Synthesis of Δ^3-1-Methylene-1-carbacephems

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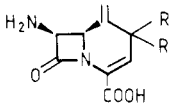
The total synthesis of (±)-1-methylene-2,2-dimethyl-7-amino-1-carbacephem-4-carboxylic acid (**1**) is described. The reaction scheme was essentially that described by Christensen et al. for the synthesis of (±)-1-carbacephems. In vitro antibacterial activities of the 7-phenoxyacetyl and 7-D-α-phenylglycyl derivatives of **1** were compared with those of 7-(phenoxyacetamido)desacetoxycephalosporanic acid and cefalexin. Derivatives of **1** were 2–4 times less active against most of the sensitive organisms than the corresponding 7-aminodesacetoxycephalosporanic acid analogues. The activity of the 7-D-α-phenylglycyl derivative of **1** however was about 20 times lower than that of cefalexin when measured against *Staphylococcus aureus* ATCC 6538P.

A number of cephem analogues in which the sulfur atom has been replaced by oxygen,[1] a methylene,[2] or a hydroxymethylene group[3] have been described. In the present work we want to investigate the synthesis of Δ^3-1-methylene-1-carbacephems. These compounds have an exocyclic double bond in the 1-position and they differ from the thia counterparts by a replacement of sulfur by a sp^2 carbon atom. This means a significant increase of the bond angle C-6–C-1–C-2, which may alter the conformation of the six-membered ring and eventually the reactivity of the β-lactam function. The initial objective was the preparation of (±)-Δ^3-7-amino-1-methylene-1-carbacephem-3-carboxylic acid (**1a**) (the natural or 6*R*,7*S* configuration is given in all schemes), which can be converted into biologically active compounds by N-acylation. The synthetic scheme used for the synthesis of **1a** was essentially that reported by Christensen et al.[4] for the preparation of Δ^3-1-carbacephem.



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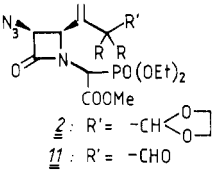
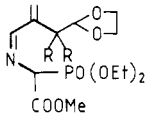


2: R' = -CH(O)(O); **11**: R' = -CHO



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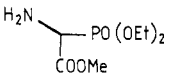
series a: R = R = H; b: R = R = Me



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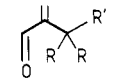
The first step in this scheme is the construction of the monocyclic β-lactam **2a** by cycloaddition of azidoacetyl chloride to the aldimine **3a**, obtained by condensation of the amine **4**[4] with 2-methylene-4,4-(ethylenedioxy)butanal (**5a**). The cycloaddition afforded cis β-lactam **2a** in a 27% yield as a mixture of diastereoisomers, together with a small amount (about 6%) of the corresponding trans isomers. The aldehyde **5a** was prepared in five steps from ethyl 4-hydroxybutyrate (**6**), which was obtained by ethanolysis of γ-butyrolactone according to Brown et al.[5] Conversion of **6** by oxidation with pyridinium chlorochromate[6] into the corresponding aldehyde **7**, followed by reaction with ethylene glycol, afforded the dioxolane **8a**. The alcohol **9a**, obtained by $LiAlH_4$ reduction of **8a**, was oxidized (pyridinium chlorochromate), yielding the aldehyde **10a**. *N,N,N',N'*-Tetramethylenediaminomethane in the presence of Ac_2O[7] was used for the introduction of the methylene group in **10a**. Other procedures for the introduction of a methylene, such as a crossed aldol condensation (CH_2O, K_2CO_3) or a Mannich reaction (CH_2O, $Me_2NH{\cdot}HCl$), were not successful.



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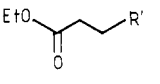
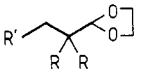
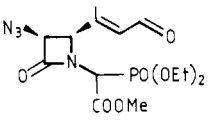


6: R' = -CH_2OH; **7**: R' = -CHO



8: R' = -COOEt *or* COOMe; **9**: R' = -CH_2OH; **10**: R' = -CHO

series a: R = R = H; b: R = R = Me



12

The next step in the Christensen scheme is the deprotection of the aldehyde function of **2a** by hydrolytic cleavage of the dioxolane group. Treatment of **2a** with acid however did not afforded the desired intermediate **11a** but resulted in a migration of the double bond with the formation of the conjugated aldehyde **12**. This means that the proposed scheme is not suitable for the synthesis of **1a**. Therefore we decided to prepare the 1-methylene-1-carbacephem **1b** with two methyl groups in the 2-position. This prevents double-bond migration during deprotection of the aldehyde function. The starting material for the preparation of the hemi-protected dialdehyde **10b** was 2,2-dimethyl-4-pentenal (**13**), which was obtained by allylation of isobutyraldehyde according to Dietl et al.[8] Conversion into the dioxolane **14** and oxidative cleavage ($NaIO_4/KMnO_4$) of the double bond afforded the ester **8b**, which was reduced to **9b** and oxidized. Treatment of **10b** with formaldehyde in the presence of K_2CO_3 afforded the aldehyde **5b**. It should be noted that the alcohol **9b** is not stable at room temperature. It converts into a substituted tetrahydrofuran by spontaneous trans-ketalization. Yields observed for the preparation of **9b** and **10b** were somewhat higher than those obtained for similar reactions in the **a** series. This may be due to incomplete extraction of **9a** and **10a** from aqueous solutions.

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(2) Reference 1, p 82.
(3) Bremner, J. A. S.; Colving, E. W.; Gallacher, G.; MacLeod, A. *Tetrahedron Lett.* **1983**, *24*, 3782.
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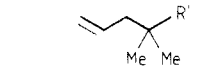
Table I. In Vitro Antibiotic Activities in Terms of Minimum Inhibitory Concentrations (μg/mL)[a]

	B. subtilis NCTC 8236	*S. lutea* ATCC 9341	*S. aureus* ATCC 6538P	*E. coli* ESS
17[b]	1.5	2	4	1.5
phenoxyacetyl-ADCA	1	1	1	1
18[b]	1.5	0.12	8	5
cefalexin	1	0.03	0.3	1

[a] Tested by the agar dilution method in diagnostic sensitivity test agar (Oxoid). The inoculum used contained 10^5–10^6 cfu/spot delivered by a multipoint inoculator. [b] The 1-methylene-1-carbacephems described in this work are racemic mixtures. The values given in the table are "corrected". This means that only one-half of the observed MIC values are considered.

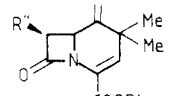
Cycloaddition of azidoacetyl chloride to the Schiff base **3b** was almost stereospecific and afforded 60% of the (±)-cis isomer **2b** together with 3% of the trans isomer. NMR spectra showed that each of these compounds are mixtures of two diastereoisomers (in a ratio of 55:45 for **2b**), due to the presence of a chiral center in the 1′-position. Separation of the diastereoisomers of **2b** is not necessary since the chiral center in 1′ is lost upon formation of the bicyclic β-lactam structure. The free aldehyde **11b** obtained by acid hydrolysis of the ketal function was cyclized under Wittig–Horner conditions (NaH in diglyme), affording the 7-azido-1-methylene-1-carbacephem **15** in a 72% yield (based on **2b**). Reduction of the azido function with H_2S/Et_3N in CH_2Cl_2 followed by hydrolysis (pH 11.9 in THF/H_2O) of the methyl ester function of **16** gave the 7-amino-1-methylene-1-carbacephem-3-carboxylic acid **1b** in a 63% yield (based on **15**). The yield seems to be satisfactory for this purpose; therefore other protecting groups of the carboxylic function were not investigated.



13: R′ = -CHO

14: R′ = -CH(O—O)

series a: R = R = H
b: R = R = Me



15: R′ = Me, R″ = N_3
16: R′ = Me, R″ = NH_2
17: R′ = H, R″ = ØOCH$_2$CONH-
18: R′ = H, R″ = D-ØCHNH$_2$CONH-

To evaluate antibacterial activity of the 2,2-dimethyl-1-methylene-1-carbacephem structure, the 7-amino function of **1b** was acylated with phenoxyacetyl and D-phenylglycyl groups. Phenoxyacetylation conducted in standard reaction conditions yielded **17**. The D-(α-aminophenylacetamido)cephem **18** was obtained by using a method similar to that reported by Dane et al.[9] for the preparation of ampicillin. Thus the condensation product (Dane's salt) of D-phenylglycine (potassium salt) and methyl acetoacetate was reacted with ethyl chloroformate. N-Acylation of the triethylamine salt of **1b** with the mixed anhydride afforded crude **18**, which was purified by XAD-2 column chromatography.

In vitro activities of the two 1-methylene-1-carbacephem **17** and **18** are given in Table I. To evaluate the influence of the exocyclic double bond on the activity of 1-carbacephems, MIC values of **17** and **18** should be compared with their counterparts in the 2,2-dimethyl-1-carbacephem series. Attempts to prepare this skeleton using the present synthetic scheme was unsuccessful. The aldehyde **10b** did not condense even under vigorous conditions with (±)-methyl α-amino-α-(diethylphosphono)acetate. This may be due to a steric hindrance of the dioxolane group, which seems to be less pronounced in the case of a condensation of the aldehyde **5b**. The fact that **5b** contains a sp^2 carbon in the 2-position with a larger bond angle may be partly responsible for the difference in reactivity. For this reason comparison was made with MIC values obtained for (phenoxyacetamido)desacetoxycephalosporanic acid and with cefalexin. It appears that **17** is 2–4 times less active than the corresponding aminodesacetoxycephalosporanic acid analogue. When comparison of **18** with cefalexin is considered for sensitive microorganisms, decrease by a factor 4–20 was observed.

It should be noted that the presence of C-2 methyl groups reduces the activity of Δ^2-cephems.[10] Therefore it is believed that the decrease in activity, observed for **17** and **18**, is not only due to the replacement of S by >C=CH_2 but also to the presence of two methyl groups in the 2-position. The absence of the C-3 methyl group in Δ^2-cephems has little or no influence on the in vitro activity.[11]

Experimental Section

Melting points were determined with a Büchi-Tottoli apparatus and are uncorrected. Precoated Merck silica gel F254 plates were used for TLC. Column chromatography was performed on silica gel (Merck, 0.040–0.063 mm). Infrared (IR) spectra were run on a Perkin-Elmer 257 spectrophotometer. ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24 60-MHz instrument in $CDCl_3$ with tetramethylsilane as internal standard unless stated otherwise. Mass spectra (MS) were determined with an AEI MS-12 apparatus.

Ethyl 4-Oxobutyrate (7). A solution of ethyl 4-hydrobutyrate (**6**;[5] 1.3 g, 10 mmol) in CH_2Cl_2 (10 mL) was added to a stirred suspension of pyridinium chlorochromate[6] (5.37 g, 25 mmol), containing NaOAc (0.41 g, 5 mmol). After 2 h Et_2O (50 mL) was added and the supernatant was decanted. The black precipitate was washed with Et_2O (2 × 25 mL), and the combined CH_2Cl_2–Et_2O solution was washed with 5% aqueous $NaHCO_3$ (50 mL) with 1 N HCl (50 mL) and H_2O (50 mL), dried, and filtered over a layer of Florisil. Evaporation of the filtrate gave 1.02 g (7.9 mmol, 79% yield) of the title compound as a colorless oil, which was used in the following step without further purification; IR (CH_2Cl_2) $\bar{\nu}$ 1740 (ester), 1725 (ketone) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, CH_3), 2.65 (m, CH_2CH_2), 4.13 (q, J = 7 Hz, CH_2CH_3), 9.79 (s, CHO).

Ethyl 4,4-(Ethylenedioxy)butyrate (8a). A solution of ethyl 4-oxobutyrate (**7**; 6.5 g, 50 mmol) and ethylene glycol (5.06 g, 81.5 mmol) in C_6H_6 containing a catalytic amount of *p*-toluenesulfonic acid (10 mg) was refluxed for 2 h. Water was removed as it formed by means of a Dean–Stark apparatus. The reaction mixture was cooled and washed with 5% aqueous $NaHCO_3$ (2 × 20 mL) and H_2O (2 × 10 mL). Aqueous layers were extracted with C_6H_6, and the combined C_6H_6 layer was dried (Na_2SO_4) and evaporated, affording 6.45 g (74%) of the title compound (as an oil), which was used in the following step without further purification; IR (CH_2Cl_2) $\bar{\nu}$ 1735 (ester) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, CH_3), 1.9–2.3 and 2.3–2.65 (m, CH_2CH_2COOEt), 3.88 (m, OCH_2CH_2O), 4.13 (q, J = 7 Hz, CH_2CH_3), 4.93 (t, J = 4 Hz, CH).

4,4-(Ethylenedioxy)-1-butanol (9a). A solution of ethyl 4,4-ethylenedioxybutyrate (**8a**; 17.4 g, 100 mmol) in anhydrous Et_2O (20 mL) was added over a period of 2 h to a stirred suspension of $LiAlH_4$ (2.55 g) in Et_2O (50 mL). The reaction mixture was refluxed overnight, and the excess $LiAlH_4$ was decomposed with H_2O (10 mL). The Et_2O layer was decanted, and the remaining solid was washed with Et_2O (2 × 50 mL) and with EtOAc (3 × 50 mL). The combined organic layer was washed (brine 100 mL), dried (Na_2SO_4), and evaporated, affording 7.6 g (57.1 mmol, 57% yield) of the title compound (colorless oil), which was used as such in the following step; ^{1}H NMR ($CDCl_3$) δ 1.7 (m, CH_2CH_2), 3.6 (m, CH_2OH), 3.9 (m, OCH_2CH_2O), 4.86 (t, J = 3.7 Hz, CH).

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(11) Kukolja, S.; Chauvette, R. R. In "Chemistry and Biology of β-Lactam Antibiotics"; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 1, p 171.

4,4-(Ethylenedioxy)butanal (10a). 4,4-(Ethylenedioxy)-1-butanol (15 g, 114 mmol) was oxidized with pyridinium chlorochromate (61.3 g, 285 mmol) as described for the preparation of **7**, affording 8.2 g of the title compound (62.6 mmol, 55% yield) as a colorless oil, which was used in the following step without further purification; IR (CH_2Cl) $\bar{\nu}$ 1720 (aldehyde) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–2.1 and 2.25–2.6 (m, CH_2CH_2), 3.75 (m, OCH_2CH_2O), 4.83 (t, J = 3.7 Hz, CHO_2), 9.58 (t, J = 1.5 Hz, CH=O); MS, m/e 1.29 (M^+ – H).

2-Methylene-4,4-(ethylenedioxy)butanal (5a). Acetic anhydride (20 mL) was added dropwise to a solution of 4,4-(ethylenedioxy)butanal (5.2 g, 40 mmol) in *N,N,N′,N′*-tetramethyldiaminomethane (20 mL). During addition the reaction mixture was kept below 40 °C by cooling in an ice bath. The reaction mixture was stirred for 2 h at 0 °C and poured into an ice–water mixture (300 mL). After 10 min the aqueous solution was extracted with Et_2O (5 × 30 mL) and EtOAc (2 × 30 mL). The combined organic layer was washed with 5% aqueous $NaHCO_3$ and water and dried (Na_2SO_4). Evaporated afforded 4 g (28.2 mmol, 70.5% yield) of the title compound as a colorless oil, which was used as such in the following step; IR (CH_2Cl_2) $\bar{\nu}$ 1690 (aldehyde), 1630 (C=CH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (d, J = 5 Hz, CH_2CH), 3.90 (br s, OCH_2CH_2O), 5.05 (t, J = 5 Hz, CHO_2), 6.15 (s, CH=C), 6.47 (s, CH=C), 9.58 (s, CHO); MS, m/e 142 (M^+), 141 (M^+ – H).

(±)-(3*S*,4*R*,1′*S*)- and (±)-(3*S*,4*R*,1′*R*)-1-[(Methoxycarbonyl)(diethylphosphono)methyl]-3-azido-4-[3,3-(ethylenedioxy)-1-methylenepropyl]-2-azetidinone (Cis Isomers, 2a). The aldimine **3a** was obtained by condensation of 4,4-(ethylenedioxy)butanal (1.775 g, 12.5 mmol) and (±)-methyl α-amino-α-(diethylphosphono)acetate[4] (2.815 g, 12.5 mmol) in C_6H_6 (185 mL). The reaction mixture was heated to reflux temperature, and 100 mL of C_6H_6 was distilled off, in order to eliminate the water that was formed during condensation. The C_6H_6 solution of **3a** was diluted with a mixture of C_6H_6–cyclohexane (2:1, 175 mL) containing triethylamine (1.615 g, 16 mmol). Azidoacetyl chloride (1.79 g, 15 mmol) in cyclohexane (50 mL) was added dropwise to the stirred solution of the aldimine over a period of 45 min. After 2 h the reaction mixture was diluted with Et_2O (200 mL) and washed with 0.5 M aqueous phosphate buffer (pH 3, 2 × 125 mL), H_2O, and brine. The organic phase was dried (Na_2SO_4) and evaporated, leaving on oil (2 g), which contained (as shown by ^1H NMR) a mixture of the cis and trans β-lactam. TLC (system cyclohexane–2-propanol, 70:30) showed two main spots (R_f 0.20 and 0.25) in a ratio of about 4:1. Column chromatography on silica gel using cyclohexane–2-propanol (3:1) as a mobile phase afforded 1.5 g (3.4 mmol, 27.5% yield) of the title compound (cis β-lactam) (R_f 0.20); IR (CH_2Cl_2) $\bar{\nu}$ 2120 (azide), 1780 (β-lactam), 1750 (ester) cm^{-1}; ^1H NMR ($CDCl_3$), 90 MHz) δ 1.34 (t, J = 7 Hz, OCH_2CH_3), 2.48 (d, J = 4.9 Hz, CH_2=CCH_2), 3.79 and 3.85 (s, COOMe), 3.89 and 3.94 (s, OCH_2CH_2O), 4.24 and 4.29 (dq, J = 7 Hz, J_P = 7.5 Hz, OCH_2CH_3), 4.62 (d, J_P = 24 Hz, CHP), 4.61 (d, J = 5 Hz, CHN_3), 4.78 (d, J = 4 Hz, CHN), 4.93 (t, J = 4.9 Hz, =CCH_2CH), 5.42 (s, CH_2=C). Double signals for the COOMe, OCH_2CH_2O, and OCH_2CH_3 protons are due to the presence of two diastereoisomers in a ratio of about 1:1.

(±)-(3*S*,4*R*,1′*S*)- and (±)-(3*S*,4*R*,1′*R*)-1-[(Methoxycarbonyl)(diethylphosphono)methyl]-3-azido-4-(3-oxo-1-methylprop-1-enyl)-2-azetidinone (Cis Isomers, 12). A solution of **2a** (1.3 g, 3 mmol) in glacial acetic acid (15 mL) and 10% aqueous H_2SO_4 (150 mL) was heated for 2 h at 50 °C. The cooled solution was saturated with NaCl and extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with 5% aqueous $NaHCO_3$ and with H_2O and dried. Evaporation afforded 1.01 g (2,5 mmol, 83% yield) of the title compound as an oil; IR (CH_2Cl_2) $\bar{\nu}$ 2120 (azide), 1782 (β-lactam), 1750 (ester), 1675 (aldehyde) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 7 Hz, OCH_2CH_3), 2.22 (s, CH_3C=), 3.85 (s, $COOCH_3$), 4.21 (m, OCH_2CH_3), 4.6–4.8 (m, CHP, CHN_3, CHN), 6.15 (d, J = 7 Hz, =CHCHO), 9.94 (d, J = 7 Hz, =CHCHO). The two diastereoisomers were not differentiated in the 60-MHz spectrum.

4,4-Dimethyl-5,5-(ethylenedioxy)-1-pentene (14). 2,2-Dimethyl-4-pentenal[8] (56 g, 500 mmol) was converted into the title compound as described in the preparation of **8a**. Purification of the crude reaction product by destillation under reduced pressure (bp 72 °C (10 mm)) afforded 58.5 g (375 mmol, 75% yield); IR (CH_2Cl_2) $\bar{\nu}$ 1645 (CH_2=CH), 1110 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (, CMe_2), 2.07 (d, J = 7 Hz, CH_2CH=), 3.86 (s, OCH_2CH_2O), 4.54 (s, CHO_2), 4.8–6.2 (m, CH_2=CH).

Methyl 3,3-Dimethyl-4,4-(ethylenedioxy)butyrate (8b). A solution of 4,4-dimethyl-5,5-(ethylenedioxy)-1-pentene (10 g, 64 mmol) in *tert*-butyl alcohol (200 mL) and H_2O (100 mL) was added gradually to a stirred solution of $NaIO_4$ (55 g, 256 mmol), $KMnO_4$ (2 g, 13 mmol), and K_2CO_3 (2.65 g, 192 mmol) in *tert*-butyl alcohol (500 mL) and H_2O (600 mL) over a period of 4 h. The reaction mixture was stirred overnight, filtered, concentrated to a volume of 500 mL, and extracted with Et_2O (2 × 100 mL). The aqueous layer was acidified to pH 3 (5 N HCl), discolored with $Na_2S_2O_3$, adjusted to pH 2, and extracted with Et_2O (6 × 150 mL). The ether layer was dried and evaporated, yielding 3,3-dimethyl-4,4-(ethylenedioxy)butyric acid, which was converted into its methyl ester by reaction with CH_2N_2 in Et_2O, affording 11.3 g (60 mmol, 94% yield) of the title compound; IR (CH_2Cl_2) $\bar{\nu}$ 1735 (ester), 1110 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (s, CMe_2), 2.99 (s, CH_2COOMe), 3.62 (s, COOMe), 3.87 (s, OCH_2CH_2O), 4.60 (s, CH).

3,3-Dimethyl-4,4-(ethylenedioxy)-1-butanol (9b). Methyl 3,3-dimethyl-4,4-(ethylenedioxy)butyrate (18.8 g, 100 mmol) was reduced with $LiAlH_4$ (2.55 g, 67 mmol) as described in the preparation of **9a**, affording 14.13 g (88.3 mmol, 88.3% yield) of the title compound; ^1H NMR ($CDCl_3$) δ 0.96 (s, CMe_2), 1.62 (t, J = 6.7 Hz, CH_2CH_2OH), ~2.9 (br s, OH), 3.67 (m, CH_2OH), 3.9 (s, OCH_2CH_2O), 4.55 (s, CH).

3,3-Dimethyl-4,4-(ethylenedioxy)butanal (10b). 3,3-Dimethyl-4,4-(ethylenedioxy)butanal (10 g, 62.5 mmol) was oxidized with pyridinium chlorochromate (33.5 g, 156 mmol) as described in the preparation of **7**, affording 8.6 g (54.4 mmol, 87% yield) of the title compound; IR (CH_2Cl_2) $\bar{\nu}$ 1720 (aldehyde), 1110 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (s, CMe_2), 2.27 (d, J = 3.2 Hz CH_2CHO), 3.83 (s, OCH_2CH_2O), 4.55 (s, CHO_2), 9.74 (t, J = 3.2 Hz, CHO).

2-Methylene-3,3-dimethyl-4,4-(ethylenedioxy)butanal (5b). Potassium carbonate (16.56, 120 mmol) was added gradually to a stirred solution of 3,3-dimethyl-4,4-(ethylenedioxy)butanal (9.5 g, 60 mmol) in 35% aqueous formaldehyde (10.3 mL, ~120 mmol) over a period of 2.5 h. After stirring for another 2 h, the reaction mixture was poured into H_2O (100 mL) and extracted with Et_2O (2 × 100 mL). The Et_2O extract was washed with water, dried, and evaporated. Destillation of the residue under reduced pressure (bp 71 °C (0.1 mm)) afforded 9 g (52.8 mmol, 88% yield) of the title compound; IR (CH_2Cl_2) $\bar{\nu}$ 1700 (CHO), 1620 (CH_2=C), 1110 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (s, CMe_2), 3.88 (s, OCH_2CH_2O), 5.22 (s, CHO_2), 6.08 (s, CH=C), 6.37 (s, CH=C), 9.57 (s, CHO).

(±)-(3*S*,4*R*,1′*S*)- and (±)-(3*S*,4*R*,1′*R*)-1-[(Methoxycarbonyl)(diethylphosphono)methyl]-3-azido-4-[3,3-(ethylenedioxy)-2,2-dimethyl-1-methylenepropyl]-2-azetidinone (Cis Isomers, 2b). Reaction of 2-methylene-3,3-dimethyl-4,4-(ethylenedioxy)butanal (4.25 g, 25 mmol) and (±)-methyl α-amino-α-(diethylphosphono)acetate (5.63 g, 25 mmol) and cycloaddition of the resulting aldimine **3b** with azidoacetyl chloride (3.58 g, 30 mmol) in the presence of triethylamine (3.23 g, 32 mmol) was conducted as described for the preparation of **2a**. TLC (system cyclohexane–2-propanol, 70:30) of the crude reaction mixture showed the presence of cis and trans β-lactams (R_f 0.25 and 0.30) in a ratio of about 20:1. Column chromatography on silica gel, using cyclohexane–2-propanol (3:1) as a mobile phase, afforded 6.9 g (15 mmol, 60% yield) of the title compound (cis β-lactam); R_f 0.25 (system cyclohexane–2-propanol, 70:30); IR (CH_2Cl_2) $\bar{\nu}$ 2120 (azide), 1785 (β-lactam), 1760 (ester) cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 1.15 (s, CMe_2), 1.36 (t, J = 7 Hz, OCH_2CH_3), 3.75 and 3.84 (s, COOMe), 3.86 (m, OCH_2CH_2O), 4.02–4.60 (m, OCH_2CH_3, CHP, CHO_2), 4.68 (d, J = 5.2 Hz, CHN_3), 4.83 and 4.95 (d, J = 5.2 Hz, CHN), 5.50 (m, CH_2=C) (double signals for COOMe and CHN protons are due to the presence of two diastereoisomers in a ratio of 55:45); MS, m/e 460 (M^+).

(±)-(3*S*,4*R*,1′*S*)- and (±)-(3*S*,4*R*,1′*R*)-1-[(Methoxycarbonyl)(diethylphosphono)methyl]-3-azido-4-(3-oxo-2,2-dimethyl-1-methylenepropyl)-2-azetidinone (Cis Isomers, 11b). Acid-catalyzed hydrolysis of the cyclic acetal function of **2b** (1.84 g, 4 mmol) in the conditions described for the preparation of **12** afforded 1.53 g (3.7 mmol, 92% yield) of the title compound

as an oil, which was used as such in the following step; TLC, R_f 0.32 (system cyclohexane–2-propanol, 70:30); IR (CH_2Cl_2) $\bar{\nu}$ 2120 (azide), 1790 (β-lactam), 1757 (ester), 1735 (aldehyde) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, CMe), 1.30 (s, CMe), 1.33 (t, J = 7 Hz, OCH_2CH_3), 3.78 and 3.84 (s, $COOCH_3$), 4.0–4.80 (m, OCH_2CH_3, CHP, CHN_3, CHN), 5.49 (d, J = 3 Hz, CH=C), 5.67 (s, CH=C), 9.36 (s, CHO).

(±)-(6*R*,7*S*)-1-Methylene-2,2-dimethyl-4-carbomethoxy-7-azido-1-carbacephem (Cis Isomer, 15). A stirred solution of **11b** (1.66 g, 4 mmol) in anhydrous ethylene glycol dimethyl ether (50 mL) containing NaH (4 mmol) was kept at room temperature under a N_2 atmosphere for 1 h. The reaction mixture was cooled (0 °C), poured into 75 mL of a cold (0 °C) 0.5 M aqueous phosphate buffer (pH 7), and extracted with CH_2Cl_2 (4 × 50 mL). The organic layer was dried and evaporated. Column chromatography of the residual oil on silica gel (30 g), using CH_2Cl_2–MeOH (98:2) as a mobile phase, afforded 0.828 g (3.16 mmol, 79% yield) of the title compound as an oil, which crystallized upon standing; mp 66 °C; TLC, R_f 0.48 (system cyclohexane–2-propanol, 70:30); IR (CH_2Cl_2) $\bar{\nu}$ 2130 (azide), 1785 (β-lactam), 1738 (ester), 1650 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, CH_3), 1.34 (s, CH_3), 3.87 (s, $COOCH_3$), 4.46 (m, H-6), 4.98 (d, J = 5.2 Hz, H-7), 5.46 (m, CH_2=C), 6.35 (s, H-3). Anal. ($C_{12}H_4O_3N_4$) C, H, N.

(±)-(6*R*,7*S*)-1-Methylene-2,2-dimethyl-7-amino-1-carbacephem-4-carboxylic Acid (1). A stream of dry H_2S gas was bubbled through a cooled (0 °C) solution of (±)-(6*R*,7*S*)-1-methylene-2,2-dimethyl-4-(carboxymethyl)-7-azido-1-carbacephem (262 mg, 1 mmol) in CH_2Cl_2 (20 mL) containing NEt_3 (0.17 mL, 1.2 mmol) for a period of 30 min. The reaction mixture was washed with 1 N NaOH, dried, and evaporated. The residue was dissolved in THF (5 mL), and 0.1 N aqueous Na_2CO_3 (5 mL) was added. The stirred solution was adjusted to pH 11.9 and maintained at this pH for 3 h by regular addition of NaOH. The precipitate of crude **1**, obtained by adjustment of the pH to 4.75, was filtered off, converted into its Na salt (pH 5.8), and purified by adsorption on a XAD-2 column (300–1000 μm, 40 × 2.5 cm) followed by elution with H_2O–MeOH (85:15). Fractions containing the carbacephem (detection at 254 nm) were pooled, and the pH was adjusted to 4.75, affording 140 mg (0.63 nmol, 63% yield) of the title compound; mp 190 °C dec; TLC, R_f 0.25 (system EtOAc–MeOH–AcOH, 100:50:5); IR (KBr) $\bar{\nu}$ 1810 (β-lactam), 1660 (CH_2=C<), 1630 (CH=CN); ^1H NMR (D_2O containing NaOD, DSSA, 90 MHz) δ 1.23 (s, CH_3), 1.29 (s, CH_3), 4.45 (4 × d, J = 5.2, 2.1, and 2.1 Hz, H-6), 4.60 (d, J = 5.2 Hz, H-7), 5.20 (dd, J = 2.1 and 0.5 Hz, CH=C<), 5.43 (d, J = 2.1 Hz, CH=C<), 6.15 (d, J = 0.5 Hz, H-3). Anal. Calcd for $C_{11}H_{14}O_3N_2$: C, 59.45; H, 6.35; N, 12.60. Found: C, 58.91; H, 6.29; N, 12.49.

(±)-(6*R*,7*S*)-1-Methylene-2,2-dimethyl-7-(phenoxyacetamido)-1-carbacephem-4-carboxylic Acid, Sodium Salt (17). A cooled (0 °C) solution of **1** (222 mg, 1 mmol) in H_2O (5 mL) and acetone (2 mL), containing NEt_3 (0.3 mL, 2 mmol), was added to a cooled (0 °C) solution of phenoxyacetyl chloride (170.5 mg, 1 mmol) in acetone (5 mL). The reaction mixture was stirred for 1 h at room temperature, acetone was evaporated, and the aqueous solution was extracted with Et_2O, acidified to pH 2, and extracted with EtOAc (3 × 10 mL). The EtOAc layer was dried and concentrated to a volume of 5 mL, and an equal volume of H_2O was added and the pH was adjusted to 6.8 with 0.1 N NaOH. Concentration of the aqueous layer afforded upon cooling 320 mg (0.84 mmol, 84% yield) of the crystalline Na salt of **17**; TLC, R_f 0.48 (EtOAc–MeOH–AcOH, 100:50:5); IR (KBr) $\bar{\nu}$ 1775 (β-lactam), 1670 (amide), 1605 (COO^-), 760, 695 (phenyl) cm^{-1}; ^1H NMR (D_2O–DSSA, 100 MHz) δ 1.25 (s, CMe_2), 4.50 (4 × d, J = 5.2, 2.3, and 2.3 Hz, H-6), 4.65 (s, OCH_2), 4.75 (dd, J = 2.3 and 0.5 Hz, CH=C<), 5.15 (d, J = 2.3 Hz, CHC<), 5.32 (d, J = 5.2 Hz, H-7), 6.03 (d, J = 0.5 Hz, H-3), 6.9–7.45 (m, phenyl); UV (H_2O) λ_{max} 254 nm ($A_{1cm}^{1\%}$ = 207). Anal. ($C_{19}H_{19}O_5N_2Na$) C, H, N.

(6*R*(*S*),7*S*(*R*))-1-Methylene-2,2-dimethyl-7-[(*R*)-α-aminophenylacetamido]-1-carbacephem-4-carboxylic Acid (18). Condensation of CH_3COCH_2COOMe and D-phenylglycine according to Long et al.[12] afforded the potassium salt of *N*-[1-methyl-2-(methoxycarbonyl)vinyl]-D-phenylglycine, which was dried in vacuo (2 h at 80 °C and $^1/_2$ h at 100 °C). A 1% solution of *N*-methylmorpholine in acetone (0.15 mL) and ethyl chloroformate (0.15 mL) in anhydrous THF (2 mL) were added successively to a stirred and cooled (−20 °C) suspension of the Dane salt (430 mg, 1.5 mmol) in anhydrous THF (10 mL). The cooled (−20 °C) suspension was stirred for 20 min under a N_2 atmosphere and a cooled (0 °C) solution of (±)-(6*R*,7*S*)-1-methylene-2,2-dimethyl-7-amino-1-carbacephem-4-carboxylic acid (**1**; 222 mg, 1 mmol) and NEt_3 (0.2 mL, 1.5 mmol) in H_2O (6 mL)/THF (5 mL) was added rapidly (30 s). The reaction mixture was stirred for 1 h at −20 °C and for 1 h at 0 °C. The N-protecting group was hydrolyzed by acidification (1 N HCl) to pH 2.3. After the mixture was stirred for 10 min at 0 °C, THF was evaporated (at a bath temperature below 20 °C), the aqueous solution was washed with Et_2O (2 × 5 mL), and its pH was adjusted 6.8 with 0.2 N NaOH. The mixture was percolated through a XAD-2 (300–1000 μm) column (40 × 2.5 cm) at a flow rate of 6 mL/min. The column effluent was monitored by means of a 254-nm UV detector. D-Phenylglycine and the 7-amino-1-methylene-2,2-dimethyl-1-carbacephem-3-carboxylic acid were eluted with water and the title compound with H_2O–MeOH (70:30). Fractions containing **18** were pooled, adjusted to pH 4.5, and concentrated, yielding 213 mg (0.6 mmol, 60%) of the title compound; mp 165 °C dec; TLC, R_f 0.48 (system BuOH–H_2O–AcOH, 80:20:20); UV (H_2O) λ_{max} 254 nm ($A_{1cm}^{1\%}$ = 262); IR (KBr) $\bar{\nu}$ 1765 (β-lactam), 1700 (amide), 1650 (CH_2=C<), 1600 (COO^-) cm^{-1}; ^1H NMR (D_2O-DCl, DSSA, 90 MHz) 1.22 (s, CH_3), 1.31 (s, CH_3), 4.32 (m, CH=C<), 4.50 (m, H-6), ~4.75 (CH=C<, hidden under HOD peak), 4.99 (d, J = 5 Hz, H-7), 5.16 (s, PhC*H*), 6.51 (br s, H-3), 7.54 (m, phenyl). Anal. Calcd for $C_{19}H_{21}O_4N_3$: C, 64.21; H, 5.96; N, 11.82. Found: C, 63.80; H, 6.08; N, 11.69.

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Registry No. (±)-**1b**, 100367-02-0; (±)-**2a** (isomer 1), 100366-92-5; (±)-**2a** (isomer 2), 100483-20-3; (±)-**2a** (isomer 3), 100483-23-6; (±)-**2a** (isomer 4), 100483-25-8; (±)-**2b** (isomer 1), 100484-51-3; (±)-**2b** (isomer 2), 100366-98-1; (±)-**3a**, 100366-91-4; (±)-**3b**, 100366-97-0; (±)-**4**, 90711-94-7; **5a**, 100366-90-3; **5b**, 100366-96-9; **6**, 999-10-0; **7**, 10138-10-0; **8a**, 86197-13-9; **8b**, 100366-94-7; **9a**, 85391-14-6; **9b**, 100366-95-8; **10a**, 82962-18-3; **10b**, 99897-03-7; (±)-**11b** (isomer 1), 100366-99-2; (±)-**11b** (isomer 2), 100483-22-5; (±)-**12** (isomer 1), 100366-93-6; (±)-**12** (isomer 2), 100483-21-4; **13**, 5497-67-6; **14b**, 87802-43-5; (±)-**15**, 100367-00-8; (±)-**16**, 100367-01-9; (±)-**17**, 100367-05-3; (±)-**17**·Na, 100367-03-1; **18** (isomer 1), 100367-04-2; **18** (isomer 2), 100483-24-7; N_3CH_2COCl, 30426-58-5; $PhOCH_2COCl$, 701-99-5; *N*-[1-methyl-2-(methoxycarbonyl)vinyl]-D-phenylglycine potassium salt, 34582-65-5.

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