2. The Synthesis of (6*R**, 7*R**)-4-Carboxy-3-hydroxy-7-phenylacetamido-2-isooxacephem

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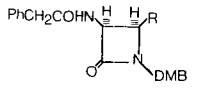
(31.VIII.83)

Summary

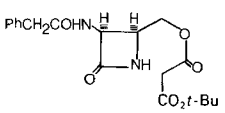
A new route to the synthesis of the title compound is described.

A low yield synthesis of the isooxacephem **7** was recently reported [1]. In this paper we wish to describe a high yield preparation of **7** using the *tert*-butyl (azetidinyl)methyl malonate **5** as a key intermediate.

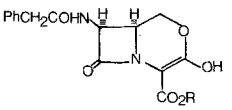
We chose *N*-dimethoxybenzyl-β-lactam **1** [2] as the starting material. Ozonolysis, followed by reductive workup gave the corresponding alcohol **2** (95%). Acylation of **2** with *t*-butyl (chloroformyl)acetate [3]/pyridine in CH_2Cl_2 afforded, after purification, ester **3** (70%). The β-lactam N-atom in **3** was conveniently deblocked by oxidative cleavage with buffered potassium persulfate [4] [5] to give **5** (63%). The IR, NMR, and elemental analysis of **5** were consistent with the proposed structure. For the cyclization of **5** to the isooxacepham skeleton it was planned to introduce a leaving group at C(α) of the malonate moiety. However, reaction of **5** with 1 equiv. of trifluoromethanesulfonyl chloride and 2 equiv. of Et_3N in CH_2Cl_2 gave, surprisingly, isooxacephem **6** (65%). The most likely explanation for the cyclization is a sequence where CF_3SO_2Cl acts as a chlorinating agent [6–8] at the potential carbanionic site, followed by a replacement of the chlorine substituent by the azetidinyl function. The hypothesis is further supported by the fact that treatment of *N*-substituted *tert*-butyl (azetidinyl)methyl malonate **3** with CF_3SO_2Cl/NEt_3 in CH_2Cl_2 at 0°, followed by standard aqueous workup, gave compound **4** (80%).



1 R = CH = CHPh
2 R = CH_2OH
3 R = $CH_2OCOCH_2COO(t\text{-Bu})$
4 R = $CH_2OCOCH(Cl)COO(t\text{-Bu})$



5



6 R = *t*-Bu
7 R = H

DMB = 2,4-dimethoxybenzyl

Reaction of **6** with trifluoroacetic acid afforded the bicyclic derivative **7** (70%). Compound **7** was in every aspect identical with the authentic sample, prepared and characterized before [1].

This work was supported by the *University Jehad Council.*

Experimental Part

General. See [9] [10].

cis-N-*(2,4-Dimethoxybenzyl)-4-hydroxymethyl-3-phenylacetamido-2-azetidinone* (**2**). The *cis-N*-(2',4'-dimethoxybenzyl)-3-phenylacetamido-4-styryl-2-azetidinone (**1**) was converted to **2** according to the procedure described for the preparation of *t*-butyl 2-(4-hydroxymethyl-2-oxo-3-phenylacetamido-1-azetidinyl)-2-(diethylphosphone)acetate [11]. IR (CH_2Cl_2): 3350 (NH), 1750 (β-lactam), 1675 (amide). ^{1}H-NMR ($CDCl_3$): 3.54 (*s*, 2H, CH_2Ph); 3.61 (*s*, 6H, $2OCH_3$); 3.81–4.41 (*m*, 4H, H–C(4), CH_2OH); 4.67 (*AB*, 2H, CH_2-N); 5.10 (*dd*, *J* = 5, 8, 1H, H–C(3)); 6.31 (*d*, *J* = 8, 1H, NH); 6.81–7.85 (*m*, 8 arom. H).

$C_{21}H_{24}N_2O_5$ (384.20) Calc. C 65.62 H 6.25 N 7.29% Found C 65.61 H 6.20 N 7.27%

tert-*Butyl* (cis-N-*(2,4-Dimethoxybenzyl)-2-oxo-3-phenylacetamido-4-azetidinyl)methyl Malonate* (**3**). Pyridine (4.80 g, 0.06 mol) was added to a solution of **2** (3.84 g, 0.01 ml) in 30 ml of dry CH_2Cl_2 at 25°. Then *tert*-butyl (chloroformyl)acetate (3.58 g, 0.02 mol) in 5 ml of CH_2Cl_2 was added. The solution was stirred for 48 h at 25°, then washed with 10% $NaHCO_3$ and H_2O, dried ($MgSO_4$), and evaporated to give impure **3** which was chromatographed on silica gel. CH_2Cl_2 eluted impurities and $CHCl_3$ gave 3.68 g (70%) of **3**. IR (CH_2Cl_2): 1775 (β-lactam), 1745 (ester), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 1.49 (*s*, 9H, $C(CH_3)_3$); 3.55 (*s*, 2H, CH_2Ph); 3.67 (*s*, 6H, $2OCH_3$); 3.89–4.21 (*m*, 3H, H–C(4), CH_2–C(4)); 4.25 (*s*, 2H, $COCH_2CO$); 4.65 (*AB*, 2H, CH_2N); 5.15 (*dd*, *J* = 5, 8, 1H, H–C(3)); 6.21 (*d*, *J* = 8, 1H, NH); 6.91–7.62 (*m*, 8 arom-H).

$C_{28}H_{34}N_2O_8$ (526.04) Calc. C 63.87 H 6.46 N 5.32% Found C 63.81 H 6.23 N 5.22%

tert-*Butyl* (cis-N-*(2,4-Dimethoxybenzyl)-2-oxo-3-phenylacetamido-4-azetidinyl)methyl 2-Chloromalonate* (**4**). To a solution of **3** (0.526 g, 1 mmol) in 15 ml of CH_2Cl_2 at 0° was added Et_3N (0.101 g, 1 mmol) and CF_3SO_2Cl (0.169 g, 1 mmol). After 2 h at 0°, the mixture was stirred for 10 h at 25°. Then, the solution was washed with H_2O, dried, and the solvent evaporated. The crude product was purified by chromatography (silica gel/$CHCl_3$) to afford **4** (80%). IR (CH_2Cl_2): 1775 (β-lactam), 1730 (ester), 1680 (amide). ^{1}H-NMR: similar to that of **3** except for COCH(Cl)CO at 5.21. MS (CI): 561 (M^+ + **1**, Cl cluster).

tert-*Butyl* (cis-*2-Oxo-3-phenylacetamido-4-azetidinyl)methyl Malonate* (**5**) was obtained from **3** according to [4] [5]: 63% yield. IR (CH_2Cl_2): 1776 (β-lactam), 1730–1750 (ester), 1681 (amide). ^{1}H-NMR ($CDCl_3$): 1.48 (*s*, 9H, $C(CH_3)_3$); 3.57 (*s*, 2H, CH_2Ph); 3.88–4.09 (*m*, 4H, H-N(1), H–C(4), CH_2-C(4)); 4.20 (*s*, 2H, $COCH_2CO$); 5.21 (*dd*, *J* = 5, 8, 1H, H–C(3)); 6.15 (*d*, *J* = 8, 1H, NH–C(3)); 7.31 (*s*, 5H, Ph).

$C_{19}H_{24}N_2O_6$ (376.24) Calc. C 60.64 H 6.38 N 7.45% Found C 60.43 H 6.30 N 7.31%

tert-*Butyl (6R*,7R*)-3-Hydroxy-8-oxo-7-phenylacetamido-4-oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate* (= *(6R*,7R*)-4-*(tert-*Butoxycarbonyl)-3-hydroxy-7-phenylacetamido-2-isooxacephem; 6)* was prepared similarly to **4** except that 2 equiv. of Et_3N were used. After purification (silica gel/AcOEt), **6** was obtained in 65% yield as a foam. IR (CH_2Cl_2): 3200–3500 (NH,OH), 1790 (β-lactam), 1755 (ester), 1735 (C=C), 1680 (amide). ^{1}H-NMR ($CDCl_3$): 1.49 (*s*, 9H, $C(CH_3)_3$); 2.30 (br., 1H, OH); 3.51 (*s*, 2H, CH_2Ph); 3.61–4.01 (*m*, 2H, 2H-C(5)); 4.09–4.52 (*m*, 2H, H–C(6), H–C(7)); 6.29 (*d*, *J* = 8, 1H, NH); 7.38 (*s*, 5H, Ph).

$C_{19}H_{22}N_2O_6$ (374.22) Calc. C 60.96 H 5.88 N 7.48% Found C 61.12 H 5.76 N 7.40%

(6R,7R*)-3-Hydroxy-8-oxo-7-phenylacetamido-4-oxa-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid (= (6R*,7R*)-4-Carboxy-3-hydroxy-7-phenylacetamido-2-isooxacephem; 7).* CF_3COOH/CH_2Cl_2 1:2 (10 ml) was added dropwise at 0–5° with in 5 min to **6** (0.37 g, 1 mmol) in 2 ml of dry CH_2Cl_2. The mixture was stirred at r.t. for 10 h, then evaporated, and the crude product crystallized from $EtOAC/Et_2O$ 1:10 to give 0.22 g (70%) of 7, m.p. 125–128°. IR and ^{1}H-NMR: identical with the ones of an authentic sample [1].

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