Tetrahedron Vol. 45, No. 3, pp. 701 to 707, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00
Pergamon Press plc

STUDIES TOWARD THE TOTAL SYNTHESIS OF 1-OXACEPHALOSPORINS 3: SYNTHESIS OF A (±)-TRANS-7-BENZOYLAMINO-3-CARBAMOYLOXYMETHYL-1-OXA-3-CEPHEM-3-CARBOXYLATE FROM 1,3-DIHYDROXYACETONE [1)]

HANS SCHMINCKE AND DIETER HOPPE*

Institut für Organische Chemie, Universität Kiel,
Olshausenstr. 40, D-2300 Kiel 1, FRG

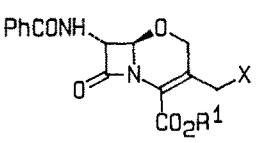
(*Received in Germany* 21 *October* 1988)

Abstract. As a first example for a novel strategy in the total synthesis of 1-oxacephalosporins the title compound **12** was constructed from 1,3-dihydroxyacetone, methyl isocyanoacetate, and azidoacetyl chloride in 10 steps. Intermediates are the N-formyl α,ß-dehydroaminoacid ester **5**, the 1,3-thiazoline-4-carboxylate **6**, the S-methyl thioformimidate **7**, the 4-azido-3-methylthio-2-azetidinone **8** and the oxazolinoazetidinone **11**. The synthesis also includes a base-induced Z/E-isomerization of unsymmetrical protected γ,γ'-dihydroxy-ß-methylbutenoate side chains in the 4-benzoylamino-2-azetidinone **9**.

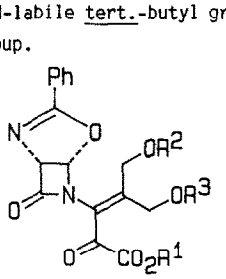
1-Oxacephalosporins are artificial ß-lactam antibiotics of high antibacterial potential.[2] As key intermediates in multi-step partial syntheses from penicillins or cephalosporins,[3,4,5,6] frequently, trans-substituted 1-oxa-3-cephem-3-carboxylates of type **A**, bearing a hetero substituent X in the 3'-position, are used (Scheme 1). Two total syntheses of racemic compounds **A** (cis or trans) are also known.[7,8]

In two preceding papers[9,10] we reported on the total synthesis of racemic oxazolinoazetidinones of type **B**, starting from 2,2-dimethyl-1,3-dioxan-5-one. These are potential precursors for **A** which bear a symmetrically protected γ,γ'-dihydroxy-ß-methylbutenoate group at N-1. All efforts to accomplish cyclo-acetalizations of the diols **C**, obtained in situ by acidic deprotection, to produce the oxacephems **A** failed due to unsupressible butenolide formation.[10] This communication deals with the successful application of the strategy on unsymmetrically protected derivatives **D**. The major disadvantage, connected with this modification of our initial strategy,[9] - the formation of E/Z-diastereoisomers - could be overcome by Z/E-equilibration of an intermediate. As the key intermediate we chose the oxazolinoazetidinone **11a** which bears an acid-labile tert.-butyl group on the (Z)-OH and the N,N-diisopropylcarbamoyloxy group[11] on the (E)-OH group.

Scheme 1



A X= hetero substituent



B $R^2 + R^3 = C(CH_3)_2$

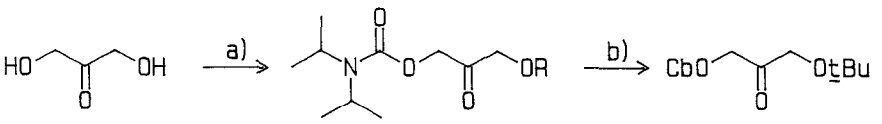
C $R^2 = R^3 = H$

D $R^2 \neq R^3$, e.g. tBu and C(=O)NiPr$_2$ (= Cb)

Synthesis of Azetidinones 9

Commercial (dimeric) 1,3-dihydroxyacetone (**1**) on acylation with N,N-diisopropylcarbamoyl chloride[12] gave the monocarbamate **2a** (38%) besides 14% of the dicarbamate **2b** (Scheme 2). The acid-catalyzed addition of 2-methylpropene to **2a** gave rise to the tert.-butyl ether **3** (60%).

Scheme 2



1 **2** **a** R = H ; 38% **3**

b R = C(=O)NiPr$_2$ (=Cb) ; 14%

a) N,N-Diisopropylcarbamoyl chloride/pyridine; 15 h at 40 °C; LC separation of **2a** and **2b**. b) 2-Methylpropene, H_2SO_4, CH_2Cl_2, 12 h at -22 °C.

The Schöllkopf formylamino-methylenation[9,13] of **3** with methyl isocyanoacetate (**4**) led to the diastereoisomeric α-amino acrylates **5a** and **5b** (70%, 4:1); Scheme 3. **5a** and **5b** (R_f = 0.54 and 0.41; ether) are easily separated on silica gel and exist in $CDCl_3$ solution as E/Z rotamers around the formamide bond,[14] stable in the NMR time-scale. The assignment is tentative; it is based on the comparison of the chemical shifts in ^{1}H NMR and the lower polarity of the major diastereoisomer **5a**, for which a more efficient intramolecular hydrogen bridging is expected.

Thiation[9] of the mixture **5a/5b** or of both the individual isomers with the Lawesson reagent[15] gave the inseparable thiazolines[16] **6a** and **6b** with 66% yield, ratio 1:4. **6a** is recognized in ^{1}H NMR by the down-field shift of the diastereotopic CH_2OCb protons ($CDCl_3$, δ = 4.36 and 4.64 ppm) compared with those of **6b** (4.19 and 4.47). The thiazolines **6** on base-induced ring-opening[17] with lithium isopropoxide in the presence of excess methyl iodide[9] afforded the methyl thioformimidate[18] **7**, which, after rapid chromatography on silica gel, immediately was subjected to the action of 2 equiv. azidoacetyl chloride/triethyl amine[9,17] to produce two trans-substituted ß-lactams **8a** and **8b** (^{1}H NMR: J_{34} = 2.4 Hz) with 92% yield in a ratio 1:4. The configurative assignment is based on a down-field shift (0.3 ppm) in ^{1}H NMR of cis-CH_2-O groups compared to those being in a trans-position to the methoxycarbonyl group in the second diastereoisomer. It was further confirmed by carrying both stereoisomers separately through the synthesis.

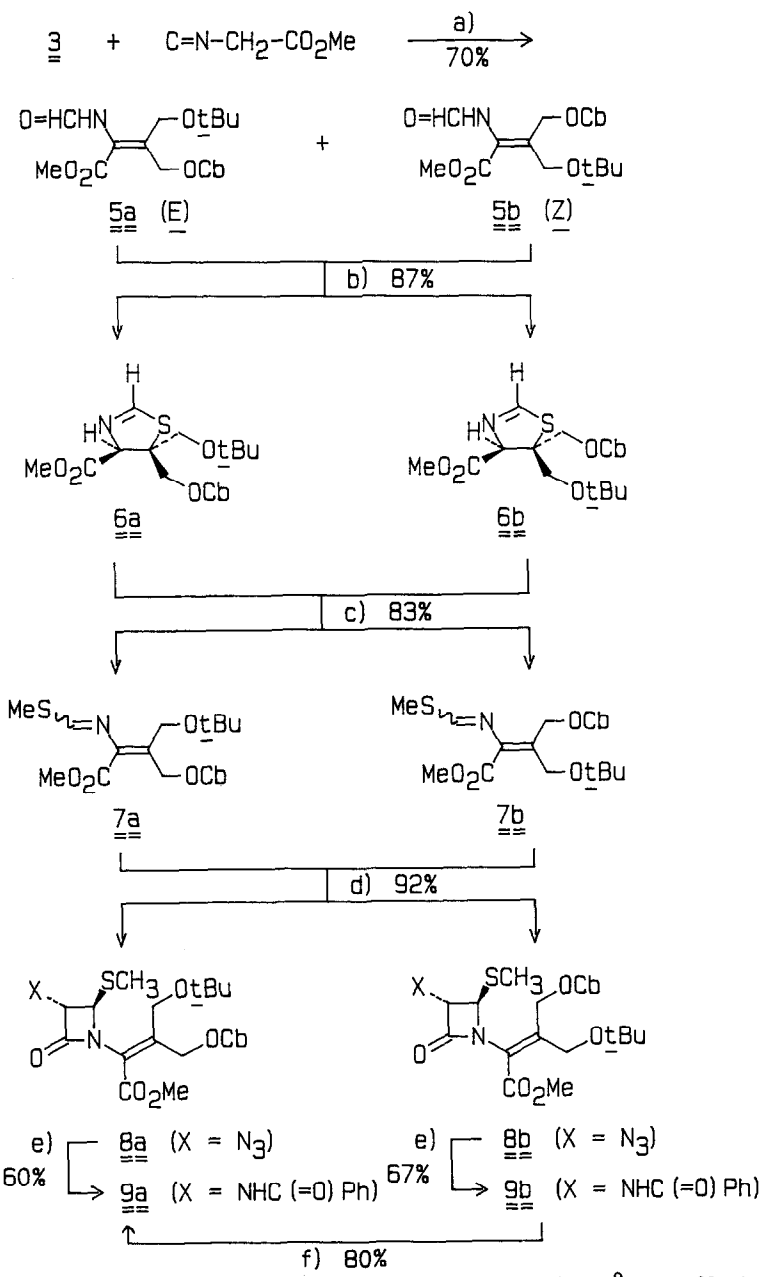
The azides **8a** and **8b** were reduced by H_2S/triethyl amine [9,19] and acylated with benzoyl chloride to give the benzamides **9a** or **9b** with 60% or 67% yield, respectively. From the (Z)-azide **9b** also 4% of the (E)-isomer **9a** was formed. The chromatographic separation of the benzamides **9a** and **9b** is easier to perform than those of the azides **8a** and **8b**, therefore the reduction/acylation sequence usually was accomplished with the E/Z mixture of **8**.

The Z/E isomerization of the double bond in **9b** is very wellcome, since **9a** is needed for the transformation into an oxacephem **12**. Here, most probably, it occurs by a reversible conjugate addition of a nucleophile (eg. thiolate). A second possibility consists in an equilibration of the γ-carbamoyloxy-substituted vinylogous ester enolates[12,20] **10b** and **10a**. Deprotonation should take place preferentially at the more acidic CH_2OCb group[11] to form anion **10b**. In the equilibrium of torsion isomers **10a** is expected to be the favored one, because here the azetidinone ring as the sterically most demanding substituent occupies an exo-position (Scheme 4). Treatment of **9b** with 1 equiv. of potassium tert.-butoxide in THF (-78 to 0 °C) and quenching the reaction mixture with acetic acid produced, after chromatographic separation, 59% **9a** besides 27% **9b**. With LDA as a base, a greater extend of decomposition was observed.

Synthesis of Oxacephem 12 and Butenolide 13

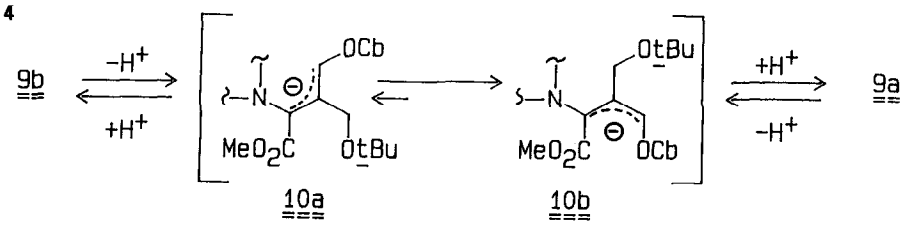
The methylthio-2-azetidinones **9a** and **9b** gave on chlorolysis and aqueous work-up with phosphate buffer,[10] followed by chromatography on silica gel, the analytically pure oxazolinoazetidinones **11a** and **11b**; yield 74% and 49%, respectively (Scheme 5). When **11a** was stirred with zinc chloride ethe-

Scheme 3



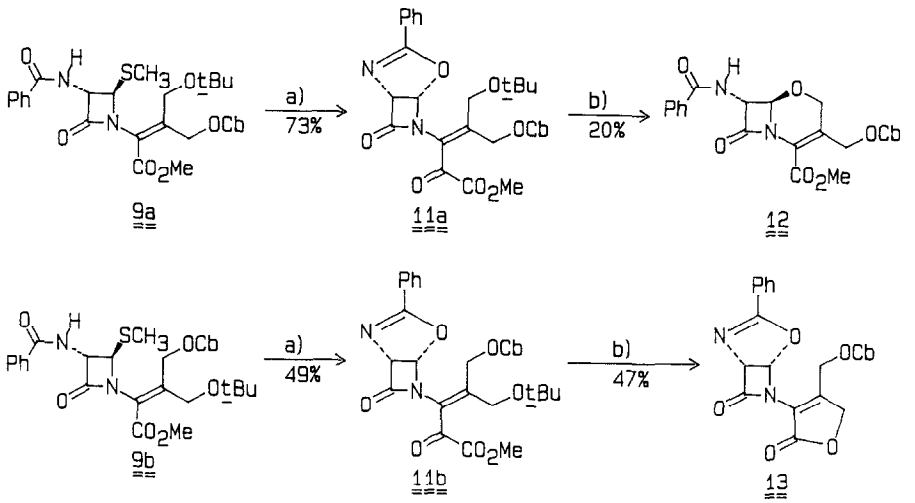
Racemates. - a) KOtBu, THF, -78 to 0 °C; HOAc. b) Lawesson reagent/Et_3N,[9] DME, 20 min at r. t. c) LiOiPr, CH_3I, THF/hexane.[9] d) Azidoacetyl chloride/Et_3N, CH_2Cl_2 at r. t. e) H_2S/Et_3N, CH_2Cl_2. Benzoyl chloride/Et_3N, CH_2Cl_2. f) KOtBu, THF, -78 °C; HOAc; yield (54% 9a) is corrected for recovered 9b (27%).

Scheme 4



rate in dichloromethane over night, the tert.-butyl group was cleaved and cyclo-acetalization of the intermediate hydroxy compound (**11a**, H for t-Bu) occurred to yield the crystalline oxacephem **12** (20%); some starting material (21%) could be recovered. The trans-substitution pattern of **12** is evident from the ^{1}H NMR by the small coupling constant of 0.9 Hz between 7-H (δ = 4.95 ppm) and 6-H (5.08 ppm).

Scheme 5



a) Cl_2; phosphate buffer pH 7.[10] b) $ZnCl_2 \cdot OEt_2$, CH_2Cl_2, 15 h at r. t.

A similar treatment of the (Z)-isomer **11b** gave rise to the butenolide **13** (47%); its structure follows from the comparison of the spectral data with those of close analogues.[10]

Although the final cyclization step is not optimized yet, the strategy, outlined here and in the accompanying papers[9,10] should be advantageous for the preparation of various oxacephem derivatives which are further modified in the 2- and 3'-position, starting from simple α-hydroxy ketones.

EXPERIMENTAL

All reactions were performed under N_2 or Ar with exclusion of air and, if necessary, in anhydrous solvents. Diethyl ether, THF, and 1,2-dimethoxyethane (DME) were distilled from $LiAlH_4$; triethyl amine, pyridine, and dimethylformamide from CaH_2; dichloromethane from P_4O_{10} prior use. - LC separations for more than 1 g were carried out with "Kieselgel 60", 0.05 - 0.2 mm, (Merck, Darmstadt, or Macherey-Nagel GmbH & Co KG, Düren), or, for less than 1 g, on "Silica 32 - 63", 0.032 - 0.063 mm, (ICN Biochemicals Eschwege) at 1 - 3 bar. - 0.1 M Phosphate buffer (pH 7) was used.

3-Hydroxy-2-oxopropyl N,N-Diisopropylcarbamate (**2a**) and 2-Oxopropan-1,3-diyl Bis(N,N-diisopropylcarbamate) (**2b**): N,N-Diisopropylcarbamoyl chloride (12) (22.31 g, 0.136 mol), 1,3-dihydroxyacetone (1) (12.28 g), and pyridine (31 mL) were stirred over night at 40 °C, poured into a mixture of ice (100 g) and 2N HCl (100 mL) and then extracted with ethyl acetate (10 x 100 mL). The solvent of the organic layers was removed and the residue purified by filtration over silica gel (130 g) with ether/hexane (1:1); yield 10.30 g (38%) **2a**, colourless oil, R_f = 0.47 (ether), besides 6.38 g (14%) **2b**, R_f = 0.38 (ether/hexane 1:1), mp 41 °C (hexane). -
2a: IR (KBr): 3400 (OH), 1750 - 1600 cm^{-1} (C=O and NC=O). - ^{1}H NMR ($CDCl_3$, 90 MHz): δ = 1.25 [d, J = 7 Hz, $(CH_3)_2CH$]; 3.15 (b, OH); 3.88 [sept, J = 7 Hz, $(CH_3)_2CH$]; 4.28 (s, CH_2OH); 4.70 ppm (s, CH_2OCb). - ^{13}C NMR ($CDCl_3$): δ = 20.51 [$(CH_3)_2CH$], 46.06 [$(CH_3)_2CH$], 66.00 and 66.39 (CH_2OCb and CH_2OH), 154.10 (OC=O), 205.52 ppm (C=O).
2b: IR (KBr): 1690 (NC=O), 1745 cm^{-1} (C=O). - ^{1}H NMR ($CDCl_3$, 60 MHz): δ = 1.20 [d, J = 6.8 Hz, $(CH_3)_2CH$]; 3.5 - 4.2 [m, $(CH_3)_2CH$]; 4.70 ppm (s, CH_2O).
$C_{17}H_{32}N_2O_5$ (344.02). Calc. C 59.43 H 9.30. Found C 59.69 H 9.46.

3-tert.-Butoxy-2-oxopropyl N,N-Diisopropylcarbamate (**3**): A mixture of the alcohol **2a** (17.65 g, 87.7 mmol) in dichloromethane (300 mL), conc. sulphuric acid (4.6 mL), and previously condensed 2-methyl-

propene (100 mL) was stirred for 12 h at -22 °C and then allowed to warm to rt (Caution! Evolvement of 2-methylpropene). Triethyl amine (20 mL) was added, the solvent removed i. vac., and the residue purified by filtration over silica gel (100 g) with ether/hexane (1:1); yield 14.4 g (60%) **3**, colourless oil, R_f = 0.63. - IR (neat): 1745 (C=O), 1700 cm^{-1} (NC=O). - ^1H NMR ($CDCl_3$, 90 MHz): δ = 1.23 (s, t-Bu); 1.23 [d, J = 6 Hz, $(CH_3)_2CH$]; 3.93 (sept, J = 6 Hz, NCH); 4.07 (s, CH_2OtBu); 4.92 (s, CH_2OCb). - ^{13}C NMR ($CDCl_3$): δ = 20.93 [$(CH_3)_2CH$], 27.23 [$(CH_3)_3C$], 46.24 [$(CH_3)_2CH$], 66.67 and 66.73 (CH_2OCb and CH_2OtBu), 74.22 [$(CH_3)_3C$], 154.71 (OC=O, 204.26 ppm (C=O).

Methyl (E)- and (Z)-3-tert.-Butoxymethyl-4-(N,N-diisopropylcarbamoyloxy)-2-(N-formylamino-2-butenoate (**5a** and **5b**): To a soln of potassium tert.-butoxide (8.35 g, 74.4 mmol) at -78 °C in THF (150 mL) methyl isocyanoacetate (13) **4** (6.71 g, 67.7 mmol) was added dropwise and the mixture stirred for 30 min. Then the ketone **3** (18.51 g, 67.7 mmol) in THF (40 mL) was added at -78 °C. After 3 h stirring the mixture was allowed to warm to rt and glacial acetic acid (5 mL) was added. The solvent was removed i. vac., the residue dissolved in dichloromethane (1000 mL), and washed with phosphate buffer (100 mL). After drying (Na_2SO_4), evaporation of the solvent, the residue was purified by filtration over silica gel (300 g) with ether; yield 17.7 g (70%) of **5a** and **5b** (4:1). A sample was separated by LC (40 g silica gel/g 5). **5a**, viscous oil, R_f = 0.54; **5b**, mp 121 °C (ether), R_f = 0.41.
5a: IR (KBr): 1740 (OC=O, 1700 - 1660 cm^{-1} (NHC=O and NC=O, Cb). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.21 [s, $(CH_3)_3C$]; 1.24 [m, $(CH_3)_2CH$]; 3.65 - 4.2 [m, $(CH_3)_2CH$]; 3.84 (s, OCH_3); 4.07 (s, CH_2OtBu); 4.75 (s, CH_2OCb); 8.18 [d, J = 10 Hz, HC=O, (N-Z)]; 8.26 [s, HC=O, (N-E)]; 9.40 [d, J = 10 Hz, NH, (N-E)]; 10.09 ppm [s, NH, (N-Z)]. - ^{13}C NMR ($CDCl_3$): δ = 20.40 and 21.40 [$(CH_3)_2CH$], 27.47 [$(CH_3)_3C$], 47 and 45 [b, $(CH_3)_2CH$], 52.23 (CH_3O), 58.91 (CH_2OCb), 60.36 (CH_2OtBu), 79.52 [$(CH_3)_3C$)], 127.85 (C-2), 129.07 (C-3), 156.45 (NC=O, Cb), 159.24 (NHC=O), 164.76 ppm (OC=O).
$C_{18}H_{32}N_2O_6$ (372.46). Calc. C 58.05 H 8.66. Found C 58.05 H 8.64.
5b: IR (KBr): 1725 (OC=O), 1705 (NCH=O), 1690 cm^{-1} (NC=O). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.19 [d, J = 7 Hz, $(CH_3)_2CH$]; 1.28 [s, $(CH_3)_3C$]; 3.88 (s, OCH_3); 4.13 [s, CH_2OtBu, (N-Z)]; 4.19 [s, CH_2OtBu, (N-E)]; 4.78 [s, CH_2OCb, (N-E)]; 4.89 [s, CH_2OCb, (N-Z)]; 8.18 [s, HC=O, (N-E)]; 8.24 [s, HC=O, (N-Z)]; 8.96 ppm (s, NH). - ^{13}C NMR ($CDCl_3$): δ = 21 [b, $(CH_3)_2CH$], 27.34 [$(CH_3)_3C$], 46 [b, $(CH_3)_2CH$], 52.49 (OCH_3), 61.51 (CH_2OtBu), 61.57 (CH_2OCb), 74.82 [$(CH_3)_3C$], 125.81 (C-2), 129.12 (C-3), 155.01 (NC=O, Cb), 158.00 (NHC=O), 163.92 ppm (OC=O).
$C_{18}H_{32}N_2O_6$ (372.46). Calc. C 58.05 H 8.66. Found C 58.08 H 8.75.

Methyl (4R*,5R*)- and (4R*,5S*)-4-tert.-Butoxymethyl-4-(N,N-diisopropylcarbamoyloxymethyl)-1,3-thiazoline-5-carboxylate (**6a** and **6b**): A soln of **5a** and **5b** (4:1) (17.66 g, 47.4 mmol) and triethyl amine (0.7 mL) in 1,2-dimethoxyethane (150 mL) was stirred with the Lawesson reagent (10.55 g, 25.1 mmol) for 20 min at rt. Then a soln of triethyl amine (33 mL) in ether (1.5 L) was added and the mixture stirred for further 20 min, washed with phosphate buffer (200 mL), dried over Na_2SO_4, evaporated, and filtrated rapidly over silica gel (300 g) with ether/pentane (1:1); yield 16.16 g (87%) of an unseparable mixture (4:1) of **6a** and **6b**. When starting from the pure diastereomers **5a** or **5b**, the same isomer ratio **6a/6b** was observed. - IR (KBr): 1749 (OC=O), 1700 - 1690 cm^{-1} (NC=O). **6a** and **6b**, ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.1 - 1.3 [m, $(CH_3)_2CH$]; 1.18 [s, $(CH_3)_3C$]; 3.62 and 3.79 (AB, J = 10 Hz, **6b**, CH_2OtBu); 3.78 (s, OCH_3); 3.7 - 4.1 [m, $(CH_3)_2CH$]; 4.19 and 4.47 (AB, J = 11 Hz, **6b**, CH_2OCb); 4.36 and 4.64 (AB, J = 11 Hz, **6a**, CH_2OCb); 4.84 (d, J = 2 Hz, **6a**, 4-H); 4.98 (d, J = 2.4 Hz, **6b**, 4-H); 8.08 (d, J = 2 Hz, **6a**, 2-H); 8.09 ppm (d, J = 2.4 Hz, **6b**, 2-H). - ^{13}C NMR ($CDCl_3$): δ = 20.86 [$(CH_3)_2CH$], 27.23 and 27.40 [$(CH_3)_3C$], 45.99 [$(CH_3)_2CH$], 52.01 (**6b**, CH_3O), 52.29 (**6a**, CH_3O), 64.76 and 65.12 (**6b**, 2 x CH_2O), 62.08 and 65.74 (**6a**, 2 x CH_2O), 66.24 (**6b**, C-5), 66.36 (**6a**, C-5), 73.63 [**6a**, $(CH_3)_3C$], 73.74 [**6b**, $(CH_3)_3C$], 79.12 (**6a**, C-4), 79.18 (**6b**, C-4), 153.94 (**6b**, NC=O), 154.44 (**6a**, NC=O), 158.97 (**6a**, C-2), 159.12 (**6b**, C-2), 168.83 ppm (OC=O).

Methyl 3-tert.-Butoxymethyl-4-(N,N-diisopropylcarbamoyloxy)-2-(N-methylthiomethylene-amino)-2-butenoate (**7**), diastereoisomers: A soln of lithium isopropoxide (42 mmol) in THF/hexane (130 mL, 4:1), chilled to -78 °C, was added dropwise into a soln of **6a** and **6b** (16.16 g, 41.59 mmol) and methyl iodide (21 mL) in THF (1000 mL) kept at rt (9). The mixture was stirred for further 4 h and phosphate buffer (200 mL) was added. The soln was concentrated at 40 °C i. vac., the residue diluted with ether (1000 mL) and water (200 mL), the aqueous layer extracted with pentane (2 x 100 mL), the combined organic layers filtrated over silica gel (100 g), and the solvent removed; yield 13.94 g (83%) of a mixture of diastereoisomers **7**, I, II, and III (77:19:4); viscous oil. The crude product was immediately used for the next step. - IR (KBr): 1730 (OC=O), 1690 (NC=O), 1570 cm^{-1} (C=N). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.21 [s, $(CH_3)_3C$]; 2.12 [d, J = 6.7 Hz, $(CH_3)_2CH$]; 2.43 (s, SCH_3, I); 2.46 (s, SCH_3, II); 3.78 (s, OCH_3, I); 3.81 (s, OCH_3, II); 3.7 - 4.1 [m, $HC(CH_3)_2$]; 4.13 (s, CH_2OtBu, I); 4.28 (s, CH_2OtBu, II); 4.42 (s, CH_2OtBu, III); 4.78 (s, CH_2OCb, III); 4.85 (s, CH_2OCb, N-Z); 5.02 (s, CH_2OCb, N-E); 8.33 (s, N=C-H, I; 8.42 ppm (s, N=C-H, II). - ^{13}C NMR ($CDCl_3$): δ = 11.38 (SCH_3, II), 11.47 (SCH_3, I), 21 [b, $(CH_3)_2CH$], 27.34 [$(CH_3)_3C$, N-E], 27.58 [$(CH_3)_3C$, N-Z], 45 [b, $(CH_3)_2CH$], 57.70 (OCH_3, I), 51.93 (OCH_3, II), 57.22 (CH_2OCb, II), 59.49 (CH_2OCb, I), 60.34 (CH_2OtBu, I), 61.44 (CH_2OtBu, II), 130.38 (C-2, II), 130.60 (C-2, I), 139.83 (C-3, I), 140.61 (C-3,II), 155.22 (NC=O, I), 155.32 (NC=O, II), 159.19 (C=N, I), 160.55 (C=N, II), 165.17 (OC=O, II), 165.17 ppm (OC=O, I).

Methyl (Z)- and (E)-(3'R*,4'S*)-2-(3-Azido-4-methylthio-2-oxo-azetidin-1-yl)-3-tert.-butoxymethyl-4-(N,N-diisopropylcarbamoyloxy)-2-butenoate (**8a** and **8b**): To crude **7** (13.94 g, 34.62 mmol) and triethyl amine (9.7 mL, 69.6 mmol) in dichloromethane (500 mL) a soln of azidoacetyl chloride (9,17) (8.31 g, 69.6 mmol) in dichloromethane (200 mL) was added dropwise within 3 h. The mixture was stirred for 1 h, washed with phosphate buffer (200 mL) and water (300 mL), the solvent removed, and the residue chromatographied over silica gel (300 g) with ether/pentane (1:1); yield 15.4 g (92%) **8a** and **8b** (1:4), yellow oil. A sample of the diastereoisomers was separated with the same eluent; **8a**: R_f = 0.43, **8b**: R_f = 0.49.
8a: IR (KBr): 2115 (N_3), 1780 (NC=O, ß-lactam), 1725 (OC=O), 1690 cm^{-1} (NC=O). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.21 [s, $(CH_3)_3C$]; 1.22 [d, J = 7 Hz, $(CH_3)_2CH$]; 2.17 (s, SCH_3); 3.7 - 4.1 [m, $(CH_3)_2CH$]; 3.84 (s, OCH_3); 4.08 and 4.15 (AB, J = 13 Hz, CH_2OtBu); 4.54 (d, J = 2 Hz, 4'-H); 4.98 (d, J = 2 Hz, 3'-H); 5.02 and 5.14 ppm (AB, J = 13 Hz, CH_2OCb). - ^{13}C NMR ($CDCl_3$): δ = 12.54 (SCH_3), 21.00

[$(CH_3)_2CH$], 27.49 [$(CH_3)_3C$], 46.01 [$(CH_3)_2CH$], 52.64 (OCH_3), 60.05 and 60.57 (CH_2OCb and CH_2OtBu), 67.20 (C-3'), 69.15 (C-4'), 74.22 [$(CH_3)_3C$], 123.16 (C-2), 146.23 (C-3), 154.87 (NC=O, Cb), 161.31 (NC=O, ß-lactam), 162.80 ppm (OC=O).

8b: IR (KBr): 2115 (N_3), 1780 (C=O, ß-lactam), 1725 (OC=O), 1690 cm^{-1} (NC=O). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.17 [s, $(CH_3)_3C$]; 1.19 [d, J = 6 Hz, $(CH_3)_2CH$]; 2.15 (s, SCH_3); 3.82 (s, OCH_3); 3.7 - 4.1 [m, $(CH_3)_2CH$]; 4.35 and 4.45 (AB, J = 12.5 Hz, CH_2OtBu); 4.79 and 4.88 (AB, J = 11 Hz, CH_2OCb); 4.54 (d, J = 2.4 Hz, 4'-H); 4.95 ppm (d, J = 2.4 Hz, 3'-H). - ^{13}C NMR ($CDCl_3$): δ = 12.44 (SCH_3), 20.94 [$(CH_3)_2CH$], 27.41 [$(CH_3)_3C$], 46 [b, $(CH_3)_2CH$], 52.44 (OCH_3), 58.94 (CH_2OCb), 69.79 (CH_2OtBu), 67.24 (C-4'), 69.27 (C-3'), 73.82 [$(CH_3)_3C$], 122.07 (C-2), 147.03 (C-3), 154.47 (NC=O, Cb), 161.56 (NC=O, ß-lactam), 163.06 ppm (OC=O).

$C_{21}H_{35}N_5O_6S$ (485.61). Calc. C 51.94 H 7.27. Found C 52.07 H 7.29.

Methyl (E)- and (Z)-(3'R*,4'S*)-2-(3-Benzoylamino-4-methylthio-2-oxo-azetidin-1-yl)-3-tert.-butoxymethyl-4-(N,N-diisopropylcarbamoyloxy)-2-butenoate (**9a** and **9b**): Through the soln of **8a** and **8b** (1:4, 15.4 g, 31.7 mmol) and triethyl amine (6.7 mL, 48 mmol) in dichloromethane (500 mL) a stream hydrogen sulfide was passed at 0 °C for 1 h. Then the solvent and excess hydrogen sulfide were removed i. vac. (8 torr) and the residue dissolved in dichloromethane (200 mL). Triethyl amine (6.7 mL) and benzoyl chloride (6.75 g, 48 mmol) were added at -22 °C and the mixture was stirred over night. Then it was washed with phosphate buffer (200 mL) and the aqueous layer extracted with dichloromethane (100 mL). The solvent was removed i. vac. and the residue separated on silica gel (1000 g) with ether/pentane (1:1); yield 7.71 g (43%) of **9b**, R_f (ether) = 0.59, mp 62 °C (ether) and 1.16 g (6.4%) of **9a**, R_f = 0.52, mp 55 °C. - The same procedure (scale 2 mmol) yielded from **9a** 60% **11a** and from **9b** 67% **11b** besides 4% **11a**.

9a: IR (KBr): 3350 (NH), 1775 (NC=O, ß-lactam), 1725 (OC=O), 1690 (NC=O, Cb), 1665 cm^{-1} (NC=O, amide). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.21 [d, J = 7 Hz, $(CH_3)_2CH$]; 1.21 [s, $(CH_3)_3C$]; 2.19 (s, SCH_3); 3.77 (s, OCH_3); 3.7 - 4.1 [m, $(CH_3)_2CH$]; 4.17 and 4.24 (AB, J = 12.6 Hz, CH_2OtBu); 5.00 and 5.18 (AB, J = 8.9 Hz, CH_2OCb); 4.99 - 5.18 (m, ABX, 3'-H and 4'-H); 7.28 (d, J = 6 Hz, N-H); 7.46, 7.54 and 7.84 ppm (m, phenyl). - ^{13}C NMR ($CDCl_3$): δ = 12.44 (SCH_3), 21.08 [$(CH_3)_2CH$], 27.58 [$(CH_3)_3C$], 46.09 [$(CH_3)_2CH$], 52.58 (CH_3O), 60.05 and 60.55 (CH_2OtBu and CH_2OCb), 62.26 (C-3'), 67.93 (C-4'), 74.12 [$(CH_3)_3C$], 123.39 (C-2), 127.27, 128.64, 132.13 and 132.90 (phenyl), 145.57 (C-3), 154.97 (NC=O, Cb), 163.30 OC=O), 164.00 (NC=O, ß-lactam), 167.14 (NC=O, amide).

$C_{28}H_{41}N_3O_7S$ (563.71) Calc. C 59.66 H 7.33. Found C 59.67 H 7.39.

9b: IR (KBr): 3340 (NH), 1775 (NC=O, ß-lactam), 1725 (OC=O), 1690 (NC=O, Cb), 1660 cm^{-1} (NC=O), amide). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.10 - 1.28 [b, $(CH_3)_2CH$]; 1.23 [s, $(CH_3)_3C$]; 2.22 (s, SCH_3); 3.82 (s, OCH_3); 3.7 - 4.1 [b, $(CH_3)_2CH$]; 4.39 and 4.48 (AB, J = 14 Hz, CH_2OtBu); 4.88 (d, J = 2 Hz, 4'-H); 4.92 and 5.03 (AB, J = 12 Hz, CH_2OCb); 5.48 (dd, J_1 = 10 Hz, J_2 = 2 Hz, 3'-H); 7.42, 7.52 and 7.94 (m, phenyl); 8.11 ppm (d, J = 10 Hz, NH). - ^{13}C NMR ($CDCl_3$): δ = 11.94 (SCH_3), 20 - 21 [$(CH_3)_2CH$], 27.49 [$(CH_3)_3C$], 45.79 - 46.95 [$(CH_3)_2CH$], 52.34 (OCH_3), 59.30 and 59.47 (CH_2OCb and CH_2OtBu), 62.44 (C-3'), 69.45 (C-4'), 73.87 [$(CH_3)_3C$], 123.86 (C-2), 127.40, 128.40, 131.84 and 133.18 (phenyl), 147.85 (C-3), 155.28 (NC=O, Cb), 163.80 (OC=O), 164.62 (NC=O, ß-lactam); 166.76 (NC=O, amide).

$C_{28}H_{41}N_3O_7S$ (563.71). Calc. C 59.66 H 7.33. Found C 59.67 H 7.30.

Isomerization of **9b** to **9a**: **9b** (0.142 g, 0.25 mmol) in THF (2 mL) were added to a soln of potassium tert.-butoxide (0.044 g, 0.25 mmol) in THF (4 mL) at -78 °C. The mixture was allowed to warm to rt before glacial acetic acid (0.4 mL) in THF was added. The solvent was removed i. vac. and the residue separated on silica gel (8 g) with ether/pentane (1:1); yield 0.083 g (59%) **9a** besides 41 mg (27%) of recovered **9b**.

Methyl (E)-(1'R*,5'S*)-3-tert.-Butoxymethyl-4-(N,N-diisopropylcarbamoyloxy-2-(7-oxo-3-phenyl-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-6-yl)-2-butenoate (**11a**): According to the procedure in ref. (10) the chlorolysis of **9a** (0.662 g, 1.17 mmol), stirring the reaction mixture with phosphate buffer (10 mL) over night, afforded after LC on silica gel (8 g) with ether/pentane (1:1); yield 0.438 g (73%) **11a**, white solid, mp 109 °C. - IR (KBr): 1785 (NC=O, ß-lactam), 1735 (OC=O), 1690 (NC=O, Cb), 1640 cm^{-1} (C=N). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.93 [s, $(CH_3)_3C$]; 1.19 [m, $(CH_3)_2CH$]; 3.76 (s, OCH_3); 3.92 and 4.05 (AB, J = 12.5 Hz, CH_2OtBu); 5.08 and 5.20 (AB, J = 13 Hz, CH_2OCb); 5.43 (d, J = 4 Hz, 1'-H); 6.23 (d, J = 4 Hz, 5'-H); 7.3 - 7.5 and 7.9 - 8.1 ppm (m, phenyl). - ^{13}C NMR ($CDCl_3$): δ = 21 [$(CH_3)_2CH$], 27.17 [$(CH_3)_3C$], 46.02 [$(CH_3)_2CH$], 52.59 (OCH_3), 59.59 (CH_2OCb), 60.21 (CH_2OtBu), 73.90 [$(CH_3)_3C$], 82.00 (C-5'), 87.60 (C-1'), 126.94 (C-2), 148.09 (C-3), 128,41, 128.45, 128.54 and 132.28 (phenyl), 154.78 (NC=O, Cb), 163.10 (OC=O), 165.14 (NC=O, ß-lactam), 166.65 ppm (C-3').

$C_{27}H_{37}N_3O_7$ (515.61). Calc. C 62.90 H 7.23. Found C 63.06 H 7.28.

Methyl (Z)-(1R*,5S*)-3-tert.-Butoxymethyl-4-(N,N-diisopropylcarbamoyloxy)-2-(7-oxo-3-phenyl-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-6-yl)-2-butenoate (**11b**): As described for **11a**, from **9b** (0.620 g, 1.20 mmol) **11b** (0.306 g, 49%) was obtained as a colourless viscous oil. - IR (KBr): 1785 (NC=O, ß-lactam), 1725 (OC=O), 1710 - 1650 cm^{-1} (NC=O, Cb, and C=N). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.15 [s, $(CH_3)_3C$]; 1.21 [d, J = 5 Hz, $(CH_3)_2CH$]; 3.15 (s, OCH_3); 3.7 - 3.9 [m, $(CH_3)_2CH$]; 4.37 and 4.45 (AB, J = 11.5 Hz, CH_2OtBu); 4.76 and 4.88 (AB, J = 13 Hz, CH_2OCb); 5.42 (d, J = 4.5 Hz, 5'-H); 5.18 (d, J = 4.5 Hz, 1'-H); 7.3 - 7.6 and 7.9 - 8.0 ppm (m, phenyl). - ^{13}C NMR ($CDCl_3$): δ = 20.84 [$(CH_3)_2CH$], 27.32 [$(CH_3)_3C$], 45.94 [$(CH_3)_2CH$], 52.29 (CH_3O), 58.60 (CH_2OtBu), 60.41 (CH_2OCb), 73.69 [$(CH_3)_3C$], 81.98 (C-5'), 88.15 (C-1'), 126.84 (C-2), 127.49, 128.28, 128.38 and 133.00 (phenyl), 154.48 (C-3), 162.64 (NC=O, Cb), 165.22 (NC=O, ß-lactam), 166.64 ppm (C=N).

$C_{27}H_{25}N_3O_6$ (515.61). Calc. C 62.89 H 7.23. Found C 63.12 H 7.37.

Methyl (1R*,8R*)-8-Benzoylamino-4-(N,N-diisopropylcarbamoyloxymethyl)-7-oxo-2-oxa-6-azabicyclo[4.2.0]oct-4-en-5-carboxylate (**12**): **11a** (0.438 g, 0.849 mmol) was dissolved in 2.2 M zinc chloride etherate in dichloromethane (2 mL) and stirred over night at rt. Dichloromethane (30 mL) was added and the mixture was washed with phosphate buffer (10 mL). The aqueous layer was extracted with dichloromethane, the solvent removed i. vac. and the residue separated on silica gel (8 g) with ether/pentane (1:1). Besides 92 mg (21%) recovered **11a**, 77 mg (20%) **12**, white solid, mp 80 °C

(ether), was obtained. - IR (KBr): 3400 (NH), 1785 (NC=O, ß-lactam); 1725 (OC=O), 1705 - 1640 cm^{-1} (NC=O, amide, and Cb). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.21 [d, J = 6.8 Hz, $(CH_3)_2CH$]; 3.88 (s, CH_3O); 3.7 - 4.1 [m, $(CH_3)_2CH$]; 4.45 and 4.59 (AB, J = 18 Hz, 3-CH_2); 4.92 and 5.15 (AB, J = 15 Hz, CH_2OCb); 4.95 (dd, J_1 = 0.9 Hz, J_2 = 7 Hz, 8-H); 5.08 (d, J = 0.9 Hz, 1-H); 7.06 (d, J = 7 Hz, NH); 7.43, 7.52 and 7.82 ppm (m, phenyl). - ^{13}C NMR ($CDCl_3$): δ = 21.00 [$(CH_3)_2CH$], 46.27 [$(CH_3)_2CH$], 52.72 (OCH_3), 60.62 (C-3), 66.06 (CH_2OCb), 64.47 (C-8), 82.74 (C-1), 123.44 (C-5), 127.55, 128.33, 130.01, 132.36 and 132.99 (phenyl and C-4), 155.03 (NC=O, Cb), 161.44 (OC=O), 162.77 (NC=O, ß-lactam), 167.78 ppm (NC=O, amide).
$C_{23}H_{29}N_3O_7$ (459.50). Calc. C 60.12 H 6.36. Found C 60.09 H 6.47.

(1R*,5S*)-6-[4-(N,N-Diisopropylcarbamoyloxymethyl)-2-oxo-2,5-dihydrofuran-3-yl]-3-phenyl-4-oxa-2,6-diazabicyclo[3.2.0]hept-3-en-7-one (13): **11b** (0.165 g, 0.320 mmol) and 2.2 M zinc chloride etherate in dichloromethane (1.46 mL) were stirred over night. Dichloromethane (10 mL) was added and the mixture washed with phosphate buffer (5 mL). After drying ($MgSO_4$) the solvent was removed i. vac. and the residue purified on silica gel (8 g) with ether/pentane (1:1); yield 64 mg (47%) **13**, white solid, mp 160 °C. - IR (KBr): 1810 - 1750 (OC=O and NC=O, ß-lactam), 1690 (NC=O, Cb), 1630 cm^{-1} (C=N). - ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.14 [d, J = 7 Hz, $(CH_3)_2CH$]; 3.65 - 4.0 [m, $(CH_3)_2CH$]; 4.85 and 4.86 (AB, J = 1 Hz, 5'-H_2); 5.20 and 5.31 (AB, J_1 = 15.5 Hz, J_2 = 1 Hz, CH_2OCb); 5.47 (d, J = 3.4 Hz, 1-H); 6.86 (d, J = 3.4 Hz, 5-H); 7.44, 7.54 and 8.02 ppm (m, phenyl). - ^{13}C NMR ($CDCl_3$): δ = 20.69 - 21.46 [$(CH_3)_2CH$], 46.56 [$(CH_3)_2CH$], 58.88 (C-5'), 69.93 (CH_2OCb), 82.42 and 84.80 (C-1 and C-5), 119.29 (C-3'), 124.45, 126.72, 128.70 and 132.37 (phenyl), 144.43 (C-4'), 154.44 (NC=O, Cb), 163.52 (NC=O, ß-lactam), 167.30 (C=N), 167.90 (OC=O).
$C_{22}H_{25}N_3O_6$ (427.46). Calc. C 61.82 H 5.89. Found C 61.96 H 5.95.

Acknowledgement - Generous support of the work by the Fonds der Chemischen Industrie is gratefully acknowledged.

REFERENCES AND FOOTNOTES

1. Dissertation H. Schmincke, University of Göttingen, 1987.
2. Review: M. Narisada, Pure Appl. Chem. **59** (1987) 459.
3. S. Wolfe, J.-B. Ducep, K. C. Tin, S.-L. Lee, Can. J. Chem. **52** (1974) 3996.
4. E. G. Brain, C. L. Branch, A. J. Eglington, J. H. C. Nayler, N. F. Osborne, M. J. Pearson, T. C. Smale, R. Southgate, P. Tolliday, in "Recent Advances in the Chemistry of ß-Lactam Antibiotics" (J. Elks, Ed.), Spec. Publ. No. 28, p. 204-213, Chem. Soc., London 1977.
5. M. Narisada, H. Onoue, W. Nagata, Heterocycles **7** (1977) 839.
6. Review: W. Nagata, M. Narisada, T. Yoshida in R. B. Morin and M. Gorman (Ed.), Chemistry and Biology of ß-Lactam Antibiotics, Vol. 2, p. 1 - 98, Academic Press, New York 1982.
7. L. D. Cama, B. G. Christensen, J. Am. Chem. Soc. **96** (1974) 7582.
8. R. A. Firestone, J. L. Fahey, N. S. Maciejewicz, G. S. Patel, B. G. Christensen, J. Med. Chem. **20** (1977) 551.
9. D. Hoppe, H. Schmincke, H.-W. Kleemann, Tetrahedron **45** (1989); the next to the last paper.
10. D. Hoppe, H. Schmincke, H.-W. Kleemann, Tetrahedron **45** (1989); preceding paper.
11. Review: D. Hoppe, Angew. Chem. **96** (1984) 930; Angew. Chem., Int. Ed. Engl. **23** (1984) 932.
12. D. Hoppe, R. Hanko, A. Brönneke, F. Lichtenberg, E. van Hülsen, Chem. Ber. **118** (1985) 2822. - The chloride is now commercially available from Merck-Schuchardt Co. and from Fluka Chemie AG.
13. U. Schöllkopf, F. Gerhart, R. Schröder, D. Hoppe, Liebigs Ann. Chem. **766** (1972) 116. - Review: D. Hoppe, Angew. Chem. **86** (1974) 878; Angew. Chem., Int. Ed. Engl. 13 (1974) 789.
14. R. Glaser, S. Gheresh, U. Schöllkopf, R. Meyer, J. Chem. Soc., Perkin 1 **1979**, 1746.
15. B. S. Pedersen, S. Scheibye, K. Clausen, S.-O. Lawesson, Bull. Soc. Chim. Belg. **87** (1978) 229.
16. U. Schöllkopf, D. Hoppe, Angew. Chem. **85** (1973) 1102; Angew. Chem., Int. Ed. Engl. **12** (1973) 1006.
17. a) D. Hoppe, M. Kloft, Liebigs Ann. Chem. **1980**, 1512. b) M. Kloft, D. Hoppe, Tetrahedron Lett. **1977**, 2141.
18. Of the four possible diastereoisomers of the azadiene **7** three are recognized by NMR in the $CDCl_3$ soln, ratio 77:19:4. An assignment was not possible. The deduction on the configuration of **7** from that of the major precursor **8b** or the major ß-lactam **8b** is not permissible, since the base-induced ring opening was shown to proceed not stereospecifically (17) and during ß-lactam formation of similar thioformimidates E/Z-isomerization of the conjugated C=C bond had been observed (17).
19. B. G. Christensen, K. Hoogsten, F. Plavac, R. W. Ratcliffe, in J. Elks (Ed.) Recent Advances in the Chemistry of ß-Lactam Antibiotics, Chem. Soc. Spec. Publ. No 28, p. 260 - 268, London 1977.
20. D. Hoppe, R. Hanko, A. Brönneke, Angew. Chem. **92** (1980) 637; Angew. Chem., Int. Ed. Engl. **19** (1980) 625.