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The Conversion of β-Amino Esters by Alkylaluminum Compounds into β-Lactams

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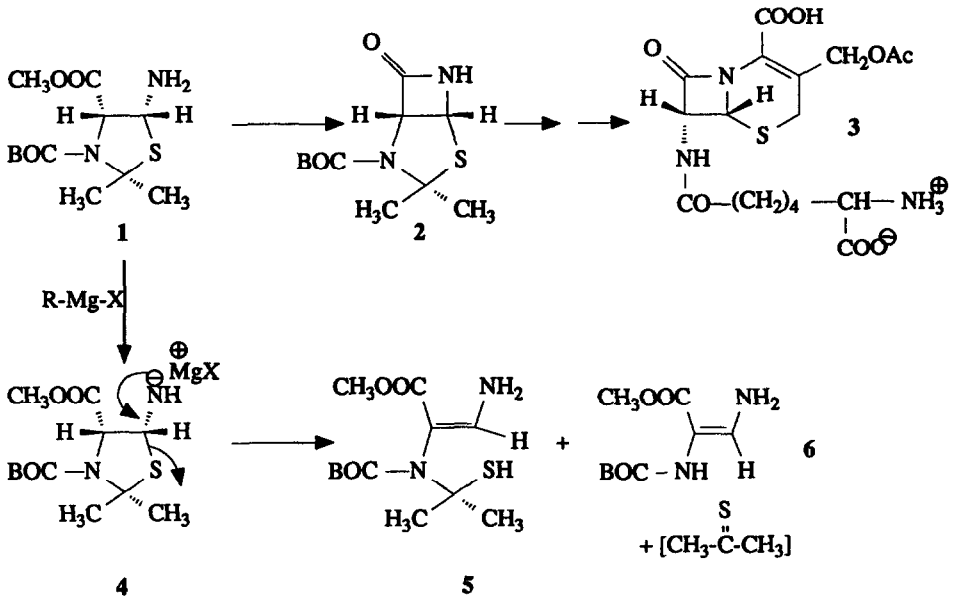
Abstract. β-Amino esters with an unsubstituted amino group such as **1** or **19** can be cyclized by two equivalents of alkylaluminum compounds such as triisobutylaluminum in yields of up to 61% to the corresponding β-lactams **2** or **20**.

A key step in the total synthesis of cephalosporin C[1] **3** was the conversion of the β-amino ester **1**,[2] derived in several steps from L-cysteine,[1] with alkylaluminum compounds into the bicyclic β-lactam **2**. Since this reaction, which was covered only very briefly in the preliminary publications,[1] might be of general interest for the preparation of β-lactams its scope and limitations are discussed in this paper.

The common method to effect such a cyclization of β-amino esters to the corresponding β-lactams is the so called Breckpot-reaction[3], in which β-amino esters are treated with two equivalents of Grignard reagents[4]. The use of the hindered mesityl Grignard reagent minimizes the competing attack on the ester carbonyl group.[5],[6] All attempts, however, to convert **1** with Grignard reagents into **2** failed since the negative charge on the nitrogen in the Grignard salt intermediate **4** induced the fragmentation of the thiazolidine ring with formation of products such as **5** and **6**, which had been observed before during attempted hydrolysis of the tributylphosphine-imine derived from **1**.[1]



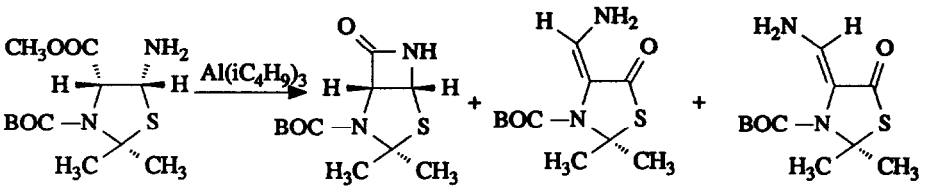
Since the Grignard reagents were too nucleophilic there was clearly a need for more electrophilic organometallic reagents, which would not fragment before closing the β-lactam ring. An obvious choice was aluminum-organic compounds[7], which had been described to form at -80° C with primary amines donor-acceptor complexes that decompose at higher temperatures with formation of alkanes and alkenes[8].

In initial experiments heating of the β-amino ester **1** with aluminum triisopropylate in toluene gave a crude product, which showed in its IR spectrum a very weak but distinct β-lactam carbonyl band at 5.63 μ as anticipated for the desired strained bicyclic β-lactam **2**. Although this result was encouraging, the aluminum alcoholates were clearly not the right reagents to form alkylaluminum amide-intermediates.

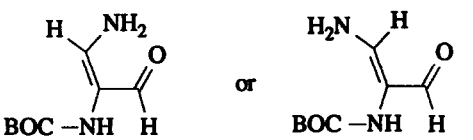
Since diisobutylaluminum hydride (DIBAH) was available, we mixed a 20% toluene solution of diisobutylaluminum hydride with a solution of **1** in toluene without cooling whereupon the reaction mixture warmed up to 40° C. After workup with ice and cyclohexane the crude product showed again the distinct β-lactam band at 5.63 μ. On repeating this reaction under controlled conditions at 0° C, however, the ester moiety in **1** was quantitatively reduced. Thus an aluminum-organic reagent had to be employed lacking a reactive hydrogen, e.g. trialkylaluminum compounds or the combination of dialkylaluminum chloride with a tert. base.

The first reaction of **1** with two equivalents of triisobutylaluminum at 0° C in abs. toluene affor-

ded a crude product, which gave after workup with ice and chromatography on silica gel a 30% yield of the desired crystalline bicyclic β-lactam **2**, the crystalline thiolactones **7** and **8**, the crystalline enaminone **9** or **10** as side products as well as 5 % starting β-amino ester **1**. The structure of the β-lactam **2** is supported by its IR bands at 2.95 (NH) and 5.63 μ (β-lactam carbonyl) as well as by its NMR and MS spectra. The structures of **2** as well as of **1** were subsequently confirmed by single crystal X-ray determination by Z.A. Gougoutas at Harvard University in summer 1965[1]. The isomeric crystalline thiolactones **7** and **8**, which could be interconverted on warming in abs. pyridine, were identified based on their characteristic IR, NMR and UV spectra, but a definite proof, which set of data belongs to either **7** or **8**, could not be obtained at that time. Likewise, the structure of the crystalline third side product could only be assigned either to **9** or **10**.

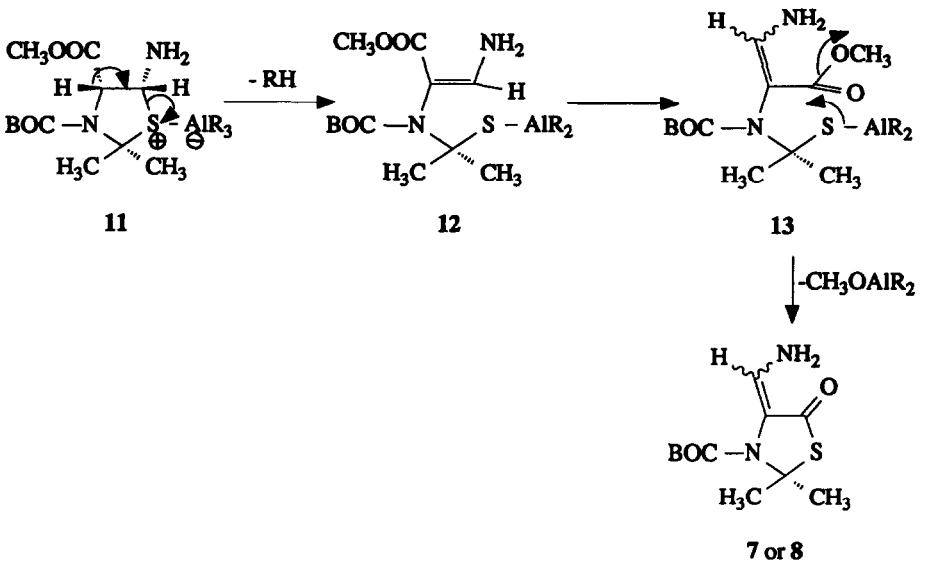


1 **2** **7** **8**



9 **10**

The formation of the thiolactones **7** and **8** can be rationalized by attack of the electrophilic trialkylaluminum on the sulfur to **11** resulting in the elimination of the sulfur aluminum complex to **12** followed by rotation of the bond between the urethane nitrogen and C-4 to **13** and recyclization with elimination of methoxy diisobutylaluminum to **7** or **8**. The formation of **9** or **10** can be explained by elimination of thioacetone from **7** or **8** and subsequent reduction of the ester- to an aldehyde group.



11 12 13

7 or 8

Variation of the reaction conditions did not give any improvement of the yield of **2**. At lower temperatures the reaction slowed down to stop at ca. -18° C. Replacement of triisobutylaluminum by the combination diethylaluminum chloride / diisopropylethylamine did neither raise the yield of **2**. Finally, dimethylaluminum chloride became available to give in combination with diisopropylethylamine at -15° C → -10° C 59 % β-lactam **2**, 10 - 15 % starting amino ester **2** as well as the aforedescribed thiolactones **7** and **8**. Later studies by colleagues in the Woodward Institute demonstrated that triethylaluminum affords similar yields of the β-lactam **2**.

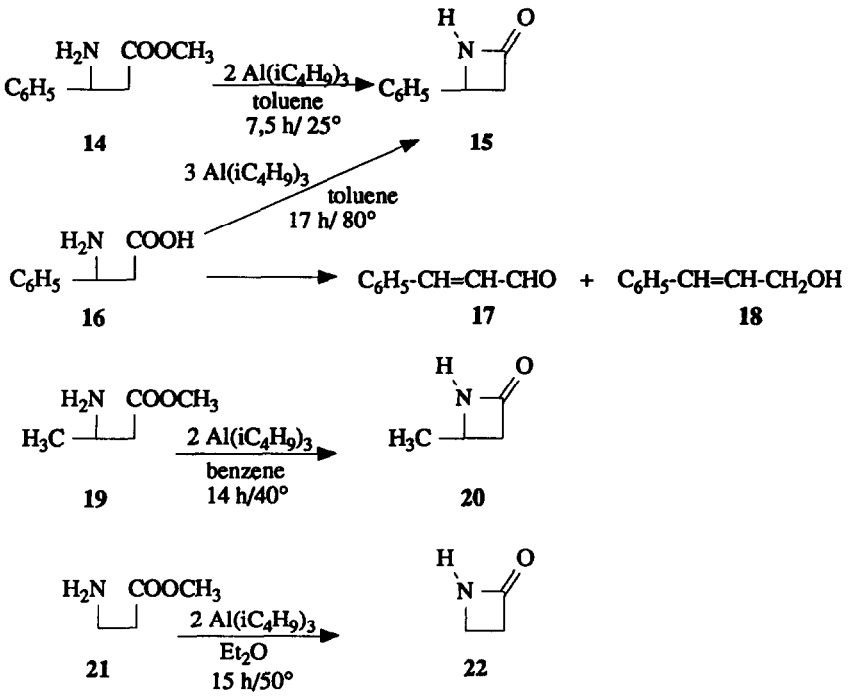
It can be anticipated that trimethylaluminum, which was not available in 1965, might be the optimal reagent for the conversion of **1** into **2** as well as the subsequently described cyclizations of β-amino esters into the corresponding β-lactams.

Scope of the Reaction

To check the generality of this new synthetic method, we treated a series of β-amino esters with two equivalents of triisobutylaluminum. Since most of these reactions were performed only once, these reactions are not optimized and the given yields can certainly be improved, particularly on using the aforementioned trimethylaluminum or the combination dimethylaluminum chloride / diisopropylethylamine.

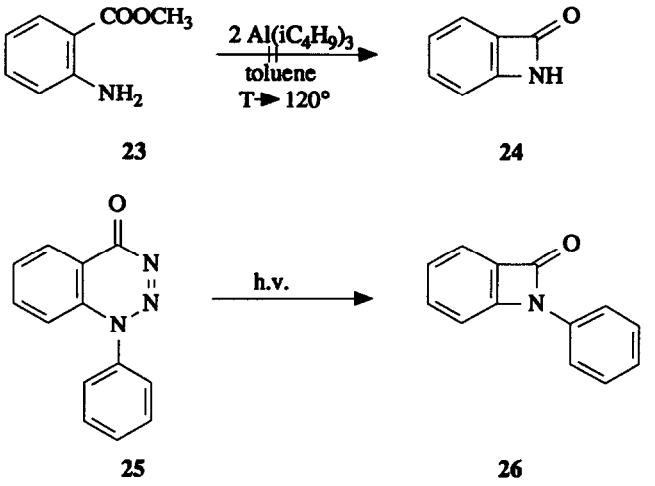
Thus D,L-methyl 3-amino-3-phenylpropionate **14** gave with triisobutylaluminum the D,L-β-lactam **15** in 30% yield, which had previously been prepared by the addition of chlorosulfonylisocyanate to styrene and subsequent hydrolysis of the N-chlorosulfonyl group[9], whereas the free D,L-3-amino-3-phe-

nylpropionic acid **16** furnished with three equivalents of triisobutylaluminum on heating to 80° C only 5.1% of **15** besides cinnamylaldehyde **17** and cinnamylalcohol **18**. D,L-Methyl 3-aminobutyrate **19** yielded 61% of the D,L-β-lactam **20**, whereas methyl 3-aminopropionate **21** gave 30% of the known crystalline β-propiolactam **22**, which had previously been prepared in 0.76% yield by the reaction of Grignard reagents with alkyl 3-aminopropionate[4a)5a)]. For subsequent preparations of β-propiolactam **22** compare ref.[5b)] and [6a)].



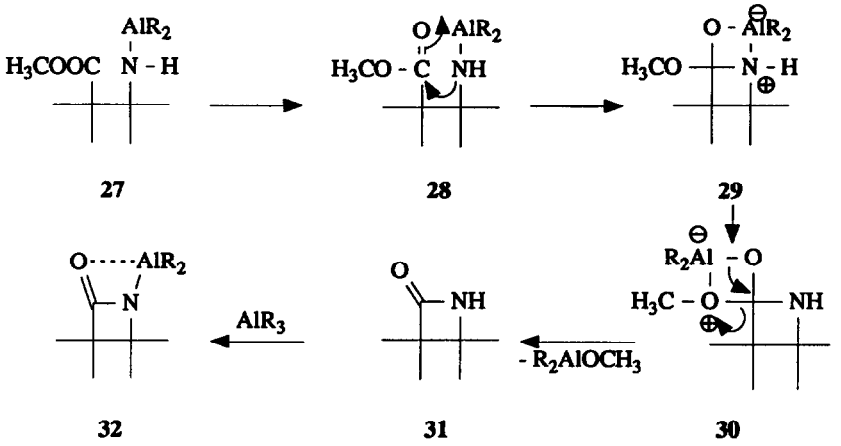
Several attempts, however, failed to convert methyl anthranilate **23** into the as yet unknown β-lactam **24**. The corresponding rather unstable N-phenyl-β-lactam **26** with a β-lactam carbonylband at 5.47 μ had been prepared by photolysis of the benzotriazinone **25**[10)].

Likewise, all attempts failed to convert any N-substituted β-amino ester with triisobutylaluminum into the corresponding N-substituted β-lactams.

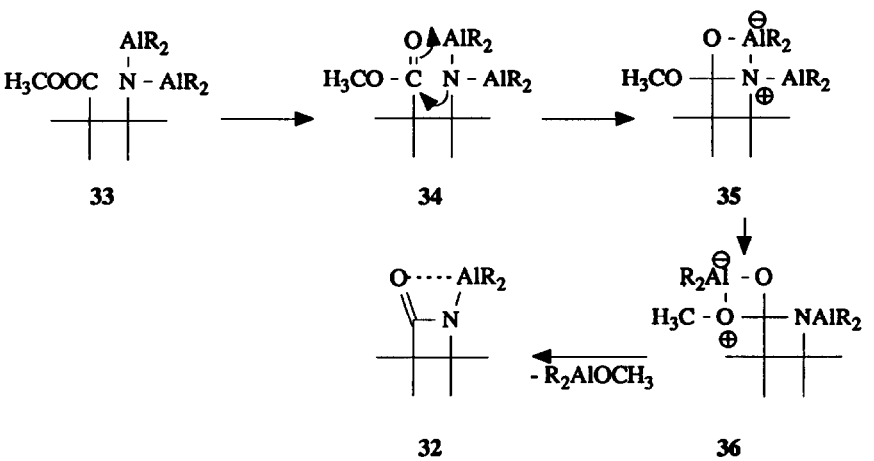


Mechanism

After addition of 2 equivalents of triisobutylaluminum to a solution of the β-amino ester **1** in toluene, the IR spectrum of the crude reaction mixture shows neither the NH band at 2.90 μ nor the β-lactam-carbonyl band at 5.63 μ. Furthermore, on addition of one equivalent of triisobutylaluminum to a solution of the β-lactam **2** in toluene at 15° C, both IR bands at 2.90 as well as 5.63 μ disappear. The crystalline β-lactam **2**, however, can be recovered unchanged after 30 min at 20° C on workup with ice in more than 80% yield.[11] The NH-group of the β-lactam moiety reacts apparently with the aluminum-organic reagent to a complex (compare **32**) with a longer wave length carbonyl frequency. As in the aforementioned Breckpot-reaction one needs two equivalents of organometallic reagent for the β-lactam synthesis: One equivalent to effect the ring closure and an additional second equivalent to form the metal complex with the NH-group of the β-lactam moiety as in **32**. Taking all these results into account there are two mechanisms possible: In the first mechanism the β-amino ester moiety reacts with <u>one</u> equivalent trialkylaluminum (or dialkylaluminum chloride - diisopropylethylamine) to form the addition complex **27**, which rearranges via **28** to the bicyclic intermediate **29** and subsequently to the bicyclic compund **30**. Elimination of methoxy dialkylaluminum to the β-lactam **31** and reaction with a second equivalent of trialkylaluminum affords finally the complex **32**.



In the second mechanism the β-amino ester reacts with <u>two</u> equivalents of the trialkylaluminum (or dialkylaluminum chloride / diisopropylethylamine) to **33**, which rearranges analogously via **34**, **35** and **36** to the aforediscussed complex **32**.



Since the size of the alkyl groups in the aluminum organic reagents seems to determine the yield of the β-lactam and N-alkylated β-amino esters fail to react with triisobutylaluminum to form the N-alkylated β-lactams, the second mechanism appears to be more probable, although no definite proof for either mechanism has as yet been provided. In the reaction of the ß-amino acid D,L-3-amino-3-phenylpropionic acid **16** three equivalents of triisobutylaluminum had to be applied to give probably via intermediates such as **33**, in which the ester methoxy group is replaced by a diisobutylaluminumoxy group, the corresponding β-lactam **32** with formation of tetraisobutyldialuminum oxide. There are, however, other and

much more efficient methods for the cyclization of β-amino acids[12].

Subsequent to these "intramolecular" reactions of dialkylaluminum amides with ester moieties to form β-lactams[13], S.M. Weinreb[14] described in 1977 very useful "intermolecular" reactions of in situ prepared dimethylaluminum amides with esters or lactones at 25 - 41° C in CH_2Cl_2 to give the corresponding carboxamides in high yields. This reaction sequence has found wide application for the preparation of amides and lactams[15], the very useful N-methyl-N-methoxyamides[16] as well as imidazolines[17].

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Varian 100 mc instrument, the IR spectra on a Perkin Elmer instrument and the Mass spectra on an Atlas CH4 spectrometer.

3-Tert.butoxycarbonyl-4,4-dimethylazetidino[3,2-d]thiazolidin -2-one (2):

a) To a solution of 59 mg (o.2 mmol) β-amino ester **1** in 2 ml abs. toluene 0.4 ml of a 20% solution of diisobutylaluminum hydride in toluene were given with a syringe at 25°C under nitrogen without cooling, whereupon the mixture warmed up to 35-40°C and turned yellow. After 20 min ice and cyclohexane were added and the aluminum hydroxide centrifuged and the cyclohexane phase decanted. The precipitated aluminum hydroxide was stirred twice with cyclohexane and centrifuged. The collected cyclohexane-phase was dried (Na_2SO_4) and evaporated to give 40 mg crude product, which showed in $CHCl_3$ solution a weak β-lactam band at 5.63 μ. Chromatography with benzene-ethyl acetate (94:6) on a column of ca. 10 g silica gel gave two fractions of 3 and 4 mg with a stronger β-lactam band at 5.63 μ.

b) To 3.832 g (13.05 mmol) β-amino ester **1** in 160 ml toluene 27.5 ml of a 0.96 molar solution of triisobutylaluminum in toluene was added slowly with a syringe under nitrogen atmosphere at 0°C. After 64 h at +7°C the reaction mixture was stirred for 2 h with ice and filtered over a layer of Celite, which was washed with toluene and chloroform. The collected organic phase was dried ($MgSO_4$) and evaporated to give 3.336 g of crude oil, which showed a strong β-lactam IR band at 5.63 μ. On keeping a solution of the crude product in 75 ml cyclohexane and 10 ml hexane at -18°C, a voluminous precipitate had formed, which was separated to give on recrystallization from cyclohexane 230 mg of the enaminone **9** or **10** mp. 142→146°C, obtained analytically pure mp. 145.5→147°C after one further recrystallization from benzene. The combined filtrate (3.1 g) was chromatographed in benzene-ethyl acetate on a column of 320 g silica gel. Elution with 450 ml 127:23→125:25 benzene-ethyl acetate mixture furnished crystalline thiolactone **7** or **8**, which was recrystallized from hexane to give 210 mg pure thiolactone mp. 105°C. Further elution with 600 ml 124:26 to 121:29 benzene-ethyl acetate mixture afforded the other thiolactone **7** or **8**, which yielded on recrystallization from hexane 180 mg pure sample, mp. 109-110°C. Elution with 750 ml 120:30→116:34 benzene-ethyl acetate furnished after evapoation and recrystallization from hexane 747 mg pure β-lactam **2**. Further elution with 600 ml 115:35→100:50 mixture yielded 200 mg crude starting β-amino ester **1**, which crystallized partly from pentane. The mother liquors and mixed fractions were combined and rechromatographed on a column of silica gel to provide additional 318 mg β-lactam **2**, combined yield of **2** = 1.184 g (35%).

c) To a solution of 5.805 g (20 mmol) amino ester **1** and 7.5 ml (43 mmol) diisopropylethylamine in 400 ml abs. toluene, which was cooled to -60° C, 35 ml of a 1.75 molar solution of dimethylaluminum chloride in abs. toluene was added slowly with a syringe and vigorous stirring under nitrogen whereupon the reaction temperature rose to -10° C. As there was still some unreacted β-amino ester after 60 min at -60° C, additional 4 ml reagent were added and the reaction mixture kept for further 30 min at -10° C. After dilution with 200 ml toluene and addition to 400 g ice and 50 ml sat. $NaHCO_3$ solution, the mixture was vigorously stirred for 10 min and filtered over a layer of Celite, which was carefully washed with CH_2Cl_2. The collected organic phase furnished after drying (Na_2SO_4) and evaporation 5.42 g crude product, which was chromatographed as aforedescribed with benzene-ethyl acetate on a column of 370 g silicagel to give 700 mg thiolactones **7** and **8**, 54 mg of a mixture of thiolactones **7** or **8** with the β-lactam **2** and finally 3.348 g crude β-lactam **2**, which provided on recrystallization 2.717 g pure crystalline β-lactam **2**, mp. 120.5° C. Rechromatography of 650 mg crude β-lactam **2** on silicagel gave further 233 mg of pure **2**. Combined yield of **2** = 3.05 g (59%).

2: mp. 120.5 (recrystallized from hexane) $[\alpha]_D$ = -274° (c = 0.522, $CHCl_3$) ^1H-NMR (CCl_4) δ 1.50 (s,

9H); 1.84 (s, 6H); 5.32 (d, J = 5Hz, 1H); 5.63 (q, J = 5Hz, 1H); 7.32 (br, 1H) MS m/z = 259 (M+1) 258 (M) 243 (M-CH_3) 231 (M-HCN) 215 (M-HNCO), 203, 159, 144, 142, 125, 114, 102, 100, 57, IR (CH_2Cl_2) μ = 2.95, 5.62, 5.90, 7.25, 7.35, 7.75, 8.65, 9.36, 10.60, 11.65, 12.30; Anal.calcd for $C_{11}H_{18}N_2OS$: C, 51.15; H, 7.02; N, 10.84; Found: C, 51.23; H, 7.09; N, 10.92.
7 (or **8**): mp. 105° C λmax. (ethanol) 230 nm (8.550) 351 nm (11.550) ^{1}H-NMR ($CDCl_3$) δ 1.55 (s, 9H); 1.92 (s, 6H); 6.30(br,2H); 7.60 (tr, J = 10 - 11Hz, 1H) IR (CH_2Cl_2) μ 2.83, 3.00, 5.87, 6.03, 6.22, 6.57, 7.22, 7.32, 7.40, 8.60, 8.90, 9.90, 10.83, 11.30, 11.84; Anal.calcd for $C_{11}H_{18}N_2O_3S$: C, 51.14; H, 7.02; N, 10.84; Found: C, 51.28; H, 7.30; N, 10.70.
7 (or **8**): mp. 109 - 110° C λmax. (ethanol) 220 nm (6.800) 322 nm (13.850) ^{1}H-NMR ($CDCl_3$) δ 1.58 (s, 9H); 1.92 (s, 6H); 4.90 (d, J = 11Hz, 2H); 7.20 (tr. J = 11Hz, 1H) Anal.calcd for $C_{11}H_{18}N_2O_3S$: C, 51.14; H, 7.02; N, 10.84; Found: C, 51.41; H, 7.25; N, 10.74.
9 (or **10**): mp. 145.5 - 147° C λmax. (ethanol) 275 nm (20.480) ^{1}H-NMR ($CDCl_3$) δ 1.62 (s, 9H); 5.5 (br, 4H); 8.66 (s, 1H) MS m/z = 186, 130, 86, 84, 78, 69, 57. IR (CH_2Cl_2) μ 2.85, 2.96, 5.87, 6.19, 6.63, 7.30, 7.70, 8.65, 9.30, 11.85 Anal.calcd for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.04; Found: C, 51.36; H, 7.67; N, 14.76.

4-Phenylazetidin-2-one (15):

a) D,L-Methyl-3-amino-3-phenylpropionate-hydrochloride **14** was treated at 0° C with 10 N NaOH/CH_2Cl_2 and the CH_2Cl_2-phase dried (Na_2SO_4) and evaporated. To a solution of 304 mg (1.7 mmol) of freshly prepared methyl 3-amino-3-phenylpropionate **15** in 50 ml toluene was added at 0° C 3.4 mmol triisobutylaluminum in toluene with a syringe under nitrogen. After 24 h at 7° C and 7.5 h at 25° C the mixture was worked up with ice/CH_2Cl_2 and filtered over a layer of Celite. After washing with CH_2Cl_2, drying (Na_2SO_4), 207 mg crude product were obtained. Chromatography with benzene-ethyl acetate (4:1) on a column of silicagel gave 72 mg (29%) crystalline **15**, which was obtained analytically pure mp. 105 - 105.5° C (lit.[9]108 - 109° C) on recrystallization from hexane.

b) To a suspension of 1.657 g (10 mmol) D,L-3-amino-3-phenylpropionic acid **16**[18] in 50 ml abs. toluene was added at -18° C under nitrogen a solution of 17.2 ml (20 mmol) triisobutylaluminum in toluene with a syringe. Since there was still part of **16** undissolved after 16 h stirring at 25° C, further 9 ml (10 mmol) triisobutylaluminum solution were added, whereupon the residual undissolved **16** passed into solution and the solution turned yellow. Since a worked up sample did not show any β-lactam band after further 6 h at 25° C, the reaction mixture was heated for 17 h at 80° C and then worked up with ice/$CHCl_3$. Chromatography of the crude reaction product (608 mg) on a column of 100 g silicagel gave on elution with 200 ml benzene-ethyl acetate (95:5 → 91:9) 147 mg of pure cinnamylaldehyde **17**. Further elution with 200 ml of 87:13 → 86:14 mixture afforded 28 mg of crude cinnamylalcohol **18**, whereas 600 ml 77:23 → 70:30 mixture furnished 75 mg (5.1%) of crystalline β-lactam **15**, mp. 105 - 105,5° C from hexane.
15: mp. 105 - 105,5° C ^{1}H-NMR ($CDCl_3$) δ 2.8 (ddd, J = 1.5; 2.7; 15Hz, 1H); 3.42 (ddd, J = 3; 4.5; 15Hz; 1H); 4.73 (dd, J = 2.7; 5.4Hz; 1H); 6.6 (br, 1H); 7.38 (m, 5H) IR (CH_2Cl_2) μ 2.93, 5.70, 7.42, 8.50, 8.58, 10.30, 10.52, Anal.calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52; Found: C, 73.47; H, 6.20; N, 9,69.

D,L-4-Methylazetidin-2-one (20):

To a solution of 588 mg (5 mmol) of oily D,L-methyl 3-amino butyrate **19** (freshly prepared from **19** hydrochloride with ice-10 N NaOH/CH_2Cl_2 and the CH_2Cl_2 phase dried with Na_2SO_4) in 25 ml abs. benzene was added a solution of 2 equivalents of triisobutylaluminum in benzene. After 14 h at 40° C, workup with ice-sat. $NaHCO_3$ solution/CH_2Cl_2, filtration over a layer of Celite and washing of the Celite-layer with benzene, the phases were separated and the aqueous phase extracted with 5 x 30 ml CH_2Cl_2. The combined organic phase was dried (Na_2SO_4) and evaporated to give 260 mg (61%) of practically pure oily D,L-4-methylazetidinone **20**, a sample of which was redistilled at 90 - 100° / 0,5 mm to furnish the analytical sample of **20**.
20: ^{1}H-NMR ($CDCl_3$) δ 2.50 (dd, J = 3 + 15Hz, 1H); 3.1 (dd, J = 5 + 15Hz, 1H); 3.75 (m, 1Hz) Anal.calcd for C_4H_7NO: C, 56.45; H, 8.29; N 16.46 Found: C, 56.34; H, 8.46; N, 16.42.

Azetidin-2-one (22):

To a solution of 1.331 g (12.9 mmol) of methyl 3-aminopropionate **21** (freshly prepared from the crystalline **21** hydrochloride with ice cold aqueous KOH/CH_2Cl_2 and the CH_2Cl_2 phase dried with Na_2SO_4) in 50 ml abs. ether there were added at 0° C under nitrogen with a syringe 28.2 ml (25.8 mmol) of a 0.917 molar solution of triisobutylaluminum in ether. After heating the solution for 15 h at 45 - 50° C bath temperature, most of the ether had evaporated. The residual viscous oil was stirred with 50 ml ether/ice cold sat. $NaHCO_3$ solution and then filtered over a layer of Celite, which was carefully washed with CH_2Cl_2. After separation of the layers, the aqueous phase was extracted three times with CH_2Cl_2 and the combined organic phase dried (Na_2SO_4) and evaporated to give 258 mg (28%) of spontanously

crystallizing azetidin-2-one **22**, which was distilled at 95°/0,1 mm to afford the analytical sample, mp. 73 → 74° C (Lit.[4a] mp. 73 → 74° C).
22: mp. 73 → 74° C ^{1}H-NMR ($CDCl_3$) δ 2.95 (m, 2H); 3.25 (m, 2H); 6.20 (br, 1H) Anal.calcd for C_3H_5NO: C, 50.69; H, 7.09; N, 19.71; Found: C, 50.63; H, 7.06; N, 19.87.

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‡deceased, July 8, 1979

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