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STEREOCHEMICAL CONTROL BY REMOTE SUBSTITUENTS IN α-ACYLIMINIUM OLEFIN CYCLISATIONS[1]

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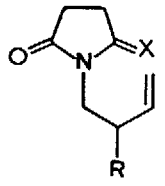
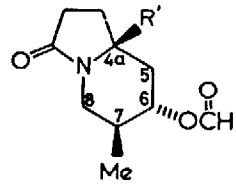
Abstract: Stereoselective cyclisation of lactams 1-4 in HCOOH leads to enantiomeric heterocycles 5-8 in excellent yields.

Recently Maryanoff and McComsey[2] described the stereoselective synthesis of substituted tetrahydroisoquinoline derivatives. The latter work prompts us to report our results on stereoselective olefin cyclisations in which the stereocontrol is exerted by remote substituents in the olefin moiety. As indicated before[3] the intermediate sec and tert cyclic α-acyliminium ions appeared to be highly reactive initiators of non-enzymatic π-cyclisations. The introduction of a chiral centre in the olefin substrate will be shown of added synthetic value for the latter technique especially with regard to the stereoselective synthesis of saturated polyheterocycles.

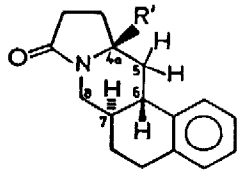
The lactams 1 to 4[4] were considered to be the key model substrates since cyclisation of the latter compounds in formic acid would indicate (i) the degree of stereoselection induced by the relatively small CH_3-substituent in lactams 1 and 2[5] and (ii) the possibility of transferring the asymmetric induction onto a second-chain linked-aromatic substituent in lactams 3 and 4.

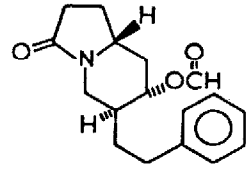
On cyclizing racemic ethoxylactam 1 in HCOOH (r.t./18 hr) 89% of the crude yield (88%) consisted of isomer 5 (by ^{1}H NMR). In addition three other stereoisomers could be detected as shown by the formate H-resonances. M.p. 5: 82-84.5° (dipe). ^{1}H NMR δ(CCl_4): 8.01 (s, 1H, O$\overset{O}{\overset{\|}{C}}$H); 4.65 (d of t, 1H, H_6; $J_{6,5eq} = 4$ Hz, $J_{6,5ax} = J_{6,7} = 11$ Hz); 4.04 (d of d, 1H, H_{8eq}; $J_{gem} = 13$ Hz, $J_{8eq,7} = 5$ Hz); 3.43-3.77





	1	2	3	4	5	R' = H
R =	Me	Me	CH_2CH_2Ph	CH_2CH_2Ph		
X =	H,OEt	OH,Me	H,OEt	OH,Me	6	R' = Me





7 R' = H

8 R' = Me

9

(m, 1H, H_{4a}); 1.26 (q, 1H, H_{5ax}; J = 12 Hz); 1.95 (d, 3H, $C\underline{H}_3$; J = 7 Hz). The high stereoselectivity encountered in the C_7-unsubstituted series[9] (isomer ratio of formates better than 9:1) was maintained in the latter ring closure. A similar observation was made in the HCOOH-cyclisation of the tert OH-lactam 2 (18 hr/r.t.), which afforded a somewhat higher yield (81%) of crude 6 again compared with the C_7-unsubstituted compound[10]. According to the ^{1}H NMR the crude yield contained 86% of one isomer 6 (formate -H). M.p. 6: 118-120° (dipe). ^{1}H NMR $\delta(CDCl_3)$: 8.08 (s, 1H, $O\underset{\underset{O}{\|}}{C}\underline{H}$); 4.93 (d of t, 1H, H_6; $J_{6,7} = J_{6,5ax} = 11$ Hz, $J_{6,5eq} = 4$ Hz); 4.10 (d of d, 1H, H_{8eq}; $J_{8eq,7} = 5$ Hz; $J_{gem} = 14$ Hz); 1.33 (s, 3H, N-C-$C\underline{H}_3$); 0.96 (d, 3H, -CHC$\underline{H}_3$; J = 6.5 Hz). A rationale for both results can be given in terms of a favoured pseudo-equatorial position for the C_7-substituent in a chair-like transition state. The avoidance of a single 1.3 diaxial C_7-Me/C_5-H interaction is assumed to be the main driving force for the observed preference.

Consecutive C-C bond formation promoted by the α-acyliminium ion has been shown to proceed through trans coplanair addition to the olefin in a synchronous[11] process. Combining this behaviour with the aforementioned asymmetric induction by a C_7-substituent would allow the stereoselective synthesis of annelated benzo[f]isoquinoline derivatives.

Thus treatment of the C_7-phenethyl olefin OEt-lactam 3 in HCOOH at r.t. for 18 hr. leads to nearly quantitative formation of racemic tetracyclic 7 solely possessing the C_6-C_7 trans configuration. The latter stereochemistry was unambiguously determined by first-order analysis of the 300 MHz spectrum, which inter alia showed H_{5ax} at δ1.15 separated from the other signals and confirmed by decoupling experiments. Only traces (<9%) of bicyclic 9 were produced resulting from intermolecular capture of the transient cation by the strongly nucleophilic reaction medium. M.p. 7: 132.0-133.5° (dipe). ^{1}H NMR δ($CDCl_3$): 7.05-7.25 (m, 4H, Ph-H); 4.20 (d of d, 1H, H_{8eq}; J_{gem} = 13 Hz; $J_{8eq,7}$ = 3.5 Hz); 3.64 (m, 1H; $J_{4a,5ax}$ = 12 Hz); 2.60 (m, 1H, H_{5eq}); 1.15 (q, 1H, H_{5ax}; J_{gem} = $J_{5ax,6}$ = 12 Hz).

By analogy upon HCOOH-treatment (120 hr/r.t.) tert OH-lactam 4 underwent complete conversion to tetracyclic 8. No trace of the bicyclic formate could be detected in ^{1}H NMR (100 MHz). M.p. 8: 121.0-123.0° (dipe). ^{1}H NMR δ($CDCl_3$): 7.05-7.23 (m, 4H, Ph-H); 4.10 (d of d, 1H, H_{8eq}; $J_{8eq,7}$ = 4 Hz, J_{gem} = 13 Hz); 1.35 (s, 1H, CH_3).

The highly uniform stereochemical outcome of the ring closure reactions of 3 and 4 imply a concerted pathway, proceeding through a product-like TS, in which the non-bonded 1.3-interactions are minimized in favor of the C_7-β-isomer.

These results point out that the presence of a chiral centre in the olefin substrate is coupled with a high degree of asymmetric induction, which in turn gives rise to the stereoselective formation of natural trans-fused-ringsystems.

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4. Starting materials are readily available via deconjugative alkylation of crotonate ester[5] and subsequent LAH-reduction to afford the homo-allyl-alcohol. The latter is coupled with succinimide by the oxidation-reduction technique[6] and the product reduced with $NaBH_4$ in presence of HCl. Upon "acid working up"[7] ethoxylactams 1 and 2 were isolated after column chromatography in almost quantitative yields prior to cyclisation. Tert hydroxylactams 3 and 4 were obtained by addition of MeMgCl at the imid carbonyl. The hydroxylactams were submitted to cyclisation as crude products to prevent decomposition upon recrystallisation or chromatography.
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