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OLEFIN CYCLISATIONS OF HINDERED α-ACYLIMINIUM IONS

B. P. WIJNBERG, W. N. SPECKAMP* and A. R. C. OOSTVEEN
Laboratory for Organic Chemistry, University of Amsterdam, P.O. Box 20241, 1000 HE Amsterdam, The Netherlands

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Abstract—Stereocontrolled $NaBH_4/H^{\oplus}$-reduction of 3,4 - *cis* - disubstituted N - alkenyl imides **1–5** leads to secondary hydroxylactams. Tertiary hydroxylactams are formed via addition of MeMgCl to imides **2** and **4**. HCOOH-Cyclisation of the hydroxylactams affords polycyclic piperidines through stereoselective α-acyliminium ring closure. Concomitant synchronous and stepwise cyclisation pathways are operative in the anti-periplanar addition of tertiary α-acyliminium ions to Me substituted olefins **8c** and **11c**.

Stereoselective heterocyclisation via α-acyliminium ions has been proven of potential value in the synthesis of alkaloids and related compounds.[1] The generally simple experimental procedure coupled with a high versatility allows the efficient preparation of a multitude of structures.[2] In continuation of our studies on the intrinsic patterns of stereochemical homogeneity it became of interest to investigate the 3,4-*cis*-disubstituted succinimides. The latter model compounds were selected to examine the effect of introducing a steric differentiation in the symmetric α-acyliminium precursor. Moreover after the determination of the cyclisation modes of varied N-alkenyl imides it was of interest to study the reactions of more complex imide substrates in order to verify and extend the earlier observed substituent effects.[3] In addition some data on the stereoselectivity of the $NaBH_4/H^{\oplus}$ reduction[4] of the succinimide derivatives also could be collected. Within the latter context it should also be mentioned that the exact determination of the stereochemical course of α-acyliminium cyclisations is only possible by starting from ω-oxylactams of known configuration.

Starting imides

As imide components tetrahydrophtalimid (**1**) and the bridged analogues *endo*-**2** and *exo*-**3** were chosen. The latter derivative was of additional interest because of the presence of an ether function which was earlier found to prevent the acid-catalyzed OH→OEt exchange in the OH-lactam[5] and therefore could potentially inhibit the HCOOH cyclisation. As a somewhat strained imide the cyclobutyl derivative **4** was selected while the effect of added steric bulk could be evaluated in the 3,4-tetrasubstituted compound **5**.[6]

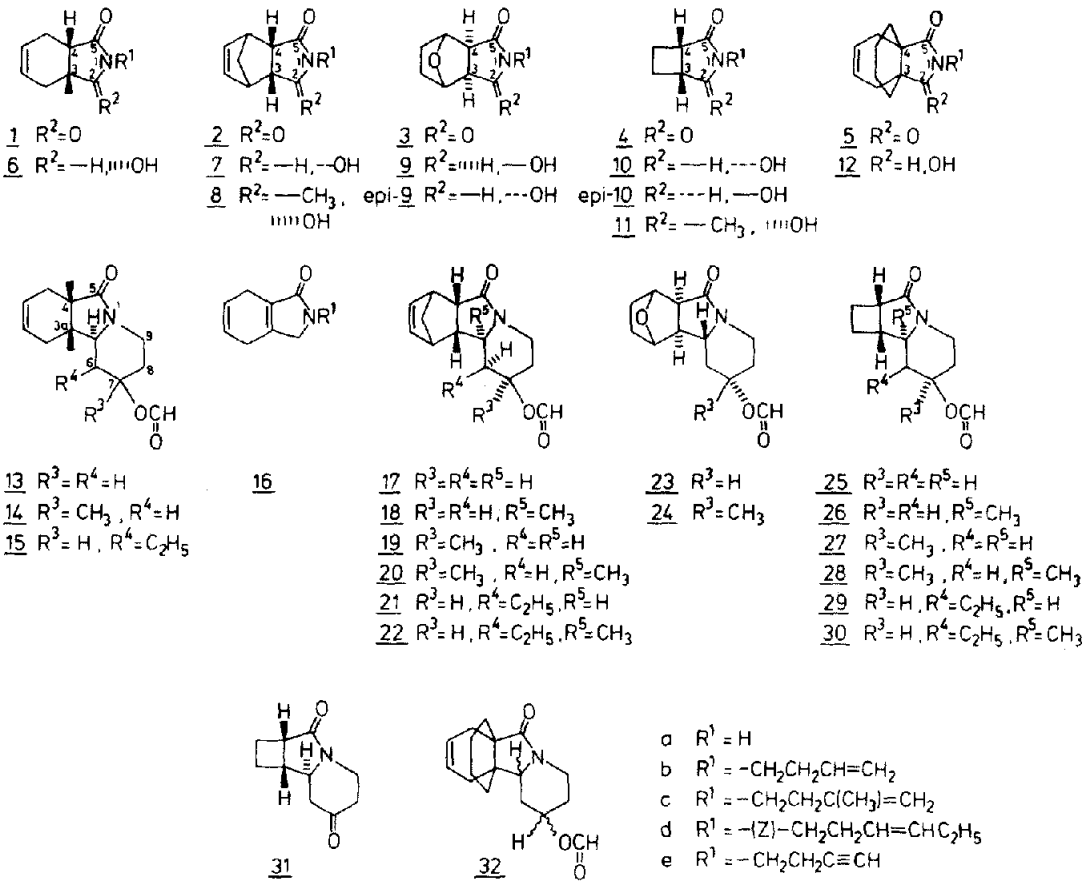
As representative unsatured N-substituents 3 - butene - 1 - ol, (*Z*) - 3 - hexene - 1 - ol, 3 - methyl - 3 - butene - 1 - ol and 3 - butyne - 1 - ol responded to the requirement of slightly different electronic character. The imides **1a–4a** were prepared by heating the corresponding anhydrides or dicarboxylic acids with ammonia at 180°. Under the latter circumstances the *endo* isomer of **2a** was obtained starting from the *endo* anhydride[7] while the *exo* diacid afforded the *exo* product **3a**.[8]

The N-substituted imides (Table 1, Experimental) were synthesized according to the oxidation-reduction procedure[9] and were obtained in yields ranging from 30–90%. Also in the case of the bulky tetrasubstituted derivative **5a** a nearly quantitative conversion into **5b** was obtained in the N-alkylation step. However, additional substitution in the olefin *viz* **5a**→**5d** caused a sharp drop in the yield.

$NaBH_4$ *Reduction and* MeMgCl *addition*

In view of the unsymmetric imide structure with respect to the plane of the ring the reduction of the imide CO might in principle give rise to the formation of two stereoisomeric OH-lactams. As has been observed earlier[10] the hydride approach will occur preferentially from the less hindered convex face of the molecule thereby leading to kinetic product formation. It was indeed found that in reductions of **2b**, **2c** and **2d** the major product, as evidenced by the δ CH–OH and J-values, was the *endo* alcohol arising from *exo* attack of the hydride. Similarly in case of the *exo* imides **3b** and **3c** the reduction was found to take place from the least hindered *endo* side, thereby affording the alcohols **9b** and **9c** as single products. Preferential hydride approach was also noticed in the reduction of **1b–1e** albeit that the size of the N-substituent seemed of additional small influence as an extra steric factor. The latter observation was confirmed by the results of the reductions of **4b**, **4c** and **4e**. Whereas **4b** and **4c** underwent preferential *exo* reduction (>90%) the smaller N-butynyl derivative **4e** afforded a 16:5 mixture of *endo* **10e** and its *exo* OH-epimer. This effect has been observed earlier[11] and may reflect a secondary conformational effect of the alkenyl vs alkynyl N-substituent. The absence of a similar N-substituent effect in the reductions of **1d** as compared with **1b** or **1c** may be accounted for in assuming a preferred "folded" conformation of the cyclohexene ring as established in the corresponding anhydride.[12] The stereochemistry of the reduction then would be mainly determined by the imposed steric effects of the carbocyclic ring.

Additional information with regard to the stereochemistry of the OH-lactams obtained as primary reduction products was derived from epimerization studies. NaOEt/EtOH treatment of OH-lactams **9c** and **10b** induced epimerization at the C_2-OH leading to the thermodynamically more stable *epi* **9c** and *epi* **10b**. Structure assignment of the latter isomers is based upon



the upfield shift of the C_2-H (0.2–0.4 ppm) and the small $J_{2,3}$-values (0-1 Hz).[13]

Reduction of the severely hindered tetrasubstituted imides **5b** and **5d** proceeded quantitatively albeit in a slow reaction. Notably the complete reduction of **5d** required 12 hr as compared to the usual 2–4 hr. The ω-OH-lactams **12b** and **12d** obtained as crystalline mixtures of epimers were not separated. Furthermore in view of the fact that most of the ω-OH-lactams in this study were obtained as solid materials which could be purified by crystallization additional conversion to ω-OEt-lactams and connecting column chromatography proved unnecessary.

Similarly the addition of MeMgCl[14] to imides **2b**, **2c** and **2d** afforded single stereoisomers of the tertiary OH-lactams **8b**, **8c** and **8d**. Although an unequivocal proof of the configuration has not been sought the fact that only one isomer is formed coupled with the information of the stereochemical course of the hydride reduction in all probability points to an *exo* attack of the organometallic. The outcome of similar additions to **4b**, **4c** and **4d** whereby mainly (> 70%) *exo* isomers of the OH-lactams **11b**, **11c** and **11d** are obtained lends extra support to the assumption of least hindered approach.

Cyclisations

All cyclisations were performed in HCOOH for reasons of comparison and good experimental outcome. Ring closure of butenyl derivatives **6b**, **7b**, **9b** and **10b** led in all cases to quantitative conversion affording 90:10 mixtures of C_7 formate epimers in which the equatorial isomers proved to be the principal products. A small difference in epimer ratio (80:20) was noted for the oxa-derivative **9b**. According to ^{1}H-NMR analysis the approach of the olefin moiety occurred exclusively from the less hindered side. As judged from the splitting of the tertiary C_2-H in compounds **13**, **17** and **23** J-values of 12.0, 3.0 and 3.5 Hz are indicated for $J_{6ax,2}$ $J_{6eq,2}$ and $J_{2,3}$ respectively. The first two values are typical for the axial position of C_2-H with respect to the 6-membered ring while the third value corresponds to a *trans* relation of C_2-H and C_3-H. In the cyclobutyl compound **25** $J_{2,3}$ becomes almost zero. The remaining C_9-H_{ax}, C_9-H_{eq} and C_7-H protons show similar δ-values and splitting patterns as observed before and a compilation of spectral data and solvent shifts are given in the Experimental. The cyclisation of **12b** proceeded more rapidly (1 hr) thereby affording a 9:1 mixture of formates. Although the major isomer presumably consists of a 1:1 mixture of C_2-stereoisomers **32**, the important conclusion from this experiment lies in the fact that N-butenyl cyclisation is possible even in a hindered tetrasubstituted imide. The relative increase in the reaction rate is most probably due to the effective blocking of the interfering α-acyliminium-enamide equilibrium.[15]

Subsequently the cyclisation of *epi* **10b** was investigated. In case the C_2-configuration of the starting ω-OH-lactam would influence the stereochemistry of the ring closure the epimer ratio in the resulting mixture of formate isomers should be different compared to the cyclisation of **10b**. After 18 hr at r.t. the product mixture obtained proved identical in all respects with that of **10b** thereby implicitly rendering the intermediacy of a planar α-acyliminium ion most likely.

Table 1. Preparation of imides

imid	yield[a]	method[d]	m.p.[e]
1a	74%	II	133-136°
1b	43%	II	57-59° (EtOH)
1c	81%	I[c], II	---
1d	90%	I[b]	---
1e	78%	I[b], II	57° (dipe*)
2a	63%	II	188-190° (EtOH)
2b	quant	I[b], II	58-59.5° (dipe)
2c	quant	I[b], II	79-80° (dipe)
2d	70%	I[b], II	32-35° (dipe)
3a	70%	II	186-189° (EtOH)
3b	89%	I[b], II	66-67° (dipe)
3c	quant	I[b], II	65-66° (dipe)
4a	74%	II	127-130° (EtOH)
4b	39%	I[c], II	40-41° (dipe)
4c	86%	I[c]	---
4d	35%	I[b]	---
4e	42%	I[b], II	30-32° (dipe/EtOAc)
5b	91%	I[b], II	76-78° (dipe)
5d	30%	I[b]	---

* Dipe = diisopropylether

a not optimized

b columnchromatographed on silicagel (act I) with EtOAc as an eluent

c columnchromatographed on silicagel (act I) with $CHCl_3$/EtOH 9/1 as an eluent

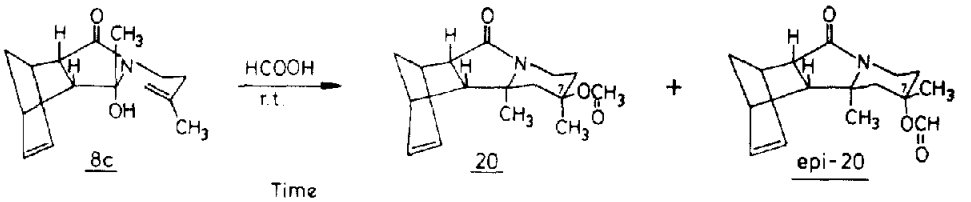
d methods of preparation I and II indicated in the experimental

e solvent of recrystallization.

The tertiary OH-lactams **8b** and **11b** upon HCOOH treatment at r.t. afforded single C_7-formate isomers **18** and **26** thus exhibiting a similar reaction pattern as found for the secondary OH-lactams. Minor differences in isomer ratio and reaction time were not further investigated.

Cyclisations of Me-olefins **6c**, **7c**, **9c** and **10c** are expected to give rise to the formation of mixtures of C_7-stereoisomers in a fast reaction. Due to the apparent nonsynchronous character of the bond formation process the reaction of the incipient carbocation is only to a minor extent proceeding under stereoelectronic control. The stereocontrol in the solvent capture by the tertiary carbenium centre will therefore grossly reflect the thermodynamic stabilities of the isomers formed. As found earlier in simple imide precursors the isomer possessing an axial C_7-Me substituent is formed to a major extent. The 60:40 isomer ratio for **14** and its C_7-epimer has been determined from ^{1}H-NMR spectral analysis of OOCH and CH_3 signals in the crude cyclisation mixtures of **6c**. A similar isomer ratio of **27** and its C_7-epimer was found in the ring closure of **10c**. In case of **7c** the major isomer **19** crystallized while in the ring closure of **10c** each of the two stereo-isomers **27** and its C_7-epimer were obtained pure by fractional crystallization. Repetition of the latter experiment in $CHCl_2COOH$ showed a 80:20 ratio of dichloro-acetates in favour of the axial Me-isomer. As could be expected on the basis of the foregoing results the ring closure of the C_2-epi isomer of **9c** provided a 60:40 mixture identical in all respects with the product of cyclisation of **9c**. This result again renders the intermediacy of an equivalent cationic initiating centre most likely and thus supports the proposed sequence of reactions. However, the following data on the ring closures of tertiary acyliminium ions also confirm the existence of a synchronous pathway for the antiperiplanar addition to the olefin linkage. Of high significance is the outcome of the ring closure of the tertiary OH-lactam **8c**. Whereas after 2 min at r.t. a mixture was formed consisting of **20** and its C_7-epimer in a ratio of 60:40 longer reaction times provoked dramatic changes. After 30 min the epimer ratio had become 50:50 (^{1}H-NMR) while after 18 hr complete conversion of **20** into its C_7-epimer (epi-**20**) was observed. Since in the epimer **20** a 1,3 diaxial relationship exists between C_2 and C_7 Me groups a possible driving force for the epimerization at C_7 might be the relief of steric hindrance. At the same time, however, from this isomerization process pertinent information with regard to the mechanism of the cyclisation may be derived. Whereas a stepwise pathway for ring closure of Me substituted alkenes cannot be excluded the present data are interpreted as in favor of a—at least partial—primary synchronous pathway leading to the kinetically formed isomer.

Epimerisation at the carbon bearing the formate residue then takes place after the cyclisation has been completed and most likely occurs via the discrete tertiary carbenium ion pathway. Comparable findings have been collected earlier[16] in cyclohexenyl derivatives. That the 1,3 diaxial interaction of C_2 and C_7 Me groups is respon-



Time	20	epi-20
2 mn	60	40
30 mn	50	50
18 hr	0	100

Scheme 1. Synchronous as non-synchronous cyclisation

sible for the instability of **20** is also demonstrated by the result of the ring closure of **11c**. Following a similar reaction behaviour the C_7-epimer of **28** is obtained after 18 hr as the sole product.

In all of the cyclisations described the approach of the nucleophile occurred from the least hindered side leading to the C_2–C_3 *anti* products. Most interesting from the point of view of steric interactions are the ring closures of (*Z*)-hexenyl lactams **6d, 7d and 10d**. The synchronous nature of the C–C bond formation implies the conservation of the (*Z*-) olefin stereochemistry in the final product. However, in the transition state leading to the cyclic material unfavorable steric interactions between axial Et substituent and lactam ring tend to hinder the cyclisation process. Therefore in substituted imides longer reaction times are necessary which tend to increase the possibility of side reactions such as enamide formation and dimerization. The latter behaviour is already manifest in the ring closure of **6d**. In addition to 75% of the expected product **15** 25% of the pyrrolinon **16d** was formed which could not be induced to cyclise by prolongation of the reaction time. On the contrary HCOOH treatment of **7d** produced a quantitative yield of **21**. Apparently the potential formation of a highly strained norbornadiene derivative is not a likely competitive process as compared to the ring closure. Yet the latter cyclisation is also remarkable in view of the rigidity and unfavourable steric interactions in the final product and illustrates once more the versatility of the α-acyliminium process. A similar result was found in the cyclisation of **10d** which afforded **29** as the sole product. On the contrary, attempts to prepare the corresponding Me substituted analogues **22** and **30** by ring closure of the tertiary hydroxylactams **8d** and **11d** all failed. This negative outcome parallels earlier findings on the behaviour of tertiary α-acyliminium ions and supposedly results from the difficulty in the attainment of the necessary alkene conformation. The latter unfavourable effect is most probably due to interactions between the (*Z*)-Et and Me groups.

In the last example the steric crowding in the tetrasubstituted lactam **12d** effectively prevents cyclisation and the starting material is recovered quantitatively. Compared with **12b** the presence of a (*Z*-) Et substituent in the olefin is the added feature which renders the bond formation impossible.

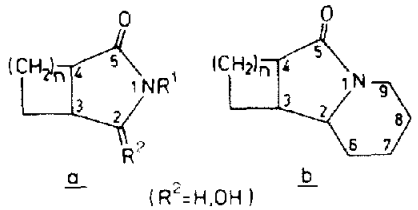
Lastly the effect of a weaker nucleophile, i.e. the butynyl substituent was investigated. In the cyclohexenyl derivative **6e** no trace of cyclic ketone was observed the exclusive product being the cyclohexadiene **16e**. On the contrary even in the relatively strained cyclobutyl derivative **10e** smooth cyclisation (60 hr/r.t.) occurred yielding the unstable ketone **31**. From these results it follows that in the absence of potentially competing processes even a weak nucleophile undergoes C–C bond formation with a hindered acyliminium ion.

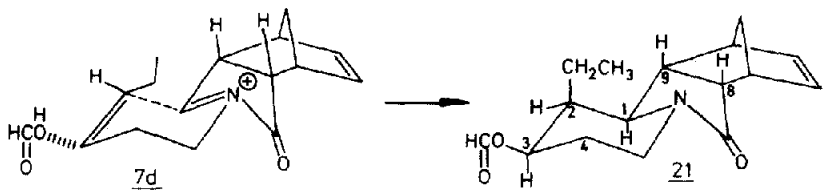
CONCLUSION

The foregoing data confirm the exceptional reactivity of the α-acyliminium ion towards carbon π-nucleophiles as a cationic initiating centre. The observed stereoselectivity in conjunction with a high versatility under mild experimental conditions mark this procedure as the method of choice in the synthesis of complex piperidine derivatives. Insofar as the mechanism of the cyclisation is concerned it can be stated that all of the results discussed before are in agreement with a nearly concerted way of bond formation.

EXPERIMENTAL

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, Bruker WM250 and Varian SC300 instruments. All cyclised products showed correct mass spectral data and were recorded on an AEI-902 or Varian Mat 711 mass spectrometer. M.ps are uncorrected. Micro-analyses were carried out by Messr. H. Pieters of the micro-analytical department of our





Scheme 2. Cyclisation of a rigid (z)-ethyl olefin

laboratory. The IUPAC-nomenclature is followed in naming the compounds. However, in the description of the ^{1}H NMR spectra an uniform numbering system is used according to the formula's **a** and **b**.

Preparation of the N–H *imides.* These were prepared by heating the corresponding anhydrides or dicarboxylic acids with ammonia at 180° during 1–3 h. After cooling the imides were obtained pure by recrystallization from EtOH (Table 1).

Preparation of the alkenols. The alkenols 3 - butene - 1 - ol, (*Z*) - 3 - hexene - 1 - ol, 3 - methyl - 3 - butene - 1 - ol and the alkynol 3 - butyn - 1 - ol were commercially available.

Preparation of the imides. These were generally prepared according to the procedure of Mitsunobu *et al.*[9]: 1 eq of alkenol, 1 eq of triphenylphosphine and 1.2–1.4 eq of the N–H imide were dissolved in freshly distilled THF. To the cooled and stirred soln 1 eq dimethylazodicarboxylate in THF was added slowly. Stirring was continued overnight at r.t. The solvent was then evaporated under reduced pressure and the residual oil was taken up in $CHCl_3$ and 5% KOH aq. The aqueous layer was extracted 3 times with $CHCl_3$. The combined organic layers were then washed with 2N HCl (3 times), $NaHCO_3$ 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 $\phi_3P\rightarrow O$ crystallized. The imides were obtained by column chromatography (I) or crystallization (II).

General procedure for the synthesis of hydroxy lactams

The $NaBH_4/H^{\oplus}$ reductions were carried out with a stirred soln of imide in EtOH at temps of 0–5° (unless otherwise indicated) with an excess of $NaBH_4$. At regular intervals (mostly 15 min) 2–3 drops of 2N HCl in EtOH were added. The reaction time was 4–5 hr. Two work-up methods were followed.

Method A (basic). After reduction the soln was poured into ice-water. Extraction with $CHCl_3$ and work-up of the extract afforded the crude product.

Method B (acidic). The excess of $NaBH_4$ was destroyed in 15–30 min at the temp of reaction by adding acid till pH = 3. The mixture was stirred for an additional 45–60 min at 0° and poured into H_2O. Extraction with $CHCl_3$ and work-up of the extract afforded the crude product.

General procedure for the synthesis of Me-*hydroxylactams*

Grignard addition reaction. To a soln of the imide in THF, a soln of 3,3 M MeMgCl in THF (2, 2 eq) was added (N_2-atmosphere) at r.t. The soln was stirred for an additional 4–5 hr. After destroying the excess Grignard reagent by adding sat NH_4Cl aq, the mixture was poured into H_2O and the product extracted with $CHCl_3$. The products were purified by recrystallization or column chromatography.

General procedure for the cyclisation reaction

The hydroxy (ethoxy) lactam was dissolved in HCOOH and the soln stirred for 18 hr (unless otherwise indicated) at r.t. The solvent was evaporated under reduced pressure at r.t. The residual oil was taken up in $CHCl_3$ and washed with dil $NaHCO_3$ aq and sat NaCl aq and dried over $MgSO_4$.

7 - *Aza* - 4 - *formyloxy* - *tricyclo*[7.4.0.0^{2,7}]*tridec* - 11 - *ene* - 8 - *one* (**13**)

(a) 8 *Aza* - 8(3 - *butenyl*) - 9 - *hydroxy* - *bicyclo*(4.3.0)*non* - 3 - *ene* - 7 - *one* (**6b**). Compound **1b** (1.22 g, 6.1 mmole) was reduced in EtOH (80 ml) with 0.73 g $NaBH_4$ at 0° during 5 hr. Work-up afforded crude **6b** which could be recrystallized from dipe; m.p. 84–89°. IR ($CHCl_3$): 3400 cm^{-1} (OH); 1685 cm^{-1} (lactam CO); ^{1}H NMR $\delta(C_6D_6)$: 5.5–6.0 (m, 3H, HC = CH, HC = CH_2), 4.8–5.15 (m, 4H, –OH; disappears with D_2O added, –N–CHOH, C=CH_2), 3.1–3.7 (m, 2H, N–CH_2), 1.7–2.5 (m, 8H, C=C–CH_2, CH–CO and CH–CHOH 3x). (Found: C, 69.44; H, 8.31; N, 6.79. Calc. for $C_{12}H_{17}O_2N$ (MW = 207.13): C, 69.54; H, 8.27; N, 6.76%).

(b) *Cyclisation of* **6b**. Compound **6b** (0.2 g, 0.96 mmole) was dissolved in 4 ml HCOOH and stirred overnight at r.t. Work-up afforded **13**. Recrystallization from dipe/ether afforded crystalline **13**; m.p. 80–83°. IR($CHCl_3$): 1680 cm^{-1} (lactam CO); 1740 cm^{-1} (ester CO). ^{1}H NMR: $\delta(CDCl_3)$: 7.98 (s, 1H, OOCH), 5.5–5.9 (m, 2H, CH=HC), 4.7–5.1 (nonet, 1H, H_7ax), 4.0–4.3 (octet, 1H, H_9eq, 2.95–3.2 (m, J_1 = 12 Hz, J_2 = 3.5 Hz, J_3 = 5 Hz, 1H, H_2ax), 2.45–2.9 (septet, 1H, H_9ax), 1.0–2–9 (m, 10H). (Found: C, 66.42; H, 7.23; N, 6.02. Calc. for $C_{13}H_{17}O_3N$ (MW = 235.12): C, 66.36, H, 7.18; N, 5.95%).

7 - *Aza* - 4 - *formyloxy* - 4 - *methyl* - *tricyclo*[7.4.0.0^{2,7}]*tridec* - 11 - *ene* - 8 - *one* (**14**)

(a) 8 - *Aza* - 8(3 - *methyl* - 3 - *butenyl*) - 9 - *hydroxy* - *bicyclo*[4.3.0]*non* - 3 - *ene* - 7 - *one* (**6c**). Compound **1c** (2.24 g, 10 mmole) was reduced in EtOH (200 ml) with 2 g of $NaBH_4$ at 0° during 6 hr. Work-up and recrystallization from dipe/EtOAc afforded crystalline **6c**; m.p. 103–105°. IR($CHCl_3$): 3400 cm^{-1} (OH); 1685 cm^{-1} (lactam CO). ^{1}H NMR: $\delta(CDCl_3)$: 5.8–6.0 (m, 2H, CH=HC), 5.12 (m, 1H, N-CHOH becomes a d (J = 9 Hz) with D_2O added), 4.65–4.85 (m, 2H, H_2C = C), 3.2–3.8 (m, 2H, N–CH_2), 2.85 (d, 1H, NCH OH disappears with D_2O added), 2.5–2.75 (m, 2H, CH–CO and CH–CHOH), 2.0–2.5 (m, 6H, –CH_2–C = C 3x), 1.75 (s, 3H, CH_2 = C(CH_3)–). (Found: C, 70.42; H, 6.81; O, 6.24. Calc. for $C_{13}H_{19}O_2N$ (MW = 221.26): C, 70.55; H, 6.65; O, 6.33%).

(b) *Cyclisation of* **6c**. Compound **6c** (0.103 g, 0.46 mmole) was dissolved in 4 ml HCOOH and stirred for 1½ hr at r.t. Work-up afforded 0.122 g (0.46 mmole, quant yield) of a 60:40 isomer ratio of **14** and its C_7-epimer. The two isomers could not be separated by column chromatography. IR ($CHCl_3$): 1720 cm^{-1} (ester CO); 1680 cm^{-1} (lactam-CO). ^{1}H NMR: δ ($CDCl_3$): 7.94 (40%) and 8.04 (60%), (2s, 1H, OOCH), 5.6–6.0 (m, 2H, CH–HC), 3.05–4.25 (m, 1H, H_9eq), 1.65 and 1.57 (s, 3H, –CH_3), 1.0–3.5 ((m, 13H).

7 - *Aza* - 4 - *formyloxy* - 5 - *ethyl* - *tricyclo*[7.4.0.0^{2,7}]*tridec* - 11 - *ene* - 8 - *one* (**15**)

(a) 8 - *Aza* - 8[(*Z*) - 3 - *hexenyl*] - 9 - *hydroxy* - *bicyclo*[4.3.0]*non* - 3 - *ene* - 7 - *one* (**6d**). Compound **1d** (1 g, 4.2 mmole) was reduced in EtOH (100 ml) with 1 g of $NaBH_4$ at 0° during 5 hr. Work-up and recrystallization from dipe afforded crystalline **6d**; m.p. 64–66°. IR ($CHCl_3$): 3400 cm^{-1} (OH); 1675 cm^{-1} (lactam CO). ^{1}H NMR: $\delta(CDCl_3)$: 5.7–6.0 (m, 2H, CH=HC), 5.25–5.6 (m, 2H, HC=CH), 5.0–5.25 (m, 1H, CHOH sharpens with D_2O added), 3.0–3.6 (m, 3H, –NCH_2, NCHOH disappears with D_2O added), 1.8–2.7 (m, 10H, C = C–CH_2 4x, –CO–CH–CH–CHOH), 0.93 (t, 3H, CH_2–CH_3). (Found: C, 71.55; H, 9.04; N, 6.02. Calc. for $C_{14}H_{21}O_2N$ (MW = 235.15): C, 71.45; H, 9.00; N, 5.95%).

(b) *Cyclisation of* **6d**. Compound **6d** (0.05 g, 0.21 mmole) was dissolved in 2 ml HCOOH and stirred for 48 hr at r.t. Work-up afforded 0.046 g (0.21 mmole, quant) of a 75:25 mixture of **15** and **16d** resp. as an oil. The two compounds could not be separated by column chromatography. IR($CHCl_3$): 1720 cm^{-1} (ester CO); 1680 cm^{-1} (lactam CO).

(b) ^{1}*H NMR of the mixture.* $\delta(CDCl_3)$: 8.07 (s, 1H, OOCH), 5.7–6.0 (m, 2H), CH=CH), 5.2–5.6 (m, 2H, –CH=CH–C_2H_5), 4.9–5.15 (m, 1H, H_7ax), 4.0–4.25 (m, 1H, H_9eq), 3.82 (s, 2H, N–CH_2–CH=CH), 3.5 (t, 2H, N–CH_2–CH_2), 3.25 (q, 1H, H_2), 2.9 (s, 4H, –C=C–CH_2–C=C–2x), 2.4–3.8 (m, 1H, H_9ax), 0.8–1.3 (m, 5H, CH_2–CH_2 2x).

8 - *Aza* - 5 - *formyloxy* - *tetracyclo*[9.2.1.0^{2,10}, 0^{3,8}]*tetradec* - 12 - *ene* - 9 - *one* (**17**)

a) 4 - *Aza* - 4(3 - *butenyl*) - 5 - *hydroxy*[5.2.1^{1,7}, 0^{2,6}]*non* - 8 - *ene* - 3 - *one* (**7b**). Compound **2b** (1 g, 4.6 mmole) was reduced in EtOH (100 ml) with 1 g of $NaBH_4$ at 0° during 5 hr. Work-up afforded 1.02 g (4.6 mmole, quant) of **7b** as an oil which crystallized upon treatment with dipe/EtOAc; m.p. 110–112°. IR($CHCl_3$): 3300 cm^{-1} (OH); 1660 cm^{-1} (lactam CO); ^{1}H NMR: $\delta(CDCl_3)$: 5.95–6.3 (m, 2H, CH=HC), 5.5–5.95 (m, 1H, CH_2= CH–), 4.9–5.3 (m, 3H, C–CH_2, NCHOH becomes a d when D_2O added), 4.3 (d, J = 7.5 Hz, 1H, –N–CH–OH; disappears with D_2O added), 28.5–3.5 (m, 6H CO–CH–CH–CHOH, –N–CH_2–, –CH 2x), 2.1–2.4 (q, 2H, CH_2–C=C), 1.48 (q, 2H). (Found: C, 71.19; H, 7.91; N, 6.50. Calc. for $C_{13}H_{17}O_2N$ (MW = 219.13): C, 71.20; H, 7.82; N, 6.39%.)

(b) *Cyclisation of* **7b**. Compound **7b** (0.05 g, 0.22 mmole) was dissolved in 3 ml HCOOH and stirred overnight at r.t. Work-up afforded 0.67 g of a 80:20 mixture of C-7 formate epimers, the

isomer with the equatorial formate could be isolated by recrystallization from dipe; m.p. 145–148°. IR ($CHCl_3$): 1720 cm^{-1} (ester CO); 1660 cm^{-1} (lactam CO). ^1H NMR: $\delta(C_6D_6)$: 7.54 (s, 1H, OOCH), 5.74–6.11 (m, 2H, CH=HC), 4.4–4.8 (m, 1H, H_7ax), 3.9–4.2 (octet, 1H, H_9eq), 2.65–2.85 (q, 1H, H_4), 2.50 (m, 1H), 3.1 (m, 1H, H_4), 2.1–2.38 (m, J_1 = 12 Hz, J_2 = 3 Hz, 1H, H_2ax), 2.02 (sextet, H_9ax, 0.5–1.85 (m, 7H). (Found: C, 68.26; H, 7.10; N, 5.86. Calc. for $C_{14}H_{17}O_3N$ (MW = 247.28): C, 67.99; H, 6.93; N, 5.66%).

8 - *Aza* - 3 - *methyl* - 5 - *formyloxy* - *tetracyclo*[9.2.1.$0^{2,10}$, $0^{3,8}$]*tetradec* - 12 - *ene* - 9 - *one* (**18**)

(a) 4 - *Aza* - 4(3 - *butenyl*) - 5 - *methyl* - 5 - *hydroxy* - *bicyclo*[5.2.1^{17}]*non* - 8 - *ene* - 3 - *one* (**8b**). To a soln of **2b** (0.3 g, 1.38 mmole) in THF (20 ml) a soln of 3.3 M MeMgCl in THF (0.92 ml, 2.2 eq) was added via a syringe (N_2 atmosphere) at r.t. The soln was stirred for 4.5 hr. Work-up afforded 0.347 g (quant yield) of crude **8b** which could be recrystallized from dipe; m.p. 93–95°. IR ($CHCl_3$): 3400 cm^{-1} (OH); 1670 cm^{-1} (lactam CO). ^1H NMR $\delta(CDCl_3)$: 5.95–6.3 (m, 2H, –HC = CH–) 5.5–5.95 (m, 1H, C=CH–), 4.9–5.15 (m, 2H, $C=CH_2$), 2.7–3.5 (m, 6H, CO–CH–CH–CH–(CCH_3)OH, –N–CH_2, –CH 2x), 2.53 (s, 1H, –CH–$C(CH_3)$OH, disappears with D_2O added), 2.1–2.4 (q, 2H, –CH_2–C=C), 1.3–1.65 (m, 2H), 1.46 (s, 3H, N–$C(CH_3)$OH. An exact mass determination gave *m/e*: 233.1384 (calc. for $C_{14}H_{19}NO_2$ *m/e*: 233.1416).

(b) *Cyclisation of* **8b**. Compound **8b** (0.173 g, 0.74 mmole) was dissolved in 12 ml HCOOH and stirred for 65 hr at r.t. Work-up afforded 0.165 g (0.63 mmole, 85%) of **20** as an oil, which crystallized upon treatment with dipe; m.p. 129.5–132°. IR($CHCl_3$): 1720 cm^{-1} (ester CO); 1660 cm^{-1} (lactam CO); ^1H NMR $\delta(CDCl_3)$: 7.97 (s, H, OOCH), 5.86–6.3 (m, 2H, –CH=CH), 5.13–5.2 (m, 1H, H_7ax), 3.9–4.05 (octet, 1H, H_9eq), 3.24 (m, 1H), 3.18 (q, 1H, H_4), 3.00 (m, 1H), 2.59 (sextet, 1H, H_9ax), 2.47 (m, 1H, H_3), 2.00 (m, 1H, H_6eq), 1.90 (m, 1H, H_6eq), 1.55 (m, 1H), 1.2–1.44 (m, 3H), 1.23 (s, 3H). An exact mass determination gave *m/e*: 261.1359 (calc. for $C_{15}H_{19}NO_3$ *m/e*: 261.1365).

8 - *Aza* - 5 - *formyloxy* - 5 - *methyl* - *tetracyclo*[9.2.1.$0^{2,10}$, $0^{3,8}$]*non* - 8 - *ene* - 3 - *one* (**19**)

(a) 4 - *Aza* - 4(3 - *methyl* - 3 - *butenyl*) - 5 - *hydroxy* - *bicyclo*[5.2.$1^{1,7}$, $0^{2,6}$]*non* - 8 - *ene* - 3 - *one* (**7c**). Compound **2c** (1 g, 4.0 mmole) was reduced in EtOH (100 ml) with 1 g of $NaBH_4$ at 0° during 5 hr. Work-up afforded **7c** (quant) which could be recrystallized from EtOAc/heptane/EtOH; m.p. 155–160°. IR($CHCl_3$): 3400 cm^{-1} (OH); 1670 cm^{-1} (lactam CO); ^1H NMR: $\delta(CDCl_3)$: 6.08–6.31 (m, 2H, –HC=CH–), 5.1–5.25 (m, –N–CHOH, becomes a d with D_2O added, J = 7 Hz), 4.73 (m, 2H, $-C=CH_2$–), 2.9–3.6 (m, 7H, –N–CH_2–, CO–CH–CH–CHOH, –CH–HC = CH–CH–N–CHOH, disappears with D_2O added), 2.2 (m, 2H, –CH_2–C = C), 1.75 (s, 3H, CH_3–C=C), 1.5 (q, 2H). (Found: C, 7183; H, 8.25. Calc. for $C_{14}H_{19}O_2N$ (MW = 233.14): C, 7207; H, 8.21%).

(b) *Cyclisation of* **7c**. Compound **7c** (0.1 g, 0.42 mmole) was dissolved in 1½ ml HCOOH and stirred for 12 hr. Work-up afforded 0.115 g (quant) of a 60:40 mixture of C_7-epimers of **19**. The isomer with the equatorial formate could be isolated by recrystallization of the mixture from dipe; m.p. 156–158°. IR($CHCl_3$): 1720 cm^{-1} (ester CO); 1660 cm^{-1} (lactam CO); ^1H NMR: $\delta(C_6D_6)$: 7.60 (s, 1H, OOCH), 5.86–6.3 (m, 2H, –CH=CH), 3.9–4.2 (octet, 1H, H_9eq), 3.18 (m, 1H), 2.6 (m, 1H), 2.38–2.72 (sextet, 1H, H_9ax), 2.08–2.20 (m. J_1 = 13 Hz, J_2 = 3 Hz, J_3 = 2.5 Hz, H_2), 1.22 (s, 3H, –CH_3), 0.5–2.0 (m, 8H). (Found: C, 68.84; C, 7.37; H, 5.37. Calc. for $C_{15}H_{19}O_3N$ (MW = 261.13): C, 68.94; H, 7.33; N, 5.37%).

8 - *Aza* - 5 - *formyloxy* - 3,5 - *dimethyl* - *tetracyclo*[9.2.1.$0^{2,10}$, $0^{3,8}$]*tetradec* - 12 - *ene* - 9 - *one* (**20**)

(a) 4 - *Aza* - 4(3 - *methyl* - 3 - *butenyl*) - 5 - *hydroxy* - 5 - *methyl* - *bicyclo*[5.2.$1^{1,7}$, $0^{2,6}$]*non* - 8 - *ene* - 3 - *one* (**8c**). To a soln of **2c** (0.318 g, 1.38 mmole) in THF (20 ml) a soln of 3.3 M MeMgCl in THF (0.92 ml, 2.2 eq) was added via a syringe (N_2 atmosphere) at r.t. The soln was stirred for 5 hr. Work-up afforded 0.298 g (1.2 mmole, 87%) of **8c** as an oil, which crystallized upon treatment with dipe; m.p. 112–114°. IR($CHCl_3$): 3400 cm^{-1} (OH); 1670 cm^{-1} (lactam CO); ^1H NMR $\delta(CDCl_3)$: 5.95–6.25 (m, 2H, –HC=CH–), 4.6–4.82 (m, 2H, $=CH_2$), 2.7–3.6 (m, 6H, CO–CH–CH–$C(CH_3)$OH, –CH_2N–, –CH–2x), 2.37 (s, 1H, –N–$C(CH_3)$OH, disappears with D_2O added), 2.05–2.3 (m, 2H, $=CH_2$–CH_2–), 1.73 (s, 3H, =C–CH_3) 1.15–1.65 (m, 2H), 1.46 (s, 3H). An exact mass determination gave *m/e*: 247.1564 (calc. for $C_{15}H_{21}NO_2$ *m/e*: 247.1572).

(b) *Cyclisation of* **8c**. Compound **8c** (0.08 g, 0.32 mmole) was dissolved in 4 ml HCOOH and stirred for 29 hr at r.t. Work-up afforded 0.089 g (quant) or **20** as an oil which crystallized upon treatment with dipe; m.p. 104–107°. IR($CHCl_3$): 1720 cm^{-1} (ester CO); 1660 cm^{-1} (lactam CO); ^1H NMR $\delta(CDCl_3)$: 1720 cm^{-1} (ester CO); 1660 cm^{-1} (lactam CO); ^1H NMR $\delta(CDCl_3)$: 8.05 (s, 1H, OOCH), 6.05–6.2 (m, 2H, CH=CH), 3.72–3.97 (m, 1H, H_9eq), 3.25–3.7 (m, 1H), 3.09–3.25 (m, 1H), 2.9–3.0 (m, 1H), 2.72–2.85 (sextet, 1H), 2.35–2.63 (d of a d, 1H), 2.33–2.345 (d of a d, 1H), 1.96–2.09 (m, 1H), 1.06–1.64 (m, 3H), 1.5 (s, 3H), 1.32 (s, 3H). An exact mass determination gave *m/e*: 275.1529 (calc. for $C_{16}H_{21}NO_3$ *m/e*: 275.1521).

8 - *Aza* - 5 - *formyloxy* - 4 - *ethyl* - *tetracyclo*[9.2.1.$0^{2,10}$, $0^{3,8}$]*tetradec* - 12 - *ene* - 9 - *one* (**21**)

(a) 4 - *Aza* - 4[(*Z*) - 3 - *hexenyl*)] - 5 - *hydroxy* - *bicyclo*[5.2.1^{17}]*non* - 8 - *ene* - 3 - *one* (**7d**). Compound **2d** (0.7 g, 2.8 mmole) was reduced in EtOH (75 ml) with 0.7 g of NaBH at 0° during 3.5 hr. Work-up afforded 0.68 g (2.8 mmole, quant) of **7d** which could be recrystallized from EtOAc; m.p. 122–124°. IR($CHCl_3$): 3400 cm^{-1} (OH); 1670 cm^{-1} (lactam CO); ^1H NMR δ ($CDCl_3$): 6.0–6.3 (m, 2H, HC=CH), 5.0–5.6 (m, 3H, –HC=CH–, N–CH–OH, sharpens with D_2O added), 2.85–3.5 (m. 7H, N–CH_2, CO–CH–CH–CHOH, –CH 2x, N–CH OH, disappears with D_2O added), 1.8–2.4 (m, 4H, –CH_2–C=C, CH_3–CH_2–C=C–), 1.48 (q, 2H), 0.94 (t, 3H, CH_2–CH_3). (Found: C, 72.94; H, 8.65; N, 5.79. Calc for $C_{15}H_{21}O_2N$ (MW = 247.33): C, 72.84; H, 8.56; N, 5.66%).

(b) *Cyclisation of* **7d**. Compound **7d** (0.1 g, 0.4 mmole) was dissolved in 1 ml HCOOH and stirred for 18 hr at r.t. Work-up afforded 0.106 g (0.4 mmole, quant) of crude **21** which could be recrystallized from dipe; m.p. 106–108°. IR ($CHCl_3$): 1720 cm^{-1} (ester CO); 1660 cm^{-1} (lactam CO); ^1H NMR $\delta(C_6D_6)$: 7.6 (s, 1H, OOCH), 5.79–6.19 (m, 2H, –CH=CH), 4.78 (m, 1H, H_7ax), 4.03 (sextet, 1H, H_9eq), 3.1 (m, 1H) 2.8 (m, 1H, H_4), 2.6 (m, 1H), 2.5 (t, $J_1 = J_2 = 3$ Hz, 1H, H_2 ax, 1.9–2.3 (m, 2H, H_3 and H_9ax), 1.61 (t, 1H), 1.44 (t, 1H), 1.34 (m, 1H), 0.94–1.34 (m, 4H), 0.89 (t, 3H). (Found: C, 69.66; H, 7.64; N, 5.20. Calc. for $C_{16}H_{21}O_3N$ (MW = 265.12): C, 69.79; H, 7.69; N, 5.09%).

4 - *Aza* - 4[(*Z*) - 3 - *hexenyl*)] - 5 - *methyl* - 5 - *hydroxy* - *bicyclo*[5.2.1^{17}]*non* - 8 - *ene* - 3 - *one* (**8d**). To a soln of **2d** (0.242 g, 1 mmole) in THF (15 ml) a soln of 3.3 M MeMgCl in THF (0.66 ml, *ca* 2.2 eq) was added via a syringe (N_2 atmosphere) at r.t. The soln was stirred for 2.5 hr. Work-up afforded 0.299 g (quant yield) of **8d** as an oil, which crystallized upon treatment with dipe; m.p. 99–101°. IR($CHCl_3$): 3400 cm^{-1} (OH); 1670 cm^{-1} (lactam CO); ^1H NMR $\delta(CDCl_3)$: 6.12–6.27 (m, 2H, –HC=CH–), 5.1–5.6 (m, 2H, CH_2–CH=CH–CH_2), 2.7–3.4 (m, 6H, CH–CH–CH–(CCH_3) OH, –N–CH_2, –CH 2x), 1.7–2.4 (m, 4H, –CH_2–C=C–CH_2), 2.15 (s, 1H, –CH–(CCH_3)OH; disappears with D_2O added), 1.9–2.4 (m, 2H), 1.44 (s, 3H, N–$C(CH_3)$OH), 0.94 (t, 3H). An exact mass determination gave *m/e*: 261.1741 (calc. for $C_{16}H_{23}NO_2$ *m/e*: 261.1729).

8 - *Aza* - 5 - *formyloxy* - 14 - *oxo* - *tetracyclo*[9.2.1.$0^{2,10}$, $0^{3,8}$]*tetradec* - 12 - *ene* - 9 - *one* (**23**)

(a) 4 - *Aza* - 4(3 - *butenyl*) - 5 - *hydroxy* - 10 - *oxo* - *bicyclo*[5.2.$1^{1,7}$, $0^{2,6}$] - *non* - 8 - *ene* - 3 - *one* (**9b**). Compound **3b** (0.4 g, 1.8 mmole) was reduced in EtOH (50 ml) with 0.5 g of $NaBH_4$ at 0° during 5 hr. Work-up afforded 0.343 g (1.5 mmole, 83%) of crude **9b** which could be recrystallized from dipe; m.p. 115–116°. IR ($CHCl_3$): 3550 cm^{-1} (OH); 1685 cm^{-1} (lactam CO). ^1H NMR $\delta(CDCl_3)$: 5.5–5.9 (m, 2H, HC = CH), 4.6–5.2 (m, 5H, N–CHOH, C = CH_2, CH–O–CH), 3.0–3.62 (m, 2H, N–CH_2), 2.95 (d, J = 12 Hz, 1H, N–CHOH, disappears with D_2O added), 2.6 (d, 2H, CO–CH–CH–CHOH), 2.3 (q, 2H, CH_2–C=C), 1.4–1.9 (m,

4H). (Found: C, 64.42; H, 7.60; N, 6.23. Calc. for $C_{12}H_{17}O_3N$ (MW = 223.12): C, 64.55; H, 7.68; N, 6.27%).

(b) *Cyclisation of* **9b**. Compound **9b** (0.05 g, 0.21 mmole) was dissolved in 1 ml HCOOH and stirred overnight at r.t. Work-up afforded (0.21 mmole, quant) of a 80:20 mixture of C_7 formate epimers. The isomer with the equatorial formate could be isolated by recrystallization from dipe: m.p. 100–105°. IR($CHCl_3$): 1720 cm^{-1} (ester CO); 1670 cm^{-1} (lactam CO); ^1H NMR of the mixture δ($CDCl_3$): 8.07 (s, 1H, OOCH, 20%), 7.98 (s, 1H, OOCH, 80%), 4.85–5.1 (m, 1H, H_7ax), 4.78 (s, 1H, CH–O–CH), 4.45 (s, 1H, CH–O–CH), 4–4.3 (octet, 1H, H_9eq), 3.4–3.9 (m, J_1 = 12 Hz, $J_2 = J_3$ = 3 Hz, 1H, H_2ax), 2.5–2.7 (sextet, 1H, H_9ax), 2.65 (d, 1H, –HC–CO–N–), 1.0–2.4 (m, 9H). (Found: C, 62.24; H, 6.79; Calc. for $C_{13}H_{17}O_4N$ (MW = 251.27): C, 62.14; H, 6.82%.)

Epimerisation of **9b**. A soln of **9b** (0.1 g, 0.45 mmole) in EtOH (15 ml) containing an excess of NaOEt (0.6 mmole) was stirred at r.t. for 3 days. The mixture was poured into H_2O and extracted with $CHCl_3$. Work-up of the filtrate afforded 0.064 g (0.27 mmole, 60%) which according to ^1H NMR δ ($CDCl_3$) was epi-**9b**. The H_2 signal was found at δ4.93 (d, J = 6Hz), 5.5–6.0 (m, 1H, C=CH), 4.5–5.2 (m, 6H, N–CH–OH, –CH–O–CH–, $C=CH_2$), 3.0–3.7 (m, 2H, N–CH_2), 2.1–2.8 (m, 4H, CH_2–C=C, CO–CH–CH–CHOH), 1.1–1.8 (m, 4H).

(c) *Cyclisation of epi-***9b**. Compound epi-**9b** (0.06 g, 0.26 mmole) was dissolved in 0.5 ml HCOOH and stirred overnight at r.t. Work-up afforded 0.067 g (0.26 mmole, quant) of a 80:20 mixture of C_7 formate epimers. Recrystallization from dipe afforded pure **23**; m.p. 100–105°. So cyclisation product of epi-**9b** gave data identical to cyclisation product of **9b**.

8 - *Aza* - 5 - *formyloxy* - 5 - *methyl* - 14 - *oxo* - *tetracyclo*[9.2.1.$0^{2,10}$, $0^{3,8}$]*tetradec* - 12 - *ene* - 9 - *one* (**24**)

(a) 4 - *Aza* - 4(3 - *methyl* - 3 - *butenyl*) - 5 - *hydroxy* - 10 - *oxo* - *bicyclo*[5.2.1^{17}, $0^{2,6}$] - *non* - 8 - *ene* - 3 - *one* (**9c**). Compound **3c** (0.75 g, 3.2 mmole) was reduced in EtOH (75 ml) with 0.7 g $NaBH_4$ at 0° during 4½ hr. Work-up afforded 0.713 g (3.0 mmole, 96%) of **9c**, which could be recrystallized from dipe/EtOAc; m.p. 148–150°. IR($CHCl_3$): 3550 cm^{-1} (OH); 1690 cm^{-1} (lactam CO). ^1H NMR δ($CDCl_3$): 5.15 (m, 1H, N–CHOH sharpens with D_2O added) 4.7–4.9 (m, 4H, CH–O–CH, $C=CH_2$), 3.0–3.8 (m, 2H, N–CH_2–), 2.97 (d, J = 13 Hz, 1H, N–CH–OH; disappears with D_2O added), 2.58–2.62 (m, 2H, CO–CH–CH–CHOH), 2.0–2.4 (t, 2H, C=C–CH_2), 1.3–1.9 (m, 7H). (Found: C, 65.63; H, 8.07; N, 5.99. Calc. for $C_{13}H_{19}O_3N$ (MW = 239.14): C, 65.80; H, 8.07; N, 5.90%).

(b) *Cyclisation of* **9c**. Compound **9c** (0.1 g, 0.42 mmole) was dissolved in 1 ml HCOOH and stirred 1 hr at r.t. Work-up afforded 0.11 g (0.42 mmole, quant) of a 60:40 mixture of the two epimers **24** and C_7-epi **24**. IR($CHCl_3$): 1720 cm^{-1} (ester CO); 1670 cm^{-1} (lactam CO). ^1H NMR of the mixture δ($CDCl_3$): 7.96 and 8.08 (s, 2H, OOCH eq and OOCH ax), 4.8 (s, 1H, CH–O–CH), 4.45 (s, 1H, CH–O–CH), 3.8–4.3 (m, 1H, H_9eq), 3.2–3.6 (m, 1H, H_2), 1.68 (s, 3H, $–CH_3$), 1.58 (s, 3H, $–CH_3$), 1.0–3.1 (m, 11H).

7 - *Aza* - 10 - *formyloxy* - *tricyclo*[5.4.0.$0^{2,5}$]*undecane* - 6 - *one* (**25**)

(a) 3 - *Aza* - 3(3 - *butenyl*) - 4 - *hydroxy* - *bicyclo*[3.2.0]*heptane* (**10b**). Compound **4b** (0.88 g, 5 mmole) was reduced in EtOH (80 ml) with 0.9 g of $NaBH_4$ at −20° during 3 hr. Work-up afforded 0.88 g (5 mmole, quant) of **10b** as an oil which crystallized upon treatment with EtOAc/dipe; m.p. 74–75°. IR($CHCl_3$): 3200 cm^{-1} (OH); 1650 cm^{-1} (lactam CO); ^1H NMR δ ($CDCl_3$): 5.5–6.0 (m, 1H, –C=CH–), 5.2–5.4 (t, 1H, N–CHOH becomes a d with D_2O added), 4.9–5.2 (m, 2H, $=CH_2$), 4.4 (d, J = 7 Hz, 1H, N–CHOH, disappears with D_2O added), 1.7–2.0 (m, 6H, CH_2–C=C and $–CH_2–CH_2$–). (Found: C, 66.34; H, 8.32; N, 7.67. Calc. for $C_{10}H_{15}O_2N$ (MW = 181.11): C, 66.27; H, 8.34; N, 7.73%).

Epimerisation of **10b**. A soln of **10b** (0.09 g, 0.15 mmole) in EtOH (15 ml) containing an excess of NaOEt (0.6 mmole) was stirred at r.t. for 3 days. The mixture was poured into H_2O and extracted with $CHCl_3$. Work-up of the filtrate afforded 0.09 g of a mixture of the hydroxy-lactam of epi-**10b** and its ethoxylactam. IR($CHCl_3$): 3400 cm^{-1} (OH); 1675 cm^{-1} (lactam CO); ^1H NMR of the mixture δ($CDCl_3$); 5.5–5.6 (m, 1H, =CH–), 5.0–5.25 (m, 3H, $C=CH_2$, –N–CH–OH, disappears with D_2O added), 4.9 (m, 1H, –N–CH–OH, sharpens with D_2O added), 4.74 (s, 1H, –N–CH–OC_2H_5), 2.6–3.9 (m, 6H, –N–CH_2– and CO–CH–CH–CHOH, OCH_2–CH_3), 1.5–2.6 (m, 6H, CH_2–C=C, $–CH_2–CH_2$), 1.2 (t, 3H).

(b) *Cyclisation of* **10b**. Compound **10b** (0.062 g, 0.34 mmole) was dissolved in 1 ml HCOOH and stirred overnight at r.t. Work-up afforded 0.072 g (0.34 mmole, quant) of a 90:10 mixture of C_7 epimers of **25** as crystalline product. The isomer with the equatorial formate could be recrystallized from dipe; m.p. 96–99°. IR($CHCl_3$): 1725 cm^{-1} (ester CO); 1670 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 8.02 (s, 1H, OOCH), 4.8–5.2 (m, 1H, H_7ax, 4.15–4.45 (q, 1H, H_9eq), 3.35–3.49 (m, J_1 = 12 Hz, J_2 = 3 Hz, J_3 = < 1 HZ, 1H, H_2), 2.65–3.0 (sextet, 1H, H_9a), 1.0–3.2 (m, 11H). (Found: C, 62.95; H, 7.22; N, 6.73. Calc. for $C_{11}H_{15}O_3N$ (MW = 209.11): C, 63.14; H, 7.23; N, 6.69%).

*Cyclisation of epi-***10b**. Compound epi-**10b** (mixture of OH and OEt lactams, 0.066 g was dissolved in 1 ml HCOOH and stirred overnight at r.t. Work-up afforded 0.05 g of a 90:10 mixture of C_7 epimers of **25** as crystalline product. The isomer with the equatorial formate could be recrystallized from dipe; m.p. 96–99°. Cyclisation of epi-**10a** gave **25** with analytical data identical to cyclisation of **10a**.

7 - *Aza* - 10 - *formyloxy* - 1 - *methyl* - *tricyclo*[5.4.0.$0^{2,5}$]*undecane* - 6 - *one* (**26**)

(a) 3 - *Aza* - 3(3 - *butenyl*) - 4 - *hydroxy* - 4 - *methyl* - *bicyclo*[3.2.0]*heptane* (**11b**). To a soln of **4b** (0.25 g, 1.39 mmole) in THF (30 ml) a soln of 3.3 M MeMgCl in THF (0.91 ml, 2.2 eq) was added via a syringe (N_2 atmosphere) at r.t. The soln was stirred for 2 hr. Work-up and column chromatography on silicagel with $CHCl_3$/acetone 4/1 as an eluent afforded 0.05 g (0.25 mmole, 18%) of **11b** as an oil. IR($CHCl_3$): 3400 cm^{-1} (OH); 1670 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 5.6–6.03 (m, 1H, CH_2=CH–), 4.9–5.23 (m, 2H, $C=CH_2$), 2.7–3.7 (m, 5H), 1.7–2.6 (m, 6H), 1.45 and 1.36 (2 xs, 3H, isomer ratio 1:2). An exact mass determination gave *m/e*: 195.1252 (calc. for $C_{11}H_{17}NO_2$ *m/e*: 195.1252 (calc. for $C_{11}H_{17}NO_2$ *m/e*: 195.1259).

(b) *Cyclisation of* **11b**. Compound **11b** (0.03 g, 0.153 mmole) was dissolved in 1½ ml HCOOH and stirred overnight at r.t. Work-up afforded 0.033 g (quant) of crystalline **26** which could be recrystallized from dipe; m.p. 116–118.5°. IR($CHCl_3$): 1725 cm^{-1} (ester CO); 1670 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 8.01 (s, 1H, OOCH), 5.41 (m, 1H, H_7ax), 4.21 (m, 1H, H_9eq), 2.82 (m, 1H, H_9ax), 1.20–3.09 (10H), 1.32 (s, 3H). An exact mass determination gave *m/e*: 223.1179 (calc. for $C_{12}H_{17}NO_3$ *m/e*: 223.1206).

7 - *Aza* - 10 - *methyl* - 10 - *formyloxy* - *tricyclo*[5.4.0, $0^{2,5}$]*undecane* - 6 - *one* (**27**)

(a) 3 - *Aza* - 3(3 - *methyl* - 3 - *butenyl*) - 4 - *hydroxy* - *bicyclo*[3.2.0]*heptane* - 2 - *one* (**10c**). Compound **4c** (1.4 g, 7 mmole) was reduced in EtOH (200 ml) with 2 g of $NaBH_4$ at −20° during 3½ hr. Work-up afforded 1.41 g (7 mmole, quant) of crystalline **10c** which could be recrystallized from dipe/EtOAc; m.p. 108–110°. IR($CHCl_3$): 3400 cm^{-1} (OH); 1680 cm^{-1} (lactam CO); ^1H NMR δ ($CDCl_3$): 5.31 (t, 1H, N-CHOH becomes a d with D_2O added), 4.7–4.8 (m, 2H, $C=CH_2$), 3.91 (d, J = 8 Hz, 1H; disappears with D_2O added), 3.1–3.8 (m, 2H, N–CH_2–), 2.8–3.15 (m, 2H, CO–CH–CH–CHOH), 1.8–2.5 (m, 6H, CH_2–C=C–CH_2–CH_2–), 1.77 (s, 3H). (Found: C, 67.58; H, 8.71; N, 7.18. Calc. for $C_{11}H_{17}O_2N$ (MW = 195.13): C, 67.66; H, 8.78; N, 7.17%).

(b) *Cyclisation of* **10c**. Compound **10c** (0.401 g, 2 mmole) was dissolved in 5 ml HCOOH and stirred for 1 hr at r.t. Work-up afforded 0.446 g (0.2 mmole, quant) of a 60:40 mixture of the two epimers **27** and C_7-epi **27** which were each obtained pure by fractional crystallization from dipe. Major isomer **27**: m.p. 78–80°. IR($CHCl_3$): 1725 cm^{-1} (ester CO); 1670 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 8.08 (s, 1H, OOCH), 4.19 (q, 1H, H_9eq), 3.54 (m, J_1 = 12 Hz, J_2 = 3 Hz, J_3 = < 1Hz, 1H, H_2), 2.98 (sextet, 1H, H_9ax), 0.8–3.2 (m, 10H), 1.54 (s, 3H).

Minor isomer C_7-epi **27**: m.p. 76–77°. IR($CHCl_3$): 1725 cm^{-1} (ester CO); 1670 cm^{-1} (lactam CO); ^1H NMR δ($CDCl_3$): 7.94 (s, 1H, OOCH), 4.24 (octet, H_9eq), 3.41 (m, J_1 = 12 Hz, J_2 = < 1Hz, 1H, H_2), 1.0–3.15 (m, 11H), 1.70 (s, 3H). (Found: C, 64.60; H,

7.73; N, 6.33. Calc. for $C_{12}H_{17}NO_2$ (MW = 223.26): C, 64.55; H, 7.68; N, 6.27%).

7 - *Aza* - 10 - *methyl* - 10 - *dichloroacetoxy* - *tricyclo*[5.4.0.0^{2,5}]*undecane* - 6 - *one*

Cyclisation of **10c** *in* $CHCl_2COOH$. Compound **10c** (0.05 g, 0.25 mmole) was dissolved in 3 ml $CHCl_2COOH$ and stirred for 1 hr at r.t. Work-up afforded 0.077 g (0.25 mmole, quant) of a 1:4 mixture of dichloro-acetates. IR($CHCl_3$): 1750 cm^{-1} (ester CO); 1660 cm^{-1} (lactam CO). ^{1}H NMR of the mixture δ($CDCl_3$): 5.9 (80%) aand 5.83 (20%) (2s, 1H, $-O_2CHCl_2$), 4.0–4.4 (m, 1H, H_9eq), 3.3–3.7 (m, 1H, H_2), 1.0–3.3 (m, 11H), 1.57 (20%) and 1.72 (80%) (two s, 3H, $-CH_3$).

7 - *Aza* - 10 - *formyloxy* - 1 - 10 - *dimethyl* - *tricyclo*[5.4.0.0^{2,5}] *undecane* - 6 - *one* (**28**)

(a) 3 - *Aza* - 3(3 - *methyl* - 3 - *butenyl*) - 4 - *hydroxy* - 4 - *methyl* - *bicyclo*[3.2.0] - *heptane* (**11c**). To a soln of **4c** (0.36 g, 1.86 mmole) in THF (15 ml) a soln of 3.3 M MeMgCl in THF (1.3 ml, 2.2 eq) was added via a syringe (N_2 atmosphere) at r.t. The soln was stirred for 4.5 hr. Work-up afforded 0.390 g (quant yield) of **11c** as an oil. IR ($CHCl_3$): 3400 cm^{-1} (OH); 1670 cm^{-1} (lactam CO); ^{1}H NMR δ($CDCl_3$): 4.7–4.85 (m, 2H, $=CH_2$), 3.75–3.88 (m, 1H, OH; disappears with D_2O added), 2.7–3.78 (m, 4H), 1.67–2.6 (m, 6H), 1.81 (s, 3H, $CH_2=C(CH_3)-$), 1.45 and 1.33 (2xs, 3H, isomer ratio, 3:1). An exact mass determination gave *m/e*: 209.1248 (calc. for $C_{12}H_{17}NO_2$ *m/e*: 207.1416).

(b) *Cyclisation of* **11c**. Compound **11c** (0.143 g, 0.68 mmole) was dissolved in 4 ml HCOOH and stirred for 18 hr at r.t. Work-up afforded 0.146 g (91%, 0.61 mmole) of **28** as an oil which crystallized upon treatment with dipe: m.p. 98–101°. IR($CHCl_3$): 1720 cm^{-1} (ester CO); 1660 cm^{-1} (lactam CO); ^{1}H NMR δ($CHCl_3$): 8.1 (s, 1H, OOCH), 3.9–4.15 (m, 1H, H_{9eq}), 2.9–3.2 (m, 2H), 1.74–2.64 (m, 7H), 1.52 (s, 3H), 1.36 (s, 3H). An exact mass determination gave *m/e*: 237.1356 (Calc. for $C_{13}H_{19}NO_3$ *m/e*: 237.1365).

7 - *Aza* - 10 - *formyloxy* - 11 - *ethyl* - *tricyclo*[5.4.0.0^{2,5}]*undecane* - 6 - *one* (**29**)

(a) 3 - *Aza* - 3[(*Z*) - 3 - *hexenyl*] - 4 - *hydroxy* - *bicyclo*[3.2.0]*heptane* (**10d**). Compound **4d** (0.2 g, 0.96 mmole) was reduced in EtOH (25 ml) with 0.4 g of $NaBH_4$ at 0° during 4 hr. Work-up afforded 0.201 g (0.96 mmole, quant) of **10d** as an oil which crystallizes upon standing at 0° and could be recrystallized from dipe; m.p. 74–75°. IR($CHCl_3$): 3400 cm^{-1} (OH); 1680 cm^{-1} (lactam CO); ^{1}H NMR δ($CDCl_3$): 5.6–5.63 (m, 3H, $-HC=CH-$, $-NCHOH$), 3.76 (d, J = 8 Hz, 1H, $-N-CH-OH$; disappears with D_2O added), 2.8–3.7 (m, 4H, $N-CH_2$, $CO-CH-CH-CHOH$), 1.8–2.53 (m, 8H), 0.95 (t, 3H). An exact mass determination gave *m/e*: 209.1419 (Calc. for $C_{12}H_{19}NO_2$ *m/e*: 209.1494).

(b) *Cyclisation of* **10d**. Compound **10d** (0.1 g, 0.47 mmole) was dissolved in 5 ml HCOOH and stirred for 24 hr at r.t. Work-up afforded 0.106 g (0.44 mmole, 94%) of **29** as an oil, which crystallizes upon standing at 0° and could be recrystallized from dipe; m.p. 78–80°. IR($CHCl_3$): 1720 cm^{-1} (ester CO); 1670 cm^{-1} (lactam CO); ^{1}H NMR δ($CDCl_3$): 8.05 (s, 1H, OOCH), 4.97–5.23 (m, 1H, H_{7ax}), 4.14–4.4 (m, 1H, H_{9eq}), 3.45 (d of a d, J_1 = 2.5 Hz, J_2 = < 1Hz, 1H, H_2), 0.8–3.1 (m, 11H), 1.01 (t, 3H). An exact mass determination gave *m/e*: 237.1359 (Calc. for $C_{13}H_{19}NO_3$ *m/e*: 237.1365).

7 - *Aza* - 10 - *formyloxy* - 1 - *methyl* - 11 - *ethyl* - *tricyclo*[5.4.0.0^{2,5}]*undecane* - 6 - *one* (**30**)

(a) 3 - *Aza* - 3[(*Z*) - 3 - *hexenyl*] - 4 - *hydroxy* - 4 - *methyl* - *bicyclo*[3.2.0]*heptane* (**11d**) To a soln of compound **4d** (0.207 g, 1 mmole) in THF (40 ml) a soln of 3.3 M MeMgCl in THF (0.7 ml, *ca* 2.2 eq) was added via a syringe (N_2 atmosphere) at r.t. The soln was stirred for 2.5 hr. Work-up afforded 0.221 g (quant yield) of **11d** as an oil. IR($CHCl_3$): 3400 cm^{-1} (OH); 1670 cm^{-1} (lactam CO). ^{1}H NMR δ($CDCl_3$): 5.2–5.7 (m, 2H, $-CH=CH-$), 2.7–3.8 (m, 5H, $N-CH_2$, $-N-(CH_3)OH$, $CO-CH-CH-C(CH_3)OH$), 1.7–2.18 (m, 8H), 1.45 and 1.35 (s, 3H, $N-(CH_3)OH$, ratio 1.25:1), 0.97 (t, 3H). An exact mass determination gave *m/e*: 221.1427 (calc. for $C_{13}H_{19}NO_2$ *m/e*: 221.1416).

7 - *Aza* - *tricyclo*[5.4.0.0^{2,5}]*undecane* - 6,10 - *dione* (**31**)

(a) 3 - *Aza* - 3(3 - *butyn*) - 4 - *hydroxy* - *bicyclo*[3.2.0]*heptane* (**10e**). Compound **4e** (0.182 g, 1 mmole) was reduced in EtOH (20 ml) with 0.2 g of $NaBH_4$ at −20° during 5 hr. Work-up afforded 0.160 g (0.88 mmole, 88% yield) of **10e** as a 16:5 mixture of *endo*- and *exo*-isomers. The endo isomer could be isolated by recrystallization of the mixture from EtOAc/dipe; m.p. 97–98°. IR($CHCl_3$): 3400 cm^{-1} (OH); 3220 cm^{-1} (C–H); 1670 cm^{-1} (lactam CO); ^{1}H NMR δ($CDCl_3$): 5.33–5.51 (m, J_1 = 6.5 Hz, J_2 = 8Hz, 1H, $N-CH-OH$ becomes a d (J = 6.5 Hz) with D_2O added) (the *exo* epimer has a multiplet at 5–5.13 which becomes a s (J = (1.5) with D_2O added), 4.05 (d, J = 8 Hz, 1H, $N-CH-OH$; disappears with D_2O added), 3.3–3.73 (m, 2H, $-N-CH_2-$), 2.8–3.2 (m, 2H, $CO-CH-CH-CHOH$), 1.8–2.67 (m, 7H). An exact mass determination gave *m/e*: 179.0944 (Calc. for $C_{10}H_{13}NO_2$ *m/e*: 179.1016).

(b) *Cyclisation of* **10e**. Compound **10e** (0.102 g, 0.55 mmole) was dissolved in 50 ml HCOOH and stirred for 60 hr at r.t. Work-up afforded 0.086 g crude product from which **31** could be isolated pure by recrystallization from dipe/EtOAc; m.p. 123.5–124.5°. ^{1}H NMR δ($CDCl_3$): 4.4–4.68 (m, 1H, H_9eq), 3.52–3.74 (m, J_1 = 12 Hz, J_2 = 3 Hz, J_3 = ≤ 1 Hz, 1H, H_2), 2.89–3.27 (m, 2H, $-CH-CH-CO$). 1.84–2.73 (m, 9H). (Found: C, 66.89; H, 7.28; N, 7.71. Calc. for $C_{10}H_{13}NO_2$ (MW = 179.21): C, 67.02; H, 7.31; N, 7.82%).

7 - *Aza* - 4 - *formyloxy* - *tetracyclo*[7.4.4.0^{1,9}, 0^{2,7}]*heptadec* - 11 - *ene* - 8 - *one* (**32**)

(a) 12 - *Aza* - 12(3 - *butenyl*) - 13 - *hydroxy* - *tricyclo*[4.4.3.0^{1,6}]*tridec* - 3 - *ene* - 11 - *one* (**12b**). Compound **5b** (1 g, 3.8 mmole) was reduced in EtOH (100 ml) with 1 g of $NaBH_4$ at 0° during 5 hr. Work-up afforded the crude product of which 0.560 g **12b** (2.1 mmole, 50% yield) could be isolated by recrystallization from dipe/EtOAc; m.p. 130–132°. IR($CHCl_3$): 3400 cm^{-1} (OH); 1670 cm^{-1} (lactam CO). ^{1}H NMR δ($CDCl_3$): 5.4–6.0 (m, 3H, $=CH-$, $-CH=CH-$), 4.7–5.17 (m, 3H, $=CH_2$, $N-CH-OH$), 3.04–3.72 (m, 2H, $-N-CH_2-$), 3.38 (d, J = 9 Hz, 1H, $N-CH-OH$, disappears with D_2O added), 1–2.43 (m, 14H). (Found: C, 73.45; H, 8.79; N, 5.42. Calc. for $C_{16}H_{23}NO_2$ (MW = 261.17): C, 73.53; H, 8.87; N, 5.36%).

(b) *Cyclisation of* **12b**. Compound **12b** (0.1 g, 0.38 mmole) was dissolved in 2 ml HCOOH and stirred for 18 hr at r.t. Work-up afforded 0.111 g (0.38 mmole, quant yield) crude product from which **32** could be isolated pure by recrystallization from dipe; m.p. 88–95°. IR($CHCl_3$): 3400 cm^{-1} (OH); 1720 cm^{-1} (ester CO); 1670 cm^{-1} (lactam CO); ^{1}H NMR δ($CDCl_3$): 8.01 and 8.1 (s, 1H, OOCH), 5.5–5.62 (m, 2H, $-CH=CH-$), 4.7–5.1 (m, 1H, H_7ax), 4.03–4.3 (m, 1H, H_9eq), 3.38 (d of a d, J_1 = 12 Hz, J_2 = 3.5 Hz, 1H, H_2), 2.68 (d of a t, 1H, H_9ax), 1.1–2.36 (m, 16H). (Found: C, 70.50; H, 7.95. Calc. for $C_{17}H_{23}NO_3$ (MW = 289.36): C, 70.56; H, 8.01%).

12 - *Aza* - 12[(*Z*) - 3 - *hexenyl*] - 13 - *hydroxy* - *tricyclo*[4.4.3.0^{1,6}]*tridec* - 3 - *ene* - 11 - *one* (**12d**)

Compound **5d** (0.5 g, 1.7 mmole) was reduced in EtOH (50 ml) with 0.5 g of $NaBH_4$ at 0° during 12 hr. Work-up afforded 0.159 g (0.55 mmole, 32% yield) of crude **12d**, which could be recrystallized from dipe/EtOAc; m.p. 108–109°. IR($CHCl_3$): 3400 cm^{-1} (OH); 1680 cm^{-1} (lactam CO). ^{1}H NMR δ ($CDCl_3$): 5.57–5.7 (m, 2H, $CH=CH$), 5.15–5.57 (m, 2H, $-CH=CH-$), 5.01 (d, J = 8.5 Hz, 1H, $N-CH-OH$; becomes a s with D_2O added), 3.78 (d, J = 8.5 Hz, 1H, $-N-CH-OH$; disappears with D_2O added), 3.03–3.7 (m, 2H, $-N-CH_2-$), 1.1–2.5 (m, 16H), 0.94 (t, 3H, CH_2-CH_3). (Found: C, 74.84; H, 9.35; N, 4.73. Calc. for $C_{18}H_{27}NO_2$ (MW = 289.20): C, 74.70; H, 9.40; N, 4.84%).

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