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STEREOCONTROLLED SYNTHESIS OF FUNCTIONALIZED 1-AZASPIRANS

EFFICIENT SYNTHESIS OF PERHYDROHISTRIONICOTOXIN†

H. E. SCHOEMAKER[1] and W. N. SPECKAMP*

Laboratory of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

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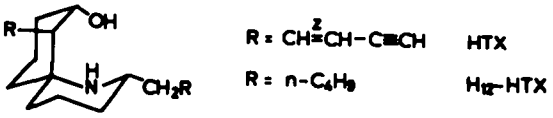
Abstract—A formal total synthesis of perhydrohistrionicotoxin (H_{12}-HTX) is described based on a stereocontrolled α-acyliminium ion-olefin cyclisation. In the key step of the synthesis three asymmetric C atoms (C_6, C_7 and C_8) are introduced in a single operation leading to the formation of the spiro formate ester **15**. Compound **15** is converted to the spirothiolactam alcohol **17**, a known precursor of H_{12}-HTX.

The versatility of the synthetic approach is further demonstrated by the stereocontrolled syntheses of other functionalized 1-azaspirans, *viz* the 6-*Endo*-Trig products **20** and **24** and the 5-*Exo*-Trig products **26** and **28**. The formation of the latter two compounds is remarkable with respect to the mechanism.

^{13}C NMR data of a series of 1-azaspirans are provided, which *inter alia* show the existence of a conformational equilibrium in 1-azaspiro alcohol **16**. Mass spectral criteria are used for assignment of 5-*Exo*- or 6-*Endo*-cyclisation products.

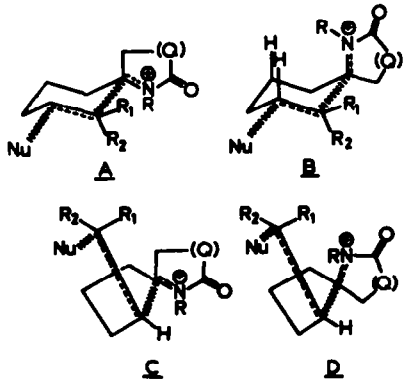
Histrionicotoxin[2] (HTX) and its congeners are used in studies concerning the mechanisms involved in the transsynaptic transmission of neuromuscular impulses. Perhydrohistrionicotoxin (H_{12}-HTX) exhibits a similar behaviour and has been shown[3] to bind selectively to a particular part of the cholinergic receptor which regulates the ion transport mechanisms (ion-conductance modulator)without affecting the binding of acetylcholine to the receptor.



In connection with this remarkable biological activity a general and stereoselective synthesis of H_{12}-HTX and structurally related compounds seem to be of high interest, especially because of the scarcity of material from natural sources. The general interest in this astonishingly simple and yet highly active type of compound is also reflected in recent[4,5] elegant total syntheses.‡

A general approach for the stereocontrolled synthesis of functionalized 1-aza-spirans is outlined in Scheme 1. As was already shown[4,5] compound **2** (Q = $-CH_2-CH_2-$, $R = R_2 = H$, $R_1 = Bu^n$) is a convenient precursor for H_{12}-HTX.

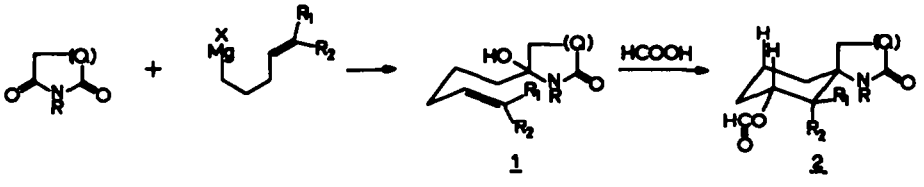
Supposedly the key-step **1**→**2** in which the final C–C bond is formed and the desired stereochemistry is incorporated (3 asymmetric C atoms) proceeds through a chairlike transition state **A** with synchronous formation of the new C–C and C–O bonds as is depicted in Fig. 1.



The alternative transition states **B**, **C** and **D** (Fig. 1) were considered less likely (*vide infra*) in the initial stage of

†Dedicated to Prof. Dr. E. Havinga on the occasion of his 70th birthday.

‡After completion of our own work a formal total synthesis of H_{12}-HTX based upon an almost identical scheme was reported by Evans and Thomas[6].

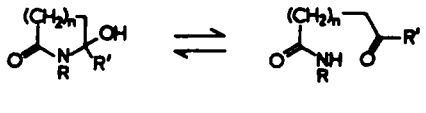


Scheme 1.

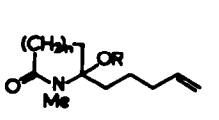
our investigation. In order to test the synthetic approach[7] outlined in Scheme 1 some model experiments were carried out. Reaction of 1 eq of N-methylsuccinimide with 1.15 eq of 4-pentenylmagnesium iodide afforded after aqueous workup a 2:1 mixture of the hydroxy compound **3** and unreacted N-methylsuccinimide. In an attempt to convert **3** to the presumably more stable ethoxy-derivative **4** the slightly unstable enamide **5** was formed quantitatively. However, upon separation of the 2:1 mixture of **5** and N-methylsuccinimide only a 42% yield of enamide **5** was obtained due to decomposition during column chromatography. Cyclisation of either the enamide **5** or the hydroxy compound **3** yielded the spirocyclic formate ester **8** in a highly stereo-selective manner (yield >95%). It is assumed that compound **8** is formed via transition state **A**. Transition state **B** is considered less likely in view of the marked steric interactions of the N-Me substituent with the 1,3 diaxial protons of the newly formed cyclohexane ring. Compound **8** was hydrolysed (KOH/EtOH/H_2O) to the azaspiro alcohol **9**.

used as the starting material. The desired *cis*-relationship between the OH group and the C–N bond at C_6 was expected to result from a stereocontrolled reaction proceeding through transition state **A**. In this manner a H_{12}-HTX precursor is formed in one single step with the correct relative stereochemical configurations at the C atoms C_6, C_7 and C_8.

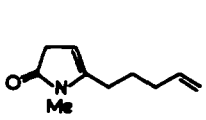
Initially, experiments were carried out with N-methylglutarimide for the following reasons; (i) due to the Me-substituent the reaction presumably proceeds through transition state **A**. (ii) From earlier studies[7,8] on Grignard additions to N–H and N–Me imides it can be inferred that in the tautomeric equilibrium **E** acyclic forms dominate in the case of N–H imides. Thus, N-



E



3 R=H, n=1
4 R=Et, n=1
6 R=H, n=2



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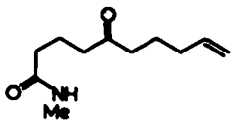

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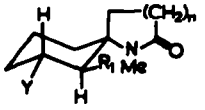


	n	Y	R_1
8	1	OCHO	H
9	1	OH	H
10	2	OCHO	H
11	2	OH	H
12	2	I	H
13	2	OCHO	Bu^n
14	2	OH	Bu^n

The corresponding glutarimide adduct **6** was found to ring-open extremely fast to the keto-amide **7**, while the latter form was difficult to cyclize back. Therefore the experimental procedure had to be modified. Thus, after completion of the Grignard reaction between N-methylglutarimide and 4-pentenylmagnesium iodide, the etheral solvent was evaporated, the residue dissolved in HCOOH and the solution stirred for 40 hr at 35–40°. Work-up and column chromatography afforded two spirocyclic products, **10** (45% yield) and **12** (15% yield). In all probability the formyloxy-group and the C–N bond in compound **10** have a *cis*-relationship. Hydrolysis of **10** afforded the crystalline alcohol **11**. The second spirocyclic product, also formed in a stereospecific manner, proved to be the slightly unstable iodo compound **12**. Presumably formation of compound **12** proceeds through transition state **A** (Fig. 1) with I^- acting as the nucleophile.

In view of the promising results of the model studies our attention now focussed upon the synthesis of H_{12}-HTX using an analogous scheme. Since the OH group at C_8 possesses a *trans*-relationship with the Bu^n-substituent at C_7, (E)-4-nonenylmagnesium bromide was methylglutarimide was reacted with (E)-4-nonenylmagnesium bromide in THF, the solvent evaporated and the residue cyclized in HCOOH at elevated temperatures. However, cyclisation experiments under a wide range of reaction conditions failed to give reasonable yields of spiro-products. A drawback of the method used is that the presence of salts in the reaction mixture, cause a lowering of the effective acid strength of the medium and this necessitates the use of elevated reaction temperatures. The salts were difficult to remove because of the fast ring-opening of the initially formed hydroxylactam to the keto-amide tautomer upon aqueous work-up.

The latter complication can in principle be avoided by synthesizing derivatives of the hydroxylactam via alkylation or acylation. Thus, after completion of the Grignard reaction, Me_2SO_4 was added at room temp. and the salts were filtered off. However, due to heterogeneous conditions in the latter reaction, the yield of **13** after cyclisation in HCOOH was very low. Slightly better results were obtained by acylation with acetic anhydride (18 hr, 70°). After filtration and evaporation of the solvent, the residue was cyclized and yields up to 20% of spiro products were obtained. After column chromato-

graphy slightly impure **13** was isolated in 10% yield. Compound **13** could be hydrolysed to the hydroxy spirolactam **14**. In view of the impractical yields the approach was slightly modified and the Grignard addition of (E)-4-nonenylmagnesium bromide to the parent glutarimide was studied. Although *a priori* the stereochemical outcome of the cyclisation reactions cannot be predicted because of a possible ring closure via transition state **B**, the latter approach has the advantage of providing in a single step a product which already had been converted to H_{12}-HTX. Thus glutarimide was reacted with 2.2 eq of (E)-4-nonenylmagnesium bromide in THF (30–35°, 20 hr). Evaporation of the solvent and cyclisation of the residue in HCOOH at 44° for 8 days afforded after column chromatography the crystalline spiroformate ester **15** in 23% yield. Because of the presence of unreacted N–H glutarimide in the crude product the reaction was repeated with a larger excess (5.9 eq) of Grignard reagent. The reaction time for the cyclisation was 14 days, the temperature 42°. Accordingly, the yield of **15** after column chromatography was raised to 30%. Compound **15** was converted into the known[4] hydroxy spirothiolactam **17** (1. P_2S_5, 2. OH) in 88% yield. Since **17** had been converted[4] into H_{12}-HTX in 70% yield, the synthesis of compound **17** constitutes a formal total synthesis of H_{12}-HTX in 18.7% overall-yield.

Compound **16**[4,5] obtained after hydrolysis of **15**, provided vital information for the structure determination of compound **15** and related 1-azaspirans (*vide infra*).

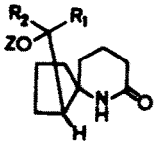
The spirocyclisation proceeded stereoselectively, only traces of isomers could be detected. In one experiment a 0.5% yield of crystalline material was obtained in addition to a 19% yield of the spiroformate **15**. This minor isomer is tentatively assigned structure **18**.

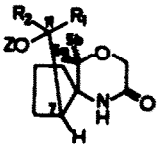
through transition state **A**. Hydrolysis of **20** afforded the crystalline hydroxy compound **21**, the C_7-epimer of the H_{12}-HTX precursor **16**. In addition, from the hydrolysis products a 0.5% yield of a crystalline isomer was obtained. Tentatively this isomer is assigned structure **23**.

Modifications in the heterocyclic ring were also investigated. Thus Grignard reaction of succinimide and (E)-4-nonenylmagnesium bromide, followed by cyclisation in HCOOH, afforded after column chromatography the oily formate **24** in about 30% yield. Hydrolysis of **24** gave the crystalline compound **25** (21% yield based on succinimide).

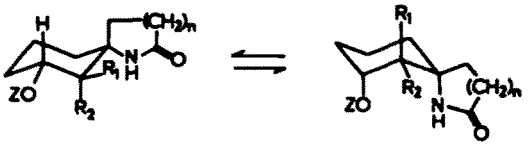
The above discussed cyclisation reactions proceeded predominantly via a 6-*Endo*-Trig[9] mode of ring closure through transition state **A**. No products formed via transition state **B** could be isolated. Small amounts of the isolated spiro compounds are formed via a 5-*Exo*-Trig[9] mode of ring closure (presumably through transition state **C** with synchronous *trans*-coplanar formation of the new C–C and C–O bonds).

However, starting from 3,5 morpholinedione and (E)-4-

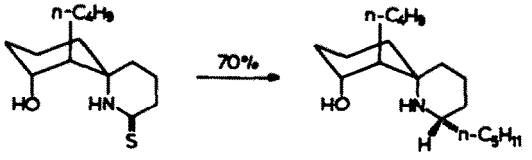




	Z	R_1	R_2	
18	CHO	Bu^n	H	**26**
19	H	Bu^n	H	**27**
22	CHO	H	Bu^n	**28**
23	H	H	Bu^n	**29**



		n	Z	R_1	R_2
15a	**15b**	2	CHO	Bu^n	H
16a	**16b**	2	H	Bu^n	H
20a	**20b**	2	CHO	H	Bu^n
21a	**21b**	2	H	H	Bu^n
24a	**24b**	1	CHO	Bu^n	H
25a	**25b**	1	H	Bu^n	H



17 H_{12}–HTX

The versatility of the α-acyliminium ion-olefin technique is illustrated by various modifications in both the heterocyclic and the olefinic synthons thereby allowing stereoselective "one-pot" syntheses of related 1-azaspirans.

Thus, reaction of glutarimide with 3 eq of (Z)-4-nonenyl-magnesium bromide followed by cyclisation in HCOOH afforded the oily spiroformate ester **29** in 22% yield. Again the cyclisation proceeded stereoselectively

nonenyl-magnesium bromide, followed by cyclisation in HCOOH only the crystalline 5-*Exo*-Trig product **26** was formed in a highly stereoselective manner (isolated yield: 41%). The cyclisation is now thought to proceed through transition state **C** with synchronous *trans*-coplanar formation of the C_6–C_7 bond and the C_{11}–O bond. No 6-*Endo*-Trig products were isolated. In a similar manner starting from 3,5-morpholinedione and (Z)-4-nonenyl-magnesium bromide the crystalline spiro compound **28**

was isolated in 47% yield after column chromatography. The structure of the latter compound was firmly established by an X-ray diffraction study[10,11c]

Structure proof and spectral data

Although spectral data and structure proofs of compounds 8–12, 15–17 and 26–29 have been published in part,[11] some additional data on those compounds of relevance for a general discussion will be given. Besides, spectral and structural characteristics of the remaining compounds are presented in more detail. Compounds 15–17 and compound 28 are considered as a reference set of materials, the structures of which were unequivocally established by comparison with the data kindly provided to us by Dr. Y. Kishi (compounds 16 and 17) or by X-ray analysis[10] (compound 28).

Structure assignment of the remaining compounds was based upon a comparison of ^1H NMR, ^{13}C NMR and mass spectral data, combined with mechanistic considerations (*vide infra*).

An important characteristic of spirolactam 16 is the existence of a conformational equilibrium 16a ⇄ 16b, which was demonstrated by variable temperature ^1H and ^{13}C NMR experiments in different solvents. In the apolar solvent $CDCl_3$ the equilibrium is shifted to conformer 16b, due to the internal H-bonding between the amide and OH functions. In the polar and protic solvent CD_3OD a fast equilibrium 16a ⇄ 16b is observed. The ^1H NMR spectrum at 37° shows the H_8 absorption at $\delta = 3.67$ while $W_{\frac{1}{2}} = 15$ Hz. At −60°, a new signal at $\delta = 4.10$ ($W_{\frac{1}{2}} = 7$ Hz) indicates the presence of conformer 16b, while the H_8 signal for 16a is observed at $\delta = 3.3$. Exact measurement of $W_{\frac{1}{2}}$ of the latter signal is obscured by overlap with the solvent signal. Upon raising the temperature of the sample, line broadening and coalescence of the H_8 signal takes place.

These phenomena are convincingly demonstrated by variable temperature ^{13}C NMR experiments. At −60°, in CD_3OD as the solvent, the two conformers are observed separately (estimated ratio 16a : 16b = 95 : 5). Upon raising the temperature of the sample line broadening and coalescence occurs (temperature range −50 to −10°). At 37° 14 sharp peaks are observed due to the fast equilibrium 16a ⇄ 16b (estimated ratio 2 : 1).

The internal hydrogen bonding was indicated by IR dilution experiments. Upon dilution (CCl_4) the absorption pattern in the regio 3000–4000 cm^{-1} remained unchanged. A free OH- stretching vibration at 3600 cm^{-1} was absent (concentration: 0.006 mole/l).

Formation of compound 20 presumably proceeds through transition state A with *trans*-coplanar addition of the α-acyliminium ion and the nucleophile to the (Z)-substituted double bond, leading to a product with a *cis*-relationship between the Bu^n-substituent, the formyloxy group and the C–N bond. The conformational equilibrium 20a ⇄ 20b is shifted completely to the conformer with an equatorial Bu^n-substituent, 20b, as is indicated by the $W_{\frac{1}{2}} = 7$ Hz for H_8 [$\delta = 4.12$ ($CDCl_3$)]. Again the *cis*-relationship between the C–N bond and the OH function in compound 21 was established by similar IR dilution experiments as described for compound 16. Compound 21 was also subjected to variable temperature ^1H and ^{13}C NMR experiments in different solvents. However, in CD_3OD as the solvent the ^1H and ^{13}C NMR spectra of 21 at temperatures varying from −60° – +50° were almost identical. From the ^1H NMR and ^{13}C NMR data no conclusive evidence for the stereochemical structure of compounds 20 and 21 could be obtained. However, the *cis*-relationship between the oxy-substituent at C_8 and the Bu^n-group at C_7 seems to be well established in view of the abundant experiences in this type of heterocyclisation with (Z)-substituted olefins. As mentioned before the *cis*-relationship between the hydroxyl and amide function in 21 was in evidence from the IR data. Representative ^{13}C NMR data for the 1-azaspiran systems discussed above are collected in Table 1.

Because complexing mainly occurs at the amide CO function in 16 shift reagent experiments with Eu(fod)$_3$ provided no further information. Only small downfield shifts were observed for the OH and CH–OH protons. On the contrary, addition of the shift reagent to compound 21 showed an upfield shift for the OH proton, indicating an OEuH-angle in the range 54.7–125.3°[13].

The marked differences in spectral behaviour of the structurally related compounds 16 and 21 indicate a large influence of the Bu^n-substituent on the conformation of the isomeric 7-butyl-8-hydroxy-1-azaspiro[5.5]undecane-

Table 1. ^{13}C NMR data on compounds 16 and 21 solvent and temperature effects

compound	solvent	temperature[a]	C_6	C_7	C_8
16	$CDCl_3$	p.t.	57.5	49.5	69.9
16	CD_3OD	p.t.	59.9	53.6	72.2
16a	CD_3OD	−60°	60.6	55.0	73.2
16b	CD_3OD	−60°	58.4	50.8[b]	70.2
21	$CDCl_3$	p.t.	57.5	47.1	66.9
21	CD_3OD	p.t.	58.6	47.9[c]	68.1
21	CD_3OD	−60°	58.7	ca 48	67.7

a. p.t. = probe temperature (37°)

b. estimated value

c. determined via the inversion-recovery method[12].

2-ones with an axial OH-substituent ($W_{\frac{1}{2}} = 7$ Hz for H_8). Out of the four possible isomers only compounds **16** and **21** have a structure compatible with an OEuH-angle in the range 54.7–125.3°.

The stereochemical structure of compounds **24** and **25** was established in an analogous fashion. The C*H*–OR signal in compound **24** (300 MHz, C_6D_6 appears as a triplet of doublets ($\delta = 4.78$, $J_1 = 8$ Hz, $J_2 = 8$ Hz, $J_3 = 3.5$ Hz) while C*H*–OR in compound **25** (100 MHz, $CDCl_3$) appears as a broad singlet at $\delta = 4.04$ ($W_{\frac{1}{2}} = 8$ Hz). The 7-azaspiro[4.5]decane-8-one structure was apparent from the mass spectral analysis (*vide infra*).

The NMR-data of compounds **18**, **19**, **22** and **23** show a remarkable resemblance with the spectral characteristics of compounds **26–29**. Compounds **18** and **19** have already been shown[6] to possess an 1-azaspiro[4.5]decane-2-one structure. From double resonance experiments (300 MHz, C_6D_6) the coupling constants $J_{H7,H11} = 5$ Hz, $J_{H11,H12a} = J_{H11,H12b} = 6$ Hz were established, hence in compound **18** H_{11} appears as a pseudo quartet at $\delta = 5.44$. In compound **26** (100 MHz, C_6D_6) H_{11} also appears as a pseudo quartet at $\delta = 5.35$, while in $CDCl_3$ or CD_2Cl_2 a triplet of doublets ($W_{\frac{1}{2}} = 15$ Hz) is observed. Similarly, in compound **19** $\delta(H_{11}) = 3.80$ ($CDCl_3$) and in compound **27** $\delta(H_{11}) = 3.88$ ($CDCl_3$).

The 1-azaspiro[4.5]decane-2-one structure of compound **23** was established by mass spectral analysis (*vide infra*). Again a close correspondance in chemical shift for H_{11} is found upon comparing the ^{1}H NMR data of compounds **23** and **29**, $\delta(H_{11}) = 3.45$–3.78 ($CDCl_3$) for compound **23** while for compound **29**: $\delta(H_{11}) = 3.45$–3.75 ($CDCl_3$). The *cis*-relationship between the C_7 side chain and the C_6–C_5 bond and the relative configuration at C_{11} in compound **28** followed from the X-ray analysis[10], thereby also confirming a cyclisation through transition state C with synchronous *trans*-coplanar attack of the α-acyliminium ion and the nucleophile to the double bond. Compound **26** is the C_{11}-epimer of compound **28**, the relative configuration at C_{11} being governed by the configuration of the double bond in the starting material. Structural assignments of compounds **18**, **19**, **22** and **23** are based upon a likely similarity in reaction mechanism. Thus, a ring closure through transition state C with synchronous *trans*-coplanar formation of the new C–C and C–O bonds furnishes the two C_{11}-epimers **18** and **22**, depending on the geometry of the double bond in the starting olefin.

^{13}C NMR *data*

Although no conclusive evidence concerning the stereochemistry of the spiro compounds can be obtained from the ^{13}C NMR data some information can be derived by comparison of the characteristic absorptions (Table 2).

Considering the ^{13}C NMR spectra taken in $CDCl_3$ as the solvent, two different types of compounds can be recognized, *viz* 5-*Exo*-Trig and 6-*Endo*-Trig products.

In the glutarimide and 3,5-morpholinedione series these two types of compounds show a typical difference in the chemical shift for the spiro C atoms. In the two 6-*Endo*-Trig type of compounds **16** and **21** δ(quat.C) = 57.5, whereas in the 5-*Exo*-Trig compounds **19** and **23**, δ(quat. C) = 64.9 and 63.8. In the oxa-series the values for compounds **27** and **29** are: δ(quat. C) = 62.5 and 62.9. Thus, the spiro C atom of a 1-azaspiro[4.5]decane system is observed at lower field than the corresponding spiro C atom of an 1-azaspiro[5.5]undecane system. The chemical shift of the spirocarbon atom in compound **25** (δ = 61.7) again indicates a spiro[4.5]decane structure. A similar difference in chemical shift of the spiro C atom is observed in the N–Me spiro compounds **9** (1-azaspiro[4.5]decane) and **11** (1-azaspiro[5.5]undecane).

A second difference in the ^{13}C NMR spectra of the 1-azaspiro[5.5]undecanes compared to the 1-azaspiro[4.5]decanes originates from the doublet around $\delta = 48$ for the *C*H–Bu^n atom in the 6-*Endo*-Trig products and the doublet around $\delta = 54$ for the C_7 atom in the 5-*Exo*-Trig products.

Finally, the *C*H–Bu and *C*H–OH absorptions also depend on the geometry of the starting olefin. Compounds **16** and **25** both are derived from the (E)-substituted alkene and show a striking resemblance in chemical shift for the carbon atoms *C*H–Bu^n (δ = ca. 49.5) and C*H*–OH (δ = ca. 69.8). In compound **21**,

Table 2. ^{13}C NMR data[a] on spiro-lactam alcohols

compound	[b] C*H*Bu^n	[b] C*H*OH	quat.C	[c] C*H*–COH	[c] C–OH
9	-	67.4	63.7	-	-
11	-	66.4	60.0	-	-
16	49.5	69.9	57.5	-	-
19	-	-	64.9	54.8	69.9
21	47.1	66.9	57.5	-	-
23	-	-	63.8	54.3	72.2
25	49.6	69.8	61.7	-	-
27	-	-	62.5	54.0	68.1
29	-	-	62.9	53.5	72.4

a. solvent : $CDCl_3$; probe temperature (37°)

b. 6-Endo - Trig products

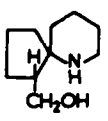
c. 5-Exo - Trig products.

derived from the (Z)-substituted alkene, these values are $\delta = 47.1$ and 66.9 respectively.

In the 5-*Exo*-Trig series the spirocompounds **19** and **27**, derived from the (E)-alkene, exhibit chemical shifts or resp. $\delta = 69.9$ and 68.1 for the *C*H–OH atoms, whereas compounds **23** and **29**, derived from the (Z)-alkene, show chemical shifts of $\delta = ca$ 72.3 for the *C*H–OH atom.

Mass spectral data

The cyclisation reactions discussed above either proceed via a 6-*Endo*-Trig or a 5-*Exo*-Trig mode of ring closure. Structure determination of the basic spiroskeleton is rather cumbersome by standard NMR techniques, necessitating the use of selective ^{13}C–$[^1H]$-decoupling experiments.



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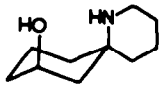

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Based on a mass spectral study of the various spiro compounds synthesized so far, notably the hydroxy spirolactams **9**, **11**, **16**, **21**, **23**, **25**, **27** and **29** combined with the published data[14] on compounds **30** and **31** an empirical rule was formulated which can be conveniently applied to distinguish between the products from 5-*Exo*-Trig and 6-*Endo*-Trig reactions. As shown from the EI Mass spectra combined with exact mass determinations the spiro compounds with a 6-membered carbocyclic ring are characterized by the $(M\text{-}43)^+$-fragment ion formed from the molecular ion by expulsion of a C_3H_7-fragment from the 6-membered carbocyclic ring (compounds **9**, **11**, **16**, **21**, **25** and **31**). On the contrary, in the spiro compounds formed via a 5-*Exo*-Trig mode of ring closure the $(M\text{-}43)^+$-ion is virtually absent, instead loss of C_3H_6 involving the C atoms from the 5-membered carbocyclic ring now being a typical fragmentation mode. The abundance of the $(M\text{-}42)^{+\cdot}$-ion is in the order of 5–35% (15 eV, rel. int). The generation of a $(M\text{–}C_3H_6)^{+\cdot}$-fragment was observed in compounds **23**, **27**, **29** and **30**. In addition, in the 5-*Exo*-Trig hydroxycompounds **23**, **27** and **29** the molecular ion loses C_4H_9 from the side chain $[(M\text{-}57)^+]$, while loss of *m/e* 57 is virtually absent in the EI-mass spectra of the corresponding 6-*Endo*-Trig type of compounds (**16**, **21** and **25**). In the 6-*Endo*-Trig type of compounds **16**, **21** and **25** possessing a n-Bu substituent a similar fragmentation will lead to the $(M\text{-}43)^+$-ion due to loss of C_3H_7 involving the C atoms of the side chain. Thus, in the latter series formation of the $(M\text{-}43)^+$-fragmentation is due to two fragmentation modes; (i) C_3H_7 is generated from the carbocyclic 6-membered ring as can be inferred from the observation of a $(M\text{–}C_3H_7)^+$-ion in the mass spectra of compounds **9**, **11** and **31** (no n-Bu substituent). (ii) The $(M\text{-}43)^+$ -ion may also originate from the molecular ion by loss of C_3H_7 from the side chain (compounds **16**, **21** and **25**). Which of these two fragmentation modes is the major process cannot be ascertained without the study of labelled (or structurally related) compounds.

CONCLUSION

The short and stereoselective synthesis of the H_{12}-HTX precursor **15** nicely illustrates the potential of the α-acyliminium ion-olefin cyclisation technique for the general preparation of this compound class. The possibility to modify both the heterocyclic and the olefinic synthons offers an attractive method for the stereoselective synthesis of a multitude of 1-azaspiro systems, functionalized both in the heterocyclic and in the carbocyclic part.

The reaction either proceeds via a 6-*Endo*-Trig type of ring closure through a chairlike transition state **A** with synchronous *trans*-coplanar formation of the new C–C and C–O bonds or via a 5-*Exo*-Trig mode of cyclisation through a transition state **C**, again with a synchronous *trans*-coplanar addition of the α-acyliminium ion and the nucleophile to the double bond. No cyclisation products arising from reactions through the transition states **B** or **D** have been found.

As observed earlier,[15] 6-membered ring formation is favoured over 5-membered ring formation in this type of biomimetic cyclisations with electronically unbiased olefins. Molecular model studies indicate only minor differences in steric interactions in the four possible transition states **A**–**D** (in the case of N–H imides). Therefore, the predominance of **A** over **B** and **C** over **D** is tentatively assumed to be governed by electronic factors also.

In the latter context the complementary relationship of the α-acyliminium ion olefin cyclisations discussed above with the both experimentally[16] and theoretically[17] studied heterolytic fragmentation may be of relevance. The course of the cyclisation reaction is controlled to a great extent by the same stereo-electronic and orbital symmetry-factors that govern the Grob-fragmentation.

At the moment the different results of the cyclisation reactions reported by Evans and Thomas[6] cannot be rationalized satisfactorily. In particular, the question of 5-*Exo*-Trig vs 6-*Endo*-Trig cyclisations in the glutarimide series and the exclusive formation of 6/5 spiro compounds in the oxa-series can only be answered by further experiments aimed at the clarification of the reaction path. In the latter context the question of kinetic vs thermodynamic control deserves special attention.

EXPERIMENTAL

IR spectra were recorded on Unicam SP 200 and Perkin Elmer 177 and 254 instruments. ^1H-NMR spectra were taken on Varian A-60, HA-100, XL-100 and 300-FT instruments. ^{13}C NMR spectra were taken on a Varian XL-100 FT instrument at 25.2 MHz. M.ps are uncorrected. Micro-analyses were carried out by Messr. H. Pieters of the micro-analytical department of our laboratory. Mass spectrometric measurements were performed at 15 and 70 eV electron energy on a Varian Mat 711 double focussing instrument. Samples were introduced into the ion source (200°) by use of a direct insertion probe (40–160°). In addition to the relevant peaks $(M\text{–}C_3H_7)^+$, $(M\text{–}C_3H_6)^{+\cdot}$, $(M\text{–}C_4H_9)^+$ and the base peak, all peaks with a relative intensity ≥20% and *m/e* ≥ 100 are given as mass spectral data.

Cis - N - Methyl - 2- formyloxy- 7- azaspiro[4.5]decane - 8 - one (**8**)

(a) N - *methyl* - 5 - (4 - *pentenyl*) - 4 - *pyrrolin* - 2 - *one* (**5**). To a soln of 4-pentenylmagnesium iodide (prepared from 248 mg of Mg and 2.06 g of 4-pentenyliodide) in 30 ml ether was added 1.00 g (8.8 mmole) of N-methylsuccinimide in THF (30 ml). The heterogeneous mixture was stirred for 20 hr at r.t. The soln is then poured into dilute aqueous NH_4Cl. The etheral layer was separated and washed with saturated aqueous NaCl. The aqueous layer was extracted 5 times with $CHCl_3$. The $CHCl_3$ extract was washed with sat NaCl aq. The combined etheral and $CHCl_3$ soln were dried over Na_2SO_4. Work-up afforded a yellowish oil which according to ^1H NMR consisted of a 2:1

mixture of 3 and N-methyl-succinimide. The oil was taken up in EtOH, the soln was acidified with 4N HCl/EtOH to pH = 3 and stirred for 2 hr at 0°. The soln was poured into dil $NaHCO_3$ aq and extracted 5 times with $CHCl_3$. The organic layer was washed with sat NaCl aq and dried over $MgSO_4$. Work-up afforded a 2:1 mixture of enamide 5 and N-methylsuccinimide. Column chromatography on silica gel (act.II) with $CHCl_3$/acetone 4:1 as eluent afforded 610 mg (3.7 mmole) of enamide 5 as an oil, yield: 42%. IR($CHCl_3$): 1670 and 1710 cm^{-1} (enamide). ^1H NMR δ ($CDCl_3$): 5.58–6.00 (m, 1H, C*H*=CH_2); 4.84–5.12 (m, 2H, CH=CH_2): 4.49–4.75 (m, 1H, N–C=CH); 2.87 (s, 3H, N–Me); 1.90–2.78 (m, 8H).

(b) *Cyclisation of* 5. Compound 5 (107 mg, 0.65 mole) was dissolved in 3 ml HCOOH and stirred for 19 hr at r.t. Work-up afforded 134 mg (0.635 mmole) of 8 as an oil, which crystallizes at temps below 7°, yield 98%. IR($CHCl_3$): 1675 and 1725 cm^{-1} (CO). ^1H NMR δ($CDCl_3$): 7.98 (s, 1H, CHO); 4.70–5.10 (m, 1H, H_2ax); 2.70 (s, 3H, N–Me); 1.05–2.48 (m, 12H). An exact mass determination gave *m/e* 211.1198. (Calc. for $C_{11}H_{17}NO_3$ *m/e* 211.1203).

Cis- N - Methyl - 2 - hydroxy - 7 - azaspiro[4.5]decane - 8 - one (9)

Hydrolysis of 8 afforded 9 in quantitative yield. IR($CHCl_3$): 1670 cm^{-1} (CO). ^1H NMR δ($CDCl_3$): 3.54–3.91 (m, 1H, H_2ax); 2.70 (s, 3H, N–Me); 1.00–2.48 (m, 13H). MS(70 eV): 183 ($C_{10}H_{17}NO_2$, M^+, 29%); 141 (22); 140 (100, $C_7H_{10}NO_2$); 124 (62); 111 (50). An exact mass determination gave *m/e* 183.1263. (Calc. for $C_{10}H_{17}NO_2$ *m/e* 183.1259).

Cis - N - Methyl - 8 - hydroxy - 1 - azaspiro[5.5]undecane - 2 - one (11)

(a) Cis - N - *Methyl - 8 - formyloxy - 1 - azaspiro[5.5]undecane - 2 - one* (10) *and* cis - N - *methyl - 8 - iodo - 1 - azaspiro[5.5]undecane - 2 - one* (12). To a soln of 4-pentenylmagnesium iodide (prepared from 245 mg of Mg and 2.10 g of 4-pentenyl iodide) in ether (50 ml) was added 635 mg (5 mmole) of N-methyl glutarimide in THF (40 ml). The heterogeneous mixture was refluxed for 4 days. The solvent was evaporated under reduced pressure and the residue was dissolved in 70 ml HCOOH and stirred for 40 hr at 35–40°. The HCOOH was evaporated under reduced pressure, the residual oil was taken up in $CHCl_3$, washed with dil $NaHCO_3$ aq and sat NaCl aq and dried over $MgSO_4$. Evaporation of the solvent and column chromatography on silica gel (act. II) with EtOAc as an eluent afforded two major fractions:

(I) 230 mg (0.75 mmole) of 12 as an unstable crystalline compound (m.p. unrecorded) yield 15%. IR($CHCl_3$): 1620 cm^{-1} (CO). ^1H NMR δ($CDCl_3$): 4.02–4.40 (m, 1H, H_8 ax); 2.93 (s, 3H, N–CH_3); 1.40–2.58 (m, 14H). ^{13}C NMR δ(d-acetone): 60.7 (s, C_6). FI-mass spectrum: M^+ = 307.

(II) 505 mg (2.24 mmole) of 10 as an oil, yield 45%. IR($CHCl_3$): 1620 and 1720 cm^{-1} (CO). ^1H NMR δ ($CDCl_3$): 7.96 (s, 1H, CHO); 4.73–5.10 (m, 1H, H_8 ax); 2.85 (s, 3H, N–Me); 1.20–2.50 (m, 14H).

(b) *Hydrolysis of compound* 10 *afforded the crystalline hydroxy compound* 11 m.p.: 142–144° (i-prop-ether). IR($CHCl_3$): 1620 cm^{-1} (CO lactam). ^1H NMR δ($CDCl_3$): 3.58–3.95 (m, 1H, H_8 ax); 2.90 (s, 3H, N–Me); 1.00–2.55 (m, 15H). MS (70 eV): 197 (M^+, $C_{11}H_{19}NO_2$, 31%); 155 (18); 154 (100, $C_8H_{12}NO_2$); 138 (30); 126 (58); 125 (56); 112 (54, $C_6H_{10}NO$); 110 (28). (Found: C, 66.9; H, 9.7; N, 7.1. $C_{11}H_{19}NO_2$ M = 197.27. Calc.:C, 66.97; H, 9.71; N, 7.10%).

General procedure for the synthesis of compound 15–29

(a) *Grignard addition reaction and cyclisation.* The Grignard reagent was prepared from 243 mg of Mg (10 mmole) and 2.3 g of (E)- or (Z)-4-nonenyl bromide[18]. To soln of the Grignard reagent in 50 ml of THF a soln of the imide in THF (30 ml) was added (N_2-atmosphere). The initially formed ppt re-dissolved and the soln was stirred for 18 hr at 20–25°. After evaporation of the THF, the residue was dissolved in 100 ml HCOOH and stirred for 8–14 days at 42–44°. Evaporation of the solvent afforded a brown oil, which was taken up in $CHCl_3$/dil $NaHCO_3$ aq. The aqueous layer was extracted 6 times with $CHCl_3$. The combined organic layers were washed with sat NaCl aq and dried over $MgSO_4$. Work-up and column chromatography on silicagel (act.II) with EtOAc as an eluent afforded the spiro formate esters.

(b) *Hydrolysis of the spiro formate esters.* The spiro formate esters were dissolved in KOH/EtOH/H_2O (0.3 g of KOH, 6 ml H_2O, 6 ml EtOH) and stirred for 6 hr at r.t. The soln was neutralized with 2N HCl and extracted with $CHCl_3$ (7 times). The combined organic layers were washed with sat NaCl aq and dried over $MgSO_4$. Work-up afforded the mostly crystalline hydroxy compounds in 95–100% yield.

(6*S*, 7*S*, 8*S*)- *and* (6*R*, 7*R*, 8*R*) 7 - *n- butyl - 8 - hydroxy - 1 - azaspiro[5.5]undecane - 2 - one* 16

(a) 7 - *n - butyl - 8 - formyloxy - 1 - azaspiro[5.5]undecane - 2 - one* (15). Cyclisation of the Grignard addition product of N–H glutarimide (190 mg, 1.68 mmole) and (E)-4-nonenylmagnesium bromide in 100 ml HCOOH (14 days, 42°) afforded after work-up and column chromatography the crystalline spiro formate ester 15 (133 mg, 0.50 mmole), yield 30%. m.p.: 144–146° (iprop-ether). IR($CHCl_3$): 1640 and 1720 cm^{-1} (CO). ^1H NMR δ(C_6D_6): 8.40 (br.s, 1H, NH); 7.68 (s, 1H, C*H*O); 4.65–5.00 (t of d, 1H, H_8ax); 0.80–2.40 (m, 22H). ^{13}C NMR δ($CDCl_3$): 171.9 (s, NCO); 160.1 (d, HCO); 74.0 (d, C_8); 58.5 (s, C_6); 50.6 (d, C_7). (Found: C, 67.4; H, 9.5; N, 5.2. $C_{15}H_{25}NO_3$ M = 267.36. Calc.: C, 67.38; H, 9.43; N, 5.24%).

Compound 18 was isolated as a minor product in this cyclisation reaction (5 mg). m.p.: 124–126° (iprop-ether). IR($CHCl_3$): 1645 and 1715 cm^{-1} (CO) ^1H NMR δ(C_6D_6): 8.42 (br.s, 1H, NH); 7.83 (s, 1H, C*H*O); 5.44 (m, 1H, H_{11}) 0.80–2.60 (m, 22H). ^{13}C NMR δ($CDCl_3$): 73.0 (d, C_{11}); 64.2 (s, C_6); 52.1 (d, C_7). An exact mass determination gave *m/e* 267.1842 (Calc. for $C_{15}H_{25}NO_3$: *m/e* 262.1834).

(b) *Hydrolysis of compound* 15 *afforded the crystalline hydroxy compound* 16. m.p.: 135–136° (iprop-ether). IR(KBr): 1640 cm^{-1} (CO lactam). ^1H NMR δ($CDCl_3$): 8.55 (br.s, 1H, NH); 5.23 (br.d, 1H, OH); 4.05 (m, $W_{\frac{1}{2}}$ = 8 Hz, 1H, H_8eq); 0.88 (br.t, 3H, CH_3) 1.1–2.5 (m, 19H). MS (70 eV): 239 (M^+, $C_{14}H_{25}NO_2$, 41%); 197 (6); 196 (35, $C_{11}H_{18}NO_2$); 182 (2); 168 (16, $C_9H_{14}NO_2$); 150 (24); 124 (53, $C_7H_{10}NO$); 112 (100, $C_6H_{10}NO$); 111 (50, C_6H_9NO). (Found: C, 70.3; H, 10.5; N, 5.9. $C_{14}H_{25}NO_2$ M = 239.25. Calc.: C, 70.25; H, 10.53; N, 5.85%). Hydrolysis of 18 afforded the crystalline 19 (m.p. unrecorded). IR(CCl_4): 1655 cm^{-1}. ^1H NMR δ($CDCl_3$): 5.66 (br.s, 1H, NH); 3.80 (m, 1H, H_{11}); 0.70–2.40 (m, 23H).

(6*S*, 7*S*, 8*S*)- *and* (6*R*, 7*R*, 8*R*) 7- *n - Butyl - 8 - hydroxy - 1 - azaspiro[5.5]undecane - 2 - thione* (17)

A suspension of 15 (18 mg, 0.0674 mmole) and P_2S_5 (36 mg) in 3 ml of C_6H_6 was refluxed for 1 hr. After cooling, the soln was diluted with CH_2Cl_2 and washed with 10% Na HCO_3 aq. The organic layer was dried over $MgSO_4$ and concentrated. To a soln of the residual oil in 10 ml of MeOH was added 0.6 ml of 1N NaOH at r.t. The soln was stirred for 1 hr at r.t., 0.2 ml of AcOH was added and the solvent was evaporated under reduced pressure. Filtration through a short silica gel column (EtOAc) furnished 15 mg (0.059 mmole) of the thiolactam alcohol 17, yield 88%. m.p.: 162–165°. IR($CHCl_3$): 1520 cm^{-1} (NC=S). ^1H NMR δ ($CDCl_3$): 4.07 (m, 1H, H_8eq); 2.5–3.2 (m, 2H); 1.00–2.2 (m, 18), 0.90, (br.t, 3H, CH_3). An exact mass determination gave *m/e* 255.1667. (Calc. for $C_{14}H_{25}$ NOS, *m/e* 255.1657).

(6*S*, 7*R*, 8*S*)- *and* (6*R*, 7*S*, 8*R*) 7- *n - Butyl - 8 - hydroxy - 1 - azaspiro[5.5]undecane - 2 - one* (21)

(a) 7- n - *Butyl - 8 - formyloxy - 1 - azaspiro[5.5]undecane - 2 - one* (20). Cyclisation of the Grignard addition product of NH glutarimide (375 mg 3.32 mmole) and (Z)-4-nonenylmagnesium bromide in 100 ml HCOOH (8 days, 44°) afforded after work-up and column chromatography the oily ester 20 (180 mg, 0.68 mmole), yield 22%. IR($CHCl_3$): 1640 and 1720 cm^{-1} (CO). ^1H NMR δ($CDCl_3$): 8.12 (s, 1H, CHO); 6.61 (br.s 1H, NH); 5.34 (m, $W_{\frac{1}{2}}$ = 7 Hz, 1H, H_8eq); 0.70–2.40 (m, 22H). ^{13}C NMR δ($CDCl_3$): 71.0 (d, C_8); 56.5 (s, C_6); 46.4 (d, C_7).

(b) *Hydrolysis of compound* 20 *afforded the crystalline spiro* lactam alcohol 21 m.p.: 127–129° (iprop-ether). IR(CCl_4): 1635 cm^{-1}. ^1H NMR δ($CDCl_3$): 8.10 (br.s. 1H, NH); 4.12 (m,

$W_{\frac{1}{2}}$ = 7 Hz, 1H, H_8eq); 3.96 (m, 1H, OH); 0.80–2.40 (m, 22H). *MS*(70 eV): 239 (M^+, $C_{14}H_{25}NO_2$ 33%), 197 (8); 196 (48, $C_{11}H_{18}NO_2$); 182 (2); 168 (21); 150 (21); 124 (50); 112 (100, $C_6H_{10}NO$); 111 (44). (Found: C, 70.3; H, 10.6; N, 5.9. $C_{14}H_{25}NO_2$ M = 239.35. Calc.: C, 70.25; H, 10.53; N, 5.85%).

Compound **23** was obtained (6 mg) after hydrolysis of a second column fraction containing the ester **22** and some unidentified products m.p.: 130–132° (iprop-ether). IR($CHCl_3$): 1635 cm^{-1}. ^1H NMR δ($CDCl_3$): 6.30 (br.s, 1H, NH); 3.64 (m, $W_{\frac{1}{2}}$ = 20 Hz, 1H, H_{11}); 0.80–2.50 (m, 23H). MS (70 eV): 239 (M^+, $C_{14}H_{25}NO_2$, 21%); 197 (12, $C_{11}H_{19}NO_2$); 196 (3); 182 (13, $C_{10}H_{16}NO_2$); 151 (29); 150 (28); 127 (21); 124 (61); 112 (100, $C_6H_{10}NO$); 111 (81, C_6H_9NO). An exact determination gave *m/e* 239.1879. (Calc. for $C_{14}H_{25}NO_2$: *m/e* 239.1882).

(1R, 2R, 6R)- and (1S, 2S, 6S) 1- n - Butyl - 2 - hydroxy - 7 - azaspiro[4.5]decane - 8 - one (**25**)

(a) *- 1 - n - Butyl - 2 - formyloxy - 7 - azaspiro[4.5]decane - 8 - one* (**24**) Cyclisation of the Grignard addition product of NH succinimide (190 mg, 1.92 mmole) and (E) - 4 - nonenylmagnesium bromide in 100 ml HCOOH (14 days, 42°) afforded after work-up and column chromatography 155 mg of the oily ester **24** (slightly impure). IR($CHCl_3$): 1680 and 1720 cm^{-1} (CO). ^1H NMR δ(C_6D_6): 7.90 (br.s, 1H NH): 7.70 (s, 1H, *CHO*); 4.60–5.00 (t of d, 1H, H_2ax); 0.70–2.30 (m, 20H).

(b) *Hydrolysis of compound* **24** (20 mg) afforded after crystallization from iprop-ether alcohol **25** (12 mg, 0.053 mmole), yield 21% based upon NH succinimide. m.p.: 138–141°. IR(KBr): 1670 cm^{-1} (CO). ^1H NMR δ($CDCl_3$) 7.54 (br.s, 1H, NH); 4.04 (m, $W_{\frac{1}{2}}$ = 8 Hz, H_2 eq); 3.52 (br.s, 1H, OH) 0.60–2.50 (m, 20H). MS (70 eV): 225 (M^+, $C_{13}H_{23}NO_2$, 20%); 208 (20); 183 (6); 182 (35, $C_{10}H_{16}NO_2$); 164 (29); 151 (21); 137 (32, $C_8H_{11}NO$); 136 (37); 111 (20); 110 (100, C_6H_8NO). An exact mass determination gave *m/e* 225.1712. (Calc. for $C_{13}H_{23}NO_2$: *m/e* 225.1720).

(6S, 7S, 11S)- and (6R, 7R, 11R) 7 - (1 - Hydroxy - pentyl) - 1 - aza - 4 - oxaspiro[4.5]decane - 2 - one (**27**)

(a) *(6S, 7S, 11S)- and (6R, 7R, 11R) 7 - (1 - Formyloxy - pentyl) - 1 - aza - 4 - oxaspiro [4.5]decane - 2 - one* (**26**). Cyclisation of the Grignard addition product of 3.5 morpholinedione (200 mg, 1.74 mmole) and (E)-4-nonenylmagnesium bromide in 100 ml HCOOH (10 days, 42°) afforded after work-up and column chromatography the crystalline spiro formate ester **26** (190 mg, 0.71 mmole), yield 41%. m.p.: 99–101° (iprop-ether). IR ($CHCl_3$): 1660 and 1715 cm^{-1} (CO). ^1H NMR δ($CDCl_3$): 8.04 (s, 1H, *CHO*); 7.88 (br.s, 1H, NH); 5.21 (m, $W_{\frac{1}{2}}$ = 15 Hz 1H, H_{11}); 4.09 (AB, 2H, $2H_3$); 3.64 (AB, $\delta(H_{3a})$ = 3.83, $\delta(H_{3b})$ = 3.44 J_{AB} = 12 Hz); 0.70–2.20 (m, 16H). ^{13}C NMR δ($CDCl_3$): 169.8 (s, C_2); 160.6 (d, CHO); 71.7 (d, C_{11}); 62.6 (s, C_6); 50.9 (d, C_7). An exact mass determination gave *m/e* 269.1627. (Calc. for $C_{14}H_{23}NO_4$: *m/e* 269.1627).

(b) *Hydrolysis of compound* **26** afforded the spiro lactam alcohol **27** IR($CHCl_3$): 1665 cm^{-1} (CO). ^1H NMR δ($CDCl_3$): 7.49 (br.s, 1H, NH); 4.18 (AB, $\delta(H_{3a})$ = 4.24, $\delta(H_{3b})$ = 4.12, J_{AB} = 16 Hz); 3.79 (AB, $\delta(H_{5a})$ = 4.14, $\delta(H_{5b})$ = 3.44 J_{AB} = 12 Hz), 3.88 (m, 1H, H_{11}); 2.91 (br. d, J = 4 Hz, OH); 0.70–2.20 (m, 16H). MS(70 eV): 241 (M^+, $C_{13}H_{23}NO_3$, 24%); 223 (37); 199 (3, $C_{10}H_{17}NO_3$); 198 (–); 184 (15, $C_9H_{14}NO_3$); 154 (22); 153 (33, $C_8H_{11}NO_2$); 152 (55); 151 (34); 150 (34); 141 (35, $C_7H_{11}NO_2$); 126 (66, $C_6H_8NO_2$); 125 (25); 124 (26); 115 (25); 114 (81, $C_5H_8NO_2$); 113 (50); 112(24); 110 (79, C_8H_{14}); 41 (100). An exact mass determination gave *m/e* 241.1667. (Calc. for $C_{13}H_{23}NO_3$: *m/e* 241.1672).

(6S, 7S, 11R)- and (6R, 7R, 11S) 7- (1 - Hydroxy - pentyl) - 1 - aza - 4 - oxaspiro[4.5]decane - 2 - one (**29**)

(a) *(6S, 7S, 11R)- and (6R, 7R, 11S) 7 - (1 - Formyloxy - pentyl) - 1 - aza - 4 - oxaspiro - [4.5]decane - 2 - one* (**28**). Cyclisation of the Grignard addition product of 3.5 morpholinedione (200 mg, 1.74 mmole) and (z) - 4 - nonenylmagnesium bromide in 100 ml HCOOH (14 days, 42°) afforded after work-up and column chromatography, the crystalline ester **28** (218 mg, 0.81 mmole), yield 47%. m.p.: 106–108° (iprop-ether). IR($CHCl_3$): 1665 and 1715 cm^{-1} (CO). ^1H NMR δ($CDCl_3$): 8.07 (s, 1H, *CHO*); 6.99 (br.s, 1H, NH); 5.19 (m, $W_{\frac{1}{2}}$ = 19 Hz, 1H, H_{11}); 4.05 (AB, $\delta(H_{3a})$ = 4.08 $\delta(H_{3b})$ = 4.02, J_{AB} = 17 Hz); 3.72 (AB, $\delta(H_{5a})$ = 3.88, $\delta(H_{5b})$ = 3.56, J_{AB} = 12 Hz); 0.70–2.36 (m, 16H). ^{13}C NMR δ($CDCl_3$): 169.3 (s, C_2); 160.4 (d, *CHO*); 73.5 (d, C_{11}); 62.4 (s, C_6); 50.1 (d, C_7). An exact mass determination gave *m/e* 269.1627 (Calc. for $C_{14}H_{23}NO_4$: *m/e* 269.1627).

(b) *Hydrolysis of compound* **28** afforded the spirolactam alcohol **29** IR($CHCl_3$): 1665 cm^{-1}. ^1H NMR δ($CDCl_3$): 7.63 (m, 1H, NH); 4.14 (AB, 2H, $2H_3$); 3.80 (AB, $\delta(H_{5a})$ = 4.03, $\delta(H_{5b})$ = 3.57, J_{AB} = 12 Hz); 3.45–3.75 (m, 1H, H_{11}); 2.82 (m, 1H, OH); 0.75–2.20 (m, 16 H). MS (70 eV): 241 (M^+, $C_{13}H_{23}NO_3$, 61); 223 (65); 199 (4, $C_{10}H_{17}NO_3$); 198 (4); 194 (20); 193 (28); 184 (48); 166 (40); 155 (26); 154 (31); 153 (50); 152 (73); 151 (41); 141 (46); 127 (23); 126 (80); 125 (37); 124 (29); 115 (31); 114 (97); 113 (59); 112 (31); 110 (100). An exact mass determination gave *m/e* 241.1667 (Calc. for $C_{13}H_{23}NO_3$: *m/e* 241.1667).

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