Antipodal forms of cephem derivatives *via* stereochemical manipulations of the cephalosporin nucleus

Francesco De Angelis,*[a] Cristina Mozzetti,[b] Alessandra Di Tullio[a] and Rosario Nicoletti[b]

[a] *Dipartimento di Chimica, Ingegneria Chimica e Materiali, Università dell'Aquila, Coppito, L'Aquila, I-67010 Italy. E-mail: deangelis@axscaq.aquila.infn.it*

[b] *Dipartimento di Chimica,Università di Roma 'La Sapienza', Roma, Italy*

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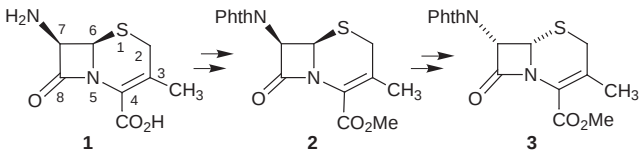
Two complementary strategies have been developed in order to convert a cephalosporin derivative, characterized by the 'natural' absolute configuration of the two stereogenic centers, into its enantiomer, as an optically pure compound.

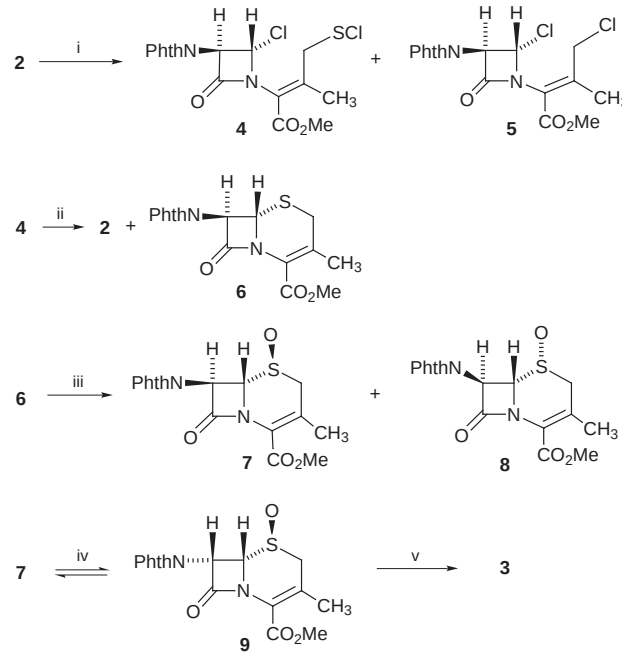
In the field of bioactive molecules asymmetry plays a fundamental role;[1] chiral drugs, in particular, are developed as single enantiomers,[2] since the optical antipode of the active compound must be regarded as a different substance with possible different biological targets. In the course of our studies aimed at developing cephem derivatives with altered biological activity, we sought a means of synthesizing, in homochiral form, bis-epimeric (relative to the stereochemistry of the natural compound) cephalosporins, starting from a commonly available β-lactam precursor (Scheme 1). Totally stereoselective syntheses of β-lactams with altered chirality have already been described by other research groups, but they have principally focused their attention on penam derivatives, usually in mono-epimeric forms, or on monobactam compounds.[3] A route to a cephalosporin enantiomer has been recently disclosed, where 6-aminopenicillanic acid (6-APA) has been used as the starting material.[4] Here we report on two alternative strategies which lead to the cephalosporin enantiomers of natural occurring (6*R*,7*R*)-cephalosporins, starting from 7-aminodesacetoxy-cephalosporanic acid (7-ADCA) **1**. In view of this target we have explored pathways to both epimeric forms, at C-6 and C-7, of the protected cephem derivative **2** obtained from **1**, followed by epimerization of the other stereogenic center to finally produce the cephalosporin antipodal form **3**.

The first strategy we describe here (Scheme 2) for the epimerization at the C-6 position exploits the well-known chlorinolysis of the thiazolidine ring of penicillins first developed by Kukolja,[5] followed by reconstruction of the isomerically modified skeleton.[6] Although this procedure is also cited by other authors,[4,7] and also worked well in our hands on penam derivatives, it failed when, in our case, it was applied on the cephem derivative, leaving the substrate **2** unreacted in the presence of added chloride ion, or it led to decomposition products under forced conditions. After many exploratory reactions, **2** was converted in high yields into a 2 : 3 mixture of the azetidinone sulfenyl chloride **4** and the chloro derivative **5** by reaction with an equimolar amount of chlorine and a slight excess amount of $TiCl_4$, at −15 °C. The two compounds were then isolated by chromatography over deactivated silica gel. In marked contrast to the penam congeners,[5] in our case only the *trans* isomers were produced. It is also worth noting that the allylic sulfenyl chloride **4**, in the presence of chlorine or of a Lewis acid, is highly susceptible to nucleophilic displacement of SCl_2 with formation of the unwanted derivative **5**. This compound in fact can also be readily prepared from **4** by treatment with 1 equiv. of chlorine. On the other hand, **4** formed as the only isolable product when **2**, as a solid powder, was rapidly treated with an excess of freshly distilled sulfuryl chloride, at 0 °C, and practically at the same time the reaction quenched with a large amount of toluene. The ring closure step was performed by treatment of **4** with 1 equiv. of $SnCl_2$ dihydrate, in dioxane, at the reflux temperature for 15 min to give a 1 : 2 mixture of the *cis*/*trans* isomers **2** and **6**, which were separated by chromatography on silica gel.

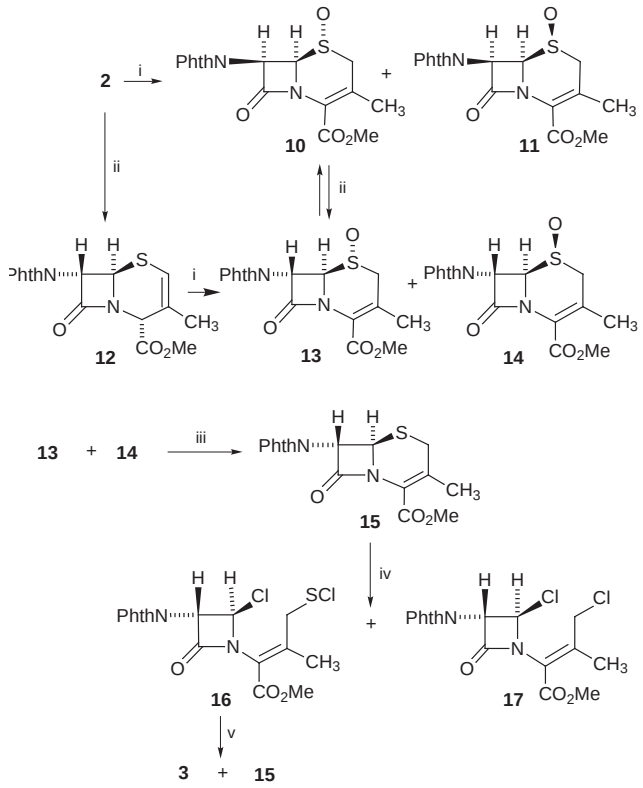


Scheme 1

Oxidation of **6** with MCPBA gave a 1 : 1 mixture of the two sulfoxide epimers **7** and **8**,[8] which were separated by taking advantage of their marked difference in solubility. The (1*R*)-sulfoxide **8**, in contrast to its epimer **7**, is practically insoluble at room temperature in many solvents such as methanol, acetone and THF; **7** in fact was completely recovered as a pure compound by treating the reaction mixture with EtOAc. Compound **7** was then equilibrated by base to partially give the stereoisomer **9** (a 2 : 1 mixture in favour of **7**), with a *cis* arrangement of the β-lactam hydrogens. The equilibrium position between the two epimers, verified also by starting from the *cis* isomer, was slowly reached with Et_3N in CH_2Cl_2, but very rapidly with a stronger base like DBU; in both cases there



Scheme 2 *Reagents and conditions*: i, $Cl_2/TiCl_4$, CH_2Cl_2, −15 °C, 87% (**4** : **5** *ca.* 2 : 3) [or SO_2Cl_2 (instant treatment), 0 °C, to give only **4**, 66%]; ii, $SnCl_2 \cdot 2H_2O$, 1,4-dioxane, reflux, 15 min, 45% (**6** : **2** *ca.* 2 : 1); iii, MCPBA, $CHCl_3$, 25 °C, 3 h, 95% (**7** : **8** *ca.* 1 : 1); iv, DBU, CH_2Cl_2, 25 °C, immediate reaction (**9** : **7** *ca.* 1 : 2); v, PBr_3, CH_2Cl_2, 0 °C, immediate reaction, 52%.



Scheme 3 *Reagents and conditions*: i, MCPBA, $CHCl_3$, 25 °C, 3 h (**10** : **11** *ca*. 9 : 1, 78%; **13** : **14** *ca*. 1 : 1, 84%); ii, DBU, CH_2Cl_2, 25 °C (**2** to **12**, 2 h; **13** : **10**, *ca*. 2:1, immediate reaction); iii, PBr_3, CH_2Cl_2, 0 °C, 10 min, 90%; iv, Cl_2, CH_2Cl_2, −15 °C, 10 min, 70% (**16** : **17** *ca*. 5 : 2)[or SO_2Cl_2 (instant treatment), 0 °C, 60% (**16** : **17** *ca*. 5 : 1)]; v, $SnCl_2{\cdot}2H_2O$, 1,4-dioxane, reflux, 15 min, 47% (**3** : **15** *ca*. 1 : 2).

is no loss of material and the remaining *trans* isomer was quantitatively recovered by chromatography. (1*R*)-Sulfoxide **8**, probably because of its very low solubility even in DMSO, does not seem to undergo equilibration at any observable rate. Finally, reduction of **9** with PBr_3[9] gave the enantiomer **3** of derivative **2** of 7-ADCA as an optically pure compound. As expected, the enantiomers gave equal and opposite CD spectra, thus showing also the stereochemical correctness of the individual reaction steps.[10] It is worth pointing out that the 7-phthalimido group, besides being relatively chemically stable, could play an important role in determining the isomer ratio in the epimerization steps. It is also easily removable,[11] thus giving potential access to pharmacologically useful 7-amidic substitution.

In order to complete the general strategy to the stereochemical manipulation of the cephem nucleus, we have also developed a complementary, which, *mutatis mutandis*, ideally represents the 'mirror image' of the one we have just described (see Scheme 3). Partial epimerization at C-7 was realized by base treatment of the cephalosporin (1*R*)-sulfoxide derivative **10**:[9] **13**, which is the enantiomer of **7**, formed in 65% yield, the remaining 35% being the starting *cis* isomer **10**. More conveniently, complete epimerization at C-7 in **2** occurred by treatment with DBU to give the Δ^2-derivative **12**. Oxidation of **12** to the sulfoxides **13** and **14** was the necessary step in order to obtain retro-isomerization of the double bond to Δ^3. Compound **15**, which is the optical antipode of **6**, was obtained by PBr_3 reduction at the sulfoxide moieties of the two S-1 epimers. According to this procedure, the overall yield from **2** to **15** was practically quantitative.

The enantiomer **16** of the sulfenyl chloride **4** was then obtained (together with **17**) by chlorinolysis (Cl_2 or SO_2Cl_2) of the C-6–S-1 bond. In this case, the presence of $TiCl_4$ was not only unnecessary, but even lowered the reaction rate and yields. Pure **16** then followed the same destiny as its enantiomer **4**: ring closure gave a 2 : 1 mixture of **15** together with, once more, the required enantiomer **3** of the natural cephem derivative **2**. Chromatographic separation afforded **3** as a chemically and optically pure material (overall yield 6.0%, starting from **2**; recovered isomers, to be re-used in the reaction sequel, were not taken into account), which showed identical chemical–physical properties to the sample obtained by the other reaction pathway.[10]

In conclusion, the present work describes a versatile 'circular' strategy, exemplified by two complementary reaction sequences, to convert a natural cephalosporin derivative into its optical antipode. The chemical transformations involved, even if the overall efficiency of the routes is low due to the yields of some stages being poor, appear significative in the cephalosporin chemistry context. Along the reaction paths, in fact, all the possible stereoisomers of cephalosporin sulfides and sulfoxides, susceptible of further chemical elaborations, have been encountered.[12]

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Notes and references

1 E. J. Ariens, *Med. Res. Rev.*, 1986, **6**, 451.
2 S. C. Stinson, *Chem. Eng. News*, 1992, **70**, 46; 1993, **71**, 38.
3 A. Vlietinck, E. Roets, P. Claes, G. Janssen and H. Vanderhaeghe *J. Chem. Soc., Perkin Trans. 1*, 1973, 937; J. E. Baldwin, R. Y. Chan and J. D. Sutherland, *Tetrahedron Lett.*, 1994, **35**, 5519; D. R. Wagle, C. Garai, M. G. Monteleone and A. K. Bose, *Tetrahedron Lett.*, 1988, **29**, 1649; C. Somoza and O. A. Mascaretti, *Tetrahedron*, 1988, **44**, 7007.
4 T. Fekner, J. E. Baldwin, R. M. Adlington and C. J. Schofield, *Chem. Commun.*, 1996, 1989.
5 S. Kukolja, *J. Am. Chem. Soc.*, 1971, **93**, 6267.
6 S. Kukolja, *J. Am. Chem. Soc.*, 1971, **93**, 6269.
7 J. E. Baldwin and D. P. Hesson, *J. Chem. Soc., Chem. Commun.*, 1976, 667; R. G. Micetich, R. Singh, W. O. Merlo, D. M. Tetteh, C. C. Shaw and R. B. Morin, *Heterocycles*, 1984, **22**, 2757.
8 At difference with our case, it is well-known [R. D. G. Cooper and D. O. Spry, in *Cephalosporins and Penicillins, Chemistry and Biology*, ed. E. H. Flynn, Academic Press, New York and London, 1972, p. 209] that oxidation with MCPBA of *N*-phthalimido-*cis*-penam and cephem derivatives affords almost exclusively the (1*R*)-sulfoxide.
9 C. F. Murphy and J. A. Webber, in *Cephalosporins and Penicillins, Chemistry and Biology*, ed. E. H. Flynn, Academic Press, New York and London, 1972, p. 137.
10 Spectral data in agreement with the reported structures were obtained for all compounds. In particular, the *cis* and *trans* arrangements of the β-lactam protons, as well as the chirality at S-1 of the sulfoxide derivatives, were precisely indicated by ^{1}H NMR spectroscopy: P. V. De Marco and R. Nagarajan, in *Cephalosporins and Penicillins, Chemistry and Biology*, ed. E. H. Flynn, Academic Press, New York and London, 1972, p. 330 and pp. 349–353: *Selected data* for **8**: mp = 176–179 °C; $[\alpha]_{365}$ + 238, $[\alpha]_D$ + 1 (*c* 0.2, EtOH); δ_H(200 MHz, $CDCl_3$) 2.38 (s, 3H), 3.28 (AB system, *J* 14, 2H), 3.86 (s, 3H), 5.15 (d, *J* 4, 1H), 5.75 (d, *J* 4, 1H), 7.88 (m, 4H); ν_{max}(Nujol)/cm^{-1} 1787 (br, C=O β-lactam), 1729 (br, C=O ester and imide); *m*/*z* (EI) 358 [M$^+$].
11 S. Kukolja and S. R. Lammert, *J. Am. Chem. Soc*., 1975, **97**, 5582; T. Kamiya, M. Hashimoto, O. Nakaguchi and T. Oku, *Tetrahedron*, 1979, **35**, 323.
12 The only epimer absent in the routes described is the enantiomer of sulfoxide **11**, which can be obtained, together with **9**, by direct oxidation of **3**.

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