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ORIGINAL PAPER

A novel synthetic route to 7-MAC from 7-ACA

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Abstract An efficient and practical seven-step procedure is described for the synthesis of (6*R*,7*S*)-benzhydryl-7-amino-7-methoxy-3-((1-methyl-1*H*-tetrazol-5-ylthio) methyl)-8-oxo-5-thia-1-aza-bicyclo [4.2.0]oct-2-ene-2-carboxylate (7-MAC, **3**) with overall yield of 49 %. This synthesis features a convenient and highly selective method for the introduction of 7α-methoxy group to cephalosporin nucleus in **10** using MeOLi/*t*-BuOCl in THF.

Keywords Antibiotics · Esterification · Isomerization · 7α-Methoxycephalosporins · Stereoselectivity synthesis

Introduction

Much attention has been focused on the synthesis of 7α-methoxycephalosporin drugs such as cefbuperazone (**1**) and cefmetazole (**2**) (Fig. 1) due to their effective activity against many pathogenic microorganisms and resistant Gram-negative bacteria [1–3]. Although many synthetic routes to 7α-methoxycephalosporins and their analogues have been documented to date [4–32], the strategy, utilizing (6*R*,7*S*)-benzhydryl-7-amino-7-methoxy-3-((1-methyl-1*H*-tetrazol-5-ylthio)methyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0] oct-2-ene-2-carboxylate (7-MAC, **3**) as an advanced intermediate, is an attractive and reliable process in the synthesis of 7α-methoxycephalosporins. A tremendous efforts have been devoted to the search for the efficient preparation of this chiral intermediate with possible industrial development [10–12, 19–37]. However, their industrial application is hampered by the lack of a convenient and highly selective installization of 7α-methoxy group to cephalosporin nucleus. The development of practical procedure for the synthesis of **3** from 7-aminocephalosporanic acid (7-ACA, **4**) is still in high demanded.

We reported herein an efficient procedure for the synthesis of **3** from 7-ACA **4** which comprises the convenient and highly selective introduction of 7α-methoxy group in **10** in the presence of MeOLi/MeOH and *t*-BuOCl in THF.

Compound **6** was prepared with 91 % yield from the commercially available 7-aminocephalosporanic acid (7-ACA, **4**) upon treatment with 5-mercapto-1-methyl-1*H*-tetrazole in anhydrous MeCN to afford **5** according to the reported procedure [37, 38]. Regioselective acylation of **5** with phenylacetyl chloride in the presence of Na_2CO_3 in acetone/H_2O to afford the amide **6** in almost quantitative yield (Scheme 1).

With compound **6** in hand, the next step is the esterification of **6** for the preparation of **9**. In the synthesis of cephalosporin antibiotics, diphenyldiazomethane was generally utilized as a masking group of the carboxylic group in cephalosporin nucleus [33–36], the unavailability and hazard property of this reagent make this reaction unacceptable on a large scale preparation of compound **9**. We used diphenylmethanol instead of diphenyldiazomethane for this purpose. Compound **6** reacted with diphenylmethanol in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 at −20 °C. As excepted, the reaction proceeded smoothly. Surprisingly, the unnatural Δ^3 isomer **7** was isolated in almost

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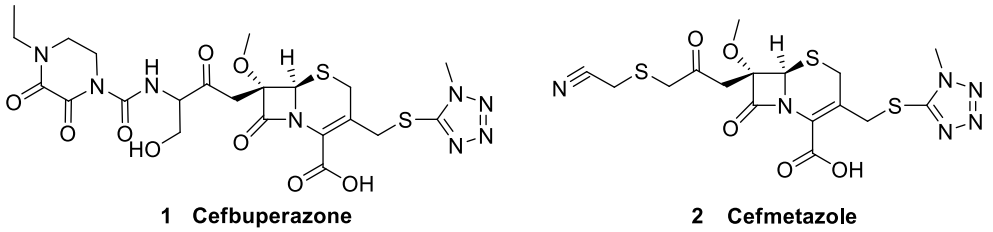
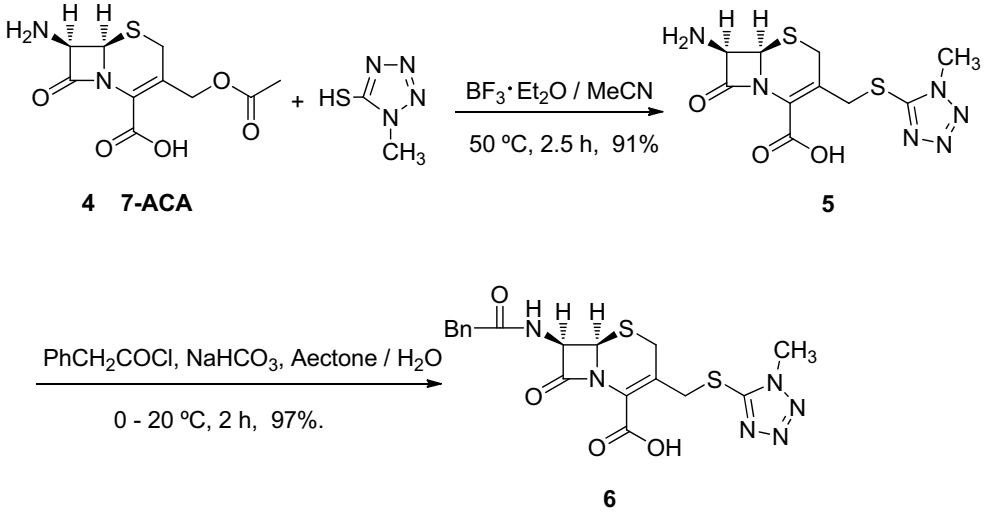


Fig. 1 Sturcture of cefbuperazone and cefmetazole

Scheme 1 The approach to the synthesis of compound **6**



100 % yield, instead of the desired normal Δ^2 isomer **9** (Scheme 2).

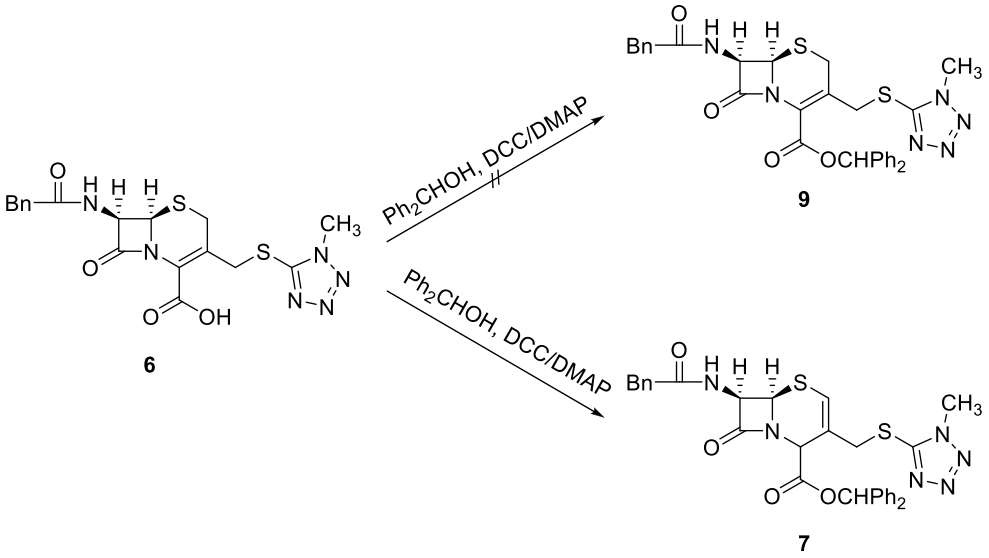
Identification of these isomers was carried out by the characteristics of these isomers. (1) In the NMR spectra of product, single peaks near 5.22 and 6.53 ppm replace the methylene protons between 3.50 and 3.60 ppm adjacent to the sulfur in the normal Δ^2-cephalosporin isomer suggested the presence of lone protons at C-2 and C-4, respectively; (2) In the dept 135° spectra, two negative peaks show that there are only two methylene in the molecule **7**, however, in the normal Δ^2-cephalosporin series, there should be three (Fig. 2).

Gratifyingly, the desired Δ^2 isomer **9** could, in turn, easily come through a double bond shift under the chemoselective oxidation/reduction strategy. Strategic transformations include a chemoselective oxidation of thioether bond of Δ^3 isomer **7** to Δ^2 sulfoxide isomer **8** [39] and subsequent reduction of **8** [40] to come back to the Δ^2 sulfide isomer **9**. As expected, the reaction of *m*-CPBA-mediated chemoselective oxidation and PCl_3-mediated reduction proceeded smoothly to afford the normal Δ^2 isomer **9**, which was outlined in Scheme 3.

Among the various reaction conditions for conversion of **9** to 7α-methoxy product **10**, as summarized in Table 1, the maximum yield (71 %) was obtained via using MeOLi/MeOH and *t*-BuOCl in THF at −78 °C. Some other halogenating reagents such as NBS and NCS were also successfully employed as reagents for the introduce methoxy group reaction under the similar reaction conditions in moderate yields.

Deprotection of **10** proceeded smoothly with PCl_5/C_5H_5N in CH_2Cl_2 at 0 °C for 90 min followed by addition MeOH to afford the desired product **3** in 91 % yield (Scheme 4). In this step, the use of a slight excess of PCl_5 and pyridine, each in equiv. molar ratio, over the amount of ester gave optimum yields of side-chain cleavage.

In conclusion, we have successfully developed a novel synthetic process for the synthesis of 7-MAC **3** in seven steps and in 49.2 % total yield from readily accessible 7-ACA, which appears to be more compatible with industrial scale and has some advantages over the existing synthesis.



Scheme 2 The esterification reaction of compound **6**

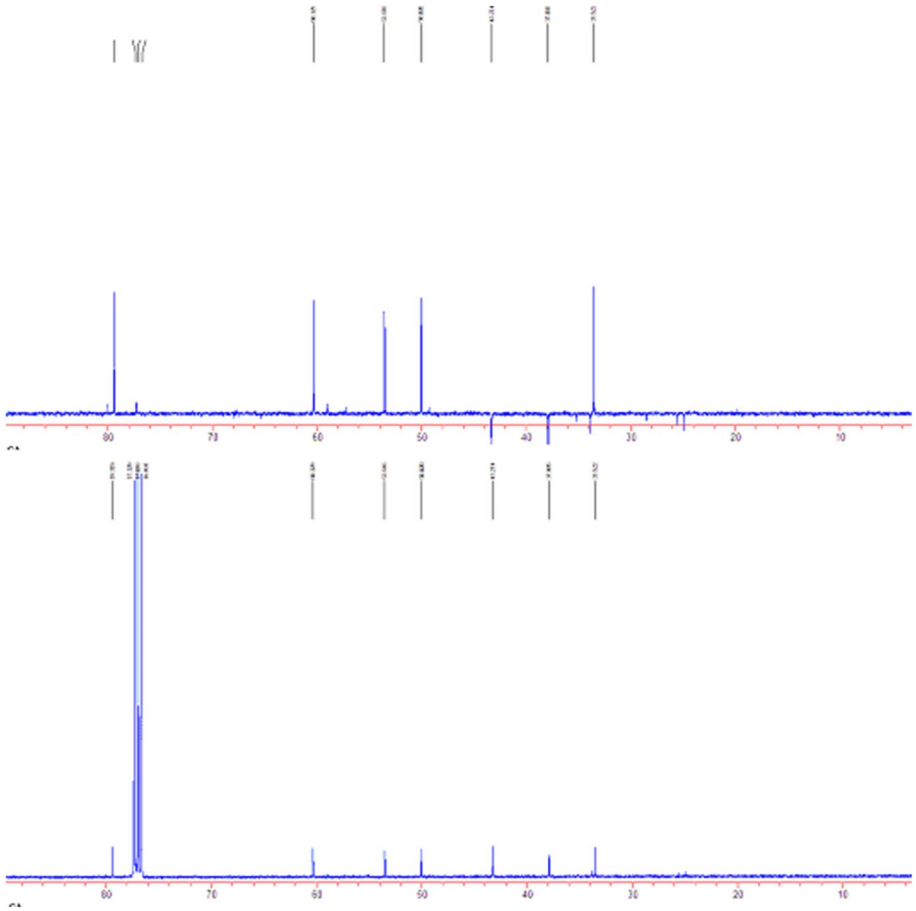
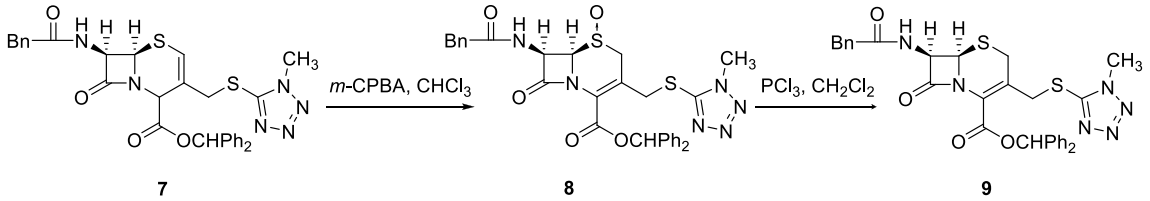


Fig. 2 Dept 135° and ^{13}C spectra of compound **7**



Scheme 3 The conversion of compound **7**–**9**

Table 1 Effects of reaction conditions on the yield of the compound **10**

Entry	Halogenating reagents	Reaction temp. (°C)	Yield (%)
1	*t*-BuOCl	−78	71
2	*t*-BuOCl	−40	48
3	*N*-Bromosuccimide (NBS)	−78	64
4	*N*-Bromosuccimide (NBS)	−40	38
5	*N*-Chlorosuccimide (NCS)	−78	42

Experimental

Reagents and chemicals were obtained from commercial suppliers and used without further purification. THF was distilled from sodium benzophenone ketyl. Ethyl acetate, acetonitrile, acetone, chloroform and methylene chloride were all redistilled. Petroleum ether (PE) for column chromatography (CC) had a b.p. of 30–60 °C. Melting points (m.p.) were determined on a *WRS-1B* digital metal point apparatus. NMR spectra were measured on *Bruker AV 400* in deuteriochloroform solution or DMSO-d_6 solution with tetramethylsilane as an internal standard. Mass spectra were recorded on a *Waters Quattro Micromass* spectrometer. IR spectra were recorded on a *Jasco FT/IR-4200* spectrometer.

(6*R*,7*R*)-7-amino-3-((1-methyl-1*H*-tetrazol-5-ylthio) methyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0] oct-2-ene-2-carboxylic acid (5)

5-Mercapto-1-methyl-1*H*-tetrazole (6.32 g, 54.48 mmol) and 7-ACA (**4**, 14.8 g, 54.41 mmol) were successively added to a stirred solution of $BF_3{\cdot}Et_2O$ (23.6 g) in anhydrous acetonitrile (75 mL). The resulting solution was allowed to react at 50 °C for 2.5 h. After cooling in an ice-bath, the reaction solution was diluted with H_2O (75 mL) and adjusted to pH 4.0 by the addition of 28 % NH_4OH. Crystals that precipitated were collected by filtration, and washed with water and then acetone, to give **5** (16.3 g, 91.3 %) as earth-yellow solid. m.p.: 207–209 °C [lit. [37, 38]: 224–226 °C (dec.)]. IR (KBr): 3423, 3170, 1803, 1735, 1618, 1542, 1411, 1342, 1084 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): $\delta = 3.56$ (d, $^2J = -18$ Hz, 1H, H-4), 3.73 (d, $^2J = -18$ Hz, 1H, H-4), 3.93 (s, 3H, CH_3), 4.20 (d, $^2J = -13.6$ Hz, 1H, CH_2), 4.36 (d, $^2J = -13.6$ Hz, 1H, CH_2), 4.78 (d, $^3J = 5.2$ Hz, 1H, H-6), 4.96 (d, $^3J = 5.2$ Hz, 1H, H-7).

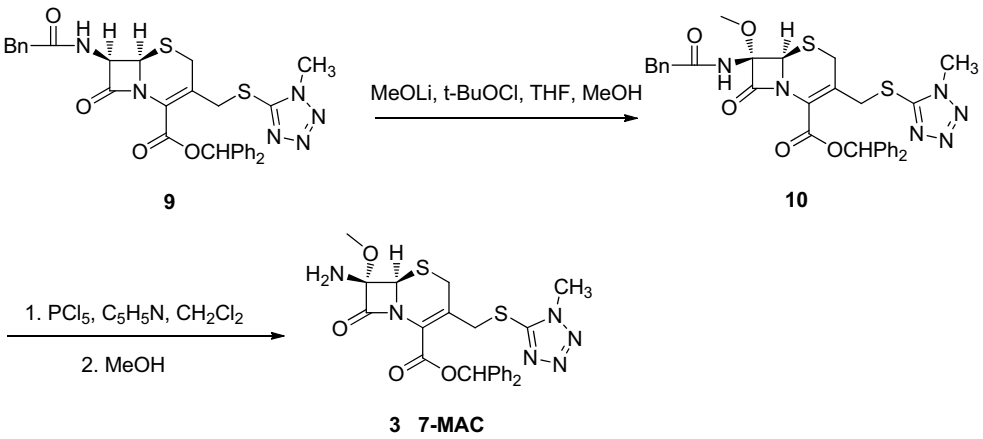
(6*R*,7*R*)-3-((1-methyl-1*H*-tetrazol-5-ylthio)methyl)-8-oxo-7-(2-phenylacetamido)-5-thia-1-aza-bicyclo [4.2.0] oct-2-ene-2-carboxylic acid (6)

Compound **5** (9.84 g, 30 mmol) was transferred into a three-necked flask, dissolved in an ice-bath solution of sodium hydrogencarbonate (6.30 g, 75 mmol) in 180 mL of water and of acetone. The mixture was treated dropwise with a solution of $PhCH_2COCl$ (5.10 g, 33 mmol) in 20 mL of acetone at 0–5 °C during a period of 40 min. After stirring for 3 h at 20 °C, the acetone was removed under reduced pressure. The aqueous solution was then poured into a separatory funnel. Ethyl acetate (180 mL) was added to this solution and acidified to pH 2.5–3.0 with 17.5 % HCl. After shaking the aqueous layer was removed, then extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water, brine, dried over anhydrous magnesium sulphate and evaporated in vacuum to give **6** (12.98 g, 97.1 %) as white solid. m.p.: 63.4–65.0 °C. IR (KBr): 3292, 3029, 2951, 1778, 1718, 1664, 1542, 1364, 1244, 1174, 1096, 730, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.48$ (d, $^2J = -18$ Hz, 1H, H-4), 3.57 (d, $^2J = -18$ Hz, 1H, H-4), 3.62 (d, $^2J = -18$ Hz, 1H, CH_2), 3.76 (d, $^2J = -18$ Hz, 1H, CH_2), 3.94 (s, 3H, CH_3), 4.25 (d, $^2J = -13.6$ Hz, 1H, CH_2), 4.35 (d, $^2J = -13.6$ Hz, 1H, CH_2), 5.06 (d, $^3J_2 = 4.8$ Hz, 1H, H-6), 5.67 (dd, $^3J_1 = 8.0$ Hz, $^3J_2 = 4.8$ Hz, 1H, H-7), 7.21–7.32 (m, 5H, ArH), 9.12 (d, $^3J_1 = 8.0$ Hz, 1H, NH), 13.68 (s, br, 1H, COOH). LC–MS: *m/z* (%) = 447 (21) $[M + H]^+$, 469 (24) $[M + Na]^+$, 330.9 (100).

(6*R*,7*R*)-benzhydryl-3-((1-methyl-1*H*-tetrazol-5-ylthio) methyl)-8-oxo-7-(2-phenylacetamido)-5-thia-1-aza-bicyclo[4.2.0]oct-3-ene-2-carboxylic (7)

To a solution of **6** (5.58 g, 12.5 mmol) in methylene chloride (25 mL) was added diphenylmethanol (2.3 g, 12.5 mmol)

Scheme 4 Synthesis of target compound **7-MAC**



and dicyclohexylacrbodiimide (DCC, 2.58 g, 12.5 mmol) while stirring at −20 °C, then the catalyst 4-dimethylaminopyridine (DMAP, 0.08 g) was added to the mixture. The color of the resulting mixture changed to black immediately. After reaction completion as monitored by TLC, the mixture was filtered and the solvent was removed under reduced pressure to give **7** (7.58 g, 99.1 %) as white solid. m.p.: 144.6–146.2 °C. IR (KBr): 3303, 3031, 2951, 1781, 1752, 1719, 1661, 1542, 1388, 1250, 1167, 1097, 744, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.59$ (d, $^2J = -16$ Hz, 1H, CH_2), 3.64 (d, $^2J = -18$ Hz, 1H, CH_2), 3.84 (s, 3H, CH_3), 3.89 (d, $^2J = -14.4$ Hz, H-4), 4.21 (d, $^2J = -14.4$ Hz, 1H, H-4), 5.17 (d, $^3J_2 = 4.0$ Hz, 1H, H-6), 5.22 (s, 1H, H-2), 5.59 (dd, $^3J_1 = 8.8$ Hz, $^3J_2 = 4.0$ Hz, 1H, H-7), 6.10 (d, $^3J_1 = 8.8$ Hz, 1H, NH), 6.53 (s, 1H, H-4), 6.91 (s, 1H, CH), 7.25–7.37 (m, 15H, ArH). LC–MS: *m/z* (%) = 613 (100) $[M + H]^+$, 635 (21) $[M + Na]^+$, 331 (15), 167 (62).

(6*R*,7*R*)-benzhydryl-3-((1-methyl-1*H*-tetrazol-5-ylthio) methyl)-8-oxo-7-(2-phenylacetamido)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate 1-oxide (8)

Compound **7** (1.02 g, 1.67 mmol) was dissolved in chloroform (10 mL), cooled in ice-bath, and stirred while 85 % *m*-chloroperbenzoic acid (0.38 g, 2.20 mmol) in chloroform (2 mL) was added dropwise during a period of 30 min. After stirring 6 h at 0 °C. The reaction mixture was washed with saturated $NaHCO_3$ and brine. The organic solution was dried over anhydrous magnesium sulphate and evaporated in vacuum to give **8** (1.03 g, 98.2 %) as yellow solid. m.p.: 124.1–126.3 °C. IR (KBr): 3367, 3031, 2929, 1793, 1751, 1719, 1685, 1676, 1627, 1542, 1509, 1381, 1245, 1064, 1032, 750, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.38$ (d, $^2J = -19.2$ Hz, 1H, H-4), 3.51 (d, $^2J = -15.2$ Hz, 1H, CH_2), 3.65 (d, $^2J = -15.2$ Hz, 1H, CH_2), 3.70 (s, 3H, CH_3), 3.96 (d, $^2J = -14.4$ Hz, 1H, H-4), 4.05 (d, $^2J = -13.6$ Hz, 1H, CH_2), 4.36 (d, $^2J = -13.6$ Hz, 1H, CH_2), 4.37 (d, $^3J_2 = 4.8$ Hz, 1H, H-6), 5.98 (dd, $^3J_1 = 10.0$ Hz, $^3J_2 = 4.8$ Hz, 1H, H-7), 6.71 (d, $^3J_1 = 10.0$ Hz, 1H, NH), 6.84 (s, 1H, CH), 7.15–7.39 (m, 15H, ArH). LC–MS: *m/z* (%) = 629 (71) $[M + H]^+$, 651 (100) $[M + Na]^+$, 347 (48), 167 (79).

(6*R*,7*R*)-benzhydryl-3-((1-methyl-1*H*-tetrazol-5-ylthio) methyl)-8-oxo-7-(2-phenylacetamido)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate (9)

Compound **8** (1.67 g, 3 mmol) was dissolved in methylene chloride (18 mL) containing PCl_3 (2.06 g, 15 mmol). The solution was heated under reflux for 3 h. After cooling to room temperature, the reaction was neutralized with a saturated solution of aqueous $NaHCO_3$, washed with water, and dried over anhydrous magnesium sulphate. Removal of solvent in vacuo yielded reduced material **9** (1.64 g, 89.2 %) as yellow solid. m.p.: 101.3–103.2 °C. IR (KBr): 3423, 3170, 2938, 1803, 1735, 1719, 1654, 1637, 1617, 1543, 1524, 1475, 1411, 1342, 1084, 1064, 745, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.52–3.66 (m, 3H, CH_2 + H-4), 3.77 (s, 3H, CH_3), 4.17 (d, $^2J = -13.6$ Hz, 1H, CH_2), 4.27 (d, $^2J = -13.6$ Hz, 1H, CH_2), 4.88 (d, $^3J_2 = 4.8$ Hz, 1H, H-6), 5.83 (dd, $^3J_1 = 9.2$ Hz, $^3J_2 = 4.8$ Hz, 1H, H-7), 6.71 (d, $^3J_1 = 9.2$ Hz, 1H, NH), 6.84 (s, 1H, CH), 7.17–7.36 (m, 15H, ArH). LC–MS: *m/z* (%) = 613 (100) $[M + H]^+$, 635 (21) $[M + Na]^+$, 331 (15), 167 (62).

(6*R*,7*S*)-benzhydryl-7-methoxy-3-((1-methyl-1*H*-tetrazol-5-ylthio)methyl)-8-oxo-7-(2-phenylacetamid-o)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate (10)

A solution of **9** (0.51 g, 0.83 mmol) in THF (5 mL) was added to a stirred mixture of LiOMe (0.11 g, 2.92 mmol),

THF (1.5 mL) and MeOH (4 mL) at −78 °C under dry N_2. After 2 min *t*-butyl hypochlorite (0.2 mL, 1.67 mmol) was added and after a further 20 min the mixture was poured into iced water (40 mL) containing NH_4Cl and $Na_2S_2O_5$ then extracted with EtOAc (3 × 15 mL). The combined extracts were washed with saturated NaCl, dried and evaporated. The crude product was purified by CC (SiO_2, petroleum ether/AcOEt 7:6) to afford pure **10** (0.38 g, 71.3 %) as yellow solid. m.p.: 74–102 °C. IR (KBr): 3289, 3030, 2936, 1776, 1720, 1701, 1686, 1543, 1509, 1496, 1381, 1241, 1085, 1031, 750, 699 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.42 (s, 3H, CH_3), 3.45–3.72 (m, 3H, CH_2 + H-4), 3.83 (s, 3H, CH_3), 4.26 (d, ^2J = −13.6 Hz, 1H, CH_2), 4.44 (d, ^2J = −13.6 Hz, 1H, CH_2), 4.99 (s, 1H, H-6), 6.21 (s, 1H, NH), 6.89 (s, 1H, CH), 7.25–7.44 (m, 15H, ArH). LC–MS: *m/z* (%) = 643 (17) $[M + H]^+$, 665 (100) $[M + Na]^+$, 545 (52), 361 (29), 167 (68).

(6*R*,7*S*)-benzhydryl-7-amino-7-methoxy-3-((1-methyl-1*H*-tetrazol-5-ylthio) methyl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0] oct-2-ene-2-carboxylate (3)

Pyridine (0.25 g, 3.1 mmol) was added to a suspension of PCl_5 (0.65 g, 3.1 mmol) in methylene chloride (8 mL) at 5 °C, and the mixture was stirred at room temperature for 30 min. **10** (1.93 g, 3 mmol) was added to reaction mixture at 5 °C and stirred at 5–8 °C for 2 h. Then, methanol (2 mL) was quickly added to reaction mixture at −30 °C and the resulting solution was stirred at −10 °C for 2 h. After removing the solvent in vacuo, the residue was added to a mixture of water and diethyl ether. The separated aqueous layer was adjusted to pH 7.5 with 20 % Na_2CO_3, and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous magnesium sulphate and evaporated to give **3** (1.43 g, 91.0 %) as yellow solid. m.p.: 119.6–121.2 °C (lit. [41]: 120–124 °C). IR (KBr): 3374, 3031, 2944, 1774, 1721, 1656, 1637, 1626, 1496, 1475, 1454, 1377, 1250, 1236, 1170, 1097, 1009, 744, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (s, 3H, CH_3O), 3.56 (d, ^2J = −16.8 Hz, 1H, H-4), 3.63 (d, ^2J = −6.8 Hz, 1H, H-4), 3.84 (s, 3H, CH_3), 4.28 (d, ^2J = −13.6 Hz, 1H, CH_2), 4.48 (d, ^2J = −13.6 Hz, 1H, CH_2), 4.84 (s, 1H, H-6), 6.93 (s, 1H, CH), 7.26–7.49 (m, 10H, ArH). ESI–MS: *m/z* (%) = 525 (4) $[M + H]^+$, 547 (28) $[M + Na]^+$, 215 (69), 167 (100).

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