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HIGHLY STEREOSELECTIVE METHOXYLATION AT THE SEVEN POSITION OF CEPHALOSPORINS

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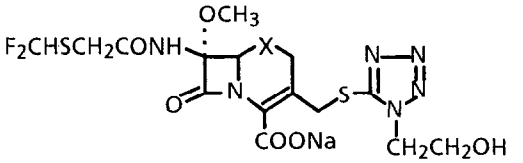
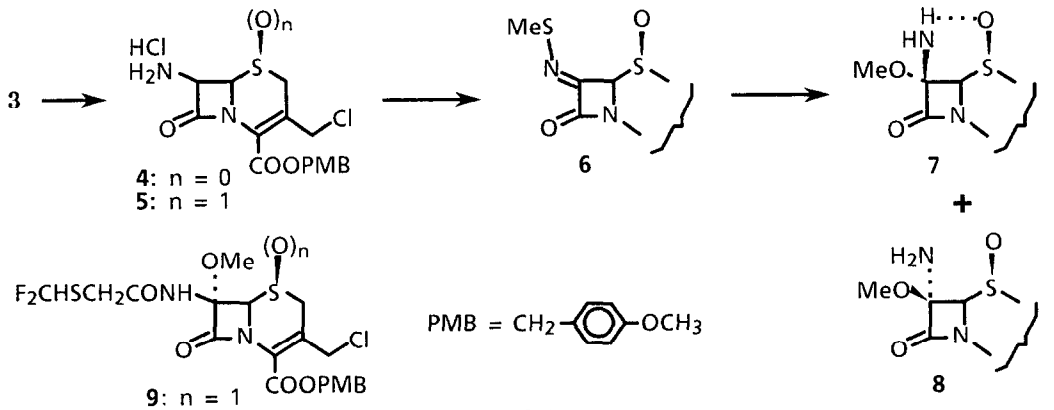
Abstract: Addition reaction of methanol to 7-methylsulfeniminocephem 1β-oxide derivatives (**6** and **12**) under acidic conditions gave exclusively 7β-amino-7α-methoxycephem 1β-oxides (**7**) stabilized by the formation of an intramolecular hydrogen bond between the 7β-amino and the oxygen atom at the 1-position.

In the course of our development studies on Flomoxef (6315-S) **1**, a new member of the 1-oxacephem antibiotics,[1] we had to prepare enough of the corresponding 1-thia congener **2** for study of its biological properties. While several methods were available for introducing a methoxy group into the 7-position of cephalosporins,[2] they were not satisfactory as to the yield of **2** and the preparative procedures. Here we report a new stereoselective methoxylation which consists of an industrially practicable reaction sequence via 7β-amino-7α-methoxycephem 1β-oxide **7** stabilized by the formation of an intramolecular hydrogen bond.



1 : X = O
2 : X = S

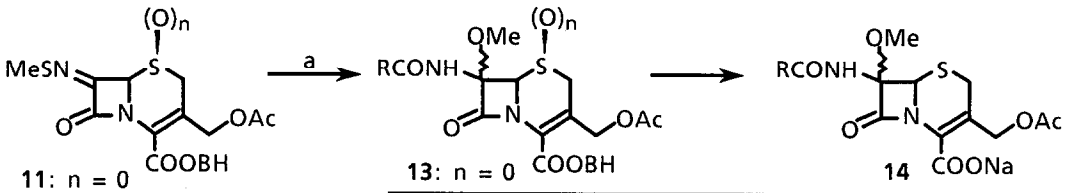
As outlined in Scheme 1, *p*-methoxybenzyl 7β-phenylacetamido-3-chloromethylcephalosporinate **3**[3] underwent a conventional side-chain cleavage reaction to give the amine hydrochloride **4**. On subsequent treatment with 40% AcOOH, **4** was converted to the 1-oxide **5** as a single product, with the orientation of the S–O bond being unambiguously determined as β by phenylacetylation of **5** followed by identification with an authentic sample prepared by oxidation of **3** with *m*-chloroperbenzoic acid.[4] The crystalline sulfenimine **6**[5] could be obtained from **5** in 93% yield according to the procedure developed by the Squibb group[2d] using 3 molar eqiv. of methylsulfenyl chloride. The key reaction for introducing a methoxy group could be achieved stereoselectively by treating **6** with a mixed solution of methanol and T.H.F. containing 2 molar eqiv. of hydrochloric acid at –20°C.



Scheme 1

T.l.c. product analysis of the methoxyamines formed indicated that they were a mixture consisting of a less polar main product (**7**) (Rf = 0.20; benzene:AcOEt = 1:2) and a trace amount of a more polar by-product (**8**) (Rf = 0.05). Acylation of the mixture with difluoromethylthioacetyl chloride gave the desired 7α-methoxy compound (**9**)[6] in the isolated yield of 62.3% from **6**, but the 7β-methoxy epimer[7] in only 1% yield.

Reduction of **9** with a combination of KI and acetyl chloride produced the sulfide **10** in 96% yield. Substitution at C–3′, deprotection and preparation of the sodium salt gave the final product **2**[1] in an overall yield of 32% from the starting material **3**.



11: n = 0
12: n = 1

BH = $CHPh_2$

R = F_2CHSCH_2

	a Temp	Time	13 (Yield)	14 α : β (Ratio)	
12	−20°C	50 min	70.0%	99.9	0.1
11	0°C	40	83.6	87.4	12.6
11	−20°C	40	86.5	83.7	16.3

In order to confirm the advantage of our new method, we carried out the addition reaction of methanol to 7-methylsulfeniminocephem compound **11** and its 1-oxide **12** derived from 7-ACA benzhydryl ester. The methoxyamines formed were immediately acylated to give **13** or the oxide, one of which was reduced to the sulfide **13**. The epimer ratios at the C–7 position were determined by HPLC after their conversion to the sodium carboxylate **14** as shown in Table.

The Table clearly shows that the presence of 1β-oxide markedly raised the stereoselective introduction of the methoxy group from the α side. This high ratio would be attributable to the formation of a hydrogen bond between the 7β-amino and the oxygen of the S-oxide which prevents attack of nucleophiles from the β-side and also plays a role in stabilizing the 7β-amino-7α-methoxycephem compounds formed.[8] In addition, we found no trace of Δ^2 isomers, which have been frequently observed in the methoxylation cases, throughout the reaction sequence given in Scheme 1.

We concluded that our new methoxylation method offers the advantages of high yields, easy handling and broad applicability for a variety of 3′-substituted cephalosporins.

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2. a) J. T. Baldwin, F. J. Urban, R. D. G. Cooper and F. L. Jose, *J. Am. Chem. Soc.*, 1973, **95**, 2401. b) H. Yanagisawa, M. Fukushima, A. Ando and H. Nakano, *Tetrahedron Lett.*, 1975, 2705. c) Y. Sugimura, K. Iino, Y. Iwano, T. Saito and T. Hiraoka, *ibid.*, 1976, 1307. d) E. M. Gordon, H. W. Chang, C. M. Cimarusti, B. Toeplitz and J. Z. Gougoutas, *J. Am. Chem. Soc.*, 1980, **102**, 1690.
3. Purchased from Otsuka Chemical Co., Ltd.
4. R. D. G. Cooper, P. V. Demorco, C. F. Murphy and L. A. Spangle, *J. Chem. Soc. (C)* 1970, 340.
5. Compound **6**; m.p. 174-178°C; ^{1}H-NMR (90 MHz, d_6-DMSO) δ: 2.88 (s, 3H); 3.70 (s, 3H); 3.49 and 3.99 (ABq, J = 18 Hz, 2H); 4.47 and 4.58 (ABq, J = 11.7 Hz, 2H); 5.20 and 5.28 (ABq, J = 11.7 Hz, 2H); 5.68 (s, 1H); 6.91 and 7.37 (ABq, J = 9 Hz, 4H).
6. Compound **9**: m.p. 181-182°C: ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.43 (s, 3H); 3.23-3.77 (m, 2H); 3.53 (s, 2H); 3.77 (s, 3H); 4.22 and 4.58 (ABq, J = 12.6 Hz, 2H); 4.65 (s, 1H); 5.24 (s, 2H); 6.93 (t, J = 56.7 Hz, 1H); 6.87 and 7.33 (ABq, J = 9.0 Hz, 4H); 7.98 (s, 1H).
7. Epimer of Compound **9**: m.p. 143-147°C: ^{1}H-NMR ($CDCl_3$) δ: 3.53 (s, 3H); 3.36 and 3.70 (ABq, J = 18 Hz, 2H); 3.50 (s, 2H); 3.78 (s, 3H); 4.14 and 4.83 (ABq, J = 11.7 Hz, 2H); 4.70 (s, 1H); 5.26 (s, 2H); 6.84 (t, J = 55.5, 1H); 6.87 and 7.35 (ABq, J = 9 Hz, 4H); 8.03 (s, 1H).
8. The similar stabilization was also observed in the preparation of 7β-amino-7α-methoxy-1-oxacephalosporins. Y. Sendo and M. Yoshioka, J. Chem. Soc., Chem. Comm., 1980, 1069.

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