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# THIA-ACYLIMINIUM CYCLISATIONS

## SYNTHESIS OF FIVE-MEMBERED RINGS AND MACROCYCLES

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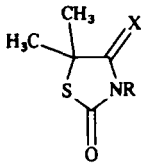
**Abstract**—Cyclisations of carbinollactams **1b–3b** afford macrocycles **4–6** in good yield by the intermediacy of N-acyliminium species. A similar process applied to lactams **21b–25b** affords the pyrrolizidine type compounds **26–35** through consecutive azonium-Cope rearrangement and N-acyliminium ring closure. Additional results are concerned with the use of aromatic rings as π-nucleophiles.

6-Membered bicyclic products obtained from N-acyliminium cyclisations of thiazolidine-derived precursors[1] can be converted in a straightforward manner to N-formyl piperidines.[2] The ease of the method coupled with its effectiveness in terms of yields and preparations of many hitherto difficult to obtain compounds invited to additional applications for which the formation of larger- and smaller-sized ring systems were studied.

*Macrocyclic cyclisations*

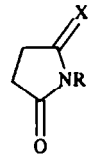
In earlier studies[1] it has been noted that for the cyclisation of olefinic and acetylenic substrates to 7- or 8-membered rings "forcing" conditions (i.e. longer reaction times and/or more elevated temperatures) are necessary, compared to reactions in which 6-membered rings are formed. This is caused by the well-known fact that formation of rings from open chains imposes a considerable loss in entropy, especially for larger rings.[3] Also, the products, when formed, possess a marked degree of angular strain compared to 6-membered rings. However, it is also known[4] that this strain is absent again when the rings attain sizes of thirteen and larger. It may therefore be anticipated that both the tridec-12-ynyl substituted imides **1** and **3** and the undec-10-enyl substituted **2** would give rise to cyclised products. As before starting materials **1a–3a** were prepared by condensation of the thiazolidinedione with an appropriate alcohol by the oxidation–reduction technique using triphenylphosphine and dimethyl azodicarboxylate.[5] Upon $NaBH_4/H^+$ reduction[6] of the imides **1a–3a** the hydroxy lactams **1b–3b** were obtained in good yields. Subsequent cyclisations were carried out in highly diluted formic acid solutions (*ca* 3 mmol/l) to prevent intermolecular reactions. Indeed under the reaction conditions employed (HCOOH, 43°, exclusion of light)[7] only cyclised products were found if the reaction was run long enough to ensure complete consumption of the starting material. Thus, after 451 hr at 43° hydroxy lactam **1b** afforded **4** in 75% yield and after 913 hr at 43° 84% of **5** was obtained from **2b**, as was obvious from signals in the $^1$H-NMR spectrum at 8.12 ppm of the formate and at 5.20–4.85 ppm of the CHOCHO proton.

A comparable result was obtained in the succinimide series, where cyclisation of **3b** (20 days, 43°, HCOOH) afforded **6** in 82% yield. The macrocyclic nature of this compound was also apparent from its melting behaviour, the ring serving as a host for a solvent molecule being incorporated. Upon prolonged drying of the crystalline material under reduced pressure the solvent molecules evaporated and the crystals liquified,

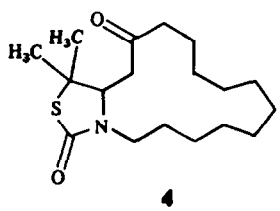


**1** R = —$(CH_2)_{11}C{\equiv}CH$
**2** R = —$(CH_2)_9CH{=}CH_2$

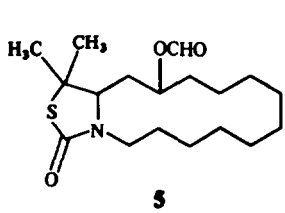
**a**: X = O
**b**: X = H,OH



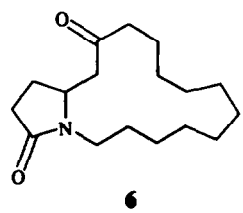
**3** R = —$(CH_2)_{11}C{\equiv}CH$



**4**

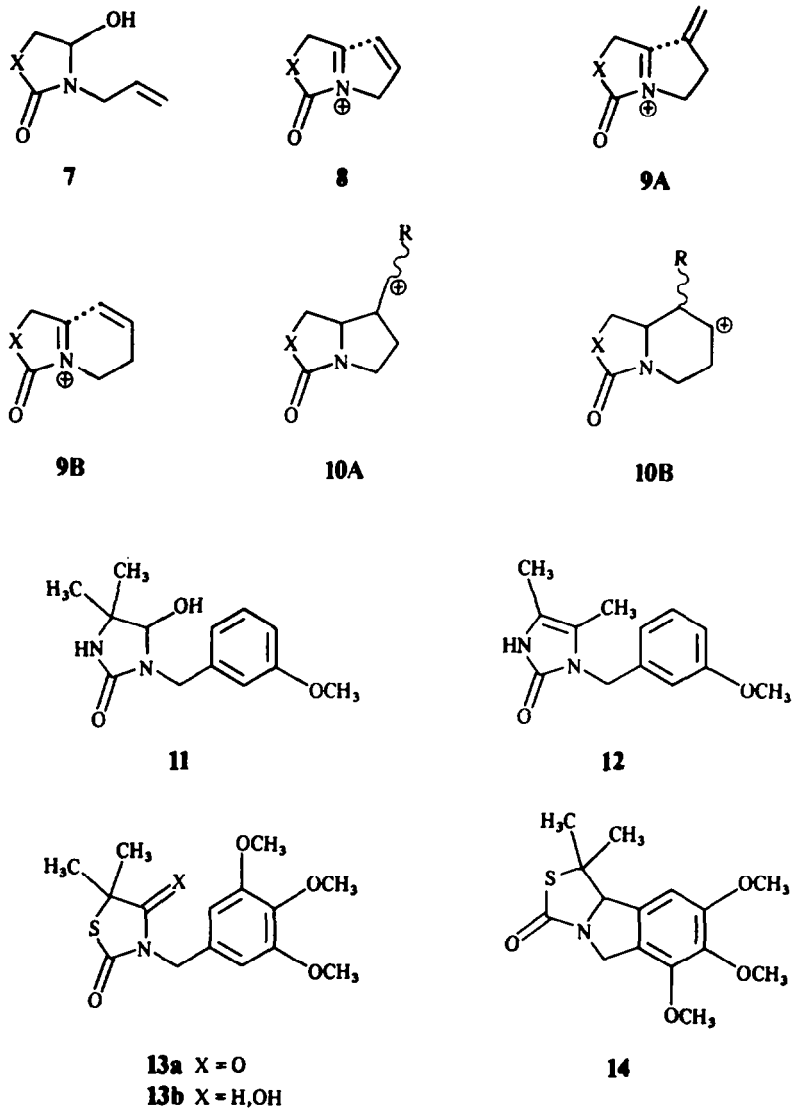


**5**



**6**

Scheme 1.




Scheme 2.

to solidify again upon continuation of the drying process. Cyclisation of **1b** and **3b** took place at the terminal acetylene carbon exclusively, resulting from the greater stability of the secondary vinyl cation relative to the primary vinyl cation which would be formed upon bond formation with the non-terminal acetylene carbon.[8]

The overall yields of the reaction sequence and the ease of the experimental procedures make this a potentially useful method for the synthesis of aza heterocycles, also in view of the number of methods available for obtaining long chain unsaturated alcohols.[9]

† This does not necessarily mean that carbenium ions are distinct intermediate species; an electron donating substituent polarising the double bond provokes a similar outcome. For clarity, only the "carbenium" effect is emphasised here, and cyclisation is depicted as a two-step process, even though in reality a considerable amount of concertedness may be present.

*Formation of 5-membered rings*[10]

Although formation of 6- and higher-membered rings is a very feasible process, formation of 5-membered rings can pose serious problems. N-allylic hydroxy lactams such as **7** are not cyclised. This is due to the fact that, to obtain a cyclised product via a 5-*endo*-Trig transition state **8**, it is necessary to force the approach of the ends of a chain of which four members have $sp^2$ hybridization, which is a highly unfavourable process.[11] Ring formation via a 5-*exo*-Trig cyclisation reaction would require a considerably less strained transition state **9A**. In the alternative 6-*endo*-Trig transition state **9B** the strain is expected to be comparable or less, so that in general 6-membered ring products are found.[2] Only if an additional stabilisation of the possible transition state **9A** would be present, formation of the 5-membered ring might be favoured.[12] Thus, if in **10** R is an electron donating group† it might be possible to promote formation of **10A** as has been demonstrated for cyclisations of olefins.[13]

For acetylenes[14] the situation is complicated by the

fact that only **10A** permits a linear vinyl cation, so that the energy difference between **10A** and **10B** will be less.[15] It is known[16] that even with activated π-nucleophiles like **11** cyclisation does not take place; instead, besides starting material only rearranged products like **12** are obtained. Surprisingly, reaction of **13b** (reflux in cyclohexane with 1.5 equiv of *p*-toluenesulfonic acid, 24 hr) afforded **14** in 84% yield. In this case the S atom presumably enlarges the thiazolidine ring, so that the angular strain in the 5/5 fused ring system which would be formed after cyclisation of the hydantoin **11** is diminished. The latter effect combined with the activation of the aromatic nucleus may suffice to effect smooth cyclisation of **13b**.

By employing a recently reported reaction type,[17] which provides for the desired array of stabilizing factors and which relies on an azonium-Cope rearrangement **15** → **16**[18] ring closure to 5/5 fused systems becomes routinely possible. Thus azonium-Cope rearrangement of the iminium ion **15** should give the iminium ion **16**, for which two modes of cyclisation are possible: 6-*endo*-Trig cyclisation would give the "normal" product **18** whereas 5-*exo*-Trig cyclisation would result in formation of the 5-membered ring product **19**. As indicated above, the factors stabilising the two carbenium ions **17** are thought to be determining in this respect. If R is an alkyl group, and stabilisation in **17A** and **17B** would be comparable, it is known[19] that **18** is formed almost exclusively. Probably the difference in annular strain is determining in this case. If, however, the R group provides a significant amount of stabilisation of the carbenium ion **17B** formation of the 5-membered ring might be competitive, and practical yields of 5/5 fused product **19** can be obtained.

Stabilising groups expected to be of value in this respect were the aryl, methoxy and dimethyl substituents. Consequently, the model compounds **21**–**25** were selected for this study. Exothermal cyclisation of **21b** (HCOOH, room temp, 5 min) led to quantitative formation of the pyrrolizidine structure **26**. The molecular structure was determined from first-order analysis of the $^1$H-NMR spectrum. The NCH bridgehead proton appeared as a multiplet ($W_{\frac{1}{2}}$ = 27.5 Hz) at 3.88 ppm, whereas the two $NCH_2$ protons were observed as a doublet of doublets (J = 8.6 and 11.0 Hz) at 3.40 ppm and a broadened triplet (J = 9.4 Hz) at 3.08 ppm. The $C_7$-H proton exhibits a multiplet around 2.72 ppm, $W_{\frac{1}{2}}$ = 34.5 Hz. Irradiation of this proton greatly influenced the signal of the bridgehead proton; thus, the *cis*-configuration was established by NOE-difference spectroscopy.[20] Likewise, HCOOH-cyclisation (room temp, 1.75 hr) of **22b** afforded the bicyclic product **27** in 66% yield as a single isomer. The structure was also derived from the $^1$H-NMR data. The NCH bridgehead proton displays a double doublet at 4.00 ppm, J = 10.0 and 7.0 Hz; the $NCH_2$ protons give a multiplet around 3.40 ppm (ddd, J = 15.5, 12.5 and 9.5 Hz), while the C-7 tertiary proton exhibits a multiplet at 2.83 ppm. The two ring Me groups give singlets at 1.53 and 1.50 ppm, while the remaining two Me groups are equivalent and give one singlet at 1.55 ppm. With NOE difference spectroscopy it was found that irradiation of the C-7 proton influenced the signal of the C-5 proton and *vice versa*; this result establishes the *cis*-relationship of these two protons. Cyclisation of the methoxy-substituted **23b** (HCOOH, room temp, 18 hr) furnished, after hydrolysis, a 5 : 1 mixture of epimers **28** in 55% yield. Most probably isomerisation occurs by acid-catalysed enolisation of the aldehyde. In addition,

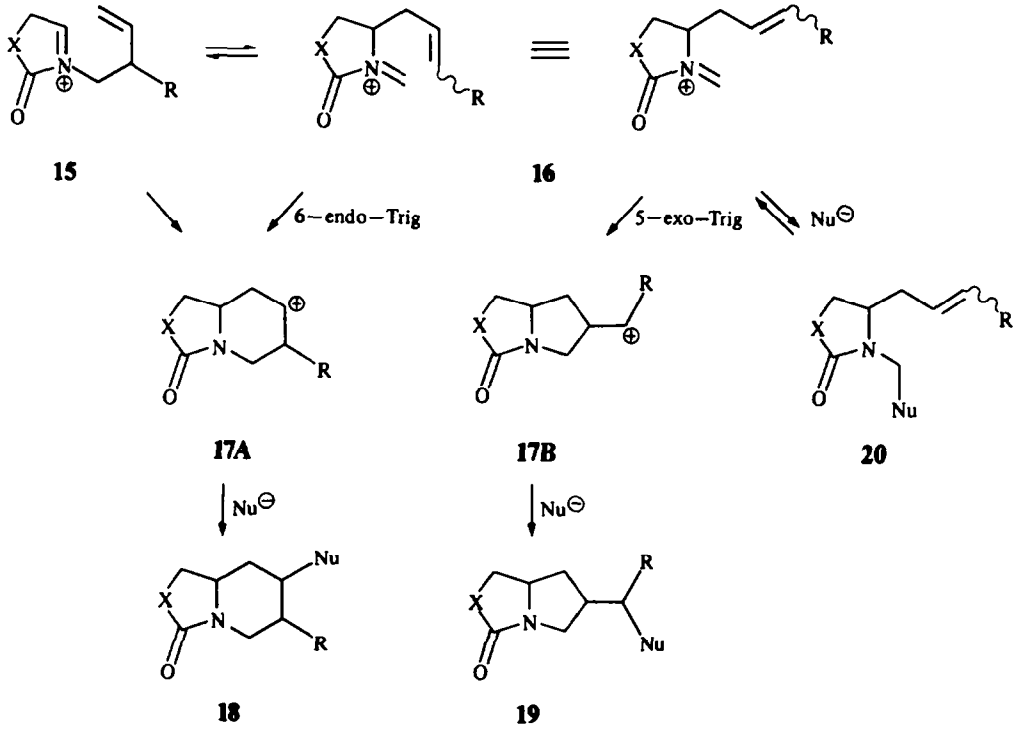
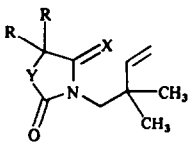
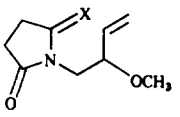


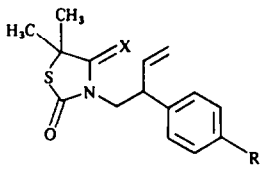

Fig. 1.



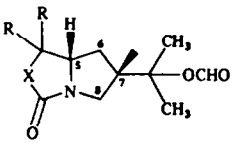
**21** Y = $CH_2$, R = H
**22** Y = S, R = $CH_3$



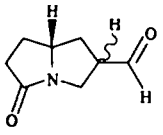
**23**
**a** X = O
**b** X = H, OH



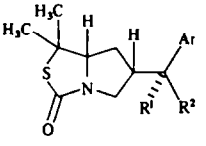
**24** R = H
**25** R = $OCH_3$



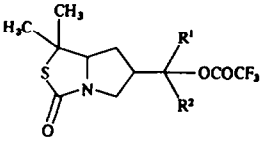
**26** X = $CH_2$, R = H
**27** X = S, R = $CH_3$



**28**



**29** $R^1$ = OCHO, $R^2$ = H, Ar = $C_6H_5$
**30** $R^1$ = H, $R^2$ = OCHO, Ar = $C_6H_5$
**32** $R^1$ = H, $R^2$ = OCHO, Ar = (p) − $C_6H_4$ − $OCH_3$
**33** $R^1$ = H, $R^2$ = Cl, Ar = (p) − $C_6H_4$ − $OCH_3$



**34** $R^1$ = $C_6H_5$, $R^2$ = H
**35** $R^1$ = $R^2$ = $CH_3$

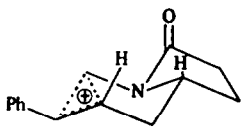
Scheme 3.

small amounts (±3%) of 5/6 fused cyclic formate were produced, as was concluded from the characteristic doublet of doublets (J = 2.9 and 14.5 Hz) at 4.38 ppm for the equatorial $NCH_2$ proton, which product originated from a 6-*endo*-Trig cyclisation of either **15** or **16** to **17A**.

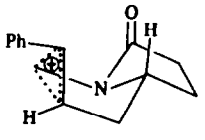
Cyclisation of the phenyl substituted hydroxy lactam **24b** afforded a product in a yield of 79% as an approximately 3 : 2 mixture of formate epimers **29** and **30**, which could be separated by fractional crystallisation. Comparison of the two $^1$H-NMR spectra led to a structure assignment, which was based on the observation of varying $\delta$-values for $C_6$ and $C_8$ protons. These differences presumably arise as a consequence of shielding influences of the formate carbonyl group in the two isomers. The differences in $C_6$-H and $C_8$-H signal positions do not arise from epimerism at C-7, since both isomers were proven to be *cis* with NOE difference spectroscopy.[21] The exclusive formation of single $C_5$-H, $C_7$-H *cis* isomers in all ring closures, leading to pyrrolizidine systems can be rationalised on the basis of a comparison of the two transition states. As indicated in Fig. 2 the *cis* isomer is due to arise from a chairlike conformation **31A** while a *trans* isomer can be expected from a boatlike form **31B** of the non-classical carbenium intermediate. Given the distinct energy differences between the two forms **31A** and **31B** the preferred reaction path clearly proceeds via **31A**.

Likewise, the methoxyphenyl hydroxy lactam **25b** was cyclised; only **32** could be crystallised from the crude reaction mixture, which is supposed to have a relative configuration as shown, from the analogy of its $^1$H-NMR spectrum with that of compound **30**. A product analogous to **29** was present according to spectral evidence, but could not be isolated. Surprisingly, upon treatment of **25b** with methanolic HCl (room temp, 17 hr) compound **33** could be isolated in low yield in which the chloride ion apparently acted as the nucleophile.[22]

In all three cyclisations of thiazolidine derivatives no trace was found of compounds resulting from trapping of the azonium-Cope intermediate, i.e. **20**. The latter product was obtained in similar cyclisations in the pyrrolidine series by treatment with trifluoroacetic acid.[21] However, $CF_3COOH$ cyclisation of **24b** (room temp, 30 min) gave **34** as the sole product in 79% yield, likewise **22b** gave only **35** in 70% yield ($CF_3COOH$, 0°, 30 min). These results reflect the fact that the ring system formed upon cyclisation of the pyrrolidine would be 5/5 fused, whereas the incorporation of a sulfur atom as in **22**, **24** and **25** makes the resulting ring system nearly 5/6 fused. The overall effect is probably an enhancement of the cyclisation step **16** → **17B** which may be relatively fast for thiazolidine systems. Further consequences of this behaviour, and synthetic applications in the field of pyrrolizidine alkaloids are under active investigation.[23]



**31A**



**31B**

Fig. 2.

## CONCLUSION

The N-acyliminium technique not only is very suitable for formation of medium-sized carbocyclic rings, it also proves very useful for the formation of macrocycles, heterocycles and even 5-membered rings. Furthermore it is indicated that the reactivity of the 5-membered ring thiazolidinium moiety corresponds closely to the behaviour of N-acyliminium ions derived from glutarimide rather than those obtained from succinimide.

## EXPERIMENTAL

IR spectra were recorded on Unicam SP 200 and Perkin–Elmer 257 instruments. $^1$H-NMR spectra were obtained with Varian A-60, HA-100, XL-100 and Bruker WM 250 instruments. Spectra were recorded in $CDCl_3$, unless otherwise indicated, and signals are given in ppm relative to TMS as an internal reference. All mass spectral data were recorded on an AEI-MS-902 or Varian Mat 711 mass spectrometer. M.ps were determined on a Leitz m.p. microscope, and are uncorrected. Micro-analyses were carried out by TNO, Utrecht, The Netherlands. In naming the compounds, IUPAC nomenclature is used.

*Preparation of starting materials*

5,5-Dimethylthiazolidine-2,4-dione was prepared from condensation of thiourea and α-bromoisobutyric acid. 12-Tridec-yn-1-ol was prepared by coupling of lithium acetylide with ω-iodoundecanoic acid[24] followed by $LiAlH_4$ reduction. 2,2-Dimethylbut-3-en-1-ol was prepared by double deconjugative alkylation[25] of ethyl crotonate followed by $LiAlH_4$ reduction. 2-Methoxybut-3-en-1-ol was prepared by acid catalysed methanolysis of butadiene monoxide; both 2-arylbut-3-en-1-ols were obtained from reaction of arylmagnesium bromide and butadiene monoxide,[26] after allylic carbonation of cinnamyl magnesium chloride[27] had failed. Other starting materials were commercially available.

*Preparation of imides*

Imides were alkylated[5] by slowly adding 1 equiv of dimethyl azodicarboxylate in freshly distilled THF to a cooled and stirred soln of 1 equiv of the imide, 1 equiv of the appropriate alcohol and 1 equiv of triphenylphosphine. Stirring was continued overnight at room temp. 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 three times with $CH_2Cl_2$, the combined organic layers were then washed twice with 2 N HCl (not for **23a**), sat $NaHCO_3$ aq, and sat NaCl aq, dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was taken up in ethyl acetate, whereupon the triphenylphosphine oxide formed partly crystallised. The coupled imides were then obtained by vacuum distillation (bulb to bulb for smaller quantities) or column chromatography (for specific details, see Table 1).

*General procedure for the synthesis of hydroxy lactams*

The $NaBH_4/H^+$ reductions were carried out with a stirred soln of imide in ethanol at temps of 0–5° with a 2-fold excess by wt of $NaBH_4$. At intervals of 15 min 3–4 drops of 2 N HCl in EtOH were added. After 4 to 5 hr of reaction the soln 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 cyclisation reaction*

The hydroxy lactam was dissolved in formic acid (unless otherwise indicated) and stirred at the specified temp. 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, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product.

16,16 - *Dimethyl* - 1 - *aza* - 17 - *thiabicyclo*[13.3.0]*octadecane* - 13,18 - *dione* **4**. (a) 4 - Hydroxy - 5,5 - dimethyl - 3 - tridec - 12 - ynyl - thiazolidin - 2 - one **1b**. 0.8 g (2.46 mmol) **1a** was reduced with 1.6 g (42.2 mmol) $NaBH_4$ to afford 0.6 g **1b** as a pale yellow oil (75%). IR ($CHCl_3$): 3340 cm$^{-1}$ (OH); 3300 cm$^{-1}$ (C≡CH); 1660 cm$^{-1}$ (CO); $^1$H-NMR: 4.67 (s, 1H, CHOH), 3.8–2.9 (m, 3H, $NCH_2$ and OH), 2.20 (m, 2H), 1.94 (m, 1H, C≡CH), 1.52 and 1.47 (s and s, 6H, 2 × $CH_3$), 1.65–1.1 (m, 18H).

(b) Cyclisation of **1b**. 0.0628 g (0.19 mmol) was dissolved in 100 ml formic acid and stirred in the dark at 43° for 451 hr. Work-up afforded 0.048 g **4** as a semisolid mass; yield 76%. IR ($CHCl_3$): 1710 cm$^{-1}$ (CO); 1665 cm$^{-1}$ (lactam CO); $^1$H-NMR: 4.04 (m, 1H, NCH), 3.62 (m, 1H, NCH), 3.34 (m, 1H, NCH), 3.0–2.45 (m, 4H), 1.55 (s, 6H, 2 × $CH_3$), 1.7–1.15 (m, 18H).[28]

11 - *Formyloxy* 14,14 - *dimethyl* - 1 - *aza* - 15 - *thiabicyclo*[11.3.0]*hexadecan* - 16 - *one* **5**. (a) 4 - Hydroxy - 5,5 - dimethyl - 3 - undec - 10 - enyl - thiazolidin - 2 - one (**2b**). 3.5 g (11.8 mmol) **2a** was reduced with 6.0 g (0.16 mmol) $NaBH_4$ to afford 3.4 g **2b** (97%) as a clear oil. IR ($CHCl_3$): 3360 cm$^{-1}$ (OH); 1655 cm$^{-1}$ (CO); $^1$H-NMR: 6.05–5.60 (m, 1H, CH=), 5.10–4.85 (m, 2H, $CH_2$=), 4.68 (br s, 1H, CHOH), 4.08 (br m, 1H, OH), 3.8–3.0 (m, 2H, $NCH_2$), 2.25–1.90 (m, 2H), 1.75–1.1 (m, 14H), 1.55 and 1.50 (s and s, 6H, 2 × $CH_3$).

(b) Cyclisation of **2b**. 0.40 g (1.34 mmol) **2b** was dissolved in 100 ml HCOOH and stirred at 43° for 913 hr. Work-up afforded 0.368 g of a TLC-homogeneous oil (84%). IR ($CHCl_3$): 1715 cm$^{-1}$ (ester CO); 1660 cm$^{-1}$ (lactam CO); $^1$H-NMR: 8.11 (s, 1H, OCHO), 5.60–5.10 (2m, combined area 1H, 2 epimers CHOCHO), 3.62 (m, 1H, $NCH_2$), 3.33 (m, 1H, NCH), 2.98 (m, 1H, $NCH_2$), 2.1–1.15 (m, 18H), 1.57 and 1.54 (s and s, 6H, 2 × $CH_3$). An exact mass determination gave 327.1866; $C_{17}H_{29}NO_3S$ requires 327.18679.

1 - *Azabicyclo*[13.3.0]*octadecane* - 13,18 - *dione* **6**. (a) 1 - Tridec - 12 - ynyl - 5 - hydroxypyrrolid - 2 - one (**3b**). Reduction of 0.51 g (1.8 mmol) **3a** with 0.49 g (12.9 mmol) $NaBH_4$ afforded, after column chromatography, 0.42 g (83%) of **3b** as an oil which crystallised upon standing; m.p. 65.5–67° (dipe).

Table 1. Preparation of N-substituted imides

| Imide | Yield (%) | Procedure for purification[a] | b.p. | m.p.[b] | IR ($cm^{-1}$)[c] | $^1$H-NMR data | |
|---|---|---|---|---|---|---|---|
| | | | | | | $NCH_2$ | $CH_3$ |
| **1a** | 81 | cg[d] | — | — | 1670/1740 | 3.61 | 1.67 |
| **2a** | 82 | vd | 134°/0.01 mm | — | 1675/1745 | 3.61 | 1.70 |
| **3a** | 94 | cg[e] | — | <20° | 1700/1775 | 3.47 | — |
| **13a** | 87 | cg[d] | — | 79–80° | 1680/1745 | 4.70 | 1.69 |
| **21a** | 49 | cg[e] | — | 72–74° | 1700/1775 | 3.41 | — |
| **22a** | 71 | vd | 120°/0.01 mm | — | 1680/1750 | 3.55 | 1.68 |
| **23a** | 12 | cg[e] | — | — | 1700/1770 | 4.14–3.52 | — |
| **24a** | 72 | vd | 132°/0.1 mm | — | 1670/1745 | 3.90 | 1.50/1.61 |
| **25a** | 57 | vd | 160°/0.2 mm | — | 1680/1745 | 3.84 | 1.47/1.58 |

[a] Procedure for purification: vd = vacuum distillation, cg = column chromatography.
[b] From dipe (diisopropylether).
[c] Imide carbonyl absorptions.
[d] On silica, eluent $CH_2Cl_2$–acetone 4:1.
[e] On silica, eluent ethyl acetate.

IR ($CHCl_3$): 3350 $cm^{-1}$ (OH); 3320 $cm^{-1}$ (C≡CH); 1675 $cm^{-1}$ (CO); $^1$H-NMR: 5.30–5.06 (m, 1H, NCHO), 3.60–2.90 (m, 2H, $NCH_2$).

(b) Cyclisation of **3b**. 0.093 g (0.33mmol) **3b** was dissolved in 100 ml HCOOH and stirred at 43° for 20 days. Work-up afforded 0.093 g (quantitative yield) of crude **6**. After column chromatography (silica, ethyl acetate) 0.077 g of **6** could be isolated (82% yield), the remainder being starting material. Compound **6** crystallised upon treatment with dipe or MeOH pentane at −16°, m.p. 46–55° (white crystals). IR ($CHCl_3$): 1705 and 1665 $cm^{-1}$ (CO); $^1$H-NMR: 4.11 (tt, J = 7.4 and 4.8 Hz, 1H, NCH), 2.95 (dd, J = 18.0 and 4.7 Hz, 1H, $C_{14}$-H), 3.50–2.94 (m, 2H, $NCH_2$), 2.49 (dd, J = 18.0 and 7.1, 1H, $H_{14}$), 2.59–2.24 (m, 5H), 1.85–1.18 (m, 19H). An exact mass determination gave 279.2199; $C_{17}H_{29}NO_2$ requires 279.21981. The compound was further characterised as its 2,4-dinitrophenylhydrazone; m.p. 207–208.5° (from EtOH). An exact mass determination gave 459.2481; $C_{23}H_{33}N_5O_5$ requires 459.24812.

1,3,5,9b - *Tetrahydro* - 7,8,9 - *trimethoxy* - 1,1 - *dimethylisoindolo*[2,1-c] - *thiazol* - 3 - *one* **14**. (a) 4 - Hydroxy - 3 - (3,4,5 - trimethoxyphenylmethyl) - 5,5 - dimethylthiazolidin - 2 - one (**13b**). 3.8 g (11.7 mmol) **13a** was reduced with 6.0 g (0.156 mmol) $NaBH_4$. Work-up afforded 3.76 g of an oil, which crystallised after addition of dipe; m.p. 124–126°; yield 98%. IR ($CHCl_3$): 3350 $cm^{-1}$ (OH); 1670 $cm^{-1}$ (CO); $^1$H-NMR: 6.55 (s, 2H, Ph), 5.2–4.75 (d of d, 1H, CHOH), 4.3–3.7 (m, 2H, $NCH_2$), 3.8 (s, 9H, 3 × $OCH_3$), 3.2 (br m, 1H, OH), 1.45 (s, 6H, 2 × $CH_3$). (Found: C, 55.5; H, 6.6; N, 4.2; S, 9.5%. $C_{15}H_{21}NO_5S$ (327.40) requires: C, 55.03; H, 6.47; N, 4.28; S, 9.79%.)

(b) Cyclisation of **13b**. 0.109 g (0.333 mmol) **13b** was dissolved in 25 ml cyclohexane with 95 mg (0.5 mmol) *p*-toluenesulfonic acid hydrate, and refluxed for 24 hr on a soxhlet charged with molecular sieves. Work-up as usual afforded 0.087 g (84%) of a brownish solid; m.p. 308–311°. IR ($CHCl_3$): 1640 $cm^{-1}$ (CO); $^1$H-NMR: 6.68 (s, 1H, Ph), 5.07 and 3.69 (AB quartet, 2H, $NCH_2Ph$), 4.31 (s, 1H, NCH), 3.95, 3.91 and 3.88 (3s, 3H each, 3 × $OCH_3$), 1.26 and 1.06 (s and s, 6H, 2 × $CH_3$).

7 - 1(1 - *Formyloxy* - 1 - *methylethyl*) - *azabicyclo*[3.3.0]*octan* - 2 - *one* **26**. (a) 1 - (2,2 - Dimethyl - 3 - but - enyl) - 5 - hydroxy - 2 - pyrrolid - one (**21b**). Reduction of (0.653 g, 3.6 mmol) **21a** with 0.96 g (25.3 mmol) $NaBH_4$ afforded, after column chromatography, 0.427 g (65%) **21b** as a yellow oil, which crystallised upon cooling; m.p. 40–50° (dec). IR ($CHCl_3$): 3350 $cm^{-1}$ (OH); 1680 $cm^{-1}$ (CO); $^1$H-NMR: 5.95 and 5.91 (each dd, 1H, CH=$CH_2$); 5.13–4.88 (m, 3H, CH=$CH_2$ and NHCO); and 0.102 g (15%) of the corresponding ethoxy lactam. IR ($CHCl_3$): 1685 $cm^{-1}$ (CO); $^1$H-NMR: 5.92 (m, 1H, CH=$CH_2$), 5.16–4.89 (m, 3H, $CH_2$=CH and NCHO), 3.43 (q, 2H, $OCH_2$), 1.23 (t, 3H, $OCH_2CH_3$), 1.06 (s, 6H, $C(CH_3)_2$).

(b) Cyclisation of **21b**. 0.420 g (2.3 mmol) **21b** was dissolved in 5 ml of HCOOH, whereupon the temp of the mixture rose up to *ca* 40°, and stirred for 5 min. Work-up furnished 0.462 g (quantitative yield) **26** as a pure crystalline compound; m.p. 58.5–60.5° (dipe). IR ($CHCl_3$): 1720 $cm^{-1}$ (ester CO); 1675 $cm^{-1}$ (lactam CO): $^1$H-NMR: 7.91 (s, 1H, OCHO), 3.88 (m, 1H, $H_5$), 3.40 (dd, J = 11.0 and 8.5 Hz, 1H, $C_8$-αH), 3.08 (br t, J = 9.1 Hz, 1H, $C_8$-βH), 2.72 (m, 1H, $H_7$), 2.63 (dt, 1H, $H_3$), 2.33 (m, 1H, $C_3$-H), 2.21 (m, 1H, $C_4$-βH), 1.97 (m, 1H, $C_6$-β), 1.73 (m, 1H, $C_4$-αH), 1.45 (s, 6H, 2 × $CH_3$), 1.29 (q, $C_6$-αH). An exact mass determination gave 211.1200; $C_{11}H_{17}NO_3$ requires 211.12082.

7 - (1 - *Formyloxy* - 1 - *methylethyl*) - 4,4 - *dimethyl* - 1 - *aza* - 3 - *thiabicyclo*[3.3.0]*octan* - 2 - *one* **27** *and* 4,4 - *dimethyl* - 7 - (1 - *methyl* - 1 - *trifluoroacetoxyethyl*) - 1 - *aza* - 3 - *thiabicyclo*[3.3.0]*octan* - 2 - *one* **35**. (a) 4 - Hydroxy - 5,5 - dimethyl - 3 - (2,2 - dimethylbut - 3 - enyl)thiazolidin - 2 - one (**22b**). 1.4 g (6.17 mmol) **22a** was reduced with 2.8 g (74 mmol) $NaBH_4$ to afford 1.32 g **22b** as a yellowish oil; yield 93%. IR ($CHCl_3$): 3340 $cm^{-1}$ (OH); 1670 $cm^{-1}$ (CO); $^1$H-NMR: 6.2–5.65 (m, 1H, CH=), 5.25–4.65 (m, 3H, $CH_2$= and CHOH), 4.3–2.9 (m, 3H, $NCH_2$ and OH), 1.55 and 1.47 (s and s, 6H, 2 × $CH_3$), 1.05 (s, 6H, 2 × $CH_3$).

(b) Cyclisation to **27**. 0.6713 g (2.9 mmol) **22b** was dissolved in 15 ml formic acid and stirred at room temp for 1.75 hr. Work-up afforded 0.499 g **27** as a white solid; m.p. 100–102°; yield 66%. IR ($CHCl_3$): 1720 $cm^{-1}$ (ester CO); 1665 $cm^{-1}$ (lactam CO); $^1$H-NMR: 8.00 (s, 1H, OCHO), 4.00 (d of d, 1H, NCH bridgehead), 3.42 (ddd, 2H, $NCH_2$), 3.0–2.7 (m, 1H, $C_7$-H), 1.85–1.50 (m, 2H), 1.55 (s, 6H, 2 × $CH_3$), 1.54 and 1.51 (s and s, 6H, 2 × $CH_3$). An exact mass determination gave 257.1089, while $C_{12}H_{19}NO_3S$ requires 257.10854.

(b) Cyclisation to **35**. 0.101 g (0.44 mmol) **22b** was dissolved in 10 ml $CH_2Cl_2$, cooled in ice, 0.313 g (6 equivs) trifluoroacetic acid was added, and the soln stirred for 0.5 hr. The soln was then poured into sat $NaHCO_3$ aq and extracted as usual to afford 0.997 g **35** as a clear oil. IR ($CHCl_3$): 1780 $cm^{-1}$ (ester CO); 1670 $cm^{-1}$ (lactam CO); $^1$H-NMR: 4.01 (d of d, 1H, NCH bridgehead), 3.50–3.30 (m, 2H, $NCH_2$), 3.0–2.8 (m, 1H, $C_7$-H), 1.80–1.50 (m, 2H), 1.58 (narrow d, 6H, 2 × $CH_3$), 1.49 and 1.45 (s and s, 6H, 2 × $CH_3$).

7 - *Formyl* - 1 - *aza* - *bicyclo*[3.3.0]*octan* - 2 - *one* **28**. (a) 1 - (2 - *Methoxybut* - 3 - *enyl*) - 5 - *hydroxypyrrolid* - 2 - *one* (**23b**). Reduction of **23a**. 0.768 g (4.2 mmol) **23a** was reduced with 1.12 g (29.5 mmol) of $NaBH_4$, affording, after column chromatography, 0.474 g (61%) of **23b** as an oil. IR ($CHCl_3$): 3380 $cm^{-1}$ (OH); 1680 $cm^{-1}$ (CO); $^1$H-NMR: 5.91–5.08 (m, 4H, $CH_2$=CH and NCHO), 3.37 and 3.34 (each s, 3H, $OCH_3$).

(b) Cyclisation of **23b**. 0.181 g (0.98 mmol) **23b** was dissolved in 5 ml HCOOH and stirred at room temp for 18 hr. Work-up furnished 83 mg (58%) of a 5:1 mixture of $C_7$-epimers **28**. The major component consisted of the $C_7$-βH isomer. IR ($CHCl_3$): 1710 $cm^{-1}$ (HC=O); 1730 and 1680 $cm^{-1}$ (CO); $^1$H-NMR: major $C_7$-epimer: 9.53 (d, 1H, CHO), 3.95 (m, 1H, NCH), 3.87 (dd, $NCH_2$), 2.62 (dt, 1H), 2.37 (m, 1H, $C_3$-H), 1.74 (m, $C_4$-αH); minor epimer: 9.62 (s, CHO).

The epimers **28** were further characterised as a mixture of 2,4-dinitrophenylhydrazones; m.p. 206.5–209.5° (from AcOH–EtOH). An exact mass determination gave 333.1074; $C_{14}H_{15}N_5O_5$ requires 333.10727.

7 - (*Formyloxyphenylmethyl*) - 4,4 - *dimethyl* - 1 - *aza* - 3 - *thiabicyclo*[3.3.0]*octan* - 2 - *one* **29** + **30** *and* 4,4 - *dimethyl* - 7 - (*phenyltrifluoroacetoxymethyl*) - 1 - *aza* - 3 - *thiabicyclo*[3.3.0]*octan* - 2 - *one* **34**. (a) 4 - Hydroxy - 5,5 - dimethyl - 3 - (2 - phenyl - 3 - but - enyl)thiazolidin - 2 - one (**24b**). Reduction of 3.0 g (10.8 mmol) **24a** with 6 g (0.16 mmol) $NaBH_4$ afforded 2.69 g (89%) **24b** as a viscous oil, which crystallised with dipe; m.p. 90–92°. IR ($CHCl_3$): 3350 $cm^{-1}$ (OH); 1660 $cm^{-1}$ (CO); $^1$H-NMR: 7.28 (m, 5H, Ph), 6.20–5.80 (m, 1H, CH=), 5.25–5.0 (m, 2H, $CH_2$=), 4.7–2.9 (m, 5H), 1.40–1.37 and 1.23–1.17 (s and s, 6H, 2 × $CH_3$) mixture of diastereomers. An exact mass determination gave 277.1136; $C_{15}H_{19}NO_2S$ requires 277.11363.

(b) Cyclisation to **29** + **30**. 0.630 g (2.27 mmol) **24b** was dissolved in 20 ml HCOOH and stirred at room temp overnight. Work-up afforded 0.55 g (79%) of a white solid mass of formate epimers (approx. 3:2). Recrystallisation from dipe–EtOH 1:2 afforded a pure compound; m.p. 193–195°, assigned structure **30**. IR ($CHCl_3$): 1725 $cm^{-1}$ (ester CO); 1660 $cm^{-1}$ (lactam CO); $^1$H-NMR (250 MHz): 8.09 (s, 1H, OCHO), 7.20–7.40 (m, 5H, Ph), 5.79 (d, 1H, CHOCHO), 4.02 (d of d, 1H, NCH bridgehead), 3.17–3.01 (m, 3H, $C_7$-H and $C_8$-H), 2.0–1.87 (m, 1H), 1.75–1.55 (m, 1H), 1.49 and 1.47 (s and s, 6H, 2 × $CH_3$). The mother liquor was chromatographed (silica, eluent $CH_2Cl_2$–acetone 4:1) and the fraction with $R_f$ 0.66 collected and recrystallised from dipe to afford the major isomer; m.p. 70–75°, which had configuration **29**; $^1$H-NMR (250 MHz): 8.06 (s, 1H, OCHO), 7.40–7.20 (m, 5H, Ph), 5.79 (d, 1H, CHOCHO), 3.97 (d of d, 1H, NCH bridgehead), 3.54–3.31 (m, 2H, $NCH_2$), 3.09 (m, 1H, $C_7$-H), 1.78–1.40 (m, 2H), 1.43 (s, 6H, 2 × $CH_3$). An exact mass determination, which for $C_{16}H_{19}NO_3S$ requires 305.10854, gave 305.1075.

(c) Cyclisation to **34**. Cyclisation at room temp of 54.8 mg (0.2 mmol) **24b** analogous to **35**, afforded 58.9 mg **34** as a clear oil (80%). $^1$H-NMR: 7.50–7.20 (m, 5H, Ph), 5.81 (d, 1H, CHOCO), 4.08 (m, 1H, NCH), 3.5–3.0 (m, 3H), 2.15–1.40 (m, 2H), 1.51 and 1.46 (s and s, 6H, 2 × $CH_3$). An exact mass

determination gave 373.0938; $C_{17}H_{18}F_3NO_3S$ requires 373.09592.

7-(*Formyloxy*-p-*methoxyphenylmethyl*)-4,4-*dimethyl*-1-*aza*-3-*thiabicyclo*[3.3.0]*octan*-2-*one* **32** *and* 7-(*chloro*-p-*methoxyphenylmethyl*)-4,4-*dimethyl*-1-*aza*-*thiabicyclo*[3.3.0]*octan*-2-*one* **33**. (a) 4-Hydroxy-3-[2-(*p*-methoxyphenyl)but-3-enyl]-5,5-dimethylthiazolidin-2-one (**25b**). 1.59 g (5.2 mmol) **25a** was reduced with 3.2 g (84.3 mmol) $NaBH_4$. Work-up afforded 1.50 g **25b** as an oil, which crystallised upon addition of dipe; m.p. 103–105°; yield 94%. IR ($CHCl_3$): 3360 $cm^{-1}$ (OH); 1660 $cm^{-1}$ (CO); $^1$H-NMR: 7.25–6.75 (2m, 4H, Ph), 6.15–5.80 (m, 1H, CH=), 5.20–4.95 (m, 2H, $CH_2$=), 3.79 (s, 3H, $OCH_3$), 4.70–2.95 (m, 5H), 1.40–1.38 and 1.25–1.22 (2s, 6H, 2 × $CH_3$) mixture of diastereomers. An exact mass determination gave 307.1251; $C_{16}H_{21}NO_3S$ requires 307.12509.

(b) Cyclisation to **32**. 0.5 g (1.63 mmol) **25b** was dissolved in 10 ml formic acid and stirred at room temp for 19 hr. Work-up afforded 0.42 g of a highly viscous oil, which upon dipe-crystallisation afforded 65 mg (12%) **32** as a white crystalline powder; m.p. 186–188°. IR ($CHCl_3$): 1720 $cm^{-1}$ (ester CO); 1665 $cm^{-1}$ (lactam CO); $^1$H-NMR: 8.10 (s, 1H, OCHO), 7.35–6.80 (2m, 4H, Ph), 5.85–5.70 (m, 1H, CHOCHO), 4.06 (d of d, NCH), 3.81 (s, 3H, $OCH_3$), 3.20–3.05 (m, 3H), 2.10–1.45 (m, 2H), 1.51 and 1.50 (s and s, 6H, 2 × $CH_3$). An exact mass determination gave 335.1192; $C_{17}H_{21}NO_4S$ requires 335.1191.

(c) Cyclisation to **33**. 0.55 g (1.79 mmol) **25b** was dissolved in 15 ml sat methanolic HCl, and stirred at room temp overnight. Work-up afforded 0.46 g of a brown oil, from which 0.0669 g white crystalline **33** was obtained upon addition of dipe and cooling; m.p. 134–137°; yield 11%. IR ($CHCl_3$): 1665 $cm^{-1}$ (CO); $^1$H-NMR: 7.35–6.80 (2m, 4H, Ph), 4.75 (m, 1H, CHCl), 4.06 (d of d, 1H, NCH), 3.81 (s, 3H, $OCH_3$), 3.20–3.0 (m, 3H), 2.35–2.1 (m, 1H), 1.80–1.40 (m, 1H), 1.52 (s, 6H, 2 × $CH_3$). An exact mass determination gave 325.09033; $C_{16}H_{20}ClNO_2S$ requires 325.09031.

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