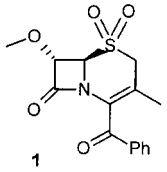
Expeditious Synthesis of 4-(*tert*-Butylcarbonyl)-7α-methoxy-3-methyl-Δ^3-cephem 1,1-Dioxide. Convenient Access to 7-Substituted Analogues

Marco Alpegiani,* Pierluigi Bissolino, Matteo D'Anello, Massimiliano Palladino, Ettore Perrone
Pharmacia & Upjohn, 20014 Nerviano (Milano), Italy
E-mail: marco.alpegiani@eu.pnu.com

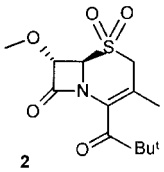
Received 10 November 1997

Abstract: A practical and efficient route leading to the synthesis of 4-(*tert*-butylcarbonyl)-7α-methoxy-3-methyl-Δ^3-cephem 1,1-dioxide (**2**), a key-intermediate in the preparation of potent inhibitors of mammalian serine proteinases, is reported. The new synthetic pathway has allowed easy access to an array of 7-substituted cephem derivatives.

In the preceding paper[1] we pointed out the pivotal role of 4-benzoyl-7α-methoxy-3-methyl-Δ^3-cephem 1,1-dioxide **1** and its 4-*tert*-butylcarbonyl counterpart **2** in the preparation of potent inhibitors of mammalian serine proteinases,[2,3] and described an innovative synthesis to obtain **1**. An improved method of synthesising **2**, and the exploitation of versatile intermediates for the introduction of various substituents at cephem C-7 position, are dealt with in the present paper.



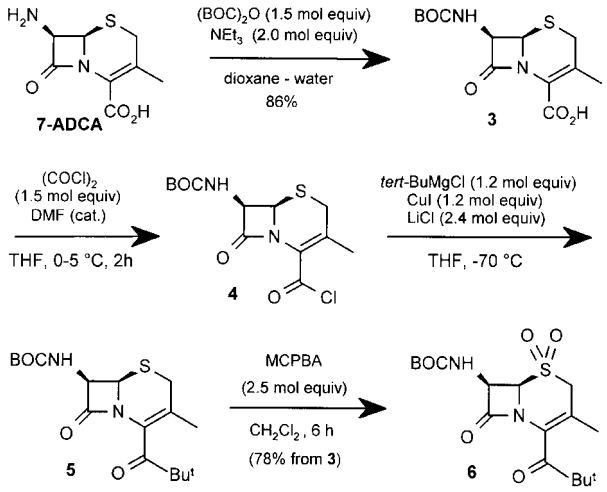
1



2

In previous approaches, when the pivaloyl moiety of cephem **2** was introduced by Grignard reaction of cephem-4-carbonyl chlorides already bearing the methoxy group at C-7α, yields ranged from poor to moderate.[2,4] Holding the electron-withdrawing substituent vicinal to the β-lactam carbonyl responsible for the unsatisfactory result, we planned to postpone the methoxylation step and perform the Grignard reaction on cephem substrates that featured a less reactive β-lactam ring. This plan worked very well indeed, and we were able to convert the cheap and commercially available 7β-amino-3-deacetoxycephalosporanic acid (7-ADCA) into 4-(*tert*-butylcarbonyl)-7α-methoxy-3-methyl-Δ^3-cephem 1,1-dioxide **2** in good overall yield, without need for chromatographic purifications (Scheme 1 and 2).

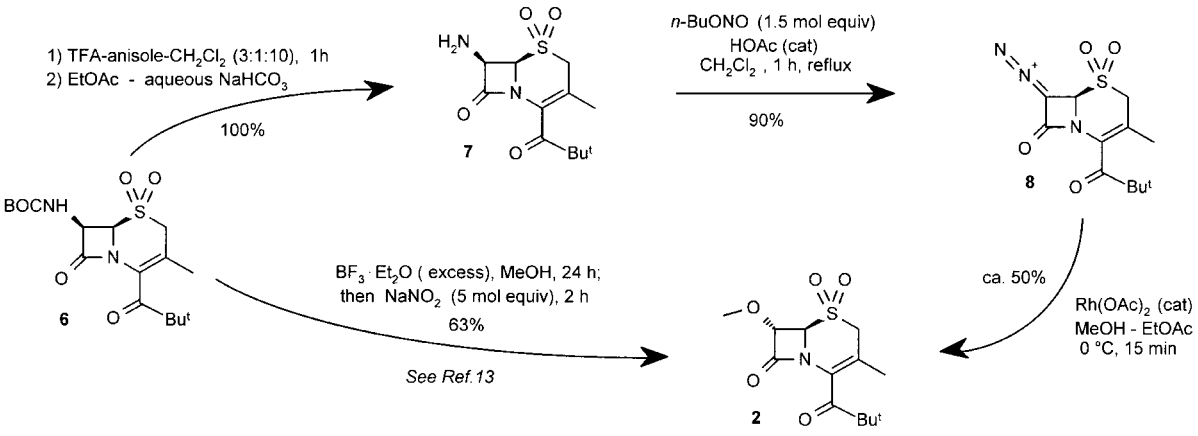
tert-Butoxycarbonylation of the 7-ADCA amino group with *tert*-butylpercarbonate efficiently produced the N-protected cephem-4-carboxylic acid **3**. Acid chloride **4**, obtained from **3** under Vilsmeier conditions, cleanly underwent the crucial reaction with *tert*-butylmagnesium chloride in the presence of copper(I) iodide and lithium chloride (THF, -70 °C) affording the crude ketone **5**,[5] whose peracid oxidation (MCPBA/ CH_2Cl_2) gave the crystalline sulfone **6** (ca. 70% yield from 7-ADCA).



Scheme 1

At this point we faced the problem of replacing the 7β-BOC group of cephem **6** with the 7α-methoxy group of the target cephem **2**. This transformation was initially realised in an efficient but lengthy way, comprising *i)* removal of the amino protecting group under acidic conditions, *ii)* diazotisation with butyl nitrite and *iii)* rhodium catalysed insertion of methanol (Scheme 2).

By applying an optimised procedure developed at Merck for large scale preparation of analogous compounds,[6] the methoxy-deamination step might be expected to proceed more efficiently in terms of yield and stereoselectivity, yet unattractive features of that protocol are the need to operate under strictly controlled conditions and to employ special equipment (flow reactor).



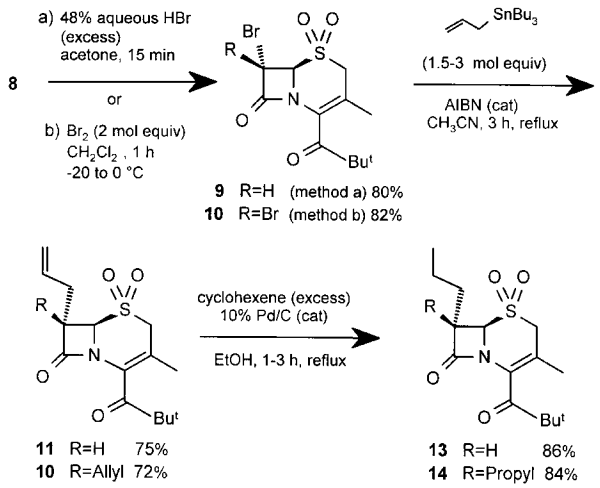
Scheme 2

Seeking a more straightforward and practical access to **2**, we endeavoured to perform deprotection, diazotisation and methoxylation steps in one pot. When **6** was exposed to the action of excess boron trifluoride etherate in methanol (24 h, r.t.)[7] and then to sodium nitrite (2 h), the 7α-methoxy derivative **2** was the preponderant reaction product (Scheme 2), moreover it could be isolated as a white powder after aqueous work-up and crystallisation from diisopropyl ether.[13]

Direct conversion of **6** to **2**, in addition to constituting an impressive short cut, does not entail the handling of potentially sensitive compounds like the diazocephem **8**.

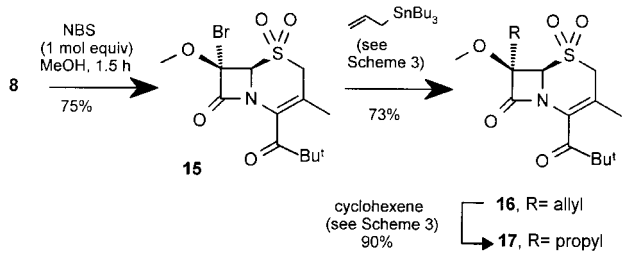
On the other hand, considering the possibility of exploiting the synthetic potential of the diazo function, cephem **8** was judged a useful intermediate for the preparation of novel C-7 substituted cephem sulfones. We aimed at converting, directly or indirectly, the diazo moiety of **8** into alkyl groups, that were expected to improve the stability of the cephem β-lactam moiety.[2]

Prepared in gram scale, **8** was stored for weeks in the fridge without apparent decomposition. Addition of hydrogen bromide or bromine smoothly took place affording 7α-bromo and 7,7-dibromo derivatives **9** and **10**, respectively (Scheme 3). Upon free-radical allylation with allyltributyltin according to the Hanessian methodology,[9] compounds **11** and **12** were obtained. Finally, transfer hydrogenation gave the propyl cephems **13** and **14**.

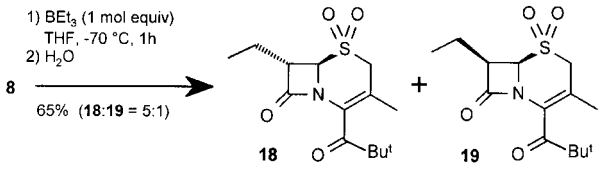


Scheme 3

When **8** was treated with N-bromosuccinimide in methanol,[10] the 7α-bromo-7β-methoxy derivative **15** was produced stereoselectively[11] (Scheme 4). Its conversion to **16** and **17** proceeded uneventfully using the aforementioned protocol.



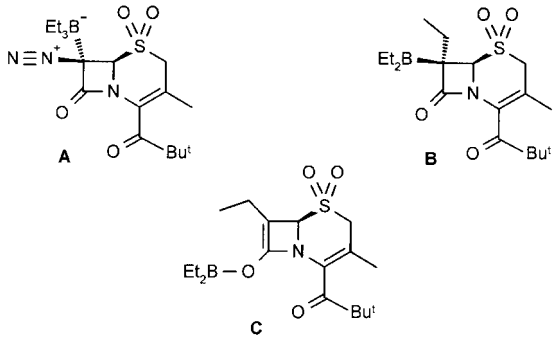
Scheme 4



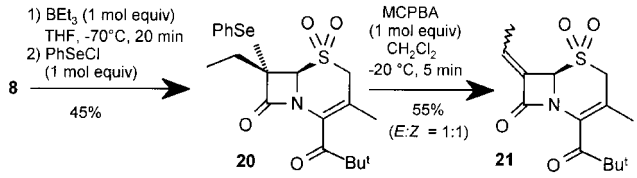
Similarly to the procedure described by Wiering and Wynberg,[12] triethylborane reacted with **8** affording an epimeric mixture of 7-ethyl compounds **18** and **19**, the *trans* isomer being predominant (Scheme 5).

Scheme 5

From a mechanistic point of view, the quaternary boron species **A** might be generated first as the result of Lewis acid - Lewis base interaction; 1,2 alkyl shift from boron to carbon with simultaneous displacement of nitrogen would then give **B**, eventually hydrolysed, possibly through the intermediacy of enolborinate **C**, to **18** and **19**.



We were intrigued by the possibility of intercepting the postulated species **C** with electrophiles other than the proton. While no desired reaction took place when methyl iodide or acetyl chloride were employed, using phenylselenyl chloride the electrophilic phenylselenyl group was selectively delivered to the C-7α position of the cephem nucleus to give **20** in satisfactory yield. The stereochemical outcome, probably originating from attack of the electrophile at the less hindered α-face, was assigned on the basis of NOE experiments.



Scheme 6

Finally, following oxidation with MCPBA (-20 °C), **20** was shown to undergo easy elimination of phenylselenenic acid, affording a 1:1 isomeric mixture of *E* and *Z* 7-ethylenecephems **21**[13] in moderate yield.

Summing up, a practical and efficient route to obtain a useful cephem synthon (*tert*-butyl ketone **2**) has been implemented. A variety of unprecedented C-7 substituted 4-ketocephems was synthesised.

Acknowledgements: We are indebted to Dr. (Mrs) Daniela Borghi (NMR spectra) and Dr. Emanuele Arlandini (MS spectra), and to Mr. Edgardo Poma and Mr. Antonio Fiumanò (technical assistance).

References and Notes

1) Alpegiani, M.; Bissolino, P.; D'Anello, M.; Perrone, E. *Synlett* **1998**, 319.

2) Alpegiani, M.; Bissolino, P.; Corigli, R.; Del Nero, S.; Perrone, E.; Rizzo, V.; Sacchi, N.; Cassinelli, G.; Franceschi, G.; Baici, A. *J. Med. Chem.* **1994**, *37*, 4003.

3) Alpegiani, M.; Bissolino, P.; Corigli, R.; Rizzo, V.; Perrone, E. *BioMed. Chem. Lett.* **1995**, *5*, 687; *ibidem* **1995**, *5*, 691.
Alpegiani, M.; Bissolino, P.; Borghi, D.; Corigli, R.; Del Nero, S.; Perrone, E.; Razzano, G.; Rizzo, V. *BioMed. Chem. Lett.* **1992**, *2*, 1127.

4) Alpegiani, M.; Bissolino, P.; Perrone, E.; Cassinelli, G.; Franceschi, G. *Tetrahedron Lett.* **1991**, *32*, 6207.

5) For analytical purposes a sample was purified by silica gel chromatography (eluting with *n*-hexane/EtOAc mixtures) to afford pure cephem **5**:
IR (KBr) ν_{max} 3320, 1780, 1725(sh), 1695 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (9H, s), 1.45 (9H, s), 1.75 (3H, d, J= 0.5 Hz), 3.09 (1H, d, J= 17.5 Hz), 3.52 (1H, br d, J= 17.5 Hz), 4.97 (1H, d, J= 4.6 Hz), 5.20 (1H, d, J= 9.1 Hz, exch. D_2O), 5.51 (1H, dd, J= 4.6 and 9.2 Hz).

6) Blacklock, T.J.; Butcher, J.V.; Sohar, P.; Lamanec, T.R.; Grabowski, E.J.J. *J. Org. Chem.* **1989**, *54*, 3907.

7) After this time complete conversion of **6** into **7** had occurred (HPLC monitoring).

8) Mother liquor removed minor contaminants together with an appreciable quantity of the C-7 epimer of **2**.

9) Hanessian, S.; Alpegiani, M. *Tetrahedron Lett.* **1986**, *27*, 4857.
Hanessian, S.; Alpegiani, M. *Tetrahedron* **1989**, *45*, 941.

10) Cama, L.D.; Leanza, W.J.; Beattie, T.R.; Christensen, B.G. *J. Amer. Chem. Soc.* **1972**, *94*, 1408.

11) The stereochemical outcome is consistent with the attack of the bromonium ion from the less hindered α-face of diazocephem **8**, and displacement of nitrogen by methanol, with inversion, of the intermediate bromodiazonium ion.[10]

12) Wiering, J.S.; Winberg, H. *J. Org. Chem*. **1976**, *41*, 1574.

13) All new compounds were fully characterised by spectroscopic means. Selected experimental and spectral data are given below:
*7*β*-tert-(Butoxycarbonyl)amino-3-deacetoxycephalosporanic acid* (**3**). Triethylamine (5.6 ml, 40 mmol) was added dropwise to a mixture of 7β-amino-3-deacetoxycephalosporanic acid (7-ADCA, 4.28 g, 20 mmol) in dioxane (80 ml) and water (40 ml). Di-*tert*-butyl dicarbonate (6.6 g, 30 mmol) was then added and the resulting mixture was stirred at r.t. for 6 h before partitioning between diethyl ether and water. The aqueous phase was acidified with 8% HCl and extracted with EtOAc. Following drying over Na_2SO_4 and evaporation of the solvent, a foamy solid was obtained which upon treatment with petroleum ether turned into a white powder (5.4 g, 86% yield). IR (KBr) ν_{max} 3600-2500, 1780, 1710 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 2.00 (3H, s), 3.33 (1H, d, J= 17.8 Hz), 3.49 (1H, d, J= 17.8 Hz), 4.98 (1H, d, J= 4.6 Hz), 5.34 (1H, dd, J= 4.6 and 8.9 Hz), 7.95 (1H, d, J= 8.9 Hz, exch. D_2O).
*7*β*-tert-Butoxycarbonylamino-4-(tert-butylcarbonyl)-3-methyl-*Δ^3*-cephem 1,1-dioxide* (**6**). A solution of **3** (4.08 g, 13 mmol) in dry THF (40 ml) was cooled to 0 °C and treated with oxalyl chloride (1.68 ml, 19.5 mmol) and DMF (70 µl, 0.9 mmol). The resulting solution was stirred for 2 h at 0-5 °C, then it was rotoevaporated to dryness (temperature of the bath <25 °C). The residue was taken up with toluene and carefully evaporated to dryness, affording crude **4** as a brownish powder (ca 4.2 g, 12.6 mmol), which was dissolved in dry THF (40 ml) and cooled to -70 °C. Separately, under a nitrogen blanket, a solution of LiCl (1.31 g, 30.9 mmol) and CuI (2.95 g, 15.5 mmol) in dry THF (20 ml) was prepared. At -70 °C 1M *tert*-butylmagnesium chloride in THF (15.5 ml, 15.5 mmol) was added dropwise. Then, *via cannula*, the cold (-70 °C) solution of acyl chloride **4** in THF was added. After stirring for 30 min at -70 °C, the reaction mixture was poured into diethyl ether and 20% NH_4Cl 1:1. The insoluble material was filtered off. The organic layer was washed twice with brine then dried over Na_2SO_4 and rotoevaporated, yielding crude **5** as a brownish foam (ca. 4.5 g, 12.6 mmol). This product was dissolved in CH_2Cl_2 (60 ml), cooled to -20 °C, and treated with 55% *meta*-chloroperbenzoic acid (9.3 g, 29.6 mmol). The resulting mixture was stirred at r.t. for 6 h. After this time, the precipitated *meta*-chlorobenzoic acid (ca. 3 g) was removed by filtration. The filtrate was sequentially washed with aqueous $NaHSO_3$ and aqueous $NaHCO_3$. After drying (Na_2SO_4), the solution was concentrated *in vacuo*. The waxy residue was treated with CH_2Cl_2-Et_2O to give the title product as a white powder (3.9 g, 78% yield from **3**). IR (KBr) ν_{max} 3400, 1780, 1700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.23 (9H, s), 1.45 (9H, s), 1.72 (3H, s), 3.54 (1H, d, J= 18.2 Hz), 3.88 (1H, d, J= 18.2 Hz), 4.79 (1H, d, J= 3.7 Hz), 5.81 (2H, m).
*4-tert-Butylcarbonyl-7*α*-methoxy-3-methyl-*Δ^3*-cephem 1,1-dioxide* (**2**). Compound **6** (1.17 g) was suspended in CH_3OH (35 ml) and treated with 50% boron trifluoride etherate (6 ml). The suspension was stirred for 24 h at r.t. To the resulting clear solution, cooled to 0 °C, sodium nitrite (1.44 g) was added and stirring was continued for 6 h at r.t. The mixture was poured into EtOAc/water and the organic layer was washed sequentially with aqueous $NaHCO_3$ and brine, then dried (Na_2SO_4). Removal of the solvent left a waxy solid, whose crystallisation from diisopropyl ether yielded the title product as a white powder (0.57 g, 63% yield). IR (KBr) ν_{max} 1780, 1690 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (9H, s), 1.70 (3H, s), 3.51 (2H, d, J= 18.1 Hz), 3.56 (3H, s), 3.93 (2H, d, J= 18.1 Hz), 4.66 (1H, m), 5.16 (1H, d, J= 1.7 Hz).
*7*β*-Amino-4-(tert-butylcarbonyl)-3-methyl-*Δ^3*-cephem 1,1-dioxide* (**7**). TFA (5 ml) was added to a suspension of **6** (1.2 g, 3.1 mmol) in CH_2Cl_2 (5 ml) and anisole (1 ml). After stirring for 1 h at r.t., the solvent was evaporated *in vacuo*. The residue was taken up in EtOAc, washed with aqueous $NaHCO_3$ and brine, then dried (Na_2SO_4). The solvent was rotoevaporated and the residue was treated with a mixture of CH_2Cl_2/diisopropyl ether. The title product was thus obtained as a white powder (0.89 g, 100% yield). IR (KBr) ν_{max} 1785, 1690 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.23 (9H, s), 1.7 l(3H, s), 3.48 (1H, d, J= 18.2 Hz), 3.87 (1H, br.d, J= 18.2 Hz), 4.71 (1H, br.d, J= 4.7 Hz), 4.80 (1H, br.d. J= 4.7 Hz).
4-tert-Butylcarbonyl-7-diazo-3-methyl-Δ^3*-cephem 1,1-dioxide* (**8**). Acetic acid (60 µl) and *tert*-butylnitrite (0.53 ml, 4.5 mmol) were sequentially added to a solution of of **7** (0.86 g, 3.0 mmol) in CH_2Cl_2 (40 ml). The reaction mixture was heated at reflux for 1 h, then poured into aqueous $NaHCO_3$. The organic layer was separated, washed with water and dried over Na_2SO_4. Removal of the solvent *in vacuo*, left an oily residue which upon treatment with petroleum ether turned into a yellow powder (0.8 g, 90% yield).
IR ($CHCl_3$) ν_{max} 2100, 1790, 1700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (9H, s), 1.78 (3H, s), 3.66 (1H, d, J= 17.1 Hz), 3.86 (1H, br.d, J= 17.1 Hz), 5.50 (1H, s).