Synthesis of a Dual-Action Cephalosporin: A Novel Approach to 3-Acyloxymethyl-3-cephems

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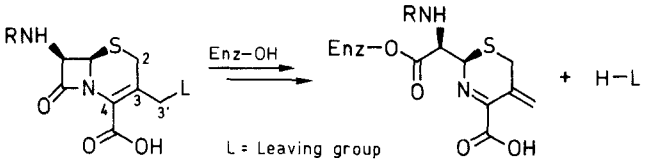
Received 11 December 1991; revised 18 February 1992

A practical synthesis of the dual-action cephalosporin **5** from 7-aminocephalosporanic acid (7-ACA), *S*-benzothiazol-2-yl (2-amino-4-thiazolyl)(methoxyimino)thioacetate (MAEM), and fleroxacin [6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, **3**] is described. Tritylated MAEM prepared in situ was coupled with 7-ACA in dichloromethane followed by hydrolysis of the acetate group to afford the 3-hydroxymethyl-3-cephem **2**. The direct acylation of **2**, which has an unprotected 4-carboxy group, with activated esters of **3** gave mixtures of the desired ester **A (4)** and the lactone **B**. The ratio of these two products was found to depend on the nature of the leaving group of the activated ester used, with the one prepared from cyclohexyl chloroformate favoring the formation of **4**. Ester **4** was isolated in more than 50% overall yield from 7-ACA. Removal of the trityl group afforded the dual-action cephalosporin **5**.

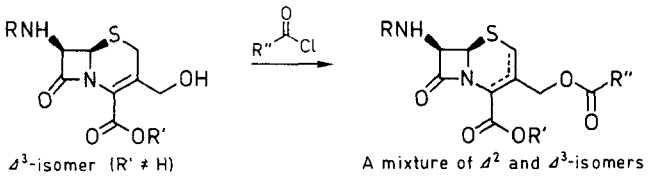
β-Lactamase-promoted opening of the β-lactam ring is the primary mode of inactivation of penicillins and cephalosporins, narrowing the spectrum of antibacterial activity exhibited by these compounds. Since the opening of the β-lactam ring of a cephalosporin leads to release of the 3′-substituent,[1] as depicted below, the incorporation of a leaving group possessing antibacterial activity against organisms which are resistant to third-generation cephalosporins should result in significant expansion of the antibacterial spectrum.



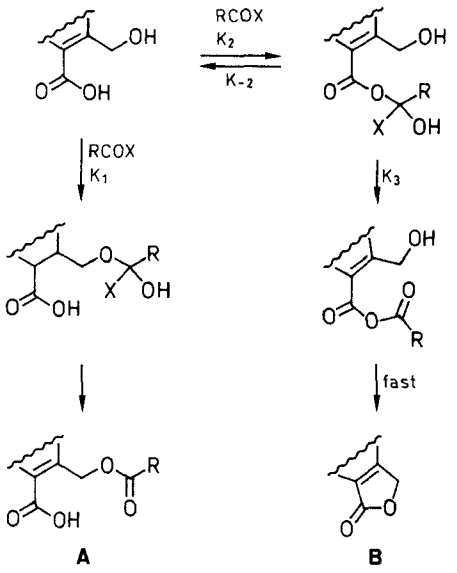
This dual-action concept[2–6] resulted in the preparation of the dual-action cephalosporin **5**[7] which incorporates into its structure both a third-generation cephalosporin acylamino moiety and an ester derived from a third-generation quinolone, fleroxacin **(3)**.[8] Compound **5** is expected to show its biological activity not only by acylating active-site serine residues of the transpeptidases responsible for cross-linking peptidoglycan, but also by DNA gyrase inhibition, the action of the quinolone portion. Compound **5** has indeed shown excellent broad spectrum activity both *in vitro* and *in vivo*[7] and has been selected for clinical development. However, the coupling of the quinolone moiety with the cephalosporin portion had not been an easy task, thus we sought to develop a new strategy to prepare this class of compounds.

The reaction of a 3-hydroxymethyl-3-cephem with an acid chloride routinely gives a mixture of Δ^3- and Δ^2-isomeric products via the double bond migration, even under slightly basic conditions.[9,10] In fact, the Δ^2-isomeric products are often more stable.[11] These isomers are not always easily separated neither by chromatographic methods nor by crystallization. Kaiser and co-workers have reported a two-step sequence to obtain the single Δ^3-isomer from the isomeric mixture[12] in which the mixture is oxidized and at the same time the double bond is isomerized back to the corresponding Δ^3-sulfoxide. Subsequent reduction of the sulfoxide produces only the Δ^3-isomer. Other strategies involve the formation of 3-iodomethyl-3-cephems[13] or 3-diazomethyl-3-cephems.[6] The reaction of a 3-iodomethyl-3-cephem with a carboxylate ion usually gives a small amount of the Δ^2-isomeric product, depending on the basicity of the nucleophilic carboxylate.[5,7,14] Moreover, the yield of the desired ester is often unsatisfactory due to the decomposition of the iodo-compound under the reaction conditions. The use of the diazo compound[6] is not practical because of its multistep preparation.

Our strategy involves the direct acylation of the 3-hydroxymethyl-3-cephem without protecting the 4-carboxy group. Since the deprotonation of this carboxylic acid reduces the acidity of the protons at the C-2 position, it should suppress the formation of the Δ^2-isomeric ester.



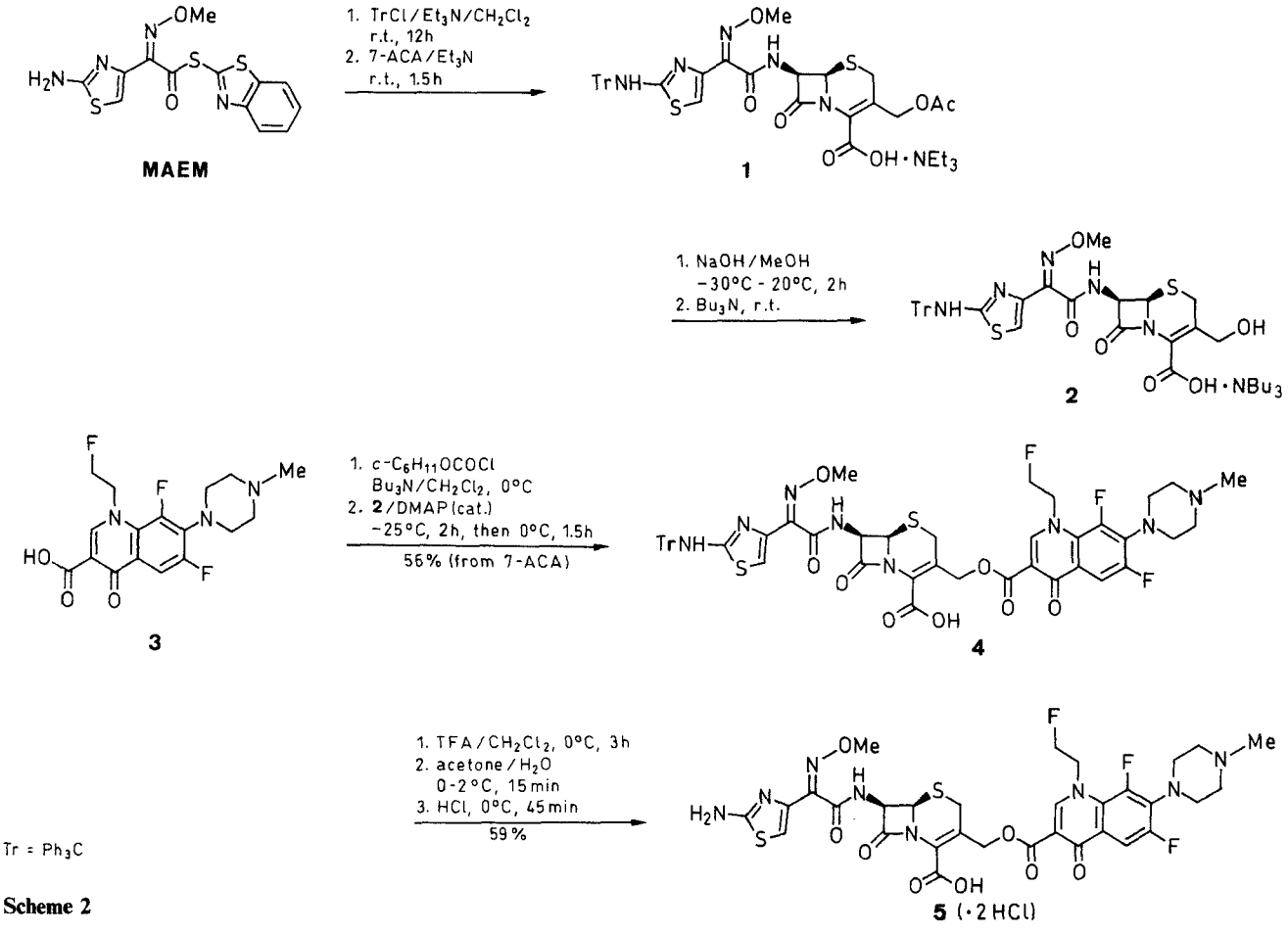
This approach also eliminates the need for protection–deprotection of the 4-carboxy group. However, this could be troublesome due to the facile formation of the five-membered lactone **B**, depicted in Scheme 1, reflecting the fact that a carboxylate is often a better nucleophile than an alcohol. In fact, treatment of such a 3-hydroxymethyl-3-cephem with acetic anhydride was reported to be a good method for the preparation of the corresponding lactone.[15] It has been reported possible, however, to obtain aroyl derivatives of a 3-hydroxymethyl-3-cephem using a large excess of an aroyl chloride in aqueous acetone at pH 8.[15] For the preparation of **5**, use of a large excess of acid chloride cannot be employed, since **3** is the most expensive ingredient. In order to test the applicability of our strategy, the 3-hydroxymethyl-3-cephem **2** was first prepared from 7-ACA.



Scheme 1

The amino group of MAEM was protected by tritylation in dichloromethane and then the addition of 7-ACA afforded the acetate **1** which was isolated as the triethylamine salt. This crude acetate **1** was subjected to hydrolysis at −20 °C in basic aqueous methanol. After acidification, the resulting alcohol slowly lactonized at room temperature; therefore the alcohol **2** was instead isolated as a tributylamine salt, which appears to be more stable and more soluble in organic solvents than the corresponding triethylamine salt.[16]

The mixed anhydride prepared from fleroxacin **3** and pivaloyl chloride was reacted with the alcohol **2** at −20 °C in dichloromethane. 4-Dimethylaminopyridine (DMAP, 0.25 equiv) was essential to promote the reaction. The desired ester **4 (A)** was obtained only as a minor product, the lactone **B** being formed preferentially in the



Scheme 2

ratio of ca. 1:2. No formation of the Δ^2-isomeric ester was observed. Even though the desired coupling product was found to be the minor one, we were actually encouraged by this result. A simplified version of the mechanism is shown in Scheme 1. When X is an acyloxy group such as pivaloyloxy group, it is reasonable to assume k_{-2} to be similar to k_3 since both leaving groups are carboxylates. When X is a good leaving group, such as chloride, k_3 should be much larger than k_{-2}, resulting in the favored formation of the lactone. Conversely, if X is a poor leaving group compared to a carboxylate, the desired ester should form preferentially since k_3 becomes much smaller than k_{-2}. Therefore, the mixed anhydride of **3** was prepared from isobutyl chloroformate. The carbonate should be a poorer leaving group than the carboxylate due to the extra oxygen which increases the electron density. As expected, the formation of the desired ester **4** **(A)** was favored over that of the lactone **B** in the ratio of ca. 4:1, and **4** was isolated by precipitation in 35% yield from 7-ACA. However, use of isobutyl chloroformate has a drawback since a significant amount of the corresponding isobutyl ester forms. In order to circumvent this problem, isopropenyl chloroformate[17] and menthyl chloroformate were tested, because the former does not produce any alcohol which would attack the activated ester, and the latter releases menthol, a poor nucleophile due to its bulkiness. Unexpectedly, when isopropenyl chloroformate was used, the lactone formation increased (**A/B** = ca. 2:1) probably because the isopropenyl carbonate is a better leaving group than an alkyl carbonate due to the partial loss of the electron density on oxygen by conjugating with the double bond. As a result, the formation of the lactone is facilitated to some extent. Menthyl chloroformate was also unsatisfactory due to the slow reaction probably caused by its bulkiness, even though the product ratio remained ca. 4:1. Finally, the activated ester prepared from cyclohexyl chloroformate was reacted with the alcohol **2**. In this case, the cyclohexanol formed during the reaction is a secondary alcohol so that the formation of the cyclohexyl ester should be small. As expected, the desired ester **4** was obtained in a comparatively high yield of 56% from 7-ACA. The ratio of **A** to **B** was again ca. 4:1.

Table. Effect of the Leaving Group X in the Reaction of **2** with the Activated Esters of **3**

X^-	**A (4)/B**[a]	Yield of **4** (%)
t-$BuCO_2^-$	1:2	~10%
$H_2C{=}C(Me)OCO_2^-$	2:1	30%
$Me_2CHCH_2OCO_2^-$	4:1	43%
c-$C_6H_{11}OCO_2^-$	4:1	56%

[a] Based on NMR analyses of the crude product.

The trityl protecting group on **4** was removed by trifluoroacetic acid (TFA) in dichloromethane to give the bis-TFA salt of **5**. On treatment of the TFA-salt with dilute hydrochloric acid in aqueous acetone, the dihydrochloride salt of **5** was obtained as a microcrystalline solid in 59% overall yield from **4**.[18] This dihydrochloride salt is used in the clinical studies.

It is worthwhile to note the effect of DMAP, which is essential for reactions of this type.[17,19,20] An acylpyridinium species has been postulated for the catalytic ability of DMAP and this convenient explanation is generally accepted.[21,22] However, the presence of such a common intermediate as an active species apparently fails to explain the difference in the selectivities observed in the reaction. Moreover, the acetylations with acetyl chloride in the presence of DMAP have been reported to proceed much more slowly than those with acetic anhydride even though 100% of the acylpyridinium species is estimated to be present at equilibrium in the case of acetyl chloride when compared to only 5–10% of such a species in the case of acetic anhydride.[21] Furthermore, it is reported that a catalytic amount of DMAP even accelerates the reaction of primary amines with (benzyloxycarbonyl) imidazole, yet it does not react with secondary amines with or without DMAP.[23] In this case the presence of an acylpyridinium species is hardly conceivable, since primary amines are believed to be more nucleophilic than DMAP and the presence of such activated species makes it difficult to rationalize the selectivity toward amines. It is more likely that in the reaction of an activated ester, DMAP catalyzes proton transfer reactions on forming tetrahedral intermediates. Although the importance of general base catalysis in acylation reactions is well known,[24] the importance of proton transfer steps is not always appreciated.

The important proton transfer reactions are intentionally neglected in Scheme 1. Therefore, it would be unrealistic to estimate the ratio of the products quantitatively from the scheme. However, the idea of leaving group controlled selectivity discussed here using this simplified scheme should provide a useful tool to understand the qualitative nature of the reaction.

In conclusion, this new strategy employing cyclohexyl chloroformate appears to offer several advantages over previously known methods for the synthesis of 3-acyloxymethyl-3-cephems even though general applicability of this strategy is yet to be seen. The dual-action cephalosporin **5** (dihydrochloride salt) was prepared in five steps in 33.0% overlal yield from 7-ACA without using any chromatographic procedures.

NMR spectra were recorded on a XL-400 instrument with TMS or CCl_3F as internal standard. Mass spectra were obtained on a VG7070-HF instrument in the positive-ion fast atom bombardment mode using thioglycerol as the solvent. HPLC analyses were carried out using a Hamilton PRP-1 column (250 mm × 4.1 mm) and MeCN/0.01 M trimethyl(tetradecyl)ammonium bromide in pH 8.2 phosphate buffer solution (37:63) as eluent.

{6*R*[6α,7β(*Z*)]}-3-(Acetoxymethyl)-7-{(methoxyimino)[2-(triphenylmethyl)amino-4-thiazolyl]acetylamino}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid (1:1) Triethylamine Salt (1):

A suspension of trityl chloride (33.5 g, 0.12 mol), MAEM (35.05 g, 0.10 mol), and Et_3N (18.1 mL, 0.13 mol) in CH_2Cl_2 (100 mL) was stirred at r. t. overnight (12 h). The resulting red solution was cooled with an ice-water bath, and then Et_3N (18.1 mL, 0.13 mol), 7-ACA (27.2 g, 0.10 mol), and CH_2Cl_2 (50 mL) were added. This mixture was stirred at r.t. for 1.5 h. The solvent was removed and the resulting solid was dried overnight at r. t. under 0.2 Torr to afford crude **1** (130 g, overweight) as a light brown solid. This material was used in the next step without any purifications.

MS: m/z = 698.1 (M + H), 720.1 (M + Na).

IR (KBr): ν = 1782 (β-lactam), 1740 (ester), 1680 cm^{-1} (amide).

^1H NMR ($CDCl_3$): δ = 1.32 (t, J = 7.3 Hz, 9 H, NEt_3), 2.02 (s, 3 H, OAc), 3.07 (q, J = 7.3 Hz, 6 H, NEt_3), 3.23 (d, J = 18.9 Hz, 1 H, SCH_2), 3.47 (d, J = 18.9 Hz, 1 H, SCH_2), 4.02 (s, 3 H, OMe), 4.91 (d, J = 12.4 Hz, 1 H, CH_2OAc), 5.02 (d, J = 4.8 Hz, 1 H, CH), 5.06 (d, J = 12.4 Hz, 1 H, CH_2OAc), 5.81 (dd, J = 8.9, 4.8 Hz, 1 H, CHNH), 6.70 (d, J = 8.9 Hz, 1 H, NH), 6.73 (s, 1 H, SCH=), 6.98 (br s, 1 H, NH), 7.26 (m, 15 H_{arom}), 12.70 (br, 1 H, CO_2H).

{6*R*[6α,7β(*Z*)]}-3-(Hydroxymethyl)-7-{(methoxyimino)[2-(triphenylmethyl)amino-4-thiazolyl]acetylamino}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid (1:1) Tributylamine Salt (2):

To a solution of crude **1** (130 g, prepared above) in MeOH (600 mL) at −30 °C was added 1.5 N NaOH (300 mL, 0.45 mol) dropwise over 1 h, keeping the temperature between −20 and −25 °C. The mixture was stirred at that temperature for an additional hour. Then, 3 N HCl (200 mL) was added dropwise at −10 to −20 °C followed by ice-cold CH_2Cl_2 (600 mL). After dissolution of the precipitate, the cold organic layer was separated and washed with 50% aq MeOH (200 mL). The organic layer was separated and Bu_3N (30 mL) was added. After warming to r.t., this solution was washed with 30% aq MeOH (100 mL) and dried. The solution was concentrated and the resulting foam was dried overnight at r.t. under 0.2 Torr. After the suspension of the crude product in Et_2O (400 mL) was stirred at r.t. for 4 h, the solid was filtered and washed with Et_2O. The solid was further dried for 24 h at r.t. under 0.2 Torr to afford crude **2** (89.7 g, overweight) as an amber solid. This material was used in the next step without any further purifications.

MS: m/z = 656.4 (M + H), 678.3 (M + Na).

IR (KBr): ν = 1778 (β-lactam), 1678 cm^{-1} (amide).

^1H NMR ($CDCl_3$): δ = 0.96 (t, J = 7.3 Hz, 9 H, NBu_3), 1.37 (sext, J = 7.4 Hz, 6 H, NBu_3), 1.69 (m, 6 H, NBu_3), 3.00 (m, 6 H, NBu_3), 3.43 (d, J = 18.6 Hz, 1 H, SCH_2), 3.52 (d, J = 18.6 Hz, 1 H, SCH_2), 3.76 (d, J = 12.4 Hz, 1 H, CH_2O), 4.06 (s, 3 H, OMe), 4.45 (d, J = 12.4 Hz, 1 H, CH_2O), 5.00 (d, J = 4.9 Hz, 1 H, CH), 5.85 (dd, J = 8.5, 4.9 Hz, 1 H, CHNH), 6.77 (s, 1 H, SCH=), 6.80 (d, J = 8.5 Hz, 1 H, NH), 7.10 (br s, 1 H, OH), 7.30 (m, 15 H_{arom}), 12.90 (br, 1 H, CO_2H).

{6*R*[6α,7β(*Z*)]}-3-{[6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyloxymethyl}-7-{(methoxyimino)[2-(triphenylmethyl)amino-4-thiazolyl]acetylamino}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid (4):

A suspension of fleroxacin **3** (36.9 g, 0.10 mol) in CH_2Cl_2 (700 mL) was cooled to 0 °C, cyclohexyl chloroformate (15.2 mL, 0.105 mol) was added followed by Bu_3N (26 mL, 0.11 mol). The resulting yellow solution was cooled to −25 °C, the crude alcohol **2** (89.7 g, 0.1 mol is assumed) was added with the aid of CH_2Cl_2 (50 mL). After dissolution of the alcohol, DMAP (3.05 g, 25 mmol) was added. The mixture was stirred at −25 °C for 2 h and then slowly warmed to 0 °C over 1.5 h. To the resulting suspension, acetone (500 mL) was added and the mixture was stirred for 20 min. The precipitate was filtered, washed with acetone (250 mL), and dried at r.t. under 0.2 Torr overnight to recover **3** (7.98 g, 22% recovery). To the combined filtrate and washes, hexane (2 L) was added. The precipitate was filtered, washed with acetone/hexane (2:1) (300 mL) and then with hexane (150 mL), and dried overnight at r.t. under 0.2 Torr. This crude product was added to CH_2Cl_2 (500 mL). To the resulting dark solution, acetone (1.5 L) was added dropwise and the precipitate was filtered and washed with acetone (300 mL) and then with Et_2O (300 mL). Drying at r.t. under 0.2 Torr for 24 h gave **4** as an off-white solid; yield: 56.8 g (56% based on 7-ACA). This material was used in the next step without any further purifications.

IR (KBr): ν = 1772 (β-lactam), 1720 (ester), 1682 (amide), 1618 cm^{-1} (ketone).

^1H NMR ($CDCl_3/CD_3OD$, 10:1): δ = 2.65 (s, 3 H, NCH_3), 2.94 (m, 4 H, NCH_2), 3.38 (d, J = 18.6 Hz, 1 H, SCH_2), 3.47 (m, 4 H, NCH_2), 3.60 (d, J = 18.6 Hz, 1 H, SCH_2), 4.01 (s, 3 H, OMe), 4.50–4.85 (m, 4 H, CH_2CH_2F), 4.98 (d, J = 12.4 Hz, 1 H, CH_2O), 5.03 (d, J = 4.8 Hz, 1 H, CH), 5.34 (d, J = 12.4 Hz, 1 H, CH_2O), 5.83 (d, J = 4.8 Hz, 1 H, CHNH), 6.69 (s, 1 H, SCH=), 7.23 (m, 15 H_{arom}), 7.64 (d, J = 12.2 Hz, 1 H, CH=CF), 8.30 (s, 1 H, NCH=C).

{6*R*[6α,7β(*Z*)]}-7-[(2-Amino-4-thiazolyl)(methoxyimino)acetylamino]-3-{[6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyloxymethyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid Bis(trifluoroacetate) Salt (5, Bis-TFA Salt):

After a mixture of TFA (114 mL) and CH_2Cl_2 (50 mL) was cooled to −10 °C, **4** (56.8 g, 56 mmol) was washed in with CH_2Cl_2 (64 mL). The mixture was stirred at 0 °C for 3 h. Stirring was stopped and hexane (228 mL) followed by Et_2O (460 mL) was added gently so as not to disturb the lower TFA layer. The two layers were then mixed by vigorous stirring causing the precipitation of a powder. The solid was filtered, washed with Et_2O (800 mL), and air-dried for 30 min to obtain the crude TFA salt of **5**. Then the crude product was added to a cold mixture of CH_2Cl_2 (300 mL) and Et_2O (40 mL). The suspension was stirred at 0 °C for 3 h. Then the solid was filtered and washed with CH_2Cl_2 (200 mL) and then with Et_2O (400 mL). The solid was dried overnight at r.t. under 0.2 Torr to afford **5** (2 TFA) as an off-white solid, which was contaminated with ca. 7% of **3**; yield: 51.9 g (93%). This material was used immediately in the next step without any further purifications.

^{19}F NMR (DMSO-d_6): δ = −74.0 (2 TFA), −120.9 (1 F_{arom}), −126.7 (1 F_{arom}), −223.7 (1 F, CH_2CH_2F).

{6R[6α,7β(*Z*)]}-7-[(2-Amino-4-thiazolyl)(methoxyimino)acetylamino]-3-{[6,8-difluoro-1-(2-fluorethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyloxymethyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid Dihydrochloride Salt (5, Dihydrochloride Salt):

To a vigorously stirring mixture of acetone (928 mL) and H_2O (271 mL) at 0–2 °C was added **5** (2 TFA) (250 g, 0.251 mol) slowly. After stirring for 15 min, the mixture was filtered through a medium-frit glass filter and the filter was washed with acetone/H_2O (1:1) (50 mL). The combined filtrate and washes are mixed with 1 N HCl (657 mL). The mixture was stirred at 0 °C for 45 min followed by the addition of cold acetone (5.33 L). The precipitate was filtered and washed with cold acetone (2.5 L). The solid was dried by suction under a high flow of N_2 for 1.5 h and at r.t. under high vacuum to give **5** (2 HCl) as an off-white solid; yield: 139 g (63%); 98.4% pure by HPLC analysis, contains 0.5% of **3**.

$C_{31}H_{31}F_3N_8O_8S_2 \cdot 2HCl \cdot 1.5H_2O$	calc.	C 43.05	H 4.20	N 12.96	S 7.41	
				F 6.59	Cl 8.20	
(864.7)	found	42.84	4.13	12.77	7.64	
				6.53	8.10	

MS: m/z = 765.8 (M + H).

^1H NMR (DMSO-d_6): δ = 2.81 (d, J = 4.4 Hz, 3 H, NH^+CH_3), 3.16 (m, 2 H, NCH_2), 3.47 (m, 2 H, NCH_2), 3.58 (m, 4 H, NCH_2), 3.71 (d, J = 18.4 Hz, 1 H, SCH_2), 3.78 (d, J = 18.4 Hz, 1 H, SCH_2), 3.92 (s, 3 H, OMe), 4.75–4.95 (m, 4 H, CH_2CH_2F), 4.99 (d, J = 13.2 Hz, 1 H, CH_2O), 5.19 (d, J = 13.2 Hz, 1 H, CH_2O), 5.20 (d, J = 4.8 Hz, 1 H, CH), 5.82 (dd, J = 8.0, 4.8 Hz, 1 H, CHNH), 6.87 n (s, 1 H, SCH=), 7.81 (d, J = 12.0 Hz, 1 H, CH=CF), 8.58 (s, 1 H, NCH=C), 9.76 (d, J = 8.0 Hz, 1 H, NH), 11.2 (br s, 1 H, CO_2H).

The authors would like to thank Dr. Ka-Kong Chan, Mr. C. Michael Delaney, and Mr. Anthony C. Specian, Jr. for their contribution in the conversion of **5** *(2 TFA) to* **5** *(2 HCl). Members of the Physical Chemistry Department are acknowledged for determination of spectra and analytical data. The encouragement and advice provided by Dr. Manfred Weigele and Dr. David L. Coffen are greatly appreciated.*

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