba analyzer mod. 1106.

General procedure for preparing cephalosporins substituted at position C-2

To a solution of 1.44 g of diisopropylamine in 20 ml of dry THF was added at −40 °C 10 ml (25 mmol) of 2.5 M *n*-BuLi in hexane, and the resulting solution was stirred for 10 min under nitrogen. The cephalosporin derivative (8.5 mmol) was added in 40 ml of dry THF and 25 ml of dry HMPA to the above mixture dropwise over a 15–30 min period. After 20–30 min 2.4 mmol of the halogen derivative as a solution in 5 ml of dry THF was added dropwise and the mixture was stirred at −40 to −45 °C for 2.5 h before being poured into EtOAc–10% aq. H_3PO_4 (100 ml each). The organic layer was washed successively with 10% aq $NaHCO_3$ and brine, dried on $MgSO_4$ and evaporated to leave an oil. The crude product was purified by SiO_2 column chromatography, using toluene–EtOAc (10 : 1 → 3 : 1 gradient technique). The side-products were isolated also in this way. In the cases of 2-crotonoyl-, 2-sorbyl-,‡ and 2-cinnamoyl-cephem derivatives (**6**, **8**, and **9**) the product could be isolated by means of crystallization from propan-2-ol instead of column chromatography.

Methyl 7β-benzamido-2α-crotonoyl-3-*c*-deacetoxycephalosporanate 1β-oxide 6 and methyl 7β-benzamido-2,2-dicrotonoyl-3-*c*-deacetoxycephalosporante 1β-oxide 7. Compound **6**: 45%, mp 181–185 °C; ν_{max}(KBr)/cm^{-1} 1792, 1728, 1378 and 1226; δ_H($CDCl_3$) 2.05 (3 H, d, J_1 1.51, CH_3), 2.15 (3 H, s, 3′-CH_3), 3.92 (3 H, s, CO_2CH_3), 4.76 (1 H, d, *J* 4.5, 6-H), 4.97 (1 H, s, 2-H), 6.29 (1 H, dd, J_1 4.5, J_2 9.0, 7-H), 6.33 (1 H, s, COC*H*), 6.41 (1 H, d, *J* 1.5, COCHC*H*), 7.12–7.30 (2 H, m, ArH), 7.40–

‡ Sorbyl = hexa-2,4-dienoyl.

7.58 (3 H, m, ArH) and 7.80 (1 H, d, *J* 9.0, N*H*); δ_C($CDCl_3$) 18.8 (crotonoyl CH_3), 19.7 (3′-CH_3), 52.7 (6-C), 59.0 (7-C), 65.4 (2-C), 70.3 (CO_2CH_3), 122.1 (3-C), 124.0 (4-C), 127.3 (arom. *C*H, 2 C), 128.7 (arom. *C*H, 2 C), 130.1 (arom. *C*H), 132.4 (crotonoyl CH), 132.5 (arom. quat. C), 149.9 (crotonoyl *C*H), 161.5 (CO), 163.3 (CO), 166.9 (CO) and 188.6 (CO) (Found: C, 57.9; H, 5.0; N, 7.0. Calc. for $C_{20}H_{20}N_2O_6S$: C, 57.68; H, 4.84; N, 6.73%).

Compound **7** (obtained from the mother liquor of compound **6** by column chromatography): 3%, mp 220–229 °C; ν_{max}(KBr)/cm^{-1} 1793, 1734, 1652 and 1522; δ_H($CDCl_3$) 1.90 (3 H, d, *J* 7.0, crotonoyl CH_3), 1.99 (3 H, d, *J* 7.0, crotonyl CH_3), 2.23 (3 H, s, 3′-CH_3), 3.89 (3 H, s, CO_2CH_3), 4.82 (1 H, d, *J* 4.5, 6-H), 5.98 (1 H, d, *J* 15.5, crotonoyl COC*H*), 6.17–6.28 (2 H, m, 7-H and crotonoyl COCHC*H*), 6.81 (1 H, d, *J* 15.0, crotonoyl COC*H*), 7.15–7.27 (1 H, m, crotonoyl COCHC*H*), 7.35 (1 H, d, *J* 9.5, N*H*), 7.45–7.58 (3 H, m, ArH) and 7.81–7.87 (2 H, m, ArH); δ_C($CDCl_3$; 360 MHz) 16.9 (3-CH_3), 18.4 and 18.7 (crotonoyl CH_3), 52.5 (6-C), 59.0 (7-C), 70.7 (CO_2CH_3), 118.3 (3-C), 120.3 (crotonoyl COCH*C*H, 121.9 (crotonoyl COCH*C*H), 124.3 (4-C), 127.3 (arom. *C*H, 2 C), 128.7 (arom. *C*H, 2 C), 132.3 (arom. *C*H), 132.5 (arom. quat. C), 137.3 (crotonoyl CO*C*H), 149.9 (crotonoyl CO*C*H) and 151.0, 161.7, 161.8, 163.5 and 166.7 (CO) (Found: C, 58.1; H, 5.0; N, 5.85. Calc. for $C_{24}H_{24}N_2O_7S$: C, 59.49; H, 4.99; N, 5.78%).

Methyl 7β-benzamido-2α-sorbyl-3-*c*-deacetoxycephalosporanate 1β-oxide 8. 55%, mp 173–176 °C; ν_{max}(KBr)/cm^{-1} 1783, 1728, 1642 and 1526; δ_H(200 MHz; [D_6]DMSO) 1.87 (3 H, d, *J* 6.0, sorbyl CH_3), 1.96 (3 H, s, 3-CH_3), 3.84 (3 H, s, CO_2CH_3), 4.67 (1 H, d, *J* 4.5, 6-H), 5.80 (1 H, s, 2-H), 5.99–6.13 (2 H, m, 7-H and sorbyl COC*H*), 6.30–6.57 (3 H, m, sorbyl COCH-C*H*C*H*C*H*), 7.44–7.67 (3 H, m, ArH), 7.84 (2 H, d, *J* 7.0, ArH) and 8.66 (1 H, d, *J* 7.5, N*H*) (Found: C, 57.0; H, 5.3; N, 6.1; S, 7.4. Calc. for $C_{22}H_{22}N_2O_6S$: C, 59.72; H, 5.01; N, 6.33; S, 7.19%).

Methyl 7β-benzamido-2α-cinnamoyl-3-*c*-deacetoxycephalosporanate 1β-oxide 9. 70%, mp 161–164 °C; ν_{max}(KBr)/cm^{-1} 1790, 1729, 1653 and 1522; δ_H(360 MHz; $CDCl_3$) 2.21 (3 H, s, 3-CH_3), 3.94 (3 H, s, CO_2CH_3), 4.83 (1 H, d, *J* 4.5, 6-H), 5.09 (1 H, s, 2-H), 6.32 (1 H, dd, J_1 4.5, J_2 10.0, 7-H), 6.96 (1 H, d, *J* 16.0, COC*H*), 7.22–7.26 (2 H, m, COCHC*H* and ArH), 7.41–7.55 (6 H, m, ArH), 7.60–7.63 (1 H, m, ArH) and 7.77–7.84 (3 H, m, ArH and N*H*); δ_C(360 MHz; $CDCl_3$) 19.8 (3-CH_3), 52.7 (6-C), 59.1 (7-C), 65.5 (2-C), 71.2 (CO_2CH_3), 122.1 (3-C), 123.5 (arom. CH), 124.1 (4-C), 127.3 (arom. CH, 2 C), 128.7 (arom. CH, 2 C), 129.2 (arom. CH, 2 C), 129.3 (arom. CH, 2 C), 132.3 (arom. CH), 132.4 (COCH*C*H) 132.5 and 133.1 (arom. quat. C) and 148.3 (CO*C*HCH), 161.5, 163.3 and 166.8 (CO) (Found: C, 61.3; H, 4.5; N, 6.0. Calc. for $C_{25}H_{22}N_2O_6S$: C, 62.75; H, 4.63; N, 5.85%).

Compounds shown in Scheme 2

All of the following compounds were prepared according to the above general procedure at −25 to −30 °C with the appropriate reagent ($BrCH_2CH{=}CH_2$, $BrCH_2CO_2Et$ or sorbyl chloride. The separation of the reaction mixture was performed with SiO_2 column chromatography (10 : 1 ⟶ 3 : 1 gradient technique).

Benzhydryl 2α-allyl-7β-(phenoxyacetamido)cephalosporanate 1β-oxide 2a. Mp 166–168 °C; ν_{max}(KBr)/cm^{-1} 3378, 1798, 1734, 1652 and 1496; δ_H(200 MHz; [D_6]DMSO) 1.93 (3 H, s, 3-CH_2OCOCH_3), 2.12–2.28 (1 H, m, 2-CH_2), 2.49–2.67 (1 H, m, 2-CH_2), 4.17 (1 H, dd, J_1 4.5, J_2 9.5, 2-CH_2CH=C*H*H), 4.69 (2 H, s, PhOCH_2CO), 4.72 and 4.89 (2 H, AB quartet, *J* 13.0, 3-CH_2), 5.13 (1 H, s, 2-H), 5.14 (1 H, d, *J* 5.0, 6-H), 5.09–5.22 (1 H, m, 2-CH_2CH=CH*H*), 5.73–5.94 (1 H, m, 2-CH_2C*H*=CH_2), 6.19 (1 H, dd, J_1 5.0, J_2 10.0, 7-H), 6.93–7.03 (5 H, m, ArH), 7.27–7.50 (11 H, m, ArH and CO_2CHPh_2) and 8.16 (1 H, d, *J* 10.0, N*H*) (Found: C, 64.5; H, 5.3; N, 4.6. Calc. for $C_{34}H_{32}N_2O_8S$: C, 64.96; H, 5.13; N, 4.46%).

Benzhydryl 4-allyl-7β-phenoxyacetamido-Δ²-cephalosporanate 1β-oxide 3a. Mp 114–116 °C; ν_{max}(KBr)/cm^{-1} 3374, 1784, 1746, 1638 and 1438; δ_H(200 MHz; [D_6]DMSO) 1.64 (3 H, s, 3-CH_2OCOCH_3), 2.85–3.13 (2 H, m, 4-CH_2CH=CH_2), 3.50–3.70 (1 H, m, 4-CH_2CH=CH_2), 4.66 (2 H, s, PhOCH_2CO), 4.69 and 4.58 (2 H, AB quartet, *J* 13.0, 3 CH_2), 5.06 (1 H, d, *J* 4.5, 6-H), 5.07 (1 H, s, 2-H), 5.00–5.16 (1 H, m, 4-CH_2CH=CH_2), 5.73 (1 H, dd, J_1 4.5, J_2 9.5, 7-H), 5.80–5.89 (1 H, m, 4-CH_2-C*H*=CH_2), 6.88 (1 H, s, CO_2CHPh_2), 6.95–7.03 (5 H, m, ArH), 7.28–7.42 (10 H, m, ArH) and 8.26 (1 H, d, 9.5, N*H*) (Found: C, 65.0; H, 5.1; N, 4.5. Calc. for $C_{34}H_{32}N_2O_8S$: C, 64.85; H, 5.13; N, 4.46%).

Benzhydryl 2,2-diallyl-7β-(phenoxyacetamido)cephalosporanate 1β-oxide 4a. Mp 53–55 °C; ν_{max}(KBr)/cm^{-1} 3396, 1794, 1748 and 1496; δ_H(200 MHz; $CDCl_3$) 1.69 (3 H, s, 3-CH_2OCOCH_3), 2.80–2.92 (1 H, m, 2-CH_2CH=CH_2), 3.20–3.50 (2 H, m, 2-CH_2CH=CH_2), 3.80–3.91 (1 H, m, 2-CH_2CH=CH_2), 4.60 (2 H, s, PhOCH_2), 4.65 (1 H, d, *J* 5.0, 6-H), 4.61 and 4.72 (2 H, AB quartet, *J* 15.0, 3-CH_2), 5.18–5.27 (4 H, m, 2-CH_2-CH=CH_2), 5.8 (1 H, dd, J_1 5.0, J_2 10.5, 7-H), 5.69–5.85 (2 H, m, 2-CH_2C*H*=CH_2), 6.90–7.06 (5 H, m, ArH), 7.24–7.47 (11 H, m, ArH and CO_2CHPh_2) and 8.07 (1 H, d, *J* 10.5, N*H*); δ_C(200 MHz; $CDCl_3$) 19.8 (3-CH_2OCOCH_3), 28.4 (2P-CH_2), 35.3 (2-CH_2), 58.8 (6-C), 59.0 (2-C), 65.0 (7-C), 65.0 (7-C), 66.4 (3-CH_2), 66.8 (PhOCH_2), 79.5 (CO_2CHPh_2), 114.8 (2 C, allylic CH), 118.3 and 120.5 (3- and 4-C), 138.0 and 138.5 (arom. quat. C), 122.1, 126.7, 126.9, 128.7, 128.9, 129.5 and 131.6 (15 C, arom. CH), 139.6 and 142.0 (2-CH_2CH=*C*H_2), 156.7 (arom. C–O) and 162.7, 165.4, 168.1 and 169.2 (CO).

Benzhydryl 2α-allyl-3-*c*-deacetoxy-7β-(phenoxyacetamido)-cephalosporanate 1β-oxide 2b. Mp 140–144 °C; ν_{max}(KBr)/cm^{-1} 3362, 1778, 1742, 1494 and 1228; δ_H(200 MHz; [D_6]DMSO) 1.77 (3 H, s, 3-CH_3), 2.03–2.20 (1 H, m, 2-CH_2), 2.84–2.96 (1 H, m, 2-CH_2), 3.80–3.90 (1 H, m, 2-CH_2CH=CH_2), 4.53 (2 H, s, PhOCH_2), 4.55 (1 H, s, 2-H), 5.13–5.19 (1 H, m, 2-CH_2-CH=CH_2), 5.20 (1 H, d, *J* 4.5, 6-H), 5.87 (1 H, dd, J_1 4.5, J_2 10.5, 7-H), 5.90–6.00 (1 H, m, 2-CH_2C*H*=CH_2), 6.69 (1 H, s, CO_2CHPh_2), 6.91–7.04 (5 H, m, ArH), 7.25–7.51 (10 H, m, ArH) and 8.28 (1 H, d, *J* 10.5, N*H*); δ_C(200 MHz; $CDCl_3$) 19.3 (3-*C*H_3), 35.2 (2-*C*H_2CH=CH_2), 58.4 (7-C), 60.8 (2-C), 64.9 (6-C), 66.9 (PhO*C*H_2), 79.5 (CO_2CHPh_2), 119.1 (3-C), 119.8 (4-C), 125.0 (2-CH_2CH=*C*H_2), 114.7, 121.9, 126.8, 127.0, 127.4, 127.9, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 129.5, 130.9 and 131.7 (15 C, arom. CH), 138.3 and 138.4 (benzhydryl arom. quat. C), 146.4 (2-CH_2*C*H=CH_2), 156.9 (PhO arom. quat. C–O) and 168.4, 166.4 and 163.7 (CO) (Found: C, 67.2; H, 5.5; N, 5.0. Calc. for $C_{32}H_{30}N_2O_6S$: C, 67.35; H, 5.30; N, 4.91%).

Benzhydryl 4-allyl-3-*c*-deacetoxy-7β-(phenoxyacetamido)-Δ²-cephalosporanate 1β-oxide 3b. Mp 125–130 °C; ν_{max}(KBr)/cm^{-1} 3372, 1782, 1740, 1494 and 1216; δ_H(200 MHz; $CDCl_3$) 1.64 (3 H, s, 3-CH_3), 2.72–2.95 (1 H, m, 4-CH_2CH=CH_2), 3.20–3.30 (1 H, m, 4-CH_2CH=CH_2), 3.80–3.90 (1 H, m, 4-CH_2CH=CH_2), 4.53 (1 H, s, 2-H), 4.56 (1 H, d, *J* 4.5, 6-H), 5.08 (2 H, s, PhOCH_2), 5.10–5.20 (1 H, m, 4-CH_2CH=CH_2), 5.84 (1 H, dd, J_1 4.5, J_2 10.5, 7-H), 5.64–6.14 (1 H, m, 4-CH_2C*H*=CH_2), 6.92–7.04 (5 H, m, ArH), 7.24–7.50 (11 H, m, ArH and CO_2CHPh_2) and 8.19 (1 H, d, *J* 10.5, N*H*); δ_C(200 MHz; $CDCl_3$) 14.3 (3-*C*H_3), 35.0 (4-*C*H_2CH=CH_2), 5.85 (7-C), 65.4 (6-C), 66.7 (4-C), 66.9 (PhO*C*H_2), 79.2 (CO_2CHPh_2), 117.6 (2-C), 118.6 (3-C), 121.9 (4-CH_2CH=*C*H_2), 114.8, 117.6, 118.6, 121.9, 123.4, 126.7, 126.9, 128.5, 128.8, 128.86, 131.4, 131.5 and 135.0 (15 C, arom. CH), 138.3 and 138.4 (arom. quat. C), 138.9 (4-CH_2CH=CH_2), 156.9 (PhO*C*H) and 163.6, 166.8 and 168.3 (CO) (Found: C, 66.4; H, 5.2; N, 4.3. Calc. for $C_{32}H_{30}N_2O_6S$: C, 67.35; H, 5.30; N, 4.91%).

Benzhydryl 2α-ethoxycarbonylmethyl-7β-(phenoxyacetamido)cephalosporanate 1β-oxide 2c. Mp 171–173 °C; ν_{max}(KBr)/cm^{-1} 3388, 1794, 1730, 1524 and 1386; δ_H(200 MHz; [D$_6$]DMSO) 1.18 (3 H, t, *J* 7.1, 2-CH$_2$CO$_2$CH$_2$C*H*$_3$), 1.89 (3 H, s, 3-CH$_2$OCOC*H*$_3$), 2.6 (1 H, dd, J_1 18.5, J_2 9.0, 2-C*H*$_2$), 2.95 (1 H, dd, J_1 18.5, J_2 3.5, 2-C*H*$_2$), 4.10 (2 H, q, *J* 7.0, 2-CH$_2$CO$_2$C*H*$_2$CH$_3$), 4.22 (1 H, dd, J_1 3.5, J_2 9.0, 2-H), 4.69 (2 H, s, PhOC*H*$_2$), 4.68 and 4.90 (2 H, AB quartet, *J* 13.0, 3-C*H*$_2$), 5.14 (1 H, d, *J* 5.0, 6-H), 6.19 (1 H, dd, J_1 5.0, J_2 9.5, 7-H), 6.92–7.01 (4 H, m, ArH), 7.26–7.51 (12 H, m, ArH and CO$_2$C*H*Ph$_2$) and 8.21 (1 H, d, *J* 9.5, N*H*) (Found: C, 62.6; H, 5.0; N, 4.0. Calc. for $C_{35}H_{34}N_2O_{10}S$: C, 62.30; H, 4.79; N, 4.15%).

Benzhydryl 7β-phenoxyacetamido-2α-sorbylcephalosporanate 1β-oxide 2d. Mp 187–190 °C; ν_{max}(KBr)/cm^{-1} 1800, 1734, 1700 and 1630; δ_H(200 MHz; CDCl$_3$) 1.90 (3 H, s), 1.90 (3 H, d, *J* 12.0, sorbyl C*H*$_3$), 4.56 (2 H, s, PhOC*H*$_2$), 4.69 (1 H, d, *J* 4.5, 6-H), 4.78 (1 H, d, *J* 6.0, 3C*H*$_2$), 4.87 (1 H, s, 2-H), 5.20–5.36 (1 H, m, sorbyl CH), 5.20 (1 H, d, *J* 6.0, 3-C*H*$_2$), 6.15–6.50 (4 H, m, 7-H and sorbyl CH), 6.89–7.13 (4 H, m, ArH), 7.26–7.52 (12 H, m, ArH and CO$_2$C*H*Ph$_2$) and 7.74 (1 H, d, *J* 11.0, N*H*) (Found: C, 64.0; H, 5.1; N, 4.2. Calc. for $C_{37}H_{34}N_2O_9S$: C, 65.09; H, 5.02; N, 4.10%).

Benzhydryl 3-*c*-deacetoxy-7β-phenoxyacetamido-2α-sorbylcephalosporanate 1β-oxide 2e. Mp 106–107 °C; ν_{max}(KBr)/cm^{-1} 3406, 1796, 1726, 1494 and 1216; δ_H(200 MHz; CDCl$_3$) 1.97 (3 H, d, *J* 4.0, sorbyl C*H*$_{34}$), 2.10 (3 H, s, 3-C*H*$_3$), 4.55 (2 H, s, PhOC*H*$_2$), 4.74 (1 H, d, *J* 5.0, 6-H), 4.90 (1 H, s, 2-H), 6.15 (1 H, dd, J_1 5.0, J_2 10.5, 7-H), 6.18–6.51 (4 H, m, sorbyl CH), 6.89–7.11 (5 H, m, ArH), 7.26–7.52 (11 H, m, ArH and CO$_2$C*H*Ph) and 7.79 (1 H, d, *J* 10.5, N*H*) (Found: C, 62.9; H, 5.1; N, 4.5. Calc. for $C_{35}H_{32}N_2O_7S$: C, 67.29; H, 5.16; N, 4.48%).

Benzhydryl 3-*c*-deacetoxy-7β-phenoxyacetamido-2,2-disorbylcephalosporanate 1β-oxide 4e. Mp 135–145 °C; δ_H(200 MHz; CDCl$_3$) 1.87 (3 H, d, *J* 6.3, sorbyl C*H*$_3$), 1.92 (3 H, d, *J* 5.0, sorbyl C*H*$_3$), 2.17 (3 H, s, 3-C*H*$_3$), 4.61 (2 H, s, PhOC*H*$_2$), 4.73 (1 H, d, *J* 4.5, 6-H), 5.82–5.96 (2 H, m, sorbyl H), 6.03 (1 H, dd, J_1 4.5, J_2 10.0, 7-H), 6.10–6.30 (4 H, m, sorbyl H), 6.47–6.84 (2 H, m, sorbyl H), 6.92–7.09 (4 H, m, ArH), 7.26–7.50 (12 H, m, ArH and CO$_2$C*H*Ph$_2$) and 7.88 (1 H, d, *J* 10.0, N*H*); δ_C(200 MHz; CDCl$_3$) 16.7, 17.5 and 18.8 (CH$_3$), 57.4 (7-C), 66.8 (PhO*C*H$_2$), 70.5 (6-C), 79.7 (CO$_2$C*H*Ph$_2$), 115.6, 119.2, 122.1, 129.4, 130.5, 138.3, 143.1 and 149.3 (sorbyl CH), 120.4 (4-C), 124.0 (3-C), 114.8, 126.9, 127.9, 128.4 and 129.7 (arom. C), 133.2 and 134.9 (arom. quat. C), 139.4 (2-C), 151.8 (arom. C–O) and 156.9, 160.6, 163.0, 168.6 and 171.1 (CO) (Found: C, 67.8; H, 5.2; N, 4.1. Calc. for $C_{41}H_{38}N_2O_8S$: C, 68.51; H, 5.29; N, 3.90%).

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