A New Convenient Synthesis of 3-Carboxycephems Starting from 7-Aminocephalosporanic Acid (7-ACA)

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New convenient syntheses of 3-carboxycephems starting from 7-ACA are reported. All three possible cephem derivatives with respect to the position of the double bond in the six-membered ring and oxidation state of the sulfur atom have been synthesized in high overall yield.

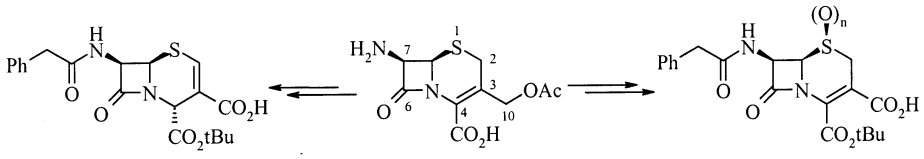
Introduction

Although several syntheses of 3-carboxycephems have been reported, no convenient general procedure for both isomers with respect to the double bond in the six-membered ring has been described so far. Spry et al.[1−4] and Peter et al.[5,6] were the first who synthesized the 3-carboxycephem derivatives from the corresponding 3-formylceph-2-ems in a sequence of reactions. In these approaches the conversion of the formyl group into the carboxyl group involved at least four separate steps. Also starting from cephalosporin thiolactones, a multi step procedure (bromination, hydrolysis, oxidation and opening of the dioxo thiophene ring) afforded the 3-carboxyceph-3-ems.[7−9] In addition, a few total syntheses have been reported.[10,11] Until now, no method for the direct oxidation of the 3-formylcephems to the 3-carboxycephems has appeared in the literature. Our interest in modifications at the C3-position of cephalosporins has led to an improved synthesis of 3-carboxycephems with the double bond in the Δ^3 as well as in the Δ^2 position.

In this paper, we describe a general synthesis for 3-carboxycephems starting from the readily available 7-aminocephalosporanic acid (7-ACA) **1** as the starting material and 3-formylcephems as the key intermediates (Scheme 1).

Results and Discussion

The general strategy for synthesizing our target compounds, viz. 3-carboxycephems **13**, **14**, **15**, starting from 7-ACA **1** involves protection of the C7-amino function and the C4-carboxyl function to allow a synthetic elaboration at C10. The amino function was protected as a phenylacetamide group because this moiety can be deprotected enzymatically and has successfully been used by others.[12−16] For the protection of the C4-carboxyl group we used the *tert*-butyl ester because this environmentally benign and economically interesting group can be easily introduced. Moreover, the re-conversion of the ester into the carboxylic acid, which may be rather problematic for these types of substrates, is high yielding in the case of the *tert*-butyl ester.[17]



13 7-ACA **1** **14** (n = 0) **15** (n = 1)

Scheme 1

The amino group of 7-ACA **1** was protected with phenylacetyl chloride under Schotten−Baumann conditions in 83% yield. Subsequently, the carboxyl group was protected as a *tert*-butyl ester by treatment with dicyclohexyl carbodiimide and *tert*-butyl alcohol using DMAP as the catalyst. The only product obtained, after recrystallisation, was the Δ^2 isomer **4** in 88% yield (Scheme 2). This is surprising since generally mixtures of the Δ^2 and Δ^3 isomers

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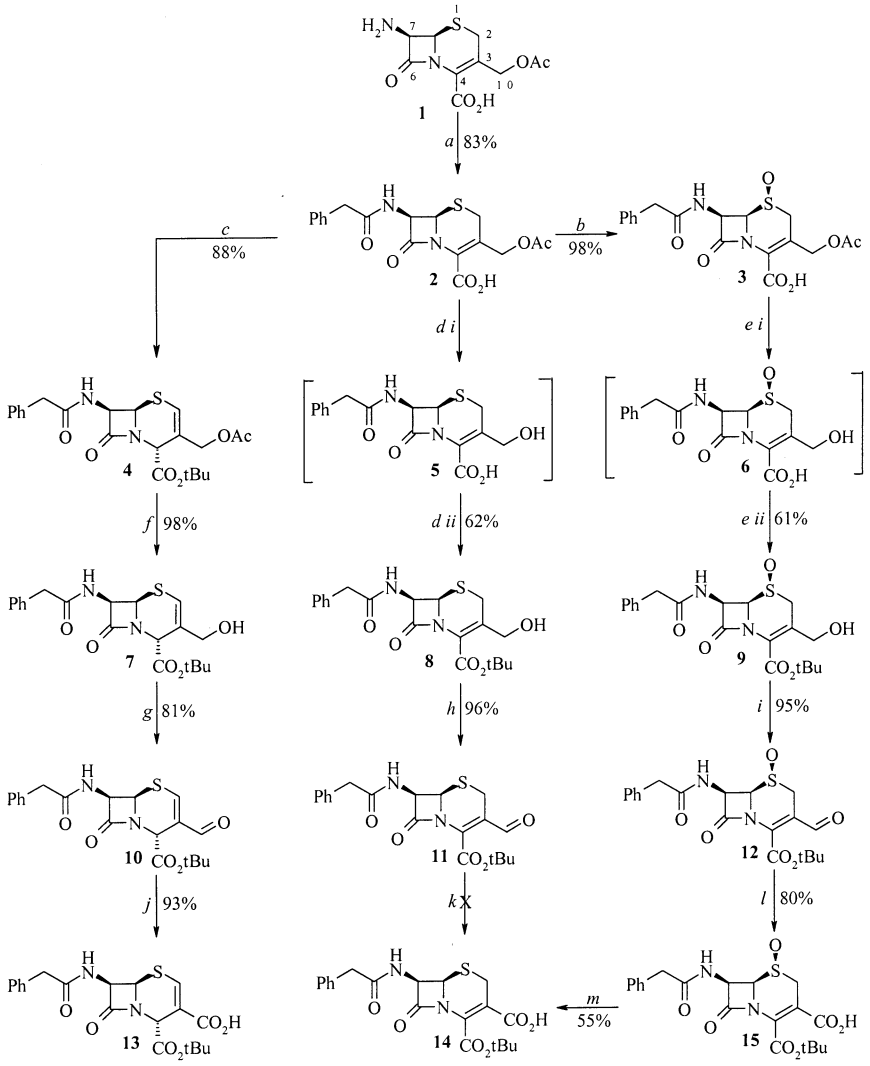

Scheme 2. a) Phenylacetyl chloride, H_2O, pH 8.0, room temp., o/n, 83%. − b) *m*-CPBA, CH_2Cl_2, 0 °C, 1.5 h, 98%. − c) *t*BuOH, DCC, DMAP (cat.), CH_2Cl_2, −30 °C → room temp., o/n, 88%. − d) i. cephalosporin acetyl hydrolase (CAH), H_2O, pH 7.5, 4−8 h, ii. isoureum (DCC, *t*BuOH), THF, o/n, 61%. − e) i. CAH, H_2O pH 7.5, 4−8 h, ii. isoureum (DCC, *t*BuOH), THF, o/n, 62%. − f) NaOH, MeOH, −20 °C, 4 h, 98%. − g) IBX, DMSO/THF, room temp., 30 h, 81%. − h) IBX, DMSO, room temp., 15′, 96%. − i) IBX, DMSO, room temp., 15′, 95%. − j) $NaClO_2$, cyclohexene, THF/phosphate buffer, 0° C, o/n, 93%. − k) $NaClO_2$, cyclohexene, THF/phosphate buffer, 0 °C, 0%. − l) $NaClO_2$, cyclohexene, THF/phosphate buffer, 0 °C, o/n, 80%. − m) AcCl, $SnCl_2$, DMF, 0 °C, 2 h, 55%

are formed due to isomerization of the double bond.[18−20] Under the basic reaction conditions the double bond had isomerized from the Δ^3 to the Δ^2 position driven by the bulky acetoxy substituent at the C(10) position. Release of steric interference between the *cis* substituents of the ceph-3-em system can be invoked to explain this phenomenon. After saponification of the acetate at C10, alcohol **7** was oxidised to aldehyde **10** with 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) analogous to the procedure of Frigerio et al.[21] in 81% yield. Other well-known oxidation reagents (e.g. MnO_2, PCC, Collins reagent, Moffat oxidation) gave lower yields, or did not react at all (e.g. TEMPO, benzimidazolium dichromate under microwave conditions and isoquinolinium dichromate). The oxidation of the 3-formyl group to the carboxyl group was accomplished in a one step procedure by treatment with sodium chlorite in THF/phosphate buffer and cyclohexene as the chlorine scavenger, affording the 3-carboxyceph-2-em **13** in 93% yield. This sequence for the conversion of 7-ACA into the 3-carboxyceph-2-em **13** only involves five steps, all of them high yielding.

In principle, the synthesis of the corresponding 3-carboxyceph-3-em **14** can be approached in a similar manner. After protection of the amino group, the acetate at C10 was hydrolyzed with an immobilized enzyme (cephalosporin acetyl hydrolase) to obtain the hydroxy acid **5** in acceptable yield. Compound **5** must be handled with great care to prevent lactonization under acidic conditions. To avoid the formation of Δ^2 by-products during the next protection step, the esterification of the C4 carboxylic acid function was performed by treatment with the isourea derived from DCC and *tert*-butyl alcohol to give the *tert*-butyl ester **8** in 62% yield.[22] As no base is required in this procedure, only Δ^3 hydroxy ester **8** is formed. Oxidation of the alcohol func-

tion at C10 to the corresponding aldehyde **11** was achieved again with IBX as the oxidizing agent in almost quantitative yield. Disappointingly, the formyl group could not be oxidized directly to the corresponding carboxy group using conditions similar to those used for the synthesis of 3-carboxyceph-2-em **13**. Opening of the β-lactam ring probably occurred by attack of a nucleophile (e.g. water) which has also been observed by others.[23] The presence of an electron-withdrawing group on the C3-position (in conjugation with the lactam moiety) also results in an enhanced chemical reactivity of the β-lactam C6 carbonyl group.[2] Since this route to the target compound **14** is not possible, a detour via sulfoxide **15** is worth considering. The results are reported below.

The synthesis of 3-carboxyceph-3-em *S*-oxide **15** started from 7-ACA by protection of the amino part (vide supra). Then sulfide **2** was oxidised to the sulfoxide **3** with *meta*-chloroperbenzoic acid in quantitative yield. Hydroxy acid **6** was obtained by enzymatic hydrolysis (cephalosporin acetyl hydrolase) of the C10 acetate and the *tert*-butyl ester of **6** was prepared by treatment with the isourea derived from DCC and *tert*-butyl alcohol to give ester alcohol **9** in an overall yield of 61%. Oxidation of the primary alcohol function at C10 to the corresponding formyl product **12** was accomplished using IBX as the oxidant similar to the conversion of **8** into **11**, again in excellent yield. Gratifyingly, this formyl compound **12** was readily oxidized to the carboxylic acid by sodium chlorite in high yield. The sulfoxide function has a stabilizing effect on this molecule as has been demonstrated before.[24] Finally, reduction of sulfoxide **15** to sulfide **14** could be accomplished by treatment with acetyl chloride in DMF and a catalytic amount of tin(II) chloride analogous to Kaiser et al.[25] Thus, the above-mentioned detour to target compound **14** via the sulfoxide route was indeed possible.

Conclusion

In conclusion, starting from the readily available 7-ACA **1**, we developed a convenient synthesis for some 3-carboxycephems, namely 3-carboxyceph-2-em **13** and 3-carboxyceph-3-em sulfide **14** and the corresponding sulfoxide **15** in high overall yields. These 3-carboxy derivatives are valuable compounds for further synthetic elaboration, to prepare new types of antibiotics.

Experimental Section

General Remarks: 100 MHz ^{1}H NMR spectra were recorded on a Bruker AC 100 spectrometer and 300 MHz ^{1}H NMR spectra and all ^{13}C NMR spectra were recorded on a Bruker AC 300 using Me_4Si as internal standard. All coupling constants are given as ^3J in Hz, unless indicated otherwise. − Melting points were measured with a Reichert Thermopan microscope and are uncorrected. − IR spectra were recorded on a Bio-Rad FTS-25 instrument. − For mass spectra a double focusing VG7070E mass spectrometer was used. − Elemental analyses were conducted on a Carlo Erba Instruments CHNSO EA 1108 element analyzer. − For the determination of optical rotations a Perkin−Elmer 241 polarimeter was used. − Solvents were dried using the following methods: dichloromethane was distilled from P_2O_5; ethyl acetate was distilled from K_2CO_3; diethyl ether was distilled from NaH; hexane and heptane were distilled from CaH_2; tetrahydrofuran was distilled from sodium prior to use. All other solvents were of analytical grade. − Thin layer chromatography (TLC) was carried out on a Merck precoated silica gel 60 F254 plates (0.25 mm). Spots were visualized with UV or using a molybdate spray. Flash chromatography was carried out at a pressure of ca. 1.5 bar, using Merck Kieselgel 60H. Column chromatography at atmospheric pressure was performed with ACROS silica gel (0.035−0.070 mm; pore diameter ca. 6 nm).

Systematic names were generated using the ACD/Name program provided by Advanced Chemistry Development Inc. (Toronto, Canada).

(7*R*,7a*R*)-3-[(Acetyloxy)methyl]-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylic Acid (2): To a solution of 7-ACA **1** (12.00 g, 44.12 mmol) in saturated aqueous $NaHCO_3$ (300 mL) and acetone (100 mL) was added phenylacetyl chloride (ca. 2 equivalents, ca. 6.0 mL) in two portions. After 17 h stirring, the reaction mixture was acidified with concentrated HCl to pH 1.5 and extracted with CH_2Cl_2 (2 × 250 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was suspended in diethyl ether and stirred for 17 h to remove phenylacetic acid (by-product). The product was filtered off, washed with diethyl ether and dried in vacuo. Phenylacetyl protected 7-ACA **2** was obtained as an off-white solid (14.20 g, 83%) and was used without any further purification. M.p. 168−171 °C (dec.). − $[\alpha]_D^{20}$ = +86 (*c* = 1.0, dioxane). − ^{1}H NMR (100 MHz, $CDCl_3$ and [D$_6$]DMSO): δ = 2.07 (s, 3 H, CH_3), 3.32 and 3.54 (qAB, *J* = 15.0 Hz, 2 H, SCH_2), 3.58 (s, 2 H, $PhCH_2$), 4.84 and 5.08 (qAB, *J* = 13.3 Hz, 2 H, C*H*$_2$OAc), 4.95 (d, *J* = 4.9 Hz, 1 H, NHCHC*H*S), 5.77 (dd, *J* = 4.8 Hz *J* = 8.5 Hz, 1 H, NHC*H*CHS), 7.29 (m, 5 H, Ph-H), 8.18 (d, *J* = 8.5 Hz, 1 H, NH), 9.64 (s, 1 H, CO_2 H). − ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 20.8 [OC(O)*C*H$_3$], 25.7 (SCH_2), 41.8 ($PhCH_2$), 57.6 (CHNH), 59.3 (CHS), 62.9 (CH_2OAc), 123.6 (=*C*CH$_2$OAc) 126.5 (=*C*CO$_2$ H), 126.7, 128.4, 129.2 and 136.0 (Ph-C), 163.0 (C=O, lactam), 165.0 (CO_2 H), 170.4 [O*C*(O)CH$_3$], 171.2 [PhCH$_2$*C*(O)]. − IR (KBr): $\tilde{\nu}$ = 3260 (broad, NH), 1782 (C=O, lactam), 1748 (C=O, acetyl), 1738 (C=O, acid), 1658 and 1535 (C=O, amide), 1345 (C−N), 1228 (C−O, acetyl) cm^{-1}. − MS (FAB$^+$, NOBA): *m*/*z* (%) = 413 (51) [M + Na]$^+$, 391 (18) [M + H]$^+$, 331 (100) [M + H − CO_2CH_3]$^+$.

(7*R*,7a*R*)-3-[(Acetyloxy)methyl]-1,6-dioxo-7-[(2-phenylacetyl)-amino]-1,6,7,7a-tetrahydro-2*H*-1λ^4-azeto[2,1-*b*][1,3]thiazine-4-carboxylic Acid (3): To a cooled (0 °C) suspension of phenylacetyl protected 7-ACA **2** (0.78 g, 2.00 mmol) in CH_2Cl_2 (50 mL) was added 1.5 equiv. of pre-dried MCPBA (0.26 g) in one portion. After additional stirring (1.5 h) the precipitate (white solid) was collected by filtration, washed with CH_2Cl_2 (2 × 25 mL) to remove MCBA, and dried in vacuo. The crude sulfoxide **3** (0.80 g, 98%) was used without any further purification. M.p. 197−198 °C (dec.). − $[\alpha]_D^{20}$ = +161 (*c* = 0.87, H_2O). − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.02 (s, 3 H, CH_3), 3.52 and 3.73 (qAB, *J* = 14.4 Hz, 2 H, $PhCH_2$), 3.56 and 3.88 (qAB, *J* = 18.5 Hz, 2 H, SCH_2), 4.59 and 5.19 (qAX, *J* = 13.1 Hz, 2 H, C*H*$_2$OAc), 4.86 (d, *J* = 4.2 Hz, 1 H, NHCHC*H*S), 5.81 (dd, *J* = 4.2 Hz *J* = 8.2 Hz, 1 H, NHC*H*CHS), 7.21−7.31 (m, 5 H, Ph-H), 8.40 (d, *J* = 8.2 Hz, 1 H, NH). − ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 20.8 [OC(O)*C*H$_3$], 41.6 ($PhCH_2$), 45.5 (SCH_2), 58.4 (CH_2OAc), 63.2 (CHS),

66.4 (CHS), 118.7 (=*C*CH_2OAc) 126.1 (=*C*CO_2H), 126.7, 128.5, 129.3 and 136.0 (Ph-C), 162.3 (C=O, lactam), 164.4 (CO_2 H), 170.3 [O*C*(O)CH_3], 171.2 [PhCH_2*C*(O)]. − IR (KBr): $\tilde{\nu}$ = 3298 (broad, NH), 1775 (C=O, lactam), 1742 (C=O, acetyl), 1723 (C=O, acid), 1658 and 1527 (C=O, amide), 1339 (C−N), 1222 (C−O, acetyl), 1035 (S=O) cm^{-1}. − MS (FAB$^+$, NOBA): *m*/*z* (%) = 429 (13) [M + Na]$^+$, 407 (3) [M + H]$^+$, 347 (12) [M + H−$COCH_3$]$^+$, 514 (100).

***tert*-Butyl (4*S*,7*R*,7a*R*)-3-[(Acetyloxy)methyl]-6-oxo-7-[(2-phenylacetyl)-amino]-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (4):** DCC (5.81 g, 28.16 mmol) was added to a cooled (−30 °C) and stirred suspension of phenylacetyl protected 7-ACA 2 (10.00 g, 25.6 mmol), *tert*-butyl alcohol (5 mL) and DMAP (200 mg) in CH_2Cl_2 (200 mL) under nitrogen. The reaction mixture was stirred for 1 h at 0 °C and for a further 15 h at room temperature. After removal of DCU by filtration, HCl (2 N) was added to the filtrate. Crude *tert*-butyl ester was obtained by extraction with CH_2Cl_2 (3 × 200 mL), washing with saturated $NaHCO_3$ (1 × 200 mL) and brine (1 × 200 mL), drying ($MgSO_4$), and concentration in vacuo. Crystallization from ethyl acetate/heptane, after treatment with active carbon, gave pure *tert*-butyl ester 4 with the Δ^2 double bond, as white needles (10.10 g, 88%). M.p. 227−229 °C, $[\alpha]_D^{20}$ = +409 (*c* = 0.53, acetone). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 [s, 9 H, C(CH_3)$_3$], 2.06 [s, 3 H, C(O)CH_3], 3.64 (s, 2 H, PhCH_2), 4.53 and 4.71 (qAB, *J* = 12.7 Hz, 2 H, C*H*$_2$OAc), 4.87 (s, 1 H, C*H*CO_2*t*Bu), 5.26 (d, *J* = 4.0 Hz, 1 H, NHCHC*H*S), 5.65 (dd, *J* = 4.0 Hz *J* = 8.7 Hz, 1 H, NHC*H*CHS), 6.23 (d, *J* = 8.7 Hz, 1 H, NH), 6.34 (s, 1 H, SCH=), 7.26−7.40 (m, 5 H, Ph-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 [OC(O)*C*H$_3$], 27.9 [C(*C*H$_3$)$_3$], 43.3 (PhCH_2), 50.6 (*C*HCO_2*t*Bu) 53.4 (CHNH), 60.2 (CHS), 65.4 (CH_2OH), 84.0 [*C*(CH_3)$_3$], 119.4 (SCH=), 121.2 (=*C*CH_2OAc) 127.6, 129.1, 129.4 and 133.6 (Ph-C), 164.2 (C=O, lactam), 165.9 (CH*C*O_2*t*Bu), 170.4 [O*C*(O)CH_3], 171.0 [PhCH_2*C*(O)]. − IR (KBr): $\tilde{\nu}$ = 3246 (broad, NH), 3058 (CH, phenyl), 1782 (C=O, lactam), 1736 (C=O, ester and acetyl), 1649 and 1560 (C=O, amide), 1387 (C−N), 1218 (C−O, acetyl) 1153 (C−O, ester) cm^{-1}. − MS (CI$^+$): *m*/*z* (%) = 446 (5) [M$^+$], 405 (3) [M + H − $COCH_3$]$^+$, 345 (14) [M + H − $COCH_3$ − C_4H_8]$^+$, 331 (60), 176 (72), 216 (95), 91 (100). − HRMS (EI, *m*/*z*): 446.15036 (calcd. for $C_{22}H_{26}N_2O_6S$: 446.15115).

***tert*-Butyl (4*S*,7*R*,7a*R*)-3-(Hydroxymethyl)-6-oxo-7-[(2-phenylacetyl)-amino]-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (7):** Sodium hydroxide (0.90 g, 22.50 mmol) in methanol (30 mL) was added under nitrogen to a cooled (−30 °C) and stirred solution of triple protected 7-ACA **4** (5.00 g, 0.011 mol) in methanol (360 mL). The reaction mixture was stirred between −30 and −20 °C for 4−5 h until TLC analysis (ethyl acetate/hexane 1:1) showed completion of the reaction. The reaction mixture was then poured into diluted HCl solution and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with brine (1 × 50 mL), water (1 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo affording crude alcohol **7** as a yellow-orange foam (4.44 g, 98%). An analytical sample was obtained after column chromatography (silica gel, ethyl acetate/heptane 2:1). M.p. 85−87 °C (dec.). − $[\alpha]_D^{20}$ = +471 (*c* = 0.525, acetone). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 [s, 9 H, C(CH_3)$_3$], 2.46 (br. s, 1 H, CH_2O*H*), 3.63 (s, 2 H, PhCH_2), 4.12 and 4.21 (dqAB, J_{AB} = 13.4 Hz *J* = 5.5 Hz, 2 H, C*H*$_2$OH,), 4.92 (d, ^4J = ≈1.0 Hz, 1 H, C*H*CO_2*t*Bu), 5.22 (d, *J* = 4.0 Hz, 1 H, NHCHC*H*S), 5.61 (dd, *J* = 4.0 Hz *J* = 8.7 Hz, 1 H, NHC*H*CHS), 6.23 (d, ^4J = ≈1.0 Hz, 1 H, SCH), 6.27 (br. s, 1 H, NH), 7.26−7.38 (m, 5 H, Ph-H), ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9 [C(*C*H$_3$)$_3$], 43.2 (PhCH_2), 50.7 (*C*HCO_2*t*Bu) 53.6 (CHNH), 60.1 (CHS), 64.9 (CH_2OH), 84.0 [*C*(CH_3)$_3$], 117.2 (SCH=), 124.3 (=*C*CH_2OH) 127.6, 129.0, 129.4 and 133.8 (Ph-C), 164.5 (C=O lactam), 166.5 (CH*C*O_2*t*Bu), 171.2 [PhCH_2*C*(O)]. − IR (KBr): $\tilde{\nu}$ = 3431 (broad, OH), 3298 (broad, NH), 1770 (C=O, lactam), 1732 (C=O, ester), 1660 and 1535 (C=O, amide), 1369 (C−N), 1151 (O−C, ester) cm^{-1}. − MS (FAB$^+$, NOBA): *m*/*z* (%) = 427 (21) [M + Na]$^+$, 404 (5) [M$^+$], 331 (35) [M + H − C_4H_8 − H_2O]$^+$, 176 (57), 57 (100). − $C_{20}H_{24}N_2O_5S$ (404.49): calcd. C 59.39, H 5.98, N 6.93, S 7.93; found C 59.39, H 5.97, N 6.83, S 8.07.

***tert*-Butyl (7*R*,7a*R*)-3-(Hydroxymethyl)-6-oxo-7-[(2-phenylacetyl)-amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (8):** Phenylacetyl protected 7-ACA **2** (4.00 g, 10.26 mmol) was dissolved in water and the pH was set to 7.0 with 0.6 M NaOH. After addition of immobilized cephalosporin acetyl hydrolase (8.00 g "wet" enzyme) the pH was maintained at pH 7.0 by addition of 0.1 M NaOH (pH stat conditions). After completion (4−6 h) the enzyme was recovered by filtration. The filtrate was acidified to pH 1.8 after cooling to 0 °C. The precipitate formed was collected by filtration and dried in vacuo or extracted (3 × 150 mL) with ethyl acetate. The combined organic layers were washed with water (2 × 50 mL) and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product **5** was dissolved in dry THF. At room temperature the carboxylic acid was esterified with isourea derived from *tert*-butyl alcohol and DCC (4 equiv.). After stirring for 17 h, DCU was removed by filtration. After addition 2 N HCl, the filtrate was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were extracted with saturated $NaHCO_3$ (1 × 75 mL) and brine (1 × 75 mL), dried ($MgSO_4$) providing *tert*-butyl ester **8** after column chromatography (silica gel, heptane/ethyl acetate 1:2) as a white solid (2.10 g, 61%). − M.p. 174−176 °C (dec.). − $[\alpha]_D^{20}$ = +83 (*c* = 0.87, acetone). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.66 (s, 9 H, C(CH_3)$_3$], 3.00 (br. s, 1 H, OH), 3.49 and 3.53 (qAB, *J* = 18.6 Hz, 2 H, SCH_2), 3.61 and 3.65 (qAB, *J* = 15.9 Hz, 2 H, PhCH_2), 3.86 (dd, *J* = 5.0 Hz *J* = 12.6 Hz, 1 H, C*H*$_2$OH), 4.46 (d, *J* = 12.6 Hz, 1 H, C*H*$_2$OH), 4.89 (d, *J* = 4.9 Hz, 1 H, NHCHC*H*S), 5.83 (dd, *J* = 4.9 Hz *J* = 9.1, 1 H, NHC*H*CHS), 6.53 (d, *J* = 9.1 Hz, 1 H, NH), 7.25−7.38 (m, 5 H, Ph-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.6 (SCH_2), 27.3 [C(*C*H$_3$)$_3$], 43.1 (PhCH_2), 57.1 (CH_2OH), 59.0 (CHNH), 61.9 (CHS), 84.0 [*C*(CH_3)$_3$], 126.5, 127.6, 129.1, 129.4, 129.9, 133.7 (=*C*CO_2*t*Bu, =*C*CH_2OH and Ph-C), 161.4 (*C*O_2*t*Bu), 164.6 (C=O, lactam), 171.3 (PhCH_2*C*(O)]. − IR (KBr): $\tilde{\nu}$ = 3409 (broad, OH), 3298 (broad, NH), 1756 (C=O, lactam), 1709 (C=O, ester), 1661 and 1536 (C=O, amide), 1367 (C−N), 1163 (C−O, ester) cm^{-1}. − MS (FAB$^+$, NOBA): *m*/*z* (%) = 427 (44) [M + Na]$^+$, 405 (17) [M + H]$^+$, 387 (42) [M + H − H_2O]$^+$, 331 (49) [M + H − C_4H_8 − H_2O]$^+$, 178 (100). − $C_{20}H_{24}N_2O_5S$ (404.49): calcd. C 59.39, H 5.98, N 6.93, S 7.93; found C 59.36, H 6.03, N 6.87, S 7.93.

***tert*-Butyl (7*R*,7a*R*)-3-(Hydroxymethyl)-1,6-dioxo-7-[(2-phenylacetyl)-amino]-1,6,7,7a-tetrahydro-2*H*-1λ^4-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (9):** The procedure as described for the preparation of the sulfide analogue was followed using phenylacetyl protected 7-ACA-sulfoxide **3** (1.50 g, 3.69 mmol), immobilized cephalosporin acetyl hydrolase (4.0 g "wet" enzyme) and isourea (4 equiv.) derived from *tert*-butyl alcohol and DCC. Workup after 4−6 h followed by purification via chromatography (silica gel, ethyl acetate) afforded *tert*-butyl ester **9** as a white solid (0.96 g, 62%). M.p. 198−199 °C (dec.). − $[\alpha]_D^{20}$ = +87 (*c* = 0.51, acetone). − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.49 [s, 9 H, C(CH_3)$_3$], 3.53 and 3.85 (qAB, *J* = 18.6 Hz, 2 H, SCH_2), 3.49 and 3.75 (qAB, *J* = 14.1 Hz, 2 H, PhCH_2), 4.07 and 4.42 (dqAB, J_{AB} = 13.9 Hz *J* = 5.6 Hz, 2 H, C*H*$_2$OH), 4.83 (d, *J* = 4.5 Hz, 1 H, NHCHC*H*S), 5.13 (t, *J* =

5.6 Hz, 1 H, CH_2OH) 5.87 (dd, J = 4.5 Hz J = 8.4 Hz, 1 H, NHC*H*CHS), 7.23−7.31 (m, 5 H, Ph-H), 8.34 (d, J = 8.4 Hz, 1 H, NH). − ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 27.7 [C(*C*H$_3$)$_3$], 41.7 (SCH_2), 45.5 ($PhCH_2$), 58.2 (CH_2OH), 60.4 (CHNH), 66.4 (CHS), 82.6 [*C*(CH$_3$)$_3$], 123.3 (=*C*CO$_2$*t*Bu), 125.7 (=*C*CH$_2$OH), 126.7, 128.5, 129.3, and 136.4 (Ph-C), 160.2 (*C*O$_2$*t*Bu), 164.2 (C=O, lactam), 171.2 [PhCH$_2$*C*(O)]. − IR (KBr): ṽ = 3509 (broad, OH), 3229 (broad, NH), 1782 (C=O, lactam), 1695 (C=O, ester), 1661 and 1541 (C=O, amide), 1327 (C−N), 1159 (C−O, ester), 1031 (S=O) cm^{-1}. − MS (FAB$^+$, NOBA): *m*/*z* (%) = 443 (18) [M + Na]$^+$, 421 (5) [M + H]$^+$, 403 (10), 387 (10), 365 (12), 347 (38), 225 (48), 91 (92), 57 (100). − $C_{20}H_{24}O_6N_2S$ (420.49): calcd. C 57.13, H 5.75, N 6.66; found C 56.73, H 5.71, N 6.62.

***tert*-Butyl (4*S*,7*R*,7a*R*)-3-Formyl-6-oxo-7-[(2-phenylacetyl)-amino]-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (10):** To a stirred solution of iodoxy benzoic acid (1.40 g, 5.00 mmol) in DMSO (8 mL) was added a solution of alcohol **7** (1.00 g, 2.48 mmol) in THF (3 mL) over a period of 3 h. The reaction mixture was stirred for an additional 30 h at room temperature. Then the reaction mixture was extracted with ethyl acetate, washed with water (3 × 15 mL), brine (1 × 15 mL), dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, ethyl acetate/hexane 3:7) to furnish aldehyde **10** (0.81 g, 81%) as a colorless solid. − M.p. 146−148 °C (dec.). − $[\alpha]_D^{20}$ = +679 (*c* = 0.30, acetone). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, C(CH$_3$)$_3$], 3.65 (s, 2 H, $PhCH_2$), 5.27 (s, 1 H, C*H*CO$_2$*t*Bu), 5.30 (d, J = 3.9 Hz, 1 H, NHCHC*H*S), 5.55 (dd, J = 3.9 Hz J = 7.6 Hz, 1 H, NHC*H*CHS), 6.22 (d, J = 7.6 Hz, 1 H, NH), 7.26−7.40 (m, 5 H, Ph-H), 7.43 (s, 1 H, SCH), 9.25 (s, 1 H, CHO). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8 [C(*C*H$_3$)$_3$], 43.1 ($PhCH_2$), 49.8 (*C*HCO$_2$*t*Bu) 53.9 (CHNH), 60.4 (CHS), 83.7 [*C*(CH$_3$)$_3$], 116.1 (=*C*CO$_2$ H), 127.7, 129.1, 129.4 and 133.5 (Ph-C), 138.0 (SCH) 163.9 (C=O, lactam), 165.7 (CH*C*O$_2$*t*Bu), 167.5 (*C*O$_2$ H), 171.5 [PhCH$_2$*C*(O)]. − IR (KBr): ṽ = 3265 (broad, NH), 1768 (C=O, lactam), 1733 (C=O, ester), 1667 and 1544 (C=O, amide), 1369 (C−N), 1152 (O−C, ester) cm^{-1}. − MS (FAB$^+$, NOBA): *m*/*z* (%) = 425 (30) [M + Na]$^+$, 403 (11) [M + H]$^+$, 347 [M + H − C_4H_8]$^+$, 178 (100). − $C_{20}H_{22}N_2O_5S$ (402.47): calcd. C 59.69, H 5.51, N 6.96 S 7.97; found C 59.73, H 5.59, N 6.93, S 7.97.

***tert*-Butyl (7*R*,7a*R*)-3-Formyl-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (11):** This compound was prepared from alcohol **8** (0.57 g, 1.41 mmol) in the same way as described for the synthesis of 3-formylceph-2-em **10** (0.54 g, 96%). An analytical sample was obtained by column chromatography (silica gel, ethyl acetate/heptane 1:1) followed by re-crystallization (diethyl ether). − M.p. 146−148 °C (dec.). − $[\alpha]_D^{20}$ = +152 (*c* = 0.51, acetone). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 [s, 9 H, C(CH$_3$)$_3$], 3.24 and 3.94 (qAB, J = 18.3 Hz, 2 H, SCH_2), 3.63 and 3.67 (qAB, J = 16.0 Hz, 2 H, $PhCH_2$), 4.99 (d, J = 5.4 Hz, 1 H, NHCHC*H*S), 5.95 (dd, J = 5.4 Hz J = 9.2 Hz, 1 H, NHC*H*CHS), 6.33 (d, J = 9.2 Hz, 1 H, NH), 7.25−7.40 (m, 5 H, Ph-H), 9.80 (s, 1 H, CHO). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (SCH_2), 27.7 [C(*C*H$_3$)$_3$], 43.2 ($PhCH_2$), 58.9 (CHNH), 59.8 (CHS), 85.8 [*C*(CH$_3$)$_3$], 122.4 (=*C*CHO), 127.7, 129.2, 129.3 and 133.5 (Ph-C), 140.2 (=*C*CO$_2$*t*Bu), 159.0 (*C*O$_2$*t*Bu), 164.7 (C=O, lactam), 171.1 [PhCH$_2$*C*(O)], 187.9 (CHO). − IR (KBr): ṽ = 3334 (broad, NH), 1795 (C=O, lactam), 1705 (C=O, ester), 1668 and 1518 (C=O, amide), 1373 (C−N), 1226 and 1161 (C−O, ester) cm^{-1}. − MS (FAB$^+$, NOBA): *m*/*z* (%) = 425 (18) [M + Na]$^+$, 403 (13) [M + H]$^+$, 347 (28) [M + H − C_4H_8]$^+$, 176 (100). − $C_{20}H_{22}N_2O_5S$ (402.47): calcd. C 59.69, H 5.51, N 6.96 S 7.97; found C 59.51, H 5.53, N 6.88, S 7.94.

***tert*-Butyl (7*R*,7a*R*)-3-Formyl-1,6-dioxo-7-[(2-phenylacetyl)-amino]-1,6,7,7a-tetrahydro-2*H*-1λ^4-azeto[2,1-*b*][1,3]thiazine-4-carboxylate (12):** This compound was prepared from alcohol **9** (0.42 g, 1.00 mmol) in the same way as described for the synthesis of 3-formylceph-2-em **10**. Purification by chromatography (silica gel, ethyl acetate/heptane 2:1) afforded **12** as a white solid (0.40 g, 95%). − M.p. 175−176 °C (dec.). − $[\alpha]_D^{20}$ = −153 (*c* = 0.48, acetone). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58 [s, 9 H, C(CH$_3$)$_3$], 2.85 (dd, J = 18.4 Hz ^4J = 1.6 Hz, 1 H, SCH_2), 3.63 (s, 2 H, $PhCH_2$), 4.40 (d, J = 18.4 Hz, 1 H, SCH_2), 4.47 (dd, J = 5.2 Hz ^4J = 1.6 Hz, 1 H, NHCHC*H*S), 6.16 (dd, J = 5.2 Hz J = 9.9 Hz, 1 H, NHC*H*CHS), 6.91 (d, J = 9.9 Hz, 1 H, NH), 7.25−7.37 (m, 5 H, Ph-H), 9.97 (s, 1 H, CHO). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.7 [C(*C*H$_3$)$_3$], 41.4 (SCH_2), 43.1 ($PhCH_2$), 60.0 (CHNH), 67.6 (CHS), 86.3 [*C*(CH$_3$)$_3$], 116.5 (=*C*CHO), 127.6, 129.0, 129.3 and 133.6 (Ph-C), 139.9 (=*C*CO$_2$*t*Bu), 158.2 (*C*O$_2$*t*Bu), 164.5 (C=O, lactam), 171.3 [PhCH$_2$*C*(O)], 188.4 (CHO). − IR (KBr): ṽ = 3324 (broad, NH), 1800 (C=O, lactam), 1705 (C=O, ester), 1672 and 1520 (C=O, amide), 1370 (C−N), 1153 (C−O, ester), 1025 (S=O) cm^{-1}. − MS (FAB$^+$, NOBA): *m*/*z* (%) = 441 (2) [M + Na]$^+$, 419 (2) [M + H]$^+$, 363 (80) [M + H − C_4H_8]$^+$, 91 (100) [$PhCH_2^+$] − HRMS (FAB, *m*/*z*): 441.1059 (calcd. for $C_{20}H_{22}N_2O_6SNa$: 441.1096).

(4*S*,7*R*,7a*R*)-4-(*tert*-Butoxycarbonyl)-6-oxo-7-[(2-phenylacetyl)-amino]-7,7a-dihydro-4*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-3-carboxylic Acid (13): Aldehyde **10** (0.80 g, 1.99 mmol) was dissolved in THF (28 mL) and cyclohexene (8 mL) was added. After cooling 0 °C a mixture of KH_2PO_4 (1.50 g) and $NaClO_2$ (1.20 g) in water (28 mL) was added. The reaction mixture was allowed to warm up to room temperature slowly and then stirred overnight. The reaction mixture was acidified with 2 N HCl and the THF was removed in vacuo. The aqueous layer was extracted with ethyl acetate (3 × 75 mL). The combined organic layer was washed with brine (1 × 50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was washed with ether to obtain acid **13** (0.77 g, 93%). An analytically pure sample could be obtained by column chromatography (silica gel, ethyl acetate/hexane 1:1). − M.p. 178−180 °C (dec.). − $[\alpha]_D^{20}$ = +535 (*c* = 1.0, acetone). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, C(CH$_3$)$_3$], 3.64 (s, 2 H, $PhCH_2$), 5.15 (d, J = 3.9 Hz, 1 H, NHCHC*H*S), 5.21 (s, 1 H, C*H*CO$_2$*t*Bu), 5.55 (dd, J = 3.9 Hz J = 7.8 Hz, 1 H, NHC*H*CHS), 6.61 (d, J = 7.8 Hz, 1 H, NH), 7.25−7.35 (m, 5 H, Ph-H), 7.74 (s, SCH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8 [C(*C*H$_3$)$_3$], 43.1 ($PhCH_2$), 49.8 (*C*HCO$_2$*t*Bu) 53.9 (CHNH), 60.4 (CHS), 83.7 [*C*(CH$_3$)$_3$], 116.1 (=*C*CO$_2$ H), 127.7, 129.1, 129.4 and 133.5 (Ph-C), 138.0 (SCH) 163.9 (C=O, lactam), 165.7 (CH*C*O$_2$*t*Bu), 167.5 (*C*O$_2$ H), 171.5 [PhCH$_2$*C*(O)]. − IR (KBr): ṽ = 3326 (broad, NH), 1805 (C=O, lactam), 1736 (C=O, ester), 1678 and 1537 (C=O, amide), 1640 (C=O, acid), 1389 (C−N) 1162 (C−O, ester) cm^{-1}. − MS (FAB$^+$, NOBA): *m*/*z* (%) = 441 (18) [M + Na]$^+$, 419 (8) [M + H]$^+$, 385 (9), 363 (32), 178 (100), 274 (100). − $C_{20}H_{22}N_2O_6S$ (418.47): calcd. C 57.40, H 5.30, N 6.69; found C 57.56, H 5.35, N 6.65.

(7*R*,7a*R*)-4-(*tert*-Butoxycarbonyl)-6-oxo-7-[(2-phenylacetyl)amino]-7,7a-dihydro-2*H*,6*H*-azeto[2,1-*b*][1,3]thiazine-3-carboxylic Acid (14): A solution of sulfoxide **15** (0.35 g, 0.73 mmol) in dry DMF (3 mL) was treated with tin(II) chloride (0.48 g, 2.75 mmol) and an excess of acetyl chloride (1.5 mL) at 0 °C for 2 h. After removal of excess acetyl chloride (in vacuo) ethyl acetate and water were added. Extraction with ethyl acetate (2 × 10 mL), drying ($MgSO_4$), and concentration in vacuo afforded the crude sulfide in nearly quantitative yield. Purification by column chromatography (silica

gel, ethyl acetate/acetone 1:1) gave sulfide **14** (0.185 g, 55%) as a white solid. An analytically pure sample was obtained by recrystallisation from diethyl ether. − M.p. 165−167 °C (dec.). − $[\alpha]_D^{20}$ = −58.8 (c = 0.32, acetone). − ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 1.51 [s, 9 H, C(CH$_3$)$_3$], 3.57 and 3.86 (qAB, J = 17.8 Hz, 2 H, SCH$_2$), 3.67 and 3.68 (qAB, J = 14.3 Hz, 2 H, PhCH$_2$), 5.17 (d, J = 5.1 Hz, 1 H, NHCHC*H*S), 5.90 (dd, J = 5.1 Hz J = 8.9 Hz, 1 H, NHC*H*CHS), 7.24−7.38 (m, 5 H, Ph-H), 8.17 (d, J = 8.9 Hz, 1 H, NH). − ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 25.0 (SCH$_2$), 27.8 [C(*C*H$_3$)$_3$], 43.0 (PhCH$_2$), 60.0 and 60.8 (CHNH and CHS), 83.6 [*C*(CH$_3$)$_3$], 110.7 (=*C*CO$_2$ H), 127.5, 129.1, 130.0 and 136.4 (Ph-C), 136.6 (=*C*CO$_2$*t*Bu), 161.7 (*C*O$_2$*t*Bu), 165.3 (C=O, lactam), 166.3 (CO$_2$ H), 171.6 [PhCH$_2$*C*(O)]. − IR (KBr): $\tilde{\nu}$ = 3298 (broad, NH), 2978 (COO−H), 1795 (C=O, lactam), 1730 (C=O, ester), 1716 (C=O, acid), 1684 and 1523 (C=O, amide) 1369 (C−N), 1155 (C−O, ester) cm^{-1}. − MS (FAB$^+$, NOBA): m/z (%) = 441 (14) [M + Na]$^+$, 419 (16) [M + H]$^+$, 363 (52) [M + H − C$_4$H$_8$]$^+$, 176 (100). − C$_{20}$H$_{22}$N$_2$O$_6$S (418.47): calcd. C 57.40, H 5.30, N 6.69; found C 57.29, H 5.30, N 6.54.

(7*R*,7a*R*)-4-(*tert*-Butoxycarbonyl)-1,6-dioxo-7-[(2-phenylacetyl)-amino]-1,6,7,7a-tetrahydro-2*H*-1λ^4-azeto[2,1-*b*][1,3]thiazine-3-carboxylic Acid (15): This compound was prepared from aldehyde **12** (0.78 g, 1.86 mmol) in the same way as described for the synthesis of 3-carboxyceph-2-em **13**. Yield after purification (0.65 g, 80%). M.p. 163−165 °C (dec.). − $[\alpha]_D^{20}$ = 9.80 (c = 0.49, acetone). − ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 1.52 [s, 9 H, C(CH$_3$)$_3$], 3.44 (dd, J = 18.1 Hz ^4J = 1.8 Hz, 1 H, SCH$_2$), 3.63 (qAB, J = 14.6 Hz, 2 H, PhCH$_2$), 4.26 (d, J = 18.1 Hz, 1 H, SCH$_2$), 4.89 (dd, J = 5.1 Hz ^4J = 1.6 Hz, 1 H, NHCHC*H*S), 6.12 (d, J = 5.1 Hz, 1 H, NHC*H*CHS), 7.25−7.40 (m, 5 H, Ph-H). − ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 27.8 [C(*C*H$_3$)$_3$], 43.1 (SCH$_2$), 44.8 (PhCH$_2$), 60.3 (CHNH), 68.1 (CHS), 83.9 [*C*(CH$_3$)$_3$], 119.7 (=*C*CO$_2$ H), 127.6, 129.3, 130.1 and 136.4 (Ph-C), 136.6 (=*C*CO$_2$*t*Bu), 161.1 (*C*O$_2$*t*Bu), 165.5 (C=O, lactam), 167.9 (CO$_2$ H), 172.6 [PhCH$_2$*C*(O)]. − IR (KBr): $\tilde{\nu}$ = 3332 (broad, NH), 2980 and 2927 (COO−H), 1793 (C=O, lactam), 1729 (C=O, ester), 1689 (C=O, acid), 1657 and 1523 (C=O, amide) 1380 (C−N), 1215 (C−O, ester), 1039 (S=O) cm^{-1}. − MS (FAB$^+$, NOBA): m/z (%) = 457 (5) [M + Na]$^+$, 434 (7) [M$^+$], 393 (13) [M + Na−C$_4$H$_8$]$^+$, 379 (14) [M + H − C$_4$H$_8$]$^+$, 57 (100). − HRMS (FAB, m/z): 457.0984 (calcd. for C$_{20}$H$_{22}$N$_2$O$_7$SNa: 457.1045).

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