Pergamon

Tetrahedron Vol. 50, No. 13, pp. 3943-3950, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0151-I

Effects of Configuration and N-Substitution on the Formation of ß-Lactams from Bicyclic Cyano-substituted Isoxazolidines

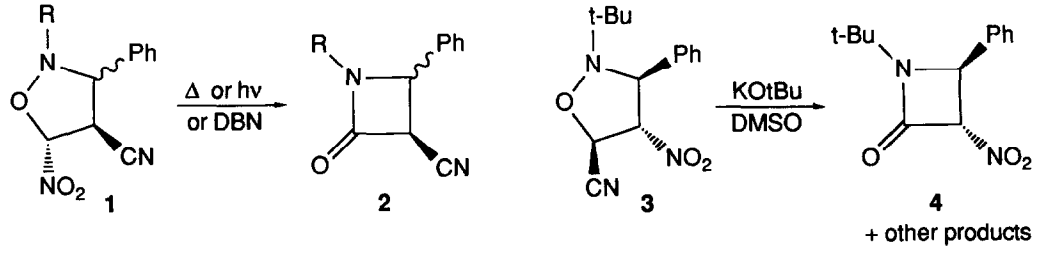
Hans Günter Aurich*, Jose-Luis Ruiz Quintero

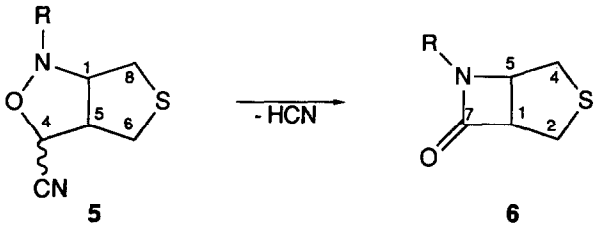
Fachbereich Chemie der Philipps-Universität Marburg, D-35032 Marburg, Germany

Abstract: The 4-cyano-substituted bicyclic compounds **10** and **11** were prepared by reaction of the aldehyde dimer **7** with a cis-trans mixture of 4-bromo crotononitrile followed by treatment with corresponding N-substituted hydroxylamines. The diastereomers **10a** and **10b** could be separated by flash chromatography. The key step in the synthesis of compounds **15** and **16** was the Wittig reaction of **13** with cyanomethylene triphenylphosphorane affording a mixture of diastereomers **14a** and **14b**, which were separated by flash chromatography. Separate Swern oxidation of **14a** and **14b**, followed by reaction with N-(4-tert-butylphenyl)hydroxylamine gave bicyclic compounds **15a** and **15b**, respectively. In the same way **16b** was prepared.
The action of lithium diisopropylamide on the N-aryl-substituted compounds **10b** and **15b** possessing an exo-hydrogen atom at 4-position converted these to the bicyclic ß-lactams **18** and **19**, respectively. In contrast neither diastereomers **10a** and **15a** with an endo-hydrogen atom, nor the N-alkyl-substituted compounds **11** or **16b**, nor compounds of type **17** were affected by LDA under equal conditions.

ß-Lactams are the subject of long-standing interest, in particular because of their significance as antibiotica.[1] Some years ago Padwa et al. described a new entry to ß-lactams starting from 4-cyano-5-nitro-isoxazolidines **1**.[2] These could be converted to ß-lactams **2** either by heating in different solvents, by irradiation in solution or by treatment with 1.5 diazabicyclo[4.3.0]non-5-ene (DBN) at room temperature. However, there are some other reaction modes for compounds **1** under similar conditions.[2] Thus, lactam formation depends strongly on the reaction conditions.

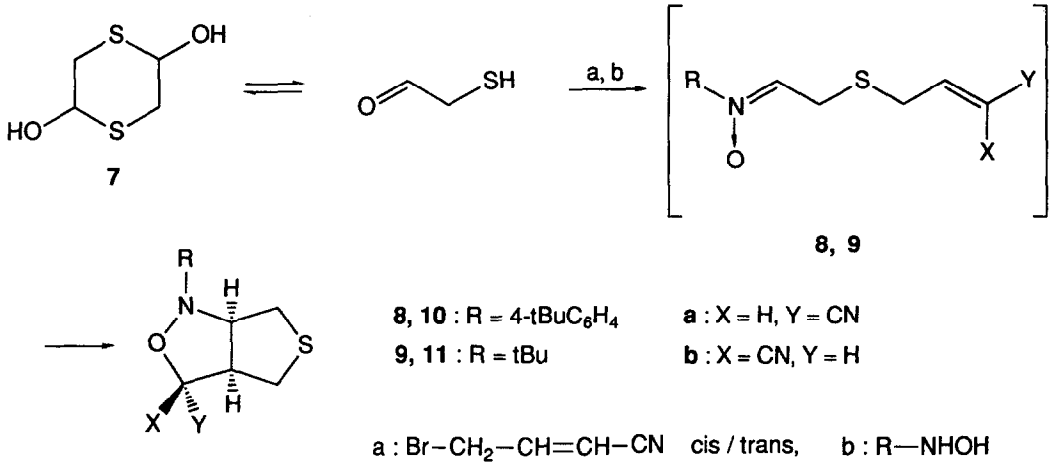
The potential of reaction pathways for the 5-cyano-4-nitro-isoxazolidine **3** is even more puzzling. The ß-lactam **4** could be isolated only as by-product in 11% yield, when **3** had been treated with potassium tert-butoxide in dimethyl sulfoxide. Taking up the finding of Padwa et al.[2] that "the isoxazolidine to ß-lactam transformation can be achieved with groups other than nitro in the 5-position of the heterocyclic ring" we suggested that bicyclic cyano-isoxazolidines of type **5** could be eventually converted to ß-lactams **6** by treatment with bases. To this end, we synthesized compounds **10**, **11**, **15** and **16** and treated them with bases as well as compounds **17** described in the preceding paper.[3]





5 **6**

Reaction of 2.5-dihydroxydithiane (7), the dimer of mercapto acetaldehyde, with a cis-trans mixture of 4-bromo crotononitrile[4] yielded the two diastereomeric 6-cyano-3-thia-hexenals, which were converted to nitrones **8** and **9** by treatment with N-4-tert-butylphenylhydroxylamine or N-tert-butylhydroxylamine, respectively. Compounds **8** and **9** underwent spontaneously an intramolecular cycloaddition[3] to afford the desired products **10** and **11**, respectively. Whereas the mixture of **10a** and **10b** could be separated by chromatography, separation of **11a** and **11b** could not be achieved.



7 **8, 9**

10, 11

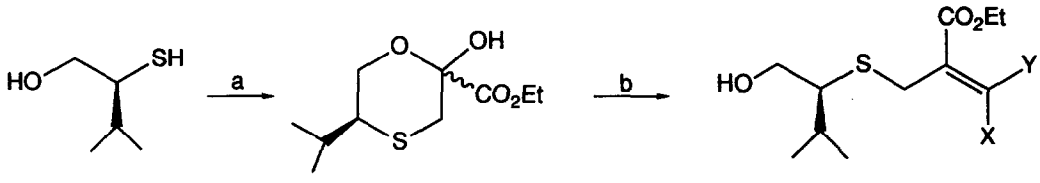
8, 10 : R = 4-tBuC$_6$H$_4$ **a** : X = H, Y = CN

9, 11 : R = tBu **b** : X = CN, Y = H

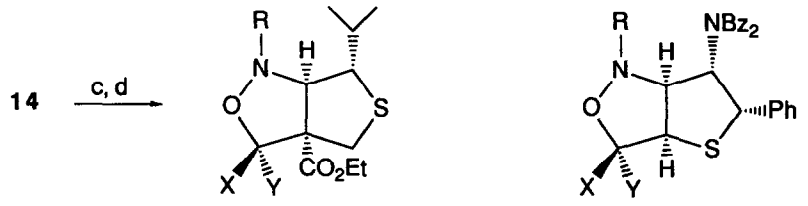
a : Br–CH$_2$–CH=CH–CN cis / trans, b : R—NHOH

Compounds **15** and **16** were prepared in the following way. Racemic 2-mercapto-3-methyl-1-butanol **12** was treated with ethyl α-bromopyruvate to give the cyclic hemiketal **13**. Reaction of the latter with cyanomethylene triphenylphosphorane[5] yielded compounds **14a** and **b** which were separated by flash chromatography. Separate Swern oxidation[6] of **14a** and **14b** followed by reaction with N-(4-tert-butylphenyl)hydroxylamine afforded compounds **15a** and **15b**, respectively, via the corresponding nitrones which underwent spontaneously an intramolecular cycloaddition. Compound **16b** was obtained in the same way from **14b** with N-benzylhydroxylamine.

The configuration of the stereoisomeric pairs **10a, 10b** and **15a, 15b** was determined by comparison of their NMR data with those of compounds **17a**, **17b** (Table 1). The configuration of **17a** and **17b** is based on the fact that they were formed from the corresponding alcohols for which definitive trans- and cis-configuration at the alkene group, respectively, had been determined from their ^{1}H-NMR coupling constants.[3]



12 **13** **14**



15, 16 **17**

15, 17 : R = 4-tBuC$_6$H$_4$ **a** : X = H, Y = CN

16 : R = tBu **b** : X = CN, Y = H

a : Br−CH$_2$−CO−CO$_2$Et b : Ph$_3$P=CH−CN

c : (COCl)$_2$, DMSO, Et$_3$N d : R−NHOH

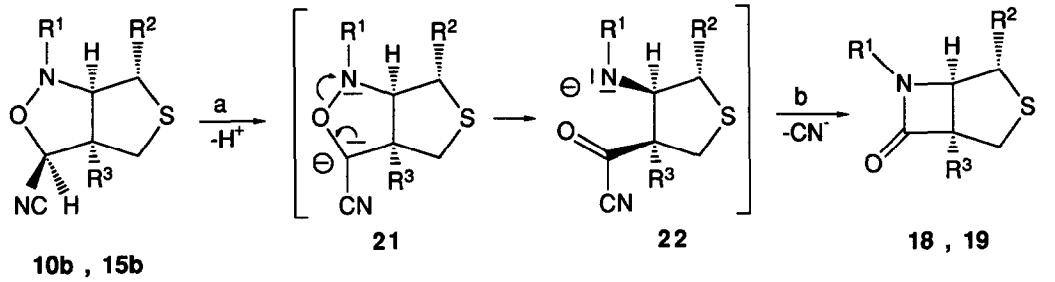
Table 1. Comparison of NMR data of bicyclic compounds **10**, **15-17** (δ in ppm, J in Hz)

	δ 4-H	δ C-4	δ CN	J 4/5
17a	4.87	74.5	116.8	3.5
17b	5.22	75.6	115.7	7.4
10a	4.63	73.2	116.5	5.0
10b	4.91	74.6	115.3	8.0
15a	4.91	79.3	114.7	-
15b	5.11	81.9	113.9	-
16b	5.30	82.2	115.0	-

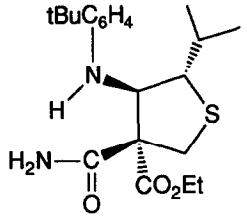
As can be seen from table 1 the proton resonance signal of 4-H appears at lower field if this proton is located in exo-position. The same is true for the C-4 signal. On the other hand, the ^{13}C NMR signal of the cyano carbon is shifted to higher field if the cyano group is in the endo-position. As expected cis-compounds **17b** and **10b** exhibit higher coupling constants J 4/5 compared to the trans compounds.

Compound **10b** was treated under various conditions with the following bases: 1.5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine, sodium ethoxide and potassium tert-butoxide. Mostly, a number of non-separable decomposition products arose.

However, treatment of **10b** with lithium diisopropylamide (LDA) in tetrahydrofuran at -78°C furnished the racemic bicyclic lactam **18** in 89% yield. In the same way compound **19** arose from the reaction of **15b** with LDA in 65% yield, along with 20% of compound **20**, which was obviously formed during the work-up procedure by the action of ammonium chloride.



10b , 15b **21** **22** **18 , 19**



20

10b , 18 : $R^1 = 4\text{-}tBuC_6H_4$ $R^2 = H$ $R^3 = H$

15b , 19 : $R^1 = 4\text{-}tBuC_6H_4$ $R^2 = iPr$ $R^3 = CO_2Et$

a : LDA -78°C b : NH_4Cl

Surprisingly, neither the diastereomeric forms **10a** and **15a** nor the N-alkyl substituted compounds **16b**, and **11a/11b** were affected by LDA at -78°C. The unchanged educts were isolated in every case. The same is true for the N-aryl substituted pair of diastereomers **17a** and **17b** in which the sulfur atom is located in position 6 of the bicyclic ring.

Following the mechanistic interpretation of Padwa[2] we suppose that the carbanion **21** initially formed by reaction with LDA undergoes ring opening to afford the amide anion **22** containing an acylcyanide moiety. Intramolecular substitution at the acylcyanide group would then yield the ß-lactam (**18/19**) with loss of cyanide anion.

The failure of compounds **10a** and **15a** to undergo the base-induced conversion, in contrast to their diastereomers **10b** and **15b**, respectively, may be rationalized by the different disposition of the 4-H atom for abstraction by the sterically hindered base. Thus, the endo-protons of **10a** and **15a** are effectively shielded by the fused heterocyclic ring system, whereas the exo-protons 4-H of **10b** and **15b** are better susceptible for the attack of the base.

On the other hand, the substituent at the nitrogen atom seems to play an important role, as is shown by the failure of compounds **11a,b** and **16b** to undergo conversion to ß-lactams. Presumably, ring opening of

carbanion **21** is only possible, if the negative charge developing at the nitrogen atom is stabilized. This can for instance occur by the aromatic N-substitutent of **10** and **15** but not by aliphatic groups as the tert-butyl group of **11** or the benzyl group of **16b**.

Under the aspects discussed so far compound **17b** should be a favorable candidate for conversion to a ß-lactam. In this case, however, it is less clear, why the conversion does not occur. The main reason for that may be the changed position of the sulfur atom within the backbone of the bicyclic compound.

Experimental Part

Elemental analyses were performed by the division Routine-Analytik, Fachbereich Chemie, University of Marburg. Spectra were recorded with following instruments: NMR: ^{1}H-NMR 300 MHz Bruker AC 300 if not quoted otherwise, or Bruker AM 400, Bruker AMX 500; ^{13}C-NMR 75 MHz Bruker AC 300. Solvent $CDCl_3$ internal standard residue of ^{1}H (δ = 7.25 ppm) or of ^{13}C (δ = 77.0 ppm) MS: Varian CH 7 (EI) and 711 (FD). - IR: Beckman IR 33 and Bruker IFS 88-FT-IR.

Formation of 4-cyano-substituted 3-oxa-7-thia-2-azabicyclo[3.3.0]octanes **10, 11**: 4-Bromocrotonitrile[4] (14.6 g , 0.1 mol mixture of cis/trans) was dropped to a suspension of 2.5-dihydroxy-1.4-dithiane (**7**) (7.6. g, 0.05 mol) and triethylamine (10.1 g, 0.1 mol) in acetone so that the temperature did not exceed 30°C. After stirring for 10 h the insoluble residue was filtered off. A solution of N-(4-tert-butylphenyl)hydroxylamine (16.5 g, 0.1 mol) or N-tert-butylhydroxylamine (8.9 g, 0.1 mol) in acetone was added to the solution of the unstable aldehyde. The reaction mixture was stirred for 5 h at room temperature. Then the solvent was removed and the product was purified by chromatography on silica gel. Compounds **10a** and **10b** were separated in this way, whereas **11a** and **11b** could be obtained only as a mixture.

(1RS/4RS/5RS) 2-(4-tert-Butylphenyl)-4-cyano-3-oxa-7-thia-2-azabicyclo[3.3.0]octane (10a): brown oil from chromatography SiO_2/CH_2Cl_2 R_F = 0.61, yield 28%. - MS(EI): m/e = 288 (7%; M^+) - IR (neat): 2251 cm^{-1}. - ^{1}H-NMR: δ = 1,28 (s, 9H, tert-Bu); 2,83 (dd, ^{2}J=12,52, ^{3}J=3,74 Hz, 1H, 8-H); 3,00 (dd, ^{2}J=12,52 Hz, ^{3}J=4,41 Hz 1H, 8'-H); 3,06 (dd, ^{2}J=12,20 Hz, ^{3}J=3,64 Hz, 1H 6-H); 3,10 (dd, ^{2}J=12,20 Hz, ^{3}J=6,88 Hz, 1H, 6'-H); 3,71 (dddd, ^{3}J=7,10 Hz, ^{3}J=6,88 Hz, ^{3}J= 5,08 Hz, ^{3}J=3,64 Hz, 1H, 5-H); 4,59 (ddd, ^{3}J=7,10 Hz, ^{3}J=4,41 Hz, ^{3}J=3,74, 1H, 1-H); 4,63 (d, ^{3}J=5,08, 1H, 4-H); 6,98 (d, 2H, aromatic H); 7,30 (d, 2H; aromatic H). - ^{13}C-NMR: δ = 31,4 (q, J=135,2 Hz, tert-Bu); 34,2 (s, $(CH_3)_3\underline{C}$), 35,0 (t, J=139,6 Hz, C-6 or C-8); 35,6 (t, J=141,1Hz, C-6 or C-8); 57,7 (d, J=138,7 Hz, C-5); 69,4 (d, J=151,1 Hz, C-1); 73,2 (d, 146,8 Hz, C-4); 116,2 (s, $\underline{C}$N); 115,9-146,4 (aromatic C).

(1RS/4SR/5RS)-2-(4-tert-Butylphenyl)-4-cyano-3-oxa-7-thia-2-azabicyclo[3.3.0]octane (**10b**): yellow solid from chromatography, SiO_2/CH_2Cl_2, yield 28%, mp 81°C from hexane/Et_2O. - $C_{10}H_{20}N_2OS$ (288,4) Calcd. C 66,63 H 6,98 N 9,71 Found C 66,07 H 6,35 N 8,92. - MS(EI): m/e = 288 (7%; M^+). - IR(KBr): 2214 cm^{-1}. - ^{1}H-NMR: δ = 1,10 (s, 9H, tert-Bu); 3,02 (dd, ^{2}J=12,4 Hz, ^{3}J=4,70 Hz, 1H; 8-H); 3,08 (dd, ^{2}J=12,60 Hz, ^{3}J=7,50 Hz, 1H; 6-H); 3,15 (dd, ^{2}J=12,4 Hz, ^{3}J=6,50 Hz, 1H, 8'-H); 3,16 (dd, ^{2}J=12,6 Hz, ^{3}J=4,9 Hz, 1H, 6'-H); 3,59 (dddd, ^{3}J=8,10 Hz, ^{3}J=8,00 Hz, ^{3}J=7,50 Hz, ^{3}J=4,90 Hz, 1H, 5-H); 4,45 (ddd, ^{3}J=8,10 Hz, J=6,5 Hz, 4,7 Hz, 1H, 1-H); 4,91 (d, J=8,00 Hz, 1H, 4-H); 7,00 (d, 2H, aromatic H); 7,28 (d, 2H, aromatic H); - ^{13}C-NMR: δ = 31,3 (q, J=132,9 Hz,$(\underline{C}H_3)_3$C); 34,1 (t, J=141,2 Hz, C-6 or C-8); 34,3 (s, $(CH_3)_3\underline{C}$); 36,8 (t, J=139.1 Hz, C-6 or C-8); 54,4 (d, J=143,8 Hz, C-5); 68,7 (d, J=151,9 Hz, C-1); 74,6 (d, J=147,3 Hz, C-4); 115,3 (s, $\underline{C}$N); 116,2-147,0 (aromatic C).

2-tert-Butyl-4-cyano-3-oxa-7-thia-2-azabicyclo[3.3.0]octane mixture of diastereomers **11a/11b**: dark brown oil from chromatography SiO_2/CH_2Cl_2, yield 52%. - MS (EI): m/e = 212 (20%), M^+). - IR (neat): 2240 cm^{-1}. - ^{1}H-NMR (400 MHz): δ = 1.09/1.11 (s, 9H, tert-Bu), 2.79 (dd, 1H, 8-H); 2.85 (dd, 1H, 8'-H); 2.87 (dd, 1H, 6-H); 2.98 (dd, 1H, 6'-H), 3.43 (m, 1H, 5-H), 3.83 (ddd, 1H, 1-H), 4.39/481 (d, 1H, 4-H). - ^{13}C-NMR: δ = 25.6/25.7 (q, tert-Bu), 27.8/32.2/32.8/38.2 (t, C-6, C-8), 56.3/56.6 (d, C-5); 57.3/58.4 (s, t-Bu); 67.4/67.7/68.1/68.4 (d, C-1, C-4); 117.0/125.3 (s, C≡N).

Ethyl-3-hydroxy-6-isopropyl-1.4-oxathiane-3-carboxylate (**13**) mixture of diastereomers. Triethylamine (0.87 g = 1.2 mmol, 8.5 mmol) was added to a solution of rac-3-methyl-2-mercapto-1-butanol (**12**) in dicthyl ether (50 ml). After 15 min a solution of the ethyl ester of bromopyruvic acid (1.79 g = 1.15 ml, 8.3 mmol) in diethyl ether (50 ml) was dropped to the stirred reaction mixture. Stirring was continued for 6 h at room temperature. Then the precipitate was filtered off, and the reaction mixture was successively extracted with saturated aqueous solution of ammonium chloride and sodium chloride. The organic layer was dried over $MgSO_4$, then the solvent was removed and the crude product was purified by chromatography on silica gel (Et_2O/EtOAc 3:1, R_f = 0.55). **13** was isolated as yellow-orange oil in 64% yield (1.24 g).

MS(EI): m/e = 234 (5%; M^+). - IR(neat): 3498, 1734 cm^{-1}. - Major diastereomer. ^{1}H-NMR: δ = 0,85 (d, ^{3}J=6,05 Hz, 3H,($C\underline{H}_3)_2$CH), 0,87 (d, ^{3}J=6,08 Hz, 3H, ($C\underline{H}_3)_2$CH); 1,18 (t, ^{3}J=7,16 Hz, 3H $OCH_2C\underline{H}_3$); 1,60 (hept, ^{3}J=7,12, ^{3}J=6,07, 1H, $(CH_3)_2C\underline{H}$); 2,58 (d, ^{2}J=13,57 Hz, 1H, 2-H); 2,72 (ddd, ^{3}J=10,66 Hz, ^{3}J=7,12 Hz, ^{3}J=3,19 Hz, 1H, 6-H); 3,18 (d, ^{2}J=13,58 Hz, 1H, 2'-H); 3,82 (dd, ^{2}J=12,01 Hz, ^{3}J=3,19 Hz, 5-H); 3,94 (dd, ^{2}J=12,01 Hz, ^{3}J=10,66 Hz, 5'-H); 4,18 (q, ^{3}J=7,16 Hz, 2H, $CO_2C\underline{H}_2CH_3$). - ^{13}C-NMR: δ = 13,9 (q, J=133,1 Hz, $CO_2CH_2\underline{C}H_3$); 20,3 (q, J=135,1 Hz, $(\underline{C}H_3)_2$CH); 20,4 (q, J=134,9 Hz, $(\underline{C}H_3)_2$CH); 29,2 (d, J=140,1 Hz, $(CH_3)_2\underline{C}$H); 33,6 (t, J=142,3 Hz, C-2); 46,1 (d, J=146,6 Hz, C-6); 62,1 (t, J=145,6 Hz, $CO_2\underline{C}H_2CH_3$); 65,2 (t, J=146,9 Hz, C-5); 90,1 (s, C-3); 169,5 (s, $\underline{C}O_2$Et).

Preparation of compounds **14a** and **14b**

Compound **13** (1.0 mg, 4.3 mmol) and (cyanomethylen)triphenylphosphorane[5] (1.4 g, 4.7 mmol) were refluxed in dry tetrahydrofuran under an argon atmosphere for 2 h. The solvent was removed under vacuum. The crude product containing triphenylphosphine oxide was purified and separated by flash chromatography (Et_2O/petroleum ether (40/60) 4:1).

Methyl E-(5RS)-2-cyanomethylene-5-hydroxymethyl-6-methyl-4-thia-heptanoate (**14a**): Orange oil, R_f = 0,41, yield 41% (45 g). - MS(EI): m/e = 257 (4%; M^+). - IR(neat): 3501, 2248, 1720 cm^{-1}. - ^{1}H-NMR: δ = 0,77 (d, ^{3}J=6,78 Hz, 3H, ($C\underline{H}_3)_2$CH); 0,85 (d, ^{3}J=6,75 Hz, 3H,($C\underline{H}_3)_2$CH); 1,17 (t, ^{3}J=7,17 Hz, 3H, $CO_2CH_2C\underline{H}_3$); 1,85 (heptd, ^{3}J=6,78 Hz, 3J=5,0 Hz 1H; $(CH_3)_2C\underline{H}$); 2,00 (s, broad, OH); 2,50 (ddd, ^{3}J=5,00 Hz, ^{3}J=7,00 Hz, 6,95 Hz, 1H, 5-H); 3,45 (dd, ^{2}J=13,86 Hz, ^{3}J=7,0 Hz, 1H, $C\underline{H}_2$OH); 3,49 (d, ^{2}J=13,05 Hz, 1H, 3-H); 3,50 (dd, ^{2}J=13,86 Hz, ^{3}J=6,95 Hz, 1H, $C\underline{H}_2$OH); 3,55 (d, ^{2}J=13,05 Hz, 1H, 3'-H); 4,15 (q, ^{3}J=7,18 Hz, 2H, $CO_2C\underline{H}_2CH_3$); 6,13 (s, 1H, C=C$\underline{H}$-CN); - ^{13}C-NMR: δ = 13,9 (q, J=127,3 Hz, $CO_2CH_2\underline{C}H_3$); 18,7 (q, J= 130,3 Hz, $(\underline{C}H_3)_2$CH); 20,3 (q, J=131,5 Hz, $CH(\underline{C}H_3)_2$); 28,9 (d, J=127,7 Hz, $\underline{C}H(CH_3)_2$); 30,7 (t, J=147,2 Hz, C-3); 56,8 (d, J=136,1 Hz, C-5); 62,7(t, J= 143,3 Hz, CH_2OH or $CO_2\underline{C}H_2CH_3$); 63,3 (t, J=143,3 Hz, CH_2OH or $CO_2\underline{C}H_2CH_3$); 106,4 (d, J=179,3 Hz,C=$\underline{C}$H-CN); 115,2 (s, $\underline{C}$N); 150,5 (s, C-2); 163,6 (s, $\underline{C}O_2$Et).

Methyl-Z-(5-RS)-2-cyanomethylene-5-hydroxymethyl-6-methyl-4-thia-heptanoate (**14b**): Red oil, R_f = 0,31, yield 30% (0,33 g). - MS(EI): m/e = 257 (4%; M^+). - IR(neat): 3551, 2243, 1726 cm^{-1}. - ^{1}H-NMR: δ = 0,86 (d, ^{3}J=6,74 Hz, $(C\underline{H}_3)_2$CH); 0,93 (d, ^{3}J=6,75 Hz, 3H, $(C\underline{H}_3)_2$CH); 1,32 (t, ^{3}J=7,10 Hz, 3H, $CO_2CH_2C\underline{H}_3$); 1,93 (heptd, ^{3}J=6,75 Hz, ^{3}J=5,50 Hz, 1H, $(CH_3)_2C\underline{H}$); 2,30 (s, broad, OH); 2,45 (ddd, ^{3}J=7,60 Hz, ^{3}J=7,41 Hz, ^{3}J=5,50 Hz, 1H; 5-H); 3,49 (d, ^{4}J=1,0 Hz, 2H, 3-H); 3,55 (dd, ^{2}J=11,25 Hz, ^{3}J=7,60 Hz, 1H, $C\underline{H}_2$OH); 3,59 (dd, ^{2}J=11,25 Hz, 7,41 Hz, 1H, $C\underline{H}'_2$OH); 4,29 (q, ^{3}J=7,10 Hz, 2H $CO_2C\underline{H}_2CH_3$); 5,88 (t, ^{4}J=1,0 Hz, 1H, C=C$\underline{H}$-CN); - ^{13}C-NMR: δ = 13,9 (q, J=125,1 Hz, $CO_2CH_2\underline{C}H_3$), 18,8 (q, J= 132,1 Hz, $(\underline{C}H_3)_2$CH); 20,3 (q, J=136,5 Hz, $(\underline{C}H_3)_2$CH); 29,3 (d, J=126,1 Hz, $(CH_3)_2\underline{C}$H); 33,8 (t, J=145,7 Hz, C-3); 56,2 (d, J=138,2 Hz, C-5); 62,4 (t, J=147,9 Hz, $\underline{C}H_2OH$ or $CO_2\underline{C}H_2CH_3$); 64,0 (t, J=145,2 Hz, $\underline{C}H_2OH$ or $CO_2\underline{C}H_2CH_3$);104,9 (d, J=177,3 Hz, C=$\underline{C}$H-CN); 114,8 (s, $\underline{C}$N); 149,7 (s, C-2); 163,3 (s, $\underline{C}O_2$Et).

Preparation of the bicyclic compounds **15** and **16**.

Swern oxidation[6] of compounds **14a/14b** and reaction of the resulting aldehydes with N-substituted hydroxylamines was performed as described in the preceding paper[3].

(1RS/4RS/5RS/8SR)-2-(4-tert-Butylphenyl)-4-cyano-5-ethoxycarbonyl-8-isopropyl-3-oxa-7-thia-2-azabicyclo[3.3.0]octane (**15a**): yellow-brown oil from flash chromatography CH_2Cl_2/ petroleum ether (40/60) 5:2, R_f = 0,54, yield 40% (0.67 g). -

$C_{22}H_{30}N_2O_3S$ (402,6) Calcd. C 65,64 H 7,76 N 6,95 Found C 65,89 H 8,11 N 7,19. - MS(FD): m/e = 402 (100%; M^+). - IR (neat): 2205, 1742 cm^{-1}. - ^{1}H-NMR: δ = 0,98 (d, ^{3}J=6,69 Hz, 3H, $CH(C\underline{H}_3)_2$); 1,02 (d, ^{3}J=6,69 Hz, 3H, $CH(C\underline{H}_3)_2$); 1,24 (t, ^{3}J=7,12 Hz, 3H, $CH_2C\underline{H}_3$); 1,29 (s, 9H, tert.-Bu); 2,02 (heptd, ^{3}J=6,69 Hz,^{3}J=6,30 Hz, 1H, $C\underline{H}(CH_3)_2$) 3,00 (d, ^{2}J=12,70 Hz, 1H, 6-H); 3,56 (d, ^{2}J= 12,70 Hz, 1H, 6'-H); 3,26 (dd, ^{3}J=6,23, ^{3}J=6,30Hz 1H, 8-H); 4,29 (q, ^{3}J=7,16 Hz, 2H, $CO_2C\underline{H}_2CH_3$) 4,89 (d, ^{3}J=6,23 Hz, 1H, 1-H); 4,91 (s, 1H, 4-H); 7,1-7,4 (m, 4H, aromatic H); ^{13}C-NMR: δ = 13,9 (q, J=125,8 Hz, $CO_2CH_2\underline{C}H_3$); 19,9 (q, J=132,7 Hz, $CH(\underline{C}H_3)_2$); 21,9 (q, J=126,3 Hz, $C(\underline{C}H_3)_2$); 31,2 (d, J=124,4 $\underline{C}H(CH_3)_2$); 31,4 (q, J=125,0, $C(\underline{C}H_3)_3$); 34,3 (s, $\underline{C}(CH_3)_3$); 39,2 (t, J=142,1 Hz, C-6); 61,7 (d, 131,8 Hz, C-8); 63,1 (t, J=151,7 Hz, $CO_2\underline{C}H_2CH_3$); 73,1 (d, J=161,1 Hz, C-1); 75,3 (s, C-5); 79,3 (d, J= 148,3 Hz, C-4); 114,7 (s, $\underline{C}N$); 117,0/125,9 (2d, aromatic C); 145,2/147,4 (2s, aromatic C) 169,2 (s, $\underline{C}O_2Et$).

(1RS/4SR/5RS/8SR)-2-(4-tert-Butylphenyl)-4-cyano-5-ethoxycarbonyl-8-isopropyl-3-oxa-7-thia-2-azabicyclo[3.3.0]octane (**15b**): yellow oil from flash chromatography CH_2Cl_2/ petroleum ether (40/60) 5:2, R_f = 0,64, yield 55% (0.93 g). - $C_{22}H_{30}N_2O_3S$ (402,6) Calcd. C 65,64 H 7,76 N 6,95 Found C 66,00 H 8,04 N 7,10. - MS(FD): m/e = 402 (100%; M^+). - IR (neat): 2210, 1738 cm^{-1}. - ^{1}H-NMR: δ = 1,07 (t, ^{3}J=7,06 Hz, 3H, $CH_2C\underline{H}_3$); 1,10 (d, ^{3}J=8,3 Hz, 6H; $CH(C\underline{H}_3)_2$); 1,28 (s, 9H, tert-Bu) 2,15(hept, ^{3}J=8,30 Hz, ^{3}J=6,40 Hz, 1H, $(CH_3)_2C\underline{H}$); 3,31 (d, ^{2}J=12,70 Hz, 1H, 6-H); 3,29 (dd, ^{3}J=6,78 Hz, ^{3}J=6,40 Hz, 1H, 8-H); 3,46 (d, ^{2}J=12,70 Hz, 1H, 6'-H); 4,08 (q, ^{3}J=7,10 Hz, 2H, $CO_2C\underline{H}_2CH_3$) 4,81 (d, ^{3}J=6,78 Hz, 1H, 1-H); 5,11 (s, 1H, 4-H) 7,0-7,3 (m, 4H, aromatic H). - ^{13}C-NMR: δ = 13,6 (q, J=127,5 Hz, $CO_2CH_2\underline{C}H_3$); 19,8 (q, J=130,5 Hz, $CH(\underline{C}H_3)_2$); 21,8 (q, J=126,0 Hz, $C(\underline{C}H_3)_2$); 31,0 (d, J=123,9 Hz,$\underline{C}H(CH_3)_2$); 31,3 (q, J=125,7 Hz, $C(\underline{C}H_3)_3$); 34,2 (s, $\underline{C}(CH_3)_3$); 37,3 (t, J=141,5, C-6); 61,5 (d, J=137,7 Hz, C-8); 62,7 (t, J=153,3 Hz, $CO_2\underline{C}H_2CH_3$); 71,8 (d, J= 159,6 Hz, C-1); 72,9 (s, C-5); 81,9 (d, J=145,4 Hz, C-4); 113,9 (s, CN); 115,3/125 (2d, aromatic C); 144,8/146,9 (2s, aromatic C); 170,1 (s, $\underline{C}O_2Et$).

(1RS/4SR/5RS/8SR)-2-Benzyl-4-cyano-5-ethoxycarbonyl-8-isopropyl-3-oxa-7-thia-2-azabicyclo[3.3.0]octane (**16b**): viscous, yellow oil from chromatography on silica gel, Et_2O/ petroleum ether (40/60) 1:3, yield 69% (0.8 g). - MS(FD): m/e = 360 (75%; M^+). - IR(neat): 2234, 1760 cm^{-1}. - ^{1}H-NMR: δ = 0,97 (d, ^{3}J=6,65 Hz, 3H, $CH(C\underline{H}_3)_2$); 1,04 (d, ^{3}J=6,65 Hz, 3H, $CH(C\underline{H}_3)_2$); 1,26 (t, ^{3}J=7,08 Hz, 3H, $CO_2CH_2C\underline{H}_3$); 1,98 (heptd, ^{3}J=6,65 Hz 3J=6,20 Hz, 1H, $C\underline{H}(CH_3)_2$); 2,93 (dd, ^{3}J=6,20 Hz, ^{3}J=3,92 Hz, 1H, 8-H); 3,14 (d, ^{2}J=12,89 Hz, 1H, 6-H); 3,32 (d, ^{2}J=12,89 Hz, 1H, 6'-H); 3,96 (d, ^{3}J=3,92 Hz, 1H, 1-H); 4,03 (s, 2H, $PhC\underline{H}_2N$); 4,24 (q, ^{3}J=7,08 Hz, 2H, $CO_2C\underline{H}_2CH_3$); 5,30 (s, 1H; 4-H); 7,20-7,37 (m, 5H, aromatic H);^{13}C-NMR: δ = 14,1 (q, $CO_2CH_2\underline{C}H_3$); 19,9 (q, $(\underline{C}H_3)_2CH$); 21,8 (q, $(\underline{C}H_3)_2CH$); 30,5 (t, C-6); 37,5 (d, $(CH_3)_2\underline{C}H$); 60,3 (t, $Ph\underline{C}H_2N$); 61,3 (d, C-8); 63,0 (t, $CO_2\underline{C}H_2CH_3$); 71,9 (d, C-1); 72,8 (s, C-5); 82,2 (d, C-4); 115,0 (s, CN), 127,2-135,4 (aromatic C); 171,3 (s, $\underline{C}O_2Et$).

Preparation of the ß-lactams **18**, **19**

(1RS/5RS)-3-Thia-6-azabicyclo[3.2.0]heptan-7-one (**18**): A 1.6 molar solution of n-butyllithium in hexane (2.14 ml, 3.8 mmol) was added to a solution of diisopropylamine (0.38 g, 0.53 ml, 3.8 mmol) in 50 ml of dry tetrahydrofuran at 0°C under argon atmosphere. The mixture was stirred for 15 min and then cooled to -78°C. A solution of compound **10b** (1.0 g, 3.5 mmol) in 10 ml of tetrahydrofuran was added slowly with a syringe. The reaction mixture which immediately coloured was stirred at -78°C for 2 h. Thereafter it had been allowed to warm up to 0°C, at which temperature it was quenched by addition of 10 ml of a 2 m solution of ammonium chloride. The organic layer was mixed with diethyl ether (100 ml) and subsequently washed by a saturated aqueous solution of sodium chloride. After drying the solution by $MgSO_4$ the solvent was removed and the crude product was subjected to chromatography on silica gel (CH_2Cl_2, R_f = 0,71). **18** was obtained in 89% yield (0,85 g) as a yellow solid, mp 86°C from hexane/diethyl ether. - $C_{15}H_{19}NOS$ (261,4) Calcd. C 68,92 H 7,32 N 5,35 Found C 68,22 H 7,48 N 5,19. - MS(FD): m/e = 261 (100%; M^+); MS(EI): m/e = 175 ($C_{10}H_{13}NCO^+$), 86 (dihydrothiophene$^+$). - IR (KBr): 1735 cm^{-1}.- -^{1}H-NMR: δ = 1,30 (s, 9H, $C(CH_3)_3$); 2,75 (dd, ^{2}J=12,40 Hz, ^{3}J=6,2Hz, 1H, 2-H); 2,80 (dd, ^{2}J=13,0 Hz, ^{3}J=3,9 Hz, 1H, 4-H); 3,19 (dd, ^{2}J=12,40 Hz, 1H, 2'-H); 3,19 (dd, ^{2}J=13,0 Hz, ^{3}J=3,9 Hz, 1H, 4'-H); 3,94 (ddd, ^{3}J=6,2 Hz, ^{3}J=4,0 Hz, 1H, 1-H); 4,71 (ddd, ^{3}J= 4,0 Hz, ^{3}J= 3,9 Hz, ^{3}J= 3,9 Hz, 1H, 5-H); 7,0-7,3 (m, 4H, aromatic H); - ^{13}C-NMR: δ = 29,6 (t, J=143,4 Hz, C-4); 31,3 (q, J=130,6 Hz,

$C(\underline{C}H_3)_3$); 33,9 (t, J=140,1 Hz, C-2); 34,4 (s, $\underline{C}(CH_3)_3$); 57,7 (d, J=146,2 Hz, C-1); 58,9 (d, J= 146,6 Hz, C-5); 116,7-126,1 (aromatic C) 163,8 (s, C-7).

(1RS/4SR/5RS)-6-(4-tert-Butylphenyl)-1-carbethoxy-4-isopropyl-3-thia-6-azabicyclo-[3.2.0]heptan-7-one **(19)** was prepared in the same way as described for **18**: orange-brown oil after chromatography on silica gel, CH_2Cl_2, R_f = 0,49 yield 65% (0.85 g). - MS(FD): m/e = 375 (100%; M^+). - IR(neat): 1781, 1725 cm^{-1}. - ^{1}H-NMR: δ = 1,03 (d, ^{3}J=6,61 Hz, 3H, $CH(C\underline{H}_3)_2$); 1,09 (d, ^{3}J=6,61 Hz, 3H, $CH(C\underline{H}_3)_3$); 1,30 (s, 9H, $(C\underline{H}_3)_3C$); 1,30 (t, ^{3}J=7,10 Hz, 3H, $CO_2CH_2C\underline{H}_3$); 1,94 (heptd, ^{3}J=6,61 Hz, ^{3}J=6,72 Hz, 1H, $C\underline{H}(CH_3)_2$); 3,16 (d, ^{2}J=12,52 Hz, 1H, 2-H); 3,22 (d, ^{2}J=12,52 Hz, 1H, 2'-H), 3,27 (d, ^{3}J=6,72 Hz, ^{3}J=0 Hz, 1H, 4-H); 4,27 (q, ^{3}J=7,10 Hz, 2H, $CO_2C\underline{H}_2CH_3$); 4,78 (s, 1H,5-H); 7,20-7,40 (2d, 4H, aromatic H); - ^{13}C-NMR: δ = 14,1 (q, J=127,4 Hz, $CO_2CH_2\underline{C}H_3$); 20,0 (q, J= 125,6 Hz, $CH(\underline{C}H_3)_2$); 20,8 (q, J= 133,8 Hz, $CH(\underline{C}H_3)_2$); 31,2 (q, J=125,7 Hz, $C(\underline{C}H_3)_3$), 31,8 (t, J = 148,4 Hz, C-2); 34,5 (s, $\underline{C}(CH_3)_3$); 54,6 (d, J = 139,9 Hz, C-4); 62.2 (t, J = 148,4 Hz, $CO_2\underline{C}H_2$-CH_3); 67,6 (d, J=157,3 Hz, C-5); 74,4 (s, C-1); 117,0/126,2 (2d, J=161,3/157,5 Hz, aromatic C); 133,8/147,6 (2s, aromatic C); 159,8 (s, C-7); 167,2 (s, $\underline{C}O_2Et$).

(2SR/3RS/4RS)-4-Aminocarbonyl-3-(4-tert-butylphenyl)amino-4-ethoxycarbonyl-2-isopropyl-tetrahydrothiophene **(20)** arose as by-product of the preparation of compound **11** in 20% yield (0.17 g), as white solid, mp 77°C after chromatography on silica gel, CH_2Cl_2, R_f = 0,29. - MS(FD): m/e = 392 (100%; M^+). - IR(KBr): 3392, 3024, 1765, 1723 cm^{-1}. - ^{1}H-NMR: δ = 0,85 (d, ^{3}J=7,40 Hz, 3H $(C\underline{H}_3)_2CH$); 0,88 (d, ^{3}J= 7,40 Hz, 3H, $(C\underline{H}_3)_2CH$), 1,27 (s, 9H, tert-Bu); 1,31 (t, ^{3}J=7,23 Hz, 3H, $CO_2CH_2C\underline{H}_3$); 1,88 (heptd, ^{3}J=7,40 Hz, ^{3}J=3,06 Hz, 1H, $C\underline{H}(CH_3)_2$); 3,26 (d, ^{2}J=12,08 Hz, 1H, 5-H); 3,42 (d, ^{2}J=12,08 Hz, 1H, 5'-H); 3,59 (dd, ^{3}J=9,43 Hz, ^{3}J=3,06 Hz, 1H, 2-H); 4,03 (dd, ^{3}J=10,89 Hz, ^{3}J=9,43 Hz, 1H, 3-H); 4,30 (q, ^{3}J=7,23 Hz, 2H, $CO_2C\underline{H}_2CH_3$); 4,68 (d, ^{3}J=10,89 Hz, 1H, ArN$\underline{H}$); 5,42 (s, broad, 2H, $CON\underline{H}_2$); 6,64 and 7,18 (dd, 4H, aromatic H); ^{13}C-NMR: δ = 13,9 (q, J=128,3 Hz, $(\underline{C}H_3)_2CH$); 15,7 (q, J= 127,2 Hz, $(\underline{C}H_3)_2CH$); 23,0 (q, J=126,3 Hz, $CO_2CH_2\underline{C}H_3$); 28,9 (d, J=123,3 Hz, $\underline{C}H(CH_3)_2$) 31,5 (q, J=125,3 Hz, $C(\underline{C}H_3)_3$); 32,7 (t, J=147,8 Hz, C-5); 34,0 (s, $\underline{C}(CH_3)_3$); 58,7 (d, J=142,2 Hz C-2); 62,1 (t, J=144,1 Hz, $CO_2\underline{C}H_2CH_3$); 64,3 (d, J=137,1 Hz, C-3); 64,7 (s, C-4), 113,9/126,3/142,2/144,0 (d,d,s,s, aromatic C); 169,6 (s, $\underline{C}ONH_2$); 171,2 (s, $\underline{C}O_2Et$).

Acknowledgment: We would like to thank the Fonds der Chemischen Industrie for financial support.

References

1. a) Davies, D.E.; Storr, R.C. in *Comprehensive Heterocyclic Chemistry*, Eds. Katritzky, A.R.; Rees, Ch. W.; Lwoski, W. Pergamon Press Oxford 1984, Vol. 7. part. 5.09, pp 247-267. b) Dürckheimer, W.; Blumbach, J.; Latrell, R.; Scheunemann, K.H., *Angew. Chem.* **1985**, *97*, 183-205; *Int. Ed. Engl.* **1985**, *24*, 180.
2. a) Padwa, A.; Koehler, K.K.; Rodriguez, A. *J. Org. Chem.* **1984**, *49*, 282-288. b) Padwa, A.; Koehler, K.K.; Rodriguez, A. *J. Am. Chem. Soc.* **1981**, *103*, 4974. c) After completion of this manuscript a paper appeared in which the formation of ß-lactams from 5-phenylthioisoxazolidines by treatment with alkyllithium is described: Di Nunno, L.; Scilimati, A. *Tetrahedron* **1993**, *49*, 10965-10976.
3. Aurich, H.G.; Ruiz Quintero, J.-L. *Tetrahedron* **1994**, *50*, preceding paper.
4. Bailey, W.J.; Bello, J. *J. Org. Chem.* **1955**, *20*, 525-529.
5. Schiemenz, G.P.; Engelhard, H. *Chem. Ber.* **1961**, *94*, 578-584.
6. a) Mancuso, A.J.; Swern, D.; *Synthesis* **1981**, 165-185. b) Marx, M.; Tidwell, T.T. *J. Org. Chem.* **1984**, *49*, 788-793.

(*Received in Germany* 21 *December* 1993; *accepted* 2 *February* 1994)