Syntheses of (6*S*,7*S*)- and (6*S*,7*R*)-deacetoxycephalosporanic acids from 6-aminopenicillanic acid

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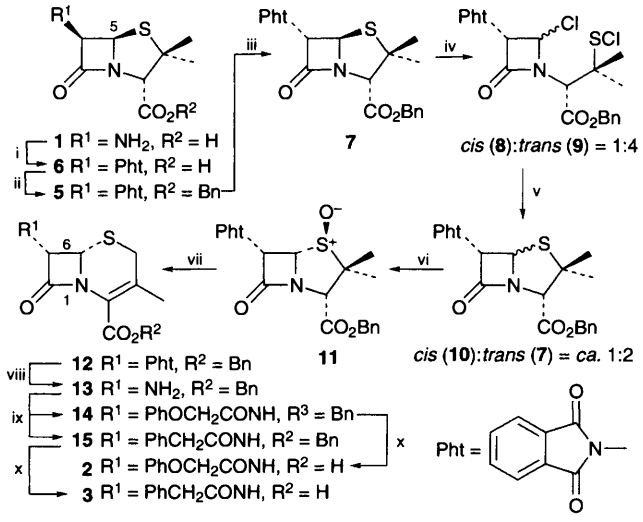
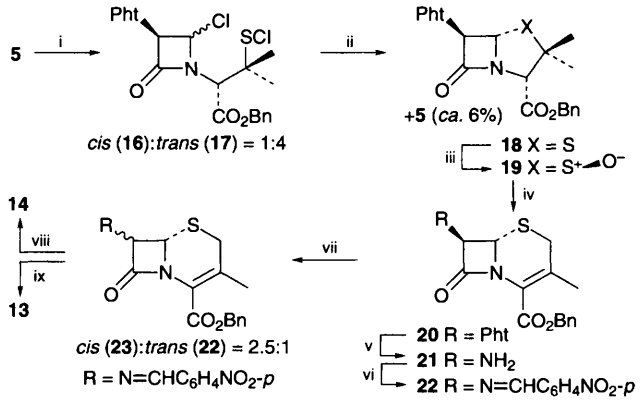
Two practical (*i.e.* applicable to multigram scale synthesis) approaches to (6*S*,7*S*)-cephalosporins (*i.e.* the enantiomers of naturally occuring cephalosporins) and the (6S)-epimers of cephalosporins from readily available (2*S*,5*R*,6*R*)-6-aminopenicillanic acid 1 are described.

In connection with our studies on the physical properties of β-lactams and their inhibition of β-lactamases we required methods for the preparation of (6*S*,7*S*)-cephalosporins, *i.e.* the enantiomers of the naturally occurring (6*R*,7*R*)-cephalosporins and (6*S*,7*R*)-cephalosporins. Here we report the first synthesis of the (6*S*,7*S*)-deacetoxycephalosporanic acids, **2** and **3**, from 6-aminopenicillanic acid (6-APA) **1**. The two successful approaches, which differ in the relative timing of the inversion of the stereochemistry at the C-5 and C-6 positions of the penicillin nucleus, are summarised in Schemes 1–3. In the first approach, epimerization of the C-6 and then C-5 positions was achieved prior to the penam sulfoxide–cephem rearrangement (Scheme 1). In the second approach (Schemes 2 and 3) the stereochemistry at the C-5 position was inverted prior to the ring expansion whereas that of the C-6 position (corresponding to the C-7 position of the cephem nucleus) was inverted subsequent to the rearrangement. A practical synthesis of (6*S*,7*R*)-deacetoxycephalosporanic acid **4** is also described (Scheme 4).[1]

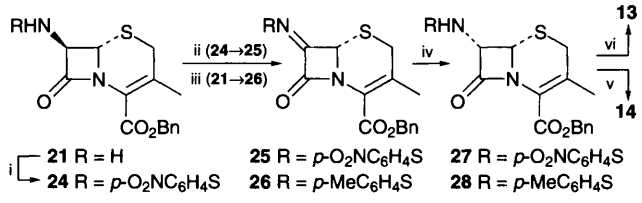
In the first approach (Scheme 1), base-promoted epimerization of the C-6 position of protected penam **5** (synthesised from **1** *via* **6**[2]) was readily accomplished using a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[3] to give its (6*S*)-epimer **7**.† Reaction of penicillin **7** with one equivalent of chlorine followed by treatment with $SnCl_2$ according to the Kukolja procedure[4] gave a mixture of starting material **7** and the



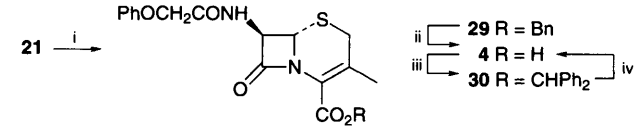
Scheme 1 *Reagents and conditions*: i, $PhtCO_3Et$, Na_2CO_3, H_2O, room temp., 2 h, 49%.; ii, $PhCH_2Br$, Et_3N, DMF, room temp., 6 h, 72%; iii, DBU (cat.), CH_2Cl_2, room temp., 90 min, 98% or NaH (1 equiv.) THF, room temp., 17 h, 85%; iv, Cl_2 (1 equiv.), CH_2Cl_2, CCl_4, room temp., 30 min; v, $SnCl_2$ (1.06 equiv.), THF, room temp., 2 h; vi, O_3, Me_2CO 0 °C then chromatographic separation, 25% over three steps (64% if based on recovered 7); vii, *p*TSA (cat.), DMF, 100 °C, 90 min, 50%; viii, $N_2H_4{\cdot}H_2O$, DMF, −15 °C, 30 min, 47%; ix, RCO_2H, DCC, THF, room temp., 2 h, 85% (R = $PhCH_2$), 98% (R = $PhOCH_2$); x, $AlCl_3$ (3 equiv.), PhOMe, DCM, $MeNO_2$, room temp., 8 h, 86% (R = $PhCH_2$), 94% (R = $PhOCH_2$)



Scheme 2 *Reagents and conditions*: i, Cl_2 (1 equiv.), CH_2Cl_2, CCl_4, room temp., 30 min. ii, $SnCl_2$ (1.06 equiv.), THF, room temp., 2 h, 93% over two steps; iii, MCPBA, $CHCl_3$, 0 °C, 1 h, 75%; iv, *p*TSA, DMF, 100 °C, 8 h, 33%; v, $N_2H_4{\cdot}H_2O$, DMF, −15 °C, 30 min, 40%; vi, *p*-nitrobenzaldehyde, $MgSO_4$, CH_2Cl_2, room temp., 8 h, 83%; vii, PhLi, THF then DMF and AcOH, −78 °C; viii, $PhOCH_2COCl$, CH_2Cl_2, room temp., 10 h, 45% over two steps from **22**; ix, *p*TSA (1.5 equiv.), H_2O (15 equiv.), EtOAc, room temp., 30 min; then crystallization from reaction mixture followed by $NaHCO_3$, 36% over two steps from **22**



Scheme 3 *Reagents and conditions*: i, *p*-nitrobenzenesulfenyl chloride, K_2CO_3, CH_2Cl_2, 0 °C, 1 h, 81%; ii, active MnO_2, C_6H_6, room temp., 1 h, 51%; iii, toluene-*p*-sulfenyl chloride (3 equiv.), propylene oxide (35 equiv.), 4 Å molecular sieves, CH_2Cl_2, 0 °C → room temp., 3 h, 75%; iv, $NaBH_4$, THF, Me_2SO, 0 °C, 10 min, 52% (**27** from **25**) or 30 min, 50% (**28** from **26**); v, $PhOCH_2COCl$, CH_2Cl_2, 0 °C, 90 min, 75%, from **27** and 82% (from **28**); vi, KI, CH_2Cl_2, MeOH, AcOH, 0 °C → room temp., 2 h, 65% (from **27**) and 75% (from **28**)



Scheme 4 *Reagents and conditions*: i, $PhOCH_2CO_2H$, DCC, THF, room temp., 2 h, 89%; ii, $AlCl_3$ (3 equiv.), PhOMe, CH_2Cl_2, $MeNO_2$, room temp., 8 h; iii, Ph_2CN_2, CH_2Cl_2, room temp., 60% over two steps; iv, $AlCl_3$ (3 equiv.), PhOMe, CH_2Cl_2, $MeNO_2$, 0 °C, 20 min, 95%

desired (5*S*,6*S*)-penam **10** in a *ca.* 2:1 ratio respectively. Separation of the mixture of penams **7** and **10** was achieved by selective oxidation of the latter with ozone[5] to give sulfoxide **11** which was readily separable from sulfide **7** (which was recycled) by flash chromatography. The higher reactivity of penam **10** towards sulfoxidation with ozone presumably reflects the decreased steric hindrance on the *exo*-face of the molecule relative to penam **7**. Morin ring expansion[6] of sulfoxide **11** afforded (6*S*,7*S*)-cephem **12**. Cleavage of the phthalimido protecting group was achieved using hydrazine[7] and the resultant amine **13** was converted through to amides **14** and **15**.[8] Removal of the benzyl ester protecting group using $AlCl_3$[9] afforded the desired deacetoxycephalosporanic acids **2** and **3**.

In the second approach (Schemes 2 and 3), penicillin **5** was converted to its (5*S*)-epimer **18** by the Kukolja protocol.[2a,4] Subsequent oxidation to (4*S*)-sulfoxide **19** followed by the Morin ring expansion gave (6*S*,7*R*)-cephem **20**. Dephthaloylation with hydrazine afforded free amine **21**. Inversion of the configuration at C-7 was achieved *via* three protocols. In the first, Schiff base **22** derived from amine **21** was converted to a *ca.* 2.5:1 mixture of Schiff bases **23** and **22**, epimeric at C-7, by reaction with phenyllithium followed by the additioin of DMF and quenching with acetic acid.[10] The mixture of Schiff bases **22** and **23** could be hydrolysed to previously obtained amines **13** and **21**,[10a,11] or acylated *in situ* to afford, after chromatographic separation, amide **14**.[11] A variation on this approach (Scheme 3) utilised the inversion of the C-7 stereochemistry of amine **21** by sterically controlled reduction of the appropriate thioximes.[12,13] Thus, amine **21** was converted to *p*-nitrobenzenesulfenamide **24** which was oxidised with active MnO_2 to afford *p*-nitrobenzenesulfenimine **25**.[12] Reduction with $NaBH_4$ gave *cis*-sulfenamide **27** along with a small amount (<5%) of its (7*R*)-epimer **24**. Alternatively, the reaction of amine **21** with 3 equiv. of toluene-*p*-sulfenyl chloride in the presence of propylene oxide and pulverised 4 Å molecular sieves furnished directly thiooxime **26** without the need for oxidation.[13] Reduction of thiooxime **26** with $NaBH_4$ afforded the desired (6*S*,7*S*)-sulfenamide **28**. Again, a small amount (<5%) of the (7*R*)-epimer was detected in the crude reaction mixture by ^1H NMR. Sulfenamides **27** and **28** could be converted either to amine **13** or to amide **14**.[12]

(6*S*,7*R*)-Deacetoxycephalosporanic acid **4** was prepared by acylation of amine **21** followed by debenzylation with $AlCl_3$ (3 equiv. of $AlCl_3$, PhOMe, CH_2Cl_2, $MeNO_2$, room temp., 8 h) (Scheme 4). In contrast to the *cis*-cephems **14** and **15**, the analogous deprotection of the benzyl ester from cephem **29** gave impure acid **4**, which was purified by flash chromatography as its benzyhydryl ester **30** and subsequently cleanly deprotected using $AlCl_3$ (3 equiv. of $AlCl_3$, PhOMe, CH_2Cl_2, $MeNO_2$, 0 °C, 20 min) to afford acid **4**.

Several points merit further discussion. The $SnCl_2$-mediated ring closure[4] of epimeric sulfenyl chlorides **16** and **17** derived from (5*R*,6*R*)-penam **5** gave, as anticipated from previous studies,[2a,4] a mixture of penams **18** and **5**, in which the former was the major product (**18**:**5**, *ca.* 16:1). In contrast, we were pleased to discover that under the same conditions the epimeric sulfenyl chlorides **8** and **9** derived from (5*R*,6*S*)-penam **7** gave a *ca.* 2:1 mixture of the starting material **7** and *cis*-penam **10**. The yield of the desired *cis*-penam **10** was sufficient for the route to be of practical use as selective oxidation of penam **10** enabled recycling of the *trans*-product **7**. The *cis*- and *trans*-benzhydryl and methyl ester analogues of benzyl esters **6** and **7** were also subjected to the Kukolja protocol.[4] High *trans*-selectivity (*trans*:*cis* > 10:1) was observed for naturally configured (2*S*,5*R*,6*R*)-penams (*e.g.* **5**). In the case of their (6*S*)-epimers (*e.g.* **7**) the selectivity was poor (*trans*:*cis*, *ca.* 2:1). For example, treatment of methyl (2*S*,5*R*,6*S*)-6-phthalimidopenicillanate according to the Kukolja protocol gave the starting material and its (5*S*)-epimer in a ratio of 2:1.‡ The ring expansion of *cis*-penam sulfoxide **11** was shown to proceed significantly faster than for *trans*-sulfoxide **19**, presumably reflecting faster formation of the appropriate sulphenic acid intermediate from the less stable *cis*-penam sulfoxide **11**.[14]

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Footnotes

† All compounds were characterised by ^1H and ^{13}C NMR (including assignment of stereochemistry by NOE experiments where appropriate), IR and MS analyses. The elemental compositions of all new isolated compounds (except **24**, **27** and **28** which were analysed by HRMS) were confirmed by combustion analysis. The structures of compounds **10**, **11**, **12**, **13** and **19** were confirmed by single-crystal X-ray crystallographic analysis.

‡ It was previously reported that this experiment resulted in recovery of starting (2*S*,5*R*,6*S*)-material only.[2a]

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