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THIA-ACYLIMINIUM - OLEFIN CYCLIZATIONS

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Abstract - Regioselective $NaBH_4/H^+$-reduction of thiazolidinediones 3 - 8 substituted at the nitrogen atom with different π-nucleophiles affords hydroxylactams 9 - 14 in good yields. The latter compounds are excellent precursors for the α-acyliminium ion 16 and can be stereoselectively cyclized in HCOOH to yield novel heterocyclic ring systems of varied structures. Because of the stereoelectronic control in the ring closure stereoselective syntheses, such as the conversion of 8a to 24, are easily accomplished.

The use of the α-acyliminium ion as a cationic initiating centre for olefin cyclizations has been well established[2]. The versatility of this intermediate, which is easily generated from cyclic imides, invited to a study of the further extension of its synthetic potential by introducing a second hetero atom in the imide ring. Especially the sulfur atom was thought to be of value in this respect[3], since it could offer a handle for the chemical transformation of the starting imide ring after the reduction and cyclization steps. The overall procedure then essentially would allow the formation of a variety of substituted azaheterocycles C and carbocycles F of defined spatial structure from non-cyclic precursors, viz. A→B→C and D→E→F (fig. 1). The chemistry of the thiazolidine α-acyliminium ions A and D is almost unexplored and their behaviour as a cationic initiating centre in olefin cyclization reactions, viz. A→B and D→E, constitutes the subject of this report.

As model compounds for this study the thiazolidinediones 1a and 1b were selected which are easily available via standard procedures[4] from α-halo carboxylic acid derivatives. The latter imides permitted the study of two

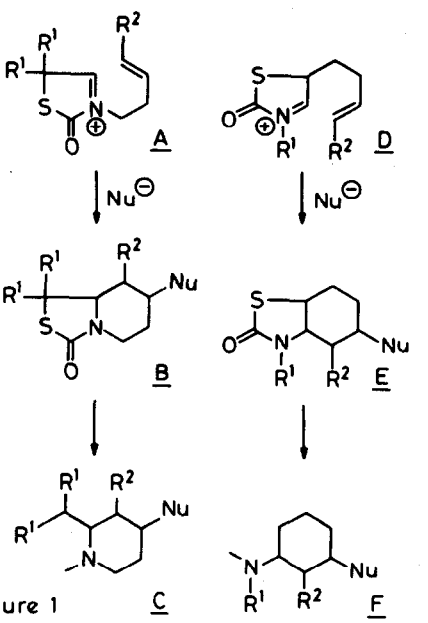
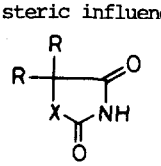


Figure 1

effects not previously encountered in the α-acyliminium cyclizations of the succinimide and glutarimide derivatives, viz. the electronic influence of the sulfur atom and secondly the steric influence of ring substituents.



1a X = S R = CH_3
b X = S R = H
2 X = CH_2 R = CH_3

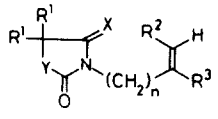
To separate these two effects, a parallel series of experiments was carried out with 2,2-dimethylsuccinimide (2). The imides 1 and 2 were coupled with a number of standard olefin or aralkyl alcohols via the oxidation-reduction procedure[5]. The coupling products 3 - 7 are easily purified by vacuum distillation affording yields up to 90%. Compounds 8 could be prepared from 5-phenylthiazolidinedione[6] by first alkylating at the most acidic position, i.e. at imide nitrogen, and subsequently alkylating at the activated ring position using potassium carbonate in dimethyl formamide as a base.

From these imides the hydroxylactams 9 - 14 are prepared by acid-catalyzed $NaBH_4$-reduction[7]. The difference in electronic character ensures that only the N−C(=O)−C-carbonyl is reduced, no trace of the S−C(=O)−N-reduced compound ever being detected, while the yield of this reaction step typically ranges from 70-80%. The OH-lactams mostly are sufficiently pure to be used in subsequent reactions without further purification.

Upon treatment with a suitable acid/nucleophile combination these N-alkenyl hydroxylactams of type 15 give the α-acyliminium species 16, which upon ring closure afford the cyclized products 17 (fig. 2).

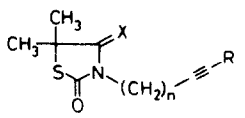
Cyclizations of olefins

The stereoselectivity of the cyclization process, which was established in the succinimide and glutarimide series[8], is also found in the thiazolidine series. In cyclizations of symmetrical thiazolidines a chair-like trans-



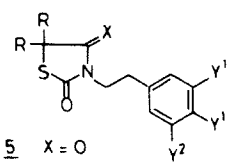
3 X = O
9 X = H,OH

	n	R^1	R^2	R^3	Y
a	2	CH_3	H	H	S
b	2	H	H	H	S
c	2	H	H	CH_3	S
d	3	CH_3	H	H	S
e	2	CH_3	C_2H_5	H	S
f	2	CH_3	$CH_2CH_2C_6H_5$	H	S
g	3	CH_3	H	H	CH_2



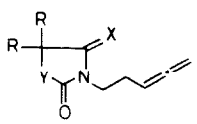
4 X = O
10 X = H,OH

	n	R
a	2	H
b	4	H
c	2	$CH_2CH_2C_6H_5$



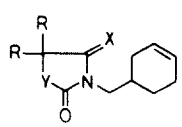
5 X = O
11 X = H,OH

	R	Y^1	Y^2
a	CH_3	H	H
b	H	H	H
c	CH_3	CH_3O	H
d	H	CH_3O	H
e	CH_3	CH_3O	CH_3O
f	H	CH_3O	CH_3O



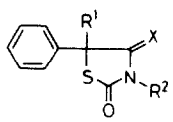
6 X = O
12 X = H,OH

	R	Y
a	H	CH_2
b	CH_3	S
c	CH_3	CH_2
d	H	S

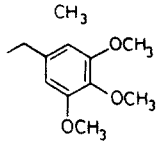
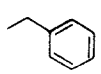


7 X = O
13 X = H,OH

	R	Y
a	CH_3	S
b	CH_3	CH_2
c	H	S



8 X = O
14 X = H,OH

	R^1	R^2
a	CH_3	(Z)-$CH_2CH_2CH{:}CHCH_2CH_3$
b		CH_3
c		CH_3
d	H	(Z)-$CH_2CH_2CH{:}CHCH_2CH_3$

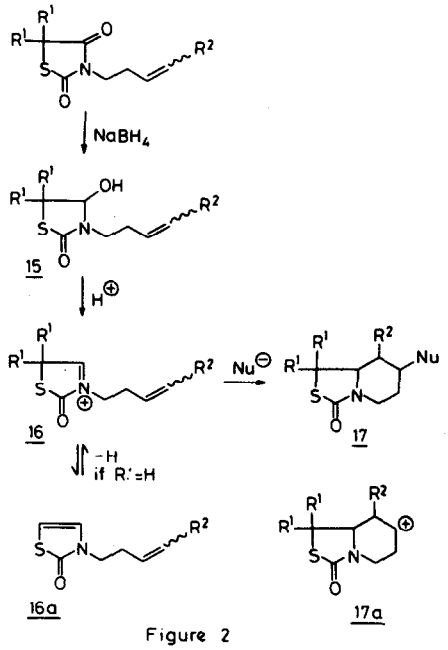


Figure 2

ition state is considered most likely. Therefore cyclization of 18 takes place via a transition state 19 to give a product of relative stereochemistry 20a, sometimes accompanied by minor amounts of its epimer 20b (fig. 3).

Thus, stirring the N-butenyl thiazolidine hydroxylactam 9a in formic acid at room temperature for 2 hours gave 21a with an epimer ratio of 3:1. The major isomer showed ^{1}H NMR-spectral data characteristic for an equatorial formate, viz. a broad CHOCHO- signal (δ 5.20-4.83) indicating an axial position for this proton. In the same manner, treatment of 9b (r.t., 142 hrs) gave 21b in a comparable epimer ratio, while cyclization of 9c, in which an intermediate of type 17a would be expected to be somewhat more stablized, indeed gave a product with a slightly larger proportion of the product with an axial formate substituent; thus, after stirring 9c in formic acid at r.t. for 18 hrs a mixture of 21c and its C-4 epimer in a ratio of 5:2 (equatorial: axial formate) was obtained.

Since formation of the 6-membered ring is obviously a favourable process it became of interest to investigate the N-pentenyl derivative in order to obtain the 7-membered ring. Therefore, 9d was stirred in formic acid for 118 hrs to give 21d as a 3:1 epimer mixture in good yield, again demonstrating the reactivity of the α-acyliminium intermediate. To further

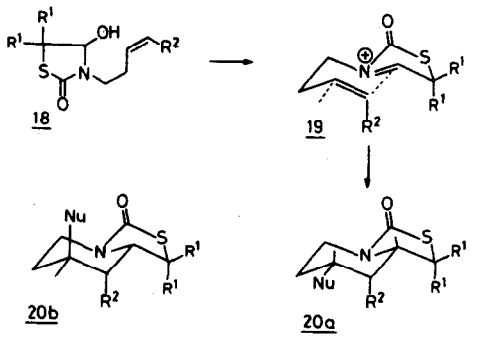
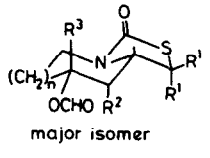


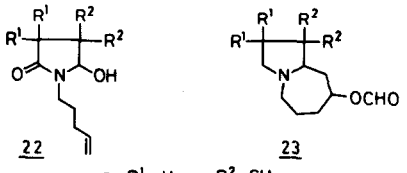
Figure 3

confirm this behaviour the succinimide 3g was prepared, which upon $NaBH_4/H^+$-reduction gave a mixture of OH-lactams 22a and 22b in a ratio of about 3:1. The regio isomers were cyclized separately, affording 23a and 23b respectively, both showing a similar epimer ratio as the thiazolidine-derived 7-membered ring. The epimer ratio in all cases is determined from ^{1}H NMR analysis by comparing the peak integrals of the formate signals and by correlating these with the signals of the quasi-axial and equatorial CHOCHO-protons.

On the contrary, in case of a (Z)-disubstituted olefin only one product with stereochemistry 20a was found, e.g. cyclization of 9e (72 hrs at r.t.) gave 21e as the sole product in 96% yield, the stereochemistry of which was established in a way similar to that of 24 (vide infra). Upon substituting the C-5 thiazolidine carbon with different substituents again high stereoselectivity in the ring closure was observed. Thus, stirring 14a in formic acid gave 24 as the sole product in 87%

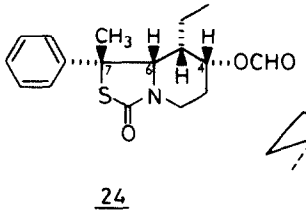


	n	R^1	R^2	R^3
21 a	1	CH_3	H	H
b	1	H	H	H
c	1	H	H	CH_3
d	2	CH_3	H	H
e	1	CH_3	C_2H_5	H



a R^1=H R^2=CH_3
b R^1=CH_3 R^2=H

yield. The relative configuration of this product was unambiguously determined from its ^{1}H NMR-spectrum. The broad signal from δ 5.29 - 5.00 of the CHOCHO-proton indicates an equatorial position for the formyloxy group. The coupling constant (J = 3 Hz) of the signal at δ = 4.77 (N-C_6H) indicates an axial-equatorial coupling, which points to an axial position of the ethyl group and finally the position at δ = 0.15 of the CH_2CH_3 protons, stemming from the shielding effect of the aromatic nucleus, establishes the cis-relationship between the phenyl and ethyl groups. This result favours the concept that reaction takes place via a chair-like transition state in which sterical hindrance is minimal, i.e. 25a and not 25b.



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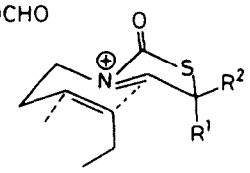
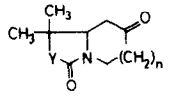


25 a $R^1 = C_6H_5$ $R^2 = CH_3$
b $R^1 = CH_3$ $R^2 = C_6H_5$

Acetylenic and aromatic cyclizations

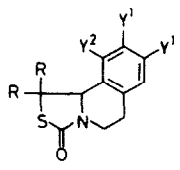
The use of acetylenes as acceptors for acyliminium ion cyclizations has been well studied[9]. In the same manner the thia-acyliminium ion proved highly reactive towards the acetylenic moiety. Thus, stirring 10a in formic acid at r.t. for 94 hrs gave the bicyclic ketone 26a (derived from the initially formed enol formate). As might be expected, the cyclization again is distinctly more difficult with increasing size of the ring to be formed; nevertheless, treatment of 10b with formic acid at 43° for 243 hrs gave the desired 5/8 ring compound 26b in 70% yield. However, the acetylenic compound 10c failed to cyclize even upon refluxing in formic acid; this anomalous behaviour is attributed to steric hindrance between the rigid linear acetylenic system and the methyl groups attached to the thiazolidine ring (see discussion below). As expected, catalytic hydrogenation of the triple bond to the (Z)-olefin 3f led to a hydroxylactam 9f which, by refluxing in formic acid for 117 hrs, could be cyclized to the thiaza steroid ring system 27. The relative configuration of this compound is inferred in analogy from its scuccinimide counterpart[10].



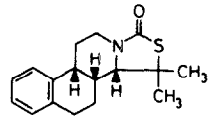
26 a n = 1 Y = S
b n = 3 Y = S
c n = 2 Y = S
d n = 2 Y = CH_2

The latter reactions also serve as an example of an aromatic nucleus acting as a scavenger for the acyliminium ion. Direct aromatic substitution with the α-acyliminium species is a feasible process as well: cyclisation of 11a to 28a could be effected by refluxing for 112 hrs in dichloromethane with p-toluenesulfonic acid. Compound 28a could also be obtained, albeit in somewhat lower yield, by refluxing 11a in formic acid. On the contrary, the unsubstituted thiazolidine 11b could not be cyclized; refluxing in formic acid gave the thiazoline 29 as the sole product in 52% yield. If, however, the aromatic moiety was made more susceptible towards electrophilic substitution by introduction of methoxy groups, cyclization of the thiazolidines 11c-11f proceeded smoothly at r.t. to give tricyclic compounds 28b-28e in high yields.

The structures of the dimethoxy compounds 28b and 28c were proven by correlating ^{1}H NMR-signals of the remaining aromatic protons with the values calculated[11]. Cyclization onto a C-benzyl substituent under formation of a 5-membered ring occurs upon refluxing 14b in a



	R	Y^1	Y^2
28 a	CH_3	H	H
b	CH_3	CH_3O	H
c	H	CH_3O	H
d	CH_3	CH_3O	CH_3O
e	H	CH_3O	CH_3O



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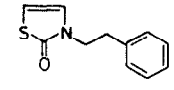

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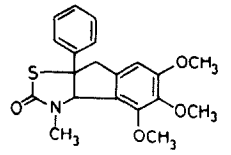

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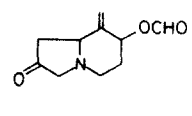

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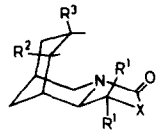
mixture of methanol and concentrated hydrochloric acid for 90 hrs, thereby affording the tricyclic compound 30 as an oil in nearly quantitative yield. If the aromatic moiety lacks the activating groups, e.g. 14c, cyclization could not be effected under these reaction conditions.

Other π-nucleophiles

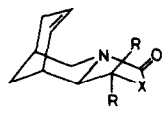
To further investigate the influence of steric factors in the cyclization process two systems possessing a certain degree of rigidity were selected. The ring closure of 12a is known[12] to lead to 31, so that the allene moiety reacts simply as a methylene substituted double bond; on the contrary, cyclization of 12b (HCOOH, reflux 93 hrs) gave the 7-membered ring compound 26c. This anomalous result is attributed to a steric hindrance between the rigid allenic system and the two methyl substituents. Indeed, a study of molecular models reveals a considerable steric interaction, sufficient to prevent reaction between the iminium centre and the non-terminal double bond of the allene. This interaction is also indicated by the observation that 12c under the same conditions cyclizes to give 26d, again emphasizing the preponderance of steric factors. Cyclization of 12d was attempted in the same way; however, due to the diminished reactivity of the unsubstituted thiazolidine system, under the forcing reaction conditions employed only decomposition products were obtained.

Another interesting result was obtained upon reaction of the cyclohexenyl methyl system 7 as the olefin moiety. Treatment of 13a with formic acid (r.t., 18 hrs) afforded a mixture of 32a (16%), 32b (34%) and 33a (50%). The product distribution was determined from the ^{1}H NMR-spectra of the crude reaction mixture, on the basis of the ratio of the integrals, which were attributed by comparison with the purified compounds or by analogy. This ring closure proceeds faster than the cyclization of (Z)-disubstituted olefins like 9e; the latter behaviour is attributed to the divergent geometry of the reaction, since this is an example of a 6-exo-trig process[13], while cyclization of 9e is a 6-endo-trig reaction.

Upon refluxing 13a in formic acid, however, only 33a was obtained in ca. 90% yield. The tendency to form this type of unsaturated compound, considering the fact that similar

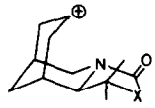


	X	R^1	R^2	R^3
32 a	S	CH_3	OCHO	H
b	S	CH_3	H	OCHO
c	CH_2	CH_3	OCHO	H
d	CH_2	CH_3	H	OCHO
e	S	H	OCHO	H
f	S	H	H	OCHO
g	S	H	OTos	H



	X	R
33 a	S	CH_3
b	CH_2	CH_3
c	S	H

34a



34b

products were detected only in trace amounts in reactions in the unsubstituted glutarimide series, is again attributed to steric hindrance; study of molecular models reveals a considerable interaction between the ring methyl groups and the cyclohexane ring. The latter repulsion is considerably reduced if the cyclohexane ring is flattened by formation of a double bond. Since the geometrical shape of the ring is somewhat modified if the sulfur atom is replaced by a methylene group the effect is less pronounced in the succinimide analogue 13b; thus, cyclization of 13b (formic acid, r.t., 19 hrs) gave a mixture of 32c (42%), 32d (42%) and 33b (16%). These results also point to the intermediacy of a cation of type 34a from which 34b can be formed through a 1,2 hydride shift, or, alternatively, a proton can be lost to give 33. That e.g. 32b is not formed by addition of formic acid to the double bond of 33a (i.e. 13a → 32a → 33a → 32b) was demonstrated by subjecting 33a to the reaction conditions (r.t. 18 hrs), which gave unchanged starting material in quantitative yield.

On the contrary, cyclization of 13c did not proceed at all in formic acid at room temperature, the enamide of type 16a being the main product. However, upon refluxing in HCOOH for 17 hrs a mixture of 32e (23%), 32f (23%) and 33c (54%) was obtained. Clearly in this case due to the absence of steric repulsion of the

methyl groups the unsaturated compound 33c is less favoured over the two formates 32e and 32f. Indeed the latter formates are stable under the reaction conditions, whereas refluxing 32b in formic acid afforded the unsaturated compound 33a in essentially quantitative yield.

Furthermore, refluxing 13c in dichloromethane with p-toluene-sulfonic acid gave, besides an amount of 33c, about 20% of 32g, again indicating the relative absence of steric strain.

Conclusion

The results mentioned above serve to indicate the reactivity of the unsubstituted thiazolidine hydroxylactam, e.g. 15, $R_1 = H$, to be somewhat lower than that of its carbocyclic counterpart under comparable reaction conditions. This effect is explained by the fact that the presence of the sulfur atom enhances the formation of the 4,5-unsaturated thiazoline enamide system 16a, which was demonstrated as an intermediate e.g. in the cyclisation of 9b, and which is less reactive than the acyliminium ion itself. Moreover, if the elimination is blocked by introduction of substituents in the 5-position, a marked degree of steric hindrance between the ring and the olefinic moiety is introduced which varies with the nature of the latter. The electronic influence of the sulfur atom appears to be of minor importance in view of the fact that gem-disubstituted succinimide derivatives show a reactivity comparable to that of the corresponding dimethyl thiazolidine compounds.

These results demonstrate the versatility of the thiazolidine system as a cationic initiating centre for the cyclization of a variety of olefins. The second important feature of these systems, viz. the possibility of transforming the cyclized products by using the sulfur atom as a chemical handle, will be reported elsewhere.

Acknowledgement

The authors wish to thank Messrs. R.C. van den Brink and R.H. Balk for a large scale preparation of starting imides.

EXPERIMENTAL SECTION

IR spectra were recorded on Unicam SP 200 and Perkin-Elmer 257 instruments. ^{1}H NMR spectra were taken on Varian A-60, HA-100, XL-100 and Bruker WM 250 instruments. All mass spectral data were recorded on an AEI-902 or Varian Mat 711 Mass spectrometer[14]. M.ps are uncorrected. Micro-analyses were carried out by TNO, Utrecht, The Netherlands.

Preparation of the imides

Imides were prepared[5] by slowly adding 1 eq. of dimethylazodicarboxylate in freshly distilled THF to a cooled and stirred solution of 1 eq. of N-H imide, 1 eq. of alkenol and 1 eq. of triphenylphosphine. Stirring was continued overnight at r.t. The solvent was evaporated under reduced pressure and the residual oil taken up in CH_2Cl_2 and 5% KOH aq. The aqueous layer was extracted 3 times with CH_2Cl_2. The combined organic layers were then washed with 2 N HCl (three times), sat. $NaHCO_3$ aq. and sat. NaCl aq., dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was taken up in EtOAc, upon which the $\emptyset_3PO$ partly crystallized. The imides were then obtained by vacuum distillation (bulb to bulb for smaller quantities) or column chromatography (see table).

Table Preparation of imides

imid	yield (%)	method[a]	b.p./m.p. (from dipe[b])
3a	62	cg	-
3b	87	vd	82°/0.004 mm
3c	80	vd	92°/0.03 mm
3d	78	vd	77°/0.04 mm
3e	81	vd	101°/0.4 mm
3g	65	bb	-
4a	79	vd	68°/0.003 mm
4b	53	vd	98°/0.15 mm
4c	99	bb	-
5a	84	vd	108°/0.005 mm
5b	17	vd	112°/0.04 mm m.p.: 97-98°
5c	81	cg	m.p.: 88.5-89.5°
5d	40	cg	m.p.: 130-131°
5e	73	cg	-
5f	47	cg	m.p.: 141-142°
6b	77	vd	75°/0.01 mm
6c	86	bb	-
6d	71	bb	-
7a	82	vd	93°/0.005 mm
7b	72	vd	124°/0.03 mm
7c	65	vd	100°/0.03 mm
8d	47	vd	150°/0.06 mm m.p.: 34-37°

a) cg = column chromatography (SiO_2, eluent CH_2Cl_2/acetone 4:1)
vd = vacuum distillation
bb = bulb to bulb distillation

b) dipe = diisopropylether

3-Methyl-5-phenylthiazolidine-2,4-dione

3.86 g (20 mmol) 5 phenylthiazolidine-2,4--dione was dissolved in 40 ml acetone, 4 g (2 eq.) of K_2CO_3 added, and 3.08 g (22 mmol, 1.1 eq.) of iodomethane added dropwise. After refluxing for 1.5 hr, the mixture was concentrated under reduced pressure, the residue taken up

in water, 3 times extracted with CH_2Cl_2, the combined organic layers washed with sat. NaCl aq., dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Yield: 4.01 g of white crystals (98%); m.p.: 97-99° (from dipe; litt.[6] m.p.: 98-99°).

General procedure for 5-alkylation of imides

To a cooled solution of 1 eq. of 3-methylthiazolidine-2,4-dione in ca. 20 ml of dry DMF, to which was added 5 eq. by weight of powdered K_2CO_3, 1.1 eq. of alkyl halide in 20 ml DMF was added dropwise. Stirring was continued for 20-40 hrs at r.t. Subsequently the reaction mixture was poured into water (250 ml), extracted with ether (5 times), the combined extracts washed with sat. NaCl aq., dried over $MgSO_4$ and after evaporation of the solvent under reduced pressure, purified by column chromatography.

compound	halide	yield (%)
8a	methyl iodide	80
8b	trimethoxybenzyl bromide	98
8c	benzyl bromide	quant.

General procedure for the synthesis of hydroxylactams

The $NaBH_4/H^+$ reductions were carried out with a stirred solution of imide in EtOH at temps of 0-5° with a twofold excess by weight of $NaBH_4$. At intervals of 15 mins 3-4 drops of 2N HCl in EtOH were added. After 4-5 hrs of reaction the solution was poured into water, extracted four times with CH_2Cl_2, the combined extracts washed with sat. NaCl aq., dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude product.

General procedure for the cyclization reaction

The hydroxylactam was dissolved in HCOOH (unless otherwise indicated) and stirred at r.t. (unless otherwise indicated). The solvent was evaporated under reduced pressure, the residue taken up in CH_2Cl_2 and washed with sat. $NaHCO_3$ aq., water, and sat. NaCl aq., and dried over $MgSO_4$.

4-Formyloxy-7,7-dimethyl-1-aza-8-thiabicyclo[4.3.0]nonan-9-one 21a

a. N-(but-3-enyl)-4-hydroxy-5,5-dimethylthiazolidin-2-one (9a)
1.108 g (5.6 mmol) 3a was reduced with 2.1 g $NaBH_4$ at 0° during 4 hrs. Work-up and purification by column chromatography (eluent EtOAc) afforded 0.79 g (77%) of 9a as an oil. IR($CHCl_3$): 3380 cm^{-1} (OH); 1675 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 6.0-5.50 (m, 1H, CH=C), 5.20-4.95 (m, 2H, CH_2=C), 4.68 (m, 2H, sharpens with D_2O, CHOH), 3.85-3.05 (m, 2H, NCH_2), 2,34 (m, 2H, CH_2C=C), 1.51 and 1.46 (s and s, 6H, CH_3 2x).

b. Cyclization of 9a. Compound 9a (0.1068 g, 0.53 mmol) was dissolved in 3 ml HCOOH and stirred for 18 hrs at r.t. Work-up afforded 0.1137 g (92%) of a solid from which the epimer with equatorial formate, m.p.: 137-138°, could be separated by crystallization from dipe/$CHCl_3$. IR($CHCl_3$): 1727 cm^{-1} (ester CO); 1670 cm^{-1} (lactam CO); ^1H NMR δ ($CDCl_3$): 8.03 (s, 1H, OCHO), 5.15-4.80 (m, 1H, CHOCHO); 4.14 (m, 1H, NCH_2 eq.), 3.31 (d of d, 1H, NCH), 2.75 (t of d, 1H, NCH_2 ax), 2.15-1.5 (m, 4H), 1.46 and 1.36 (s and s, 6H, CH_3 2x). (Found: C, 52.5%; H, 6.6%; N, 6.2%; S, 14.1%; $C_{10}H_{15}NO_3S$ (Mw 229.29) requires C, 52.4%; H, 6.6%; N, 6.1%; S, 14.0%).

4-Formyloxy-1-aza-8-thiabicyclo[4.3.0]nonan-9-one (21b)

a. N-(but-3-enyl)-4-hydroxythiazolidin-2-one (9b)
1.15 g (6.7 mmol) 3b was reduced with 2.3 g $NaBH_4$ at 0°. Work-up and purification by column chromatography (eluent $CHCl_3$/acetone 4:1) afforded 0.66 g 9b as an oil; yield: 57%. IR($CHCl_3$): 3370 cm^{-1} (OH); 1660 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 6.0-5.55 (m, 1H, CH=C), 5.30 (s, 1H, sharpens with D_2O, CHOH), 5.20-4.97 (m, 2H, CH_2=C), 4.04 (s, 1H, disappears with D_2O, OH), 3.80-3.05 (m, 4H); 2.50-2.20 (m, 2H, CH_2C=C).

b. Cyclization of 9b. Compound 9b (0.1683 g, 0.98 mmol) was dissolved in 3 ml HCOOH and stirred at r.t. for 142 hrs. Work-up afforded a mixture of epimers which could not be separated. IR($CHCl_3$): 1720 cm^{-1} (ester CO); 1670 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 5.20-4.80 (m, 3/4H, CHOCHO ax.), 4.43-4.29 (m, 1/4H, CHOCHO eq.).

4-Formyloxy-4-methyl-1-aza-8-thiabicyclo[4.3.0]nonan-9-one (21c)

a. N-(3-methylbut-3-enyl)-4-hydroxythiazolidin-2-one (9c)
1.15 g (6.2 mmol) 3c was reduced with 2.3 g $NaBH_4$. Work-up afforded 0.98 g (85%) 9c as an oil. IR($CHCl_3$): 3360 cm^{-1} (OH); 1665 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 5.30 (m, 1H, becomes d of d with D_2O, CHOH); 4.75 (m, 2H, CH_2=C); 4.36 (d, 1H, disappears with D_2O, OH); 3.95-3.05 (m, 4H); 2.28 (t, 2H, CH_2C=C); 1.75 (s, 3H, CH_3).

b. Cyclization of 9c. Compound 9c (0.250 g, 1.34 mmol) was dissolved in 3 ml of HCOOH and stirred at r.t. for 18 hrs. Work-up afforded 0.237 g of an oil, from which the epimer 21c crystallized (0.141 g; yield: 49%); m.p.: 93-94°. IR($CHCl_3$): 1720 cm^{-1} (ester CO); 1665 cm^{-1} (lactam CO). ^1H NMR δ($CDCl_3$): 4.07-3.68 (m, 2H, NCH and NCH_2 eq.), 3.43-2.18 (m, 5H), 1.70-1.30 (m, 2H), 1.58 (s, 3H, CH_3). (Found: C, 50.1%; H, 6.1%; N, 6.5%; S, 15.0%; calc. for $C_9H_{13}NO_3S$ (Mw 215.27): C, 50.2%; H, 6.1%; N, 6.5%; S, 14.9%).

5-Formyloxy-8,8-dimethyl-1-aza-9-thiabicyclo[5.3.0]decan-10-one (21d)

a. N-(pent-4-enyl)-4-hydroxy-5,5-dimethylthiazolidin-2-one (9d)
2.0 g (9.4 mmol) of 3d was reduced with 4.0 g $NaBH_4$. Work-up afforded 1.69 g (84%) 10d as a pale yellow oil. IR($CHCl_3$): 3370 cm^{-1} (OH); 1660 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 6.15-5.40 (m, 1H, CH=), 5.25-4.80 (m, 2H, CH_2=), 4.61 (s, 1H, CHOH), 3.90-2.80 (m, 3H, 2H upon addition of D_2O, NCH_2 and OH), 2.35-1.30 (m, 4H), 1.50 and 1.43 (s and s, 6H, CH_3 2x).

b. Cyclization of 9d. Compound 9d (0.161 g, 0.75 mmol) was dissolved in 15 ml HCOOH and stirred in the dark at r.t. for 118 hrs. Work-up afforded 0.1388 g of a crystalline mixture of epimers; m.p. 142-145° (76% yield). IR(KBr): 1710 cm^{-1} (ester CO); 1655 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 8.05 (s, 1H, CHO), 5.20-4.80 (m and m, 1H, CHOCHO), 4.10-3.20 (m, 2H, NCH_2 and NCH), 2.40-1.30 (m, 6H), 1.52 and 1.39 (s and s, 6H, CH_3 2x). An exact mass determination gave 243.0950; $C_{11}H_{17}NO_3S$ requires 243.0929 (8.6).

5-Ethyl-4-formyloxy-7,7-dimethyl-1-aza-8-thiabicyclo[4.3.0]nonan-9-one (21e)

a. N-(Z-hex-3-enyl)-4-hydroxy-5,5-dimethylthiazolidin-2-one (9e)
1.14 g (5.03 mmol) 3e was reduced with 2.0 g $NaBH_4$. Work-up and column chromatography (eluent: EtOAc/$CHCl_3$ 1:1) afforded 1.0358 g (90%) 9e as an oil. IR($CHCl_3$): 3380 cm^{-1} (OH); 1670 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 5.70-5.10 (m, 2H, CH=CH), 5.08 (d, 1H, disappears with D_2O, OH), 4.73 (d, 1H, CHOH), 3.8-3.0 (m, 2H, NCH_2), 2.27 (m, 2H, $NCCH_2$), 1.99 (m, 2H, CH_2C=C), 1.53 and 1.49, s and s, CH_3 2x), 0.97 (t, 3H, CH_3).

b. Cyclization of 9e. Compound 9e (0.0298 g, 0.13 mmol) was dissolved in 3 ml HCOOH and stirred at r.t. for 72 hrs. Work-up afforded 21e as a solid (0.0319 g, 96% yield); m.p. 109-110° (dipe). IR($CHCl_3$): 1715 cm^{-1} (ester CO; 1660 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 8.03 (s, 1H, CHO); 5.3-5.0 (m, 1H, CHOCHO), 4.31 (m, 1H, NCH_2 eq.), 3.19 (d, 1H, NCH), 2.82 (t of d, 1H, NCH_2 ax.), 2.3-1.6 (m, 5H), 1.55 and 1.42 (s, and s, 6H, CH_3 2x), 0.95 (t, 3H, CH_3). (Found: C, 56.2%; H, 7.4%; N, 5.3%; S, 12.3%; $C_{12}H_{19}NO_3S$ (Mw 257.34) requires C, 56.0%; H, 7.4%; N, 5.4%; S, 12.4%).

5-Formyloxy-8,8-dimethyl-1-azabicyclo[5.3.0]-decan-10-one (23a) and 5-formyloxy-9,9-dimethyl-1-azabicyclo[5.3.0]decan-10-one 23b

a. N-(pent-4-enyl)-5-hydroxy-4,4-dimethylpyrrolidin-2-one (22a) and N-(pent-4-enyl)-5--hydroxy-3,3-dimethylpyrrolidin-2-one (22b). 0,9 g (4.6 mmol) 3g was reduced with 1.8 g $NaBH_4$. Work-up afforded 0.67 g of a yellow oil, which after column chromatography (eluent CH_2Cl_2/acetone 4:1) could be separated into two fractions: 0.3839 g (42%) 22a (Rf 0.28), which crystallized upon standing; m.p. 43-46°, and 0.1065 g (11%) 22b (Rf 0.43).
22a: IR($CHCl_3$): 3340 cm^{-1} (OH); 1670 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 6.20-5.45 (m, 1H, CH=), 5.30-4.75 (m, 3H, CH_2= and CHOH), 3.80-2.90 (m, 3H, NCH_2 and OH), 2.25 and 2.10 (s and s, 2H, CH_2CON), 2.30-1.30 (m, 4H), 1.10 and 1.05 (s and s, 6H, CH_3 2x).
22b: IR($CHCl_3$): 3370 cm^{-1} (OH); 1670 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 6.20-5.40 (m, 1H, CH=), 5.30-4.75 (m, 3H, CH_2= and CHOH), 3.90-2.90 (m, 3H, NCH_2 and OH), 2.30-1.30 (m, 6H), 1.21 and 1.09 (s and s, 6H, CH_3 2x).

b. Cyclization of 22a. Compound 22a (0.1406 g, 0.71 mmol) was dissolved in 20 ml HCOOH and stirred at r.t. for 138 hrs in the dark. Work-up afforded 0.1049 g (63%) oil, which crystallized upon standing; m.p. 75-77°. IR (KBr): 1710 cm^{-1} (ester CO); 1670 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 8.06 (s, 1H, CHO), 2.22 (s, 2H, CH_2CON), 1.14 and 0.97 (s and s, 6H, CH_3 2x). An exact mass determination gave 225.1347; $C_{12}H_{19}NO_3$ requires 225.1365 (7.9).

c. Cyclization of 22b. Compound 22b (0.08 g, 0.41 mmol) was treated with HCOOH as above. Work-up afforded 0.0286 g clear oil (31%), which crystallized with dipe; m.p. 107-109°. IR(KBr): 1695 cm^{-1} (ester CO); 1680 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 8.03 (s, 1H, CHO), 1.20 and 1.12 (s and s, 6H, CH_3 2x). An exact mass determination gave 225.1347; $C_{12}H_{19}NO_3$ requires 225.1365 (7.9).

5-Ethyl-4-formyloxy-7-methyl-7-phenyl-1-aza-8-thiabicyclo[4.3.0]nonan-9-one 24

a. N-(Z-hex-3-enyl)-4-hydroxy-5-methyl-5-phenylthiazolidin-2-one 14a
1.0 g (3.5 mmol) 8a was reduced with 2 g $NaBH_4$. Work-up afforded 0.92 g (91%) 14a as a pale yellow oil. IR($CHCl_3$): 3360 cm^{-1} (OH); 1670 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 7.33 (m, 5H, Ph), 5.30-4.85 (m, 3H, sharpens with D_2O, CHOH and CH=CH), 3.80-3.0 (m, 3H, becomes 2H with D_2O, NCH_2 and OH), 2.50-1.50 (m, 4H), 1.86 and 1.80 (s and s, 3H, 2 epimers of CH_3), 0.87 (t, 3H, CH_3).

b. Cyclization of 14a. Compound 14a was dissolved in 15 ml HCOOH and stirred at r.t. for 91 hrs. Work-up afforded 0.1354 g of a pale yellow oil, which crystallized upon addition of dipe; m.p. 180-182°; yield 87%. IR($CHCl_3$): 1720 cm^{-1} (ester CO); 1665 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 7.95 (s, 1H, CHO), 7.38 (m, 5H, Ph), 5.30-5.0 (m, 1H, CHOCHO), 4.52-4.28 (m, 1H, NCH_2 eq.), 3.77 (d, 1H, NCH), 3.10-2.75 (m, 1H, NCH_2 ax.), 2.0 (s, 3H, CH_3), 2.05-1.0 (m, 5H), 0.15 (t, 3H, CH_3). (Found: C, 64.0%; H, 6.5%; N, 4.3%; S, 9.8%; $C_{17}H_{21}NO_3S$ (Mw 319.43) requires C, 63.9%; H, 6.6%; N, 4.4%; S, 10.0%).

7,7-dimethyl-1-aza-8-thiabicyclo[4.3.0]nonane--4,9-dione (26a)

a. N-(but-3-ynyl)-4-hydroxy-5,5-dimethylthiazolidin-2-one (10a)
1.01 g (5.2 mmol) 4a was reduced with 1.98 g $NaBH_4$. Work-up afforded 0.87 g (85%) 10a as a clear oil. IR($CHCl_3$): 3360 cm^{-1} (OH); 3310 cm^{-1} (C≡CH); 1660 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 4.88 (s, 1H, sharpens with D_2O, CHOH), 4.07 (s, 1H, disappears with D_2O, OH), 3.90-3.25 (m, 2H, NCH_2), 2.52 (t of d, 2H, CH_2), 2.03 (m, 1H, C≡CH), 1.58 and 1.49 (s and s, 6H, CH_3 2x).

b. Cyclization of 10a. Compound 10a was dissolved in 5 ml HCOOH and stirred at r.t. for 94 hrs. Work-up afforded a yellow oil from which 90 mg of crystalline 26a were isolated; yield: 80%; m.p. 117-118.5°. IR($CHCl_3$): 1708 cm^{-1} (CO); 1665 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 4.50-4.26 (m, 1H, NCH_2 eq.), 3.58 (d of d, 1H, NCH), 3.25-2.95 (m, 1H, NCH_2 ax.), 2.6-2.3 (m, 4H), 1.62 and 1.44 (s and s, 6H, CH_3 2x). (Found: C, 54.3%; H, 6.5%; N, 7.1%; S, 15.9%. $C_9H_{13}NO_2S$ (Mw 199.27) requires C, 54.3%; H, 6.6%; N, 7.0%; S, 16.1%).

9,9-Dimethyl-1-aza-10-thiabicyclo[6.3.0]undecane--6,11-dione 26b

a. N-(hex-5-ynyl)-4-hydroxy-5,5-dimethylthiazolidin-2-one 10b
2.5 g (11.5 mmol) 4b was reduced with 5 g $NaBH_4$. Work-up afforded 2.114 g of 10b as a pale yellow oil. IR($CHCl_3$): 3370 cm^{-1} (OH); 3330 cm^{-1} (C≡CH); 1660 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 4.67 (s, 1H, sharpens with D_2O, CHOH), 4.05 (br. s, disappears with D_2O, OH), 3.80-3.05 (m, 2H, NCH_2), 2.22 (t of d, 2H, CH_2C=), 1.95 (m, 1H, C≡CH), 1.53 and 1.47 (s and s, 6H, CH_3), 1.85-1.30 (m, 4H).

b. Cyclization of 10b. Compound 10b (0.1 g, 0.44 mmol) was dissolved in 100 ml HCOOH and stirred for 280 hrs at 43°C. Work-up afforded 90 mg of an oil, from which 70 mg 26b (70%) crystallized with dipe. IR(KBr): 1700 cm^{-1} (CO); 1660 cm^{-1} (lactam CO). ^1H NMR δ($CDCl_3$): 3.81 (d of m, 1H, NCH_2 eq.), 3.57 (d, 1H, NCH), 3.50-3.15 (m, 1H, NCH_2 ax.), 2.90-1.40 (m, 8H), 1.61 and 1.43 (s and s, 6H, CH_3 2x). (Found: C, 58.2%; H, 7.5%; N, 6.2%; S, 13.9%. Calc. for $C_{11}H_{17}NO_2S$ (Mw 227.33): C, 58.1%; H, 7.5%; N, 6.2%; S, 14.1%).

8,8-Dimethyl-1-aza-9-thiabicyclo[5.3.0]decane--5,10-dione 26c

a. N-(penta-3,4-dienyl)-4-hydroxy-5,5-dimethylthiazolidin-2-one 12b
1.0 g (4.74 mmol) 6b was reduced with 2.0 g $NaBH_4$ at -10° during 5 hrs. Work-up afforded 0.90 g (89%) 12b as an oil. IR($CHCl_3$): 3370 cm^{-1} (OH); 1960 cm^{-1} (C=C=CH_2); 1670 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 5.07 (m, 1H, CH=), 4.71 (m, 3H, sharpens with D_2O, CH_2= and CHOH), 3.90-3.10 (m, 3H, changes to 2H with D_2O, NCH_2 and OH), 2.30 (m, 2H), 1.55 and 1.49 (s and s, 6H, CH_3 2x). An exact mass determination gave 213.0826; $C_{10}H_{15}NO_2S$ requires 213.0823 (1.4).

b. Cyclization of 12b. Compound 12b (0.282 g, 1.32 mmol) was dissolved in 15 ml HCOOH and refluxed for 93 hrs. Work-up afforded 0.2454 g oil, which crystallized upon cooling; m.p. 90-92° (dipe); yield: 87%. IR(KBr): 1715 cm^{-1} (CO); 1665 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 4.45-4.15 (d of d, 1H, NCH_2 eq.), 3.66-3.48 (d of d, NCH), 3.16-2.48 (m, 5H), 2.05-1.70 (m, 2H), 1.60 and 1.43 (s and s, 6H, CH_3 2x). (Found: C, 56.5%; H, 7.2%; N, 6.6%; S, 14.7%. Calc. for $C_{10}H_{15}NO_2S$ (Mw 213.30): C, 56.3%; H, 7.1%; N, 6.6%; S, 15.0%).

8,8-dimethyl-1-azabicyclo[5.3.0]decane-5,10--dione 26d

a. N-(penta-3,4-dienyl)-5-hydroxy-4,4-dimethylpyrrolididin-2-one (12c)
1.1 g (5.7 mmol) 6c was reduced with 2.3 g $NaBH_4$. Work-up afforded 0.82 g 12c clear liquid, which crystallized upon standing; m.p. 45-48°; yield: 75%. IR($CHCl_3$): 3380 cm^{-1} (OH); 1960 cm^{-1} (C=C=CH_2); 1675 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 5.25-4.90 (m, 1H, CH=); 4.75-4.55 (m, 3H, sharpens with D_2O, CH_2= and CHOH), 3.80-3.05 (m, 3H, changes to 2H with D_2O, NCH_2 and OH), 2.50-1.80 (m, 4H), 1.14 and 1.10 (s and s, 6H, CH_3 2x). An exact mass determination gave 195.1271; $C_{11}H_{17}NO_2$ requires 195.1259 (6.1).

b. Cyclization of 12c. Compound 12c (0.126 g, 0.65 mmol) was dissolved in 15 ml HCOOH and refluxed during 138 hrs. Work-up afforded 94 mg of a brown oil, from which crystals with m.p. 50-53° were obtained. IR(KBr): 1720 cm^{-1} (CO); 1680 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 4.30 (d of d of d, 1H, NCH_2 eq.); 3.37 (d of d, 1H, NCH), 2.82 (t of d, 1H, NCH_2 ax.), 2.70-2.50 (m, 4H), 2.35 and 2.15 (d of d, AB-system, 2H, CH_2CON), 2.05-1.70 (m, 2H), 1.18 and 1.05 (s and s, 6H, CH_3 2x). An exact mass determination gave 195.1258; $C_{11}H_{17}NO_2$ 195.1259 (0.5).

N-(penta-3,4-dienyl)-4-hydroxythiazolidin-2-one 12d

Reduction of 1.0 g (5.45 mmol) 6d with 2.0 g $NaBH_4$ at -10° afforded 0.82 g of 12d as a pale yellow oil. IR($CHCl_3$): 3390 cm^{-1} (OH); 1955 cm^{-1} (C=C=CH_2); 1670 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 5.85 (d of d, 1H, CHOH), 5.10 (m, 1H, CH=), 4.75 (m, 2H, CH_2=), 4.0-3.0 (m, 5H, changes to 4H with D_2O, NCH_2, SCH_2 and OH), 2.30 (m, 2H).

N-(6-phenylhex-3-ynyl)-4-hydroxy-5,5-dimethylthiazolidin-2-one 10c

3.55 g (11.8 mmol) 4c was reduced with 7 g $NaBH_4$. Work-up afforded 3.0 yellow oil, which solidified upon addition of dipe. M.p. 74-76°; yield: 84%. IR($CHCl_3$): 3410 cm^{-1} (OH); 1670 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 7.25 (m, 5H, Ph), 4.77 (s, 1H, sharpens with D_2O, CHOH), 3.75-3.20 (m, 3H, changes to 2H with D_2O, NCH_2 and OH), 2.77 (t, 2H, $PhCH_2$), 2.45 (m, 4H), 1.49 and 1.44 (s and s, 6H, CH_3 2x). (Found: C, 67.5%; H, 7.2%; N, 4.7%; S, 10.4%. Calc. for $C_{17}H_{21}NO_2S$: C, 67.3%; H, 7.0%; N, 4.6%, S, 10.6% (Mw 303.43).

3,3-Dimethyl-1-oxo-benzo[j]-6-aza-8-thiatricyclo[7.4.0.0^{2,6}]tridecane 27

a. N-(Z-6-phenylhex-3-enyl)-5,5-dimethylthiazolidine-2,4-dione 3f
0.716 g (2.38 mmol) 4c was reduced with 31 mg 5% Pd/C/Ba_2SO_4 as catalyst in a hydrogen atmosphere. After 20 hrs the reaction mixture was filtered over Celite and the solvent evaporated under reduced pressure, affording 0.612 g (85%) 3f as a pale yellow oil. IR($CHCl_3$): 1750 cm^{-1}; 1680 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 7.20 (m, 5H, Ph), 5.65-5.15 (m, 2H, CH=CH), 3.58 (t, 2H, NCH_2), 2.80-2.10 (m, 6H), 1.64 (s, 6H, CH_3 2x).

b. N-(Z-6-phenylhex-3-enyl)-4-hydroxy-5,5--dimethylthiazolidin-2-one 9f
Compound 3f (0.7 g, 2.29 mmol) was reduced with 1.4 g $NaBH_4$. Work-up afforded 9f (0.6542 g, 92%) as an oil. IR($CHCl_3$): 3380 cm^{-1} (OH); 1670 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 7.24 (m, 5H, Ph), 5.70-5.20 (m, 2H, CH=CH), 4.87 (m, 1H, disappears with D_2O, OH), 4.61 (m, 1H, sharpens with D_2O, CHOH), 3.75-3.0 m, 2H, NCH_2), 2.8-2.2 (m, 6H), 1.50 and 1.46 (s and s, 6H, CH_3 2x).

c. Cyclization of 9f. Compound 9f was dissolved in 15 ml HCOOH and refluxed for 117 hrs. Work-up afforded 200 mg of a brown oil, which after treatment with active charcoal afforded 100 mg crystalline 27; m.p. 153-154°; yield: 41%. ^1H NMR δ($CDCl_3$): 7.15-7.10 (m, 4H, Ph), 4.25 (d of d, 1H, NCH_2 eq.), 3.39 (d, 1H, NCH), 2.97 (t of d, 1H, NCH_2 ax), 2.92-2.65 (m, 3H, PhCH 3x), 2.38-1.50 (m, 5H), 1.65 and 1.55 (s and s, 6H, CH_3 2x). An exact mass determination gave 287.13625. Calc. for $C_{17}H_{21}NOS$: 287.13437 (6.5).

1,1-Dimethyl-3-oxobenzo[d]-1-aza-8-thiabicyclo-[4.3.0]nonane 28a

a. N-(2-phenylethyl)-4-hydroxy-5,5-dimethylthiazolidin-2-one 11a
1.53 g (6.15 mmol) 5a was reduced with 3.0 g $NaBH_4$. Work-up afforded 1.27 g (82%) white solid mass; m.p. 78-79°. IR($CHCl_3$): 3360 cm^{-1} (OH); 1660 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 7.70-7.15 (m, 5H, Ph), 4.45 (d, s with D_2O, 1H, CHOH), 4.0-3.30 (m, 3H, NCH_2 and OH), 2.90 (t, 2H, $PhCH_2$), 1.39 and 1.30 (s and s, 6H, CH_3 2x). (Found: C, 62.2%; H, 6.8%; N, 5.5%; S, 12.7%; $C_{13}H_{17}NO_2S$ (Mw 251.34) requires C, 62.1%; H, 6.8%; N, 5.6%, S, 12.7%).

b. Cyclization of 11a. Compound 11a (0.516 g, 2.05 mmol) was refluxed in 50 ml CH_2Cl_2 with 1.2 g (6.3 mmol) of p-toluenesulphonic acid hydrate for 112 hrs. Work-up afforded 0.355 g crystalline 28a; m.p. 89-91°; yield 74%. IR(KBr): 1660 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 7.23 (m, 4H, Ph), 4.90 (s, 1H, NCH), 4.50-4.35 (m, 1H, NCH_2 eq.), 3.05-2.60 (m, 3H, $PhCH_2$ and NCH_2 ax.), 1.72 and 1.04 (s and s, 6H, CH_3 2x). (Found: C, 67.1%; H, 6.6%; N, 6.0%; S, 13.7%, while $C_{13}H_{15}NOS$ (Mw 233.33) requires C, 66.9%; H, 6.5%, N, 6.0%; S, 13.7%).

8,9-Dimethoxy-1,1-dimethyl-3-oxobenzo[d]-1-aza--8-thiabicyclo[4.3.0]nonane 28b

a. N-(2-(3,4-dimethoxyphenyl)ethyl)-4-hydroxy-5,5-dimethylthiazolidin-2-one 11c
1.0 g (3.24 mmol) 5c was reduced with 2.0 g

$NaBH_4$. Work-up afforded 0.91 g (90%) crystalline 11c; m.p. 142-143°. IR($CHCl_3$): 3360 cm^{-1} (OH); 1670 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 6.75 (s, 3H, Ph), 4.47 (m, 1H, CHOH), 3.70-2.40 (m, 5H), 1.40 and 1.35 (s and s, 6H, CH_3 2x). (Found: C, 57.6%; H, 6.7%; N, 4.5%; S, 10.2%; $C_{15}H_{21}NO_4S$ (Mw 311.40) requires C, 57.9%; H, 6.8%; N, 4.5%; S, 10.3%).

b. Cyclization of 11c. Compound 11c (0.113 g, 0.36 mmol) was dissolved in 15 ml HCOOH and stirred at r.t. for 113 hrs. Work-up afforded 105 mg pale yellow oil, which solidified upon standing (quant.yield); m.p. 127-130°. IR($CHCl_3$): 1660 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 6.66 (s, 2H, Ph), 4.85 (s, 1H, NCH), 4.60-4.15 (m, 1H, NCH_2 eq.), 3.83 (s, 6H, OCH_3 2x), 3.20-2.50 (m, 3H) 1.74 and 1.08 (s and s, 6H, CH_3 2x). An exact mass determination gave 293.1084; $C_{15}H_{19}NO_3S$ requires 293.1085 (0.3).

8,9-Dimethoxy-3-oxobenzo[d]-1-aza-8-thiabicyclo-[4.3.0]nonane 28c

a. N-(2-(3,4-dimethoxyphenyl)-ethyl)-4-hydroxy-thiazolidin-2-one 11d
0.64 g (2.27 mmol) 5d was reduced with 1.3 g $NaBH_4$. Work-up afforded 0.594 g (92%) 11d as a crystalline mass; m.p. 85-87° (dipe). IR($CHCl_3$): 3360 cm^{-1} (OH); 1670 cm^{-1} (CO); 1510 cm^{-1} (Ph); ^1H NMR δ($CDCl_3$): 6.63 (s, 3H, Ph), 5.05-4.80 (m, 1H, sharpens with D_2O, CHOH), 4.0-2.70 (m, 5H, changes to 4H with D_2O, OH and CH_2CH_2), 3.81 (s, 6H, OCH_3 2x), 1.12 (m, 2H, SCH_2). (Found: C, 55.0%; H, 5.9%; N, 4.9%; S, 11.1%. Calc. for $C_{13}H_{17}NO_4S$ (Mw 283.35); C, 55.1%; H, 6.0%; N, 4.9%; S, 11.3%).

b. Cyclization of 11d. Compound 11d (0.1243 g, 0.44 mmol) was dissolved in 15 ml HCOOH and stirred at r.t. for 112 hrs. Work-up afforded 0.0978 g (84%) 28c as a crystalline mass; m.p. 132-133° (dipe). IR($CHCl_3$): 1670 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 6.64 and 6.55 (s and s, 2H, Ph), 4.90 (d of d, 1H, NCH), 4.35 (m, 1H, NCH_2 eq.), 3.85 (s, 6H, CH_3O 2x), 3.62 (d of d, 1H, NCH_2 ax.), 3.15-2.60 (m, 4H). An exact mass determination gave 265.0763; $C_{13}H_{15}NO_3S$ requires 265.0772 (3.3).

8,9,10-Trimethoxy-1,1-dimethyl-3-oxobenzo[d]-1--aza-8-thiabicyclo[4.3.0]nonane 28d

a. N-(2-(3,4,5-trimethoxyphenyl)ethyl)-4-hydroxy--5,5-dimethylthiazolidin-2-one 11e
1.0 g (2.95 mmol) 5e was reduced with 2.0 g $NaBH_4$. Work-up afforded 0.84 g viscous oil, which solidified upon standing; m.p. 93-95° (dipe). IR($CHCl_3$): 3370 cm^{-1} (OH); 1660 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 6.42 (s, 2H, Ph), 4.61 (m, 1H, CHOH), 3.78 (s, 9H, OCH_3 3x), 3.80-2.65 (m, 5H), 1.39 and 1.31 (s and s, 6H, CH_3 2x). (Found: C, 56,4%; H, 6.7%; N, 4.1%; S, 9.3%; $C_{16}H_{23}NO_5S$ requires C, 56.3%; H, 6.8%; N, 4.1%; S, 9.4%).

b. Cyclization o 11e. Compound 11e (0.124 g, 0.36 mmol) was dissolved in 15 ml HCOOH and stirred at r.t. for 113 hrs. Work-up afforded 0.0686 g 28d as an oil, which solidified upon cooling; m.p. 115-116° (dipe); yield: 58%. IR($CHCl_3$): 1655 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 6.45 (s, 1H, Ph), 5.10 (s, 1H, NCH), 4.65-4.10 (m, 1H, NCH_2 eq.), 3.83 (s, 9H, OCH_3 3x), 3.50-2.50 (m, 3H), 1.65 and 1.08 (s and s, 6H, CH_3 2x). An exact mass determination gave 323.1190. Calc. for $C_{16}H_{21}NO_4S$: 323.1192 (0.6).

8,9,10-Trimethoxy-3-oxobenzo[d]-1-aza-8-thiabicyclo[4.3.0]nonane 28e

a. N-(2-(3,4,5-trimethoxyphenyl)ethyl)-4--hydroxy-thiazolidin-2-one 11f
0.326 g (1.05 mmol) 5f was reduced with 0.7 g $NaBH_4$. Work-up afforded 0.328 g 11f as a viscous oil (quant. yield). IR($CHCl_3$): 3380 cm^{-1} (OH); 1660 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 6.35 (m, 2H, Ph), 5.10-4.85 (m, 1H, sharpens with D_2O, CHOH), 4.30-2.70 (m, 5H, changes to 4H with D_2O, OH and CH_2CH_2), 3.79 (s, 9H, OCH_3 3x), 1.22 (m, 2H, SCH_2).

b. Cyclization of 11f. Compound 11f (0.193 g, 0.62 mmol) was dissolved in 30 ml CH_2Cl_2 with 0.1 g (ca. 0.5 mmol) p-toluenesulphonic acid hydrate, and refluxed for 114 hrs. Work-up afforded 0.15 g pale yellow oil, from which dipe crystallization afforded 120 mg (66%) 28e; m.p. 94.5-96.5°. IR($CHCl_3$): 1660 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 6.45 (s, 1H, Ph), 4.98 (m, 1H, NCH), 4.65-3.75 (m, 2H), 3.95 and 3.85 (s and s, 9H, OCH_3 3x), 3.25-2.40 (m, 4H). An exact mass determination gave 295.086; $C_{14}H_{17}NO_4S$ requires 295.087 (3.3)

N-(2-Phenylethyl)-4,5-thiazolin-2-one 29

a. N-(2-phenylethyl)-4-hydroxythiazolidin-2--one 11b
1.70 g (7.7 mmol) 5b was reduced with 3.5 g $NaBH_4$ at -10° for 12 hrs. Work-up afforded 0.103 g 11b as a white crystalline mass; m.p. 92-93° (dipe); yield 60%. IR($CHCl_3$): 3380 cm^{-1} (OH); 1660 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 7.26 (m, 3H, Ph), 4.9 (m, 1H, sharpens with D_2O, CHOH), 3.9-3.3 (m, 3H), 3.15-2.8 (m, 3H), 1.60 (s, 1H, disappears with D_2O, OH). (Found: C, 59.3%; H, 5.9%; N, 6.2%; S, 14.2%. Calc. for $C_{11}H_{13}NO_2S$ (Mw 223.29): C, 59.2%; H, 5.9%; N, 6.3%; S, 14.4%).

b. Compound 11b (0.047 g, 0.211 mmol) was refluxed for 88 hrs in 15 ml CH_2Cl_2 with 0.26 g (1.39 mmol) p-toluenesulphonic acid hydrate. Work-up afforded 0.046 g yellow oil, from which addition of dipe crystallized 0.0225 g 29; m.p. 140-142°; yield: 52%. IR ($CHCl_3$): 1660 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 7.25 (m, 5H, Ph), 6.11 (d and d, AB system, CH=CH), 3.92 (t, 2H, $PhCH_2$), 2.97 (t, 2H, NCH_2). (Found: C, 64.3%; H, 5.4%; N, 6.7%; S, 15.4%. $C_{11}H_{11}NOS$ (Mw 205.28) requires C, 64.4%; H, 5.4%; N, 6.8%; S, 15.6%).

5,6,7-Trimethoxy-3-methyl-2-oxo-10-phenylindano-[2,1-d]thiazolidine 30

a. N-methyl-4-hydroxy-5-phenyl-5(3,4,5-trimethoxybenzyl)thiazolidin-2-one (14b)
0.8 g (2.08 mmol) 8b was reduced with 1.5 g $NaBH_4$. Work-up afforded 0.51 g crystalline 14b; m.p. 185-187°; yield: 63%. IR(KBr): 3390 cm^{-1} (OH); 1680 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 7.60-7.05 (m, 5H, Ph), 5.94 (d, 2H, $PhOCH_3$), 5.31 (m, 1H, CHOH), 3.80, 3.64 and 3.58 (s, s and s, 9H, OCH_3 3x), 3.60-3.20 (m, 3H), 3.10 and 2.91 (s and s, 3H, NCH_3).

b. Cyclization of 14b. Compound 14b (0.1892 g, 0.486 mmol) was dissolved in a mixture of 30 ml MeOH and 5 ml conc. HCl, and refluxed for 90 hrs. Work-up afforded 0.183 g 30 as an oil (quant yield). IR($CHCl_3$): 1660 cm^{-1} (CO); ^1H NMR δ($CDCl_3$): 7.5-7.2 (m, 5H, Ph), 6.61 (s, 1H, $PhOCH_3$), 5.17 (s, 1H, NCH), 3.96 and 3.87 (s and s, 9H, OCH_3 3x), 3.73 and 3.45 (s and s, 2H, $PhCH_2$) 3.08 (s, 3H, NCH_3). An exact mass determination gave 371.1161. $C_{20}H_{21}NO_4S$ requires 371.1191 (8.0).

N-Methyl-5-benzyl-4-hydroxy-5-phenylthiazolin--2-one 14c

0.90 g (3.03 mmol) 8c was reduced with 1.8 g $NaBH_4$. Work-up afforded 0.74 g white crystalline mass; m.p. 157-158° (from dipe); yield: 82%.

IR(KBR): 3340 cm^{-1} (OH); 1640 cm^{-1} (CO); ^1H NMR $\delta(CDCl_3)$: 7.50-6.50 (m, 10H, Ph 2x), 5.22 (m, 1H, CHOH, 3.38 (d, 2H, $PhCH_2$), 2.88 (d, 3H, NCH_3). An exact mass determination gave 299.0991. Calc. for $C_{17}H_{17}NO_2S$: 299.0979 (4.0).

10-Formyloxy-3,3-dimethyl-6-aza-4-thiatricyclo-[6.3.1.$0^{2,6}$]dodecan-5-one 32b and 3,3-dimethyl--6-aza-4-thiatricyclo[6.3.1.$0^{2,6}$]dodec-10-en--5-one 33a

a. N-(cyclohex-3-enylmethyl)-4-hydroxy-5,5--dimethylthiazolidin-2-one 13a
2.15 g (9.0 mmol) 7a was reduced with 4.5 g $NaBH_4$. Work-up afforded 1.62 g 13a as a white crystalline mass; m.p. 102-103°, yield: 75%. IR(KBr): 3360 cm^{-1} (OH); 1660 cm^{-1} (CO); ^1H NMR $\delta(CDCl_3)$: 5.67 (br. m, 2H, CH=CH), 4.68 (d, 1H, changes to s with D_2O, CHOH), 3.80-2.95 (m, 3H, changes to 2H with D_2O, NCH_2 and OH), 1.90-0.50 (m, 7H), 1.57 and 1.50 (s and s, 6H, CH_3 2x). (Found: C, 59.9%; H, 7.9%; N, 5.9%; S, 13.2%. Calc. for $C_{12}H_{19}NO_2S$ (Mw 241.35): C, 59.7%; H, 7.9%; N, 5.8%; S, 13.3%).

b. Cyclization of 13a. Compound 13a (1.3767 g, 5.7 mmol) was dissolved in 30 ml HCOOH and stirred at r.t. for 18 hrs. Work-up afforded an oil, from which dipe-crystallization afforded 0.353 g (23%) 32b; m.p. 131-132°. IR(KBr): 1715 cm^{-1} (ester CO); 1660 cm^{-1} (lactam CO). ^1H NMR $\delta(CDCl_3)$: 7.99 (s, 1H, CHO), 5.60-5.22 (m, 1H, CHOCHO), 4.14 (d of m, 1H, NCH_2 eq.), 3.38 (d, 1H, NCH), 3.05 (d of m, 1H, NCH_2 ax.), 2.80-1.60 (m, 8H), 1.60 (s, 6H, CH_3 2x). (Found: C, 58.1%; H, 7.2%; N, 5.3%; S, 12.0%; $C_{13}H_{19}NO_3S$ (Mw 269.35) requires C, 58.0%; H, 7.1%; N, 5.2%; S, 11.9%).
The ^1H NMR-spectrum of the crude reaction mixture showed a second formate signal, δ 8.06, and a signal δ 5.80-5.60 (CHOCHO), indicating an axial formate (32a). Moreover, by column chromatography of the mother liquor a quantity of 33a could be obtained; a higher yield of this compound, however, was obtained by refluxing 0.0433 g 13a in 5 ml HCOOH for 17 hrs. Work-up afforded 0.0428 g oil, from which dipe-crystallization gave 36 mg crystalline 33a (90% yield). IR(KBr): 1655 cm^{-1} (CO); ^1H NMR $\delta(CDCl_3)$: 5.82 (br. m, CH=CH), 4.26 (d of m, 1H, NCH_2 eq.), 3.34 (d, 1H, NCH), 3.05 (d of m, 1H, NCH_2 ax.), 2.60-1.75 (m, 6H), 1.56 and 1.48 (s and s, 6H, CH_3 2x). (Found: C, 64.6%; H, 7.6%; N, 6.4%; S, 14.4%. Calc. for $C_{12}H_{17}NOS$ (Mw 223.33): C, 64.6%; H, 7.7%; N, 6.3%; S, 14.3%).

10-Formyloxy-3,3-dimethyl-6-azabicyclo-[6.3.1.$0^{2,6}$]dodecan-5-one 32d and 3,3-dimethyl--6-azabicyclo[6.3.1.$0^{2,6}$]dodec-10-en-5-one 33b

a. N-cyclohex-3-enylmethyl)-5-hydroxy-4,4--dimethylpyrrolidin-2-one (13b)
3.1 g (14 mmol) 7b was reduced with 6.2 g $NaBH_4$ at -5° for 5 hrs. Work-up afforded 1.40 g of a crystalline mixture of regio-isomers, from which 13b was obtained by re-crystallization from dipe in ca. 30% yield; m.p. 110-111°. IR(KBr): 3270 cm^{-1} (OH); 1670 cm^{-1} (CO); ^1H NMR $\delta(CDCl_3)$: 5.67 (br. m, 2H, CH=CH), 4.65 (d, changes to s with D_2O, 1H, CHOH), 3.39 and 3.02 (m and m, 2H, NCH_2), 2.65 (d of d, 1H, disappears with D_2O, OH), 2.35-1.60 (m, 9H), 1.16 and 1.13 (s and s, 6H, CH_3 2x). (Found: C, 70.0%; H, 9.4%; N, 6.4%; $C_{13}H_{21}NO_2$ (Mw 223.32) requires C, 69.9%; H, 9.5%; N, 6.3%).

b. Cyclization of 13b. Compound 13b (0.0675 g, 0.3 mmol) was dissolved in 5 ml HCOOH and stirred at r.t. for 19 hrs. Work-up afforded 71.5 mg clear oil, from which 15 mg (20%) 32d crystallized upon cooling; m.p. 120-122°. IR($CHCl_3$): 1715 cm^{-1} (ester CO); 1670 cm^{-1} (lactam CO); ^1H NMR $\delta(CDCl_3)$: 7.96 (s, 1H, CHO), 5.30-4.90 (m, 1H, CHOCHO), 4.12 (d, 1H, NCH_2 eq.), 3.14 (d, 1H, NCH), 2.95 (d of m, NCH_2 ax.), 2.50-1.40 (m, 10H), 1.22 and 1.15 (s and s, 6H, CH_3 2x). (Found: C, 67.1%; H, 8.6%; N, 5.5%. Calc. for $C_{14}H_{21}NO_3$ (Mw 251.33): C, 66.9%; H, 8.4%; N, 5.6%). The ^1H NMR-spectrum of the crude reaction product showed a second formate signal at δ 8.05, and a signal indicating equatorial CHOCHO at δ 5.50-5.35 (32c). Also, a quantity of 33b was indicated to be present, which compound was also prepared in the following manner:

c. 0.0469 g (0.21 mmol) 13b was dissolved in 15 ml. HCOOH and refluxed for 18 hrs. Work-up afforded 30 mg 33b as a clear oil; yield: 69%. IR($CHCl_3$): 1665 cm^{-1} (CO): ^1H NMR $\delta(CDCl_3)$: 5.82-5.65 (m, 2H, CH=CH), 4.40-4.0 (m, 1H, NCH_2 eq.), 3.08 (d, 1H, NCH), 2.50-1.70 (m, 9H), 1.14 and 1.10 (s and s, 6H, CH_3 2x). An exact mass determination gave 205.1466; $C_{13}H_{19}NO$ requires 205.1466(0.0).

11-Tosyl-6-aza-4-thiatricyclo[6.3.1.$0^{2,6}$]-dodecan-5-one (32g)

a. N-(Cyclohex-3-enylmethyl)-4-hydroxythia-zolidin-2-one (13c)
2.27 g (10.7 mmol) 7c was reduced with 5 g $NaBH_4$. Work-up afforded crystalline 13c; m.p. 83-85°; yield: 57%. IR($CHCl_3$): 3400 cm^{-1} (OH); 1660 cm^{-1} (CO); ^1H NMR $\delta(CDCl_3)$: 5.69 (br. m, 2H, CH=CH), 5.34 (m, 1H, changes to d of d with D_2O, CHOH), 4.25 (m, 1H, disappears with D_2O, OH), 3.80-3.05 (m, 4H, NCH_2 and SCH_2), 2.3-1.0 (m, 7H). (Found: C, 56.4%; H, 7.2%; N, 6.6%; S, 15.0%; $C_{10}H_{15}NO_2S$ (Mw 213.29) requires C, 56.3%; H, 7.1%; N, 6.6%; S, 15.0%).

b. Cyclization of 13c. Compound 13c (0.1445 g, 0.75 mmol) was refluxed for 24 hrs in 10 ml CH_2Cl_2 with 0.3856 g (2.4 mmol) p-toluene-sulphonic acide hydrate. Work-up afforded 0.2039 g yellow oil, from which 32g crystallized upon standing; m.p. 151-151.5°; yield: 40 mg, 16%. ^1H NMR $\delta(CDCl_3)$: 7.80 and 7.35 (m and m, 4H, Ph), 4.95-4.80 (m, 1H, CH-OTos), 4.05-3.75 (m, 3H, NCH 3x), 3.3-1.6 (m, 10H), 2.47 (s, 3H, $PhCH_3$). (Found: C, 55.6%; H, 5.8%; N, 3.9%; S, 17.6%. $C_{17}H_{21}NO_4S_2$ (Mw 367.49) requires C, 55.6%; H, 5.8%; N, 3.8%; S, 17.5%.

REFERENCES

[1]Part of the forthcoming Ph.D. thesis of J.A.M. Hamersma.
[2]W.N. Speckamp, Rec.Trav.Chim., 100, 345 (1981).
[3]For a preliminary communication see: J.A.M. Hamersma, H.E. Schoemaker and W.N. Speckamp, Tetrahedron Lett., 1347 (1979).
[4]H. Erlenmeyer and H. von Meyenburg, Helv.Chim.Acta, 20, 1388 (1937).
[5]O. Mitsunobu, M. Wada and T. Sano, J.Am.Chem. Soc., 94, 697 (1972).
[6]H. Aspelund, Acta Acad.Aboensis Math.Phys., 24, 1 (1964).
[7]J.C. Hubert, W. Steege, W.N. Speckamp and H.O. Huisman, Synth.Comm., 1, 103 (1973).
[8]E.g. H.E. Schoemaker, J. Dijkink and W.N. Speckamp, Tetrahedron, 34, 163 (1978).
[9]H.E. Schoemaker, Tj. Boer-Terpstra, J. Dijkink

and W.N. Speckamp, Tetrahedron, 36, 143 (1980).
[10]Compare J. Dijkink and W.N. Speckamp, Tetrahedron, 34, 173 (1978).
[11]M. Hesse, H. Meier and B. Zeeh, Spektroskopische Methoden in der Organischen Chemie, Georg Thieme Verlag, Stuttgart, p.188 (1979).
[12]P.M.M. Nossin and W.N. Speckamp, Tetrahedron Lett., 3289 (1981).
[13]J.E. Baldwin, J.C.S.Chem.Comm., 734 (1976).
[14]Figures given in parentheses after exact mass determinations give the absolute value of the difference between calculated and recorded masses (in ppm).