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5-Exo-Trig vs 6-Endo-Trig α-ACYLIMINIUM ION-OLEFIN CYCLISATIONS STEREOSELECTIVE SYNTHESIS OF 7-(1-FORMYLOXY-PENT-1-YL)-1-AZA-4-OXA-SPIRO[4.5]DECANE-2-ONES

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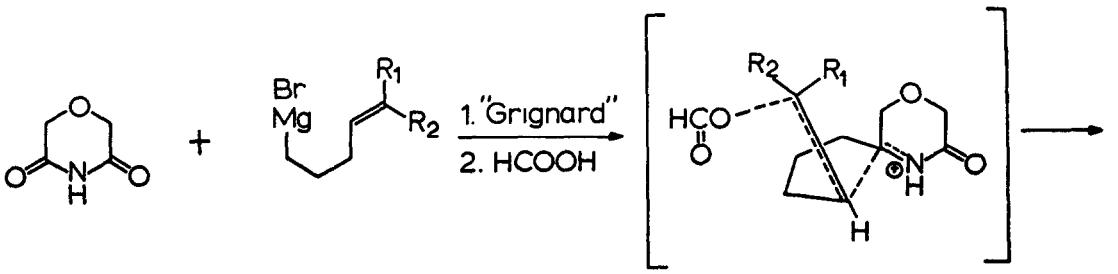
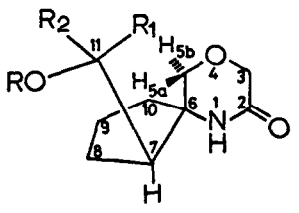
Abstract: The two C_6, C_7 trans substituted title compounds have been synthesized via stereoselective 5-Exo-Trig ringclosures starting from (E)-resp. (Z)-4-nonene-1-yl bromide and 3,5-morpholinedione.

A recent communication[2] by Evans and Thomas prompted us to report some additional results on the stereoselective formation of 1-aza-spiranes via α-acyliminium ion-olefin cyclisations. The aim of the present work was the synthesis of the 4-oxa-analogue of perhydrohistrionicotoxin via the method established before[3]. However, instead of the desired 6-Endo-Trig[4] ringclosure via a chair-form transition state with synchronous formation of the new C-C and C-O bonds the energetically favoured reaction mode in this case is a stereoselective 5-Exo-Trig[4] ringclosure leading to the unexpected 1-aza-4-oxa-spiro[4.5]decane-2-one system. The spiro[4.5]decane structure of compound 3 was unambiguously established by X-ray analysis. Structure assignment of the remaining spiro compounds was based upon a comparison of the ^1H NMR, ^{13}C NMR and mass-spectral data[5].

Thus reaction of 1 eq of 3,5-morpholinedione with 5.7 eq of (E)-4-nonene-1-yl-magnesium bromide in THF (r.t. 18 hr) followed by evaporation of the solvent and cyclisation of the residue in HCOOH (42°, 10 days) afforded after column chromatography (SiO_2, act.II, EtOAc) and crystallization from isopropylether the formate ester 1 (mp. 99-101°) in 41% yield, IR($CHCl_3$): 1660 and 1715 cm^{-1}, ^1H NMR($CDCl_3$): 8.04 (s, 1H, CHO), 5.21 (m, $W_{½}$=15 Hz, 1H, H_{11}), 3.64 (AB, $\delta(H_{5a})$=3.83, $\delta(H_{5b})$=3.44, J_{ab}=12 Hz).





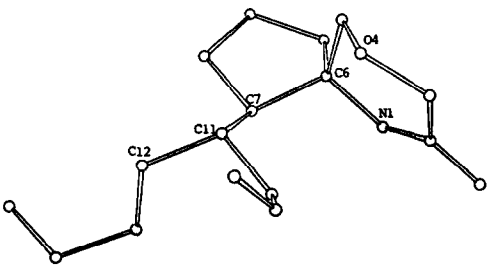
compound :	R	R_1	R_2
1	CHO	n-C_4H_9	H
2	H	n-C_4H_9	H
3	CHO	H	n-C_4H_9
4	H	H	n-C_4H_9

^{13}C NMR $\delta(CDCl_3)$: 169.8 (s, C_2), 160.6 (d, CHO), 71.7 (d, C_{11}) 62.6 (s, C_6), 50.9 (d, C_7). From double resonance and selective ^{13}C-[^{1}H]decoupling experiments it follows that the coupling constant of H_7 ($\delta = 2.01$) with H_{11} is almost zero, while the two adjacent methyleneprotons of the n-butylsubstituent ($\delta = 1.62$) possess coupling constants of approximately 5 Hz each with H_{11}.

Hydrolysis of compound 1 afforded the hydroxycompound 2. IR($CHCl_3$): 1665 cm^{-1}, ^{1}H NMR $\delta(CDCl_3)$: 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). Evidence for the cis-relationship between the C_6-C_5 bond and the C_7-C_{11} bond could be obtained by comparison of the differences $\delta(H_{5a}) - \delta(H_{5b})$ in the ^{1}H NMR spectra of compounds 1 and 2, being respectively 39 and 70 Hz. This marked influence of the C_{11}-oxysubstituent on the chemical shift of H_{5a} in all probability indicates a cis-relationship between the side chain at C_7 and the C_6-C_5 bond of the heterocyclic ring.

In a similar stereoselective manner compound 3 was formed after reaction of 1 eq of 3,5-morpholinedione with 5.7 eq of (Z)-4-nonene-1-ylmagnesium bromide in THF (r.t., 18 hr) followed by evaporation of the solvent and cyclisation of the residue in HCOOH (42°, 14 days). After column chromatography (SiO_2, act II, EtOAc) and crystallization from isopropylether the formate ester 3 (mp. 106-108°) was obtained in 47% yield. IR($CHCl_3$): 1665 and 1715 cm^{-1} (CO), ^{1}H NMR $\delta(CDCl_3)$: 8.07 (s, 1H, CHO), 5.19 (m, $W_{\frac{1}{2}}$=19 Hz, H_{11}), 3.72 (AB, $\delta(H_{5a})$=3.88, $\delta(H_{5b})$=3.56,

J_{ab}=12 Hz). ^{13}C NMR $\delta(CDCl_3)$: 169.3 (s, C_2), 160.4 (d, CHO), 73.5 (d, C_{11}), 62.5 (s, C_6), 50.1 (d, C_7). As was shown from double resonance and selective $^{13}C-[^1H]$ decoupling experiments $J_{H7,H11}$=9 Hz (δ H_7=2.18) while H_{11} is found as a multiplet due to coupling with the two adjacent methyleneprotons (δ = 1.57) of the n-butyl-substituent. Hydrolysis of compound 3 afforded the hydroxy-compound 4. IR($CHCl_3$): 1665 cm^{-1}, ^1H NMR $\delta(CDCl_3)$: 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). Comparison of the AB-system for H_{5a} and H_{5b} in compounds 3 and 4 again indicates a cis-relationship for the C_7-C_{11} bond and the C_6-C_5 bond, $\delta(H_{5a})$-$\delta(H_{5b})$=46 Hz for compound 4 and 32 Hz for compound 3. The foregoing NMR data are in good agreement with the structure established by the X-ray analysis[6] of compound 3 (Figure)



The crystallographic geometry of compound 3

From the latter analysis the 1-aza-4-oxa-spiro[4.5]decane-2-one structure was immediately apparent, together with the relative stereochemical configurations at the carbonatoms C_6, C_7 and C_{11}. Finally the ^1H NMR data indicate the structure of compound 1 as the C_{11}-epimer of compound 3.

The formation of the formate esters 1 and 3 can be explained by a 5-Exo-Trig ringclosure with synchronous trans-coplanar attack of the α-acyliminium ion and HCOOH on the double bond. The relative configuration at C_{11} therefore depends on the configuration of the starting olefin. This type of 5-Exo-Trig ringclosure (with electronically unbiased olefins) has also been observed as a secondary process in the synthesis of perhydrohistrionicotoxin[2,3] and its C_7-epimer[7], via 6-Endo-Trig ringclosures. Contrary to the observations by Evans and Thomas, however, only traces of 5-Exo-Trig products could be isolated in our own cyclisation experiments[8]. To the best of our knowledge the spiro-olefin cyclisations discussed are the first examples of a 5-Exo-Trig mode of ringclosure being favoured over a 6-Endo-Trig cyclisation via a chairform transition state, the mode

of reaction normally encountered in biomimetic olefin cyclisations with electronically unbiased olefins. From molecular model studies it is evident that minor steric interactions may profoundly influence the course of the reaction. These and other factors that possibly play a role are at the moment under active investigation.

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References

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2. D.A. Evans and E.W. Thomas, Tetrahedron Letters, 411 (1979).
   We thank Dr. Evans for sending us a preprint of this paper in advance of its publication.
3. H.E. Schoemaker and W.N. Speckamp, Tetrahedron Letters, 4841 (1978).
4. J.E. Baldwin, J.C.S. Chem.Comm., 734 (1976).
5. A mass-spectral study on a series of related 1-azaspiranes (R=H) showed a typical difference in the fragmentation of 1-azaspiranes with a five- or a six-membered carbocyclic ring. In 6-Endo-Trig type 1-azaspiranes the $(M-43)^+$-ion is observed, i.e. loss of C_3H_7 generated from the six-membered ring. However, in 5-Exo-Trig type products the $(M-43)^+$-fragment is virtually absent, instead loss of C_3H_6 generated from the five-membered ring now being a typical fragmentation mode [$(M-42)^{+\cdot}$].
   Details will be published in our full paper.
6. J.D. Schagen and A.R. Overbeek, to be published.
7. cf. ref.3, details will be published in our full paper.
8. Since Evans and Thomas perform the HCOOH-spirocyclisation with the purified enamide, it cannot be excluded that the nature of the tegen-ion plays an important role in the actual course of the reaction.

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