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BIOMIMETIC HETEROCYCLISATION OF ARYL OLEFINS ONE-STEP FORMATION OF TWO CARBON–CARBON BONDS†

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Abstract—Cyclisation of ethoxylactam **5** in formic acid at room temperature gives rise to stereospecific formation of **9**. Similar reaction of the olefin **6** possessing unnatural geometry also proceeds stereospecific and in quantitative yield to the tetracyclic product **10**. The acetylene **7** equally affords **11**. Upon Me-substitution of the olefinic double bond the cyclisation of **8** has to be carried out in trifluoroacetic acid–dichloromethane in order to obtain a 84% yield of **12** again formed with a high degree of stereoselectivity. The results are discussed on the basis of a mechanism involving synchronous bond formation.

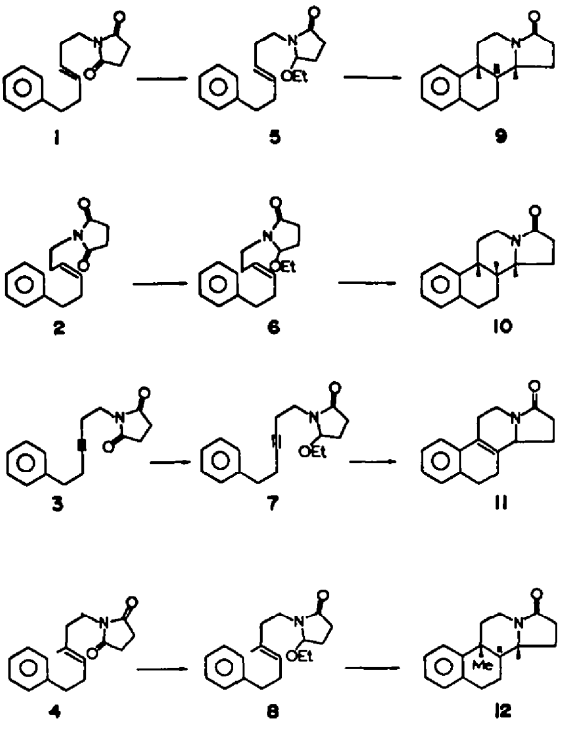
In contrast to the great number of immonium induced C–C bond formations known to-day both in biosynthetic routes to alkaloids[1] as well as in the synthesis of heterocycles,[2] reactions in which two or more C–C bonds are created in a simultaneous fashion to form part of a polyheterocyclic system are virtually unknown. Yet in view of the current interest in carbocyclic olefin cyclisations[3] it might be anticipated that the latter type of reaction offers interesting opportunities for extended synthetic applications, while in addition valuable mechanistic information may come available. Since we were engaged in studies on the heterocyclisation of monoolefins[4] in which the cyclic acylimmonium species was shown to behave as a highly reactive initiating centre for cationic olefin cyclisations, it appeared most logic to extend this work to diolefins, in particular aryl olefins of types **1–4**. The eventual ringclosed materials could be analyzed without ambiguity on the basis of previous synthetic efforts.[5]

Moreover, the compounds selected were expected to give essential data on required structural characteristics for a consistent way of describing the reaction pathway. In the latter respect expecially the Z-isomer **2** and the Me-substituted E-isomer **4** were of vital interest. Furthermore, the alkynylderivative **3** was expected to provide information on the possible incorporation of yne units in polyolefin heterocyclisations.

The following general procedure was selected for ring closure: according to the method described before[6] the imides **1–4** were reduced with $NaBH_4/H^{\oplus}$ and instantly converted into the ethoxylactams **5–8**, which were submitted to cyclisation in acid medium.

Starting materials. The imides **1–3** are synthesized as represented in Scheme 2. 4 - Phenyl - 1 - butyne **13** is obtained by coupling of benzyl bromide and propargyl magnesium bromide. The Li-acetylide of **13** is subsequently alkylated with ethyleneoxyde in DMSO. The so obtained 6 - phenyl - 3 - hexynol - 1 **14** is the starting material for the synthesis of the imides **1–3**.

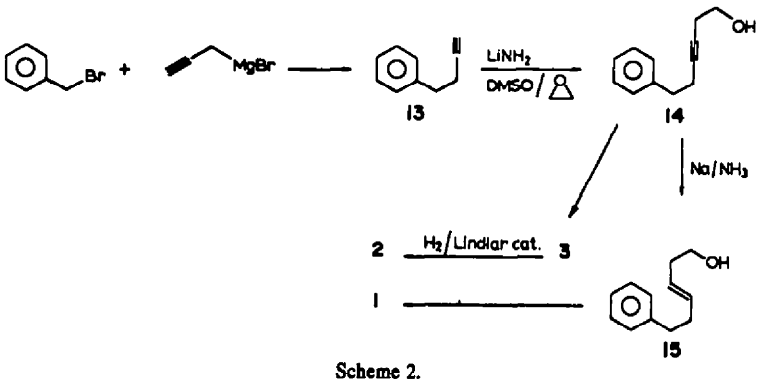
According to Mitsunobu[7] **14** is coupled with succinimide and **3** is separated from triphenylphosphoniumoxyde by fractional crystallization. An additional crop of **3** is obtained by column chromatography of the mother liquor thus giving rise to a combined yield of 69%. Hydrogenation of **3** with Lindlar catalyst leads selectively to the Z-olefin **2**. In order to synthesize the E-olefin imide **1**, alcohol **14** is treated with sodium in ammonia yielding selectively 6 - phenyl - 3 - (E) - hexanol - 1 **15** in 97% yield. Condensation of **15** with succinimide affords imide **1** in 48% yield after fractional crystallization.



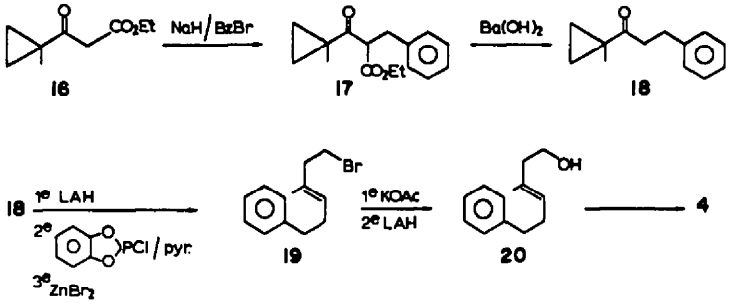
Scheme 1.

The synthesis of the Me substituted E-olefin **4** has been accomplished via a Julia–Johnson olefin synthesis,[8] as outlined in Scheme 3. The key step in this route is the efficient cyclopropylcarbinyl→homoallylic rearrange-

†Published in part; cf. J. Dijkink and W. N. Speckamp, *Tetrahedron Letters* 935 (1977).



Scheme 2.



Scheme 3.

ment, which proceeds highly stereoselectively. Alkylation of the anion of ketoester **16** with benzyl bromide gives **17**, which is decarboxylated without purification by refluxing in $EtOH/H_2O$ with $Ba(OH)_2$. The so-obtained ketone was reduced with LAH after distillation yielding carbinol **18**. Rearrangement of **18** gave bromide **19**.

Due to phosphate impurities **19** is hard to purify and therefore the product is directly converted into alcohol **20** by refluxing in DMF with K-acetate and reduction of the so formed acetate with LAH. After distillation **20** is obtained in 61% yield (from **18**). Coupling with succinimide provides **4** in 42% yield after column chromatography and crystallization.

Imides **1–4** can easily be reduced by $NaBH_4/H^{\oplus}$ at 0–5° as described in earlier papers.[9] The initially formed hydroxylactams are directly converted to the ethoxylactams, which can be purified by chromatography. Ethoxylactams **5–8** are obtained as pure oils in 77–88% yields.

Cyclisation results. Treatment of the Z- and E-olefine **5** and **6** with formic acid gave a quantitative formation of tetracyclic compounds obtained as single stereoisomers. Thus when ethoxylactam **5** is stirred in formic acid for 18 hr at room temperature the crystalline residue obtained after work-up consists of *trans - anti* - desmethoxy - 13-aza - 18 - norestrone **9**. From the ^1H NMR spectra of the crude reaction product no indication can be found for the formation of other isomeric compounds. In the same manner ethoxylactam **6** has been cyclized to the *cis - syn* - desmethoxy - 13 - aza - 18 - norestrone **10**. Again the crude reaction product consists, according to the ^1H NMR spectra, of a single isomer.

The ^1H NMR spectra of **9** and **10** show significant differences between 3.0 and 5.0 ppm, which is the region where protons at C_{12} and C_{14} absorb. Due to the anisotropy of the amide function protons at C_{12} differ largely in chemical shift.[10] This effect results in a downfield shift of H_{12} eq. Upon comparison of the ^1H NMR spectra of **9** and **10** with the spectra of the corresponding bicyclic compounds **21** and **22** (cyclisation products of E- and Z-olefins)[4] a highly significant resemblance of the spectral part between 3.0 and 5.0 ppm is observed (Fig. 1).

In particular the similar splitting patterns for the N–CH signals are quite characteristic. Molecular models of *cis* compounds **10** and **22** show some steric hindrance between protons of the pyrrolidone ring and the axial substituent at the C_8-carbon of the piperidine ring. This causes some deformation of the piperidine ring, which results in a chemical shift difference for H_{8a} (**22**) and H_{14} (**10**).

Additional support for structures **9** and **10** was found upon comparison of **9** and **10** with the 13 - aza - 18 - norestrones, synthesized[11] via reduction of the corresponding 8,9 - dehydro-compound with sodium in ammonia and hydrogenation with Pd/C catalyst.

The *trans - anti* - 13 - aza - 18 - norestrone **24** could also be obtained via an aryl olefin acylimmonium cyclisation of **23**, which was prepared according to the Julia–Johnson method starting from cyclopropylcarboethoxy methyl ketone and *m*-methoxybenzyl bromide. Cyclisation of **23** in formic acid gives the *o*- and *p*-methoxy 13 - aza - steroids **24** and **25** in a 1.8:1 ratio[12] (Scheme 4).

About the same ratio of **24** and **25** was observed upon cyclisation of **23** is dichloroacetic acid.

Cyclisation of **7** in formic acid is complete after 18 hr at room temperature. Again only one compound is formed. This product, isolated as an oil, is not very stable probably as a result of a facile hydride loss from C_{14}. After crystallisation a yield of only 53% of **11** is obtained, the mother liquor being composed of different polymeric products. Assignment of structure **11** is based upon comparison of the PMR and IR spectra of **11** and 8,9 - dehydro - 13 - aza - 18 - norestrone.[13] In the mass spectrum of **11** the main fragmentation observed is the loss of an H atom as indicated by the *m/e* of 238 (M^+-1,

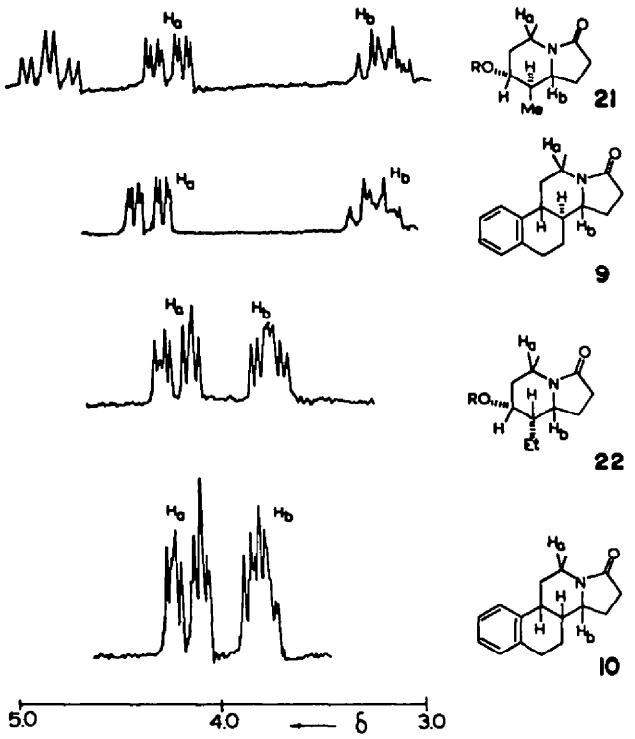
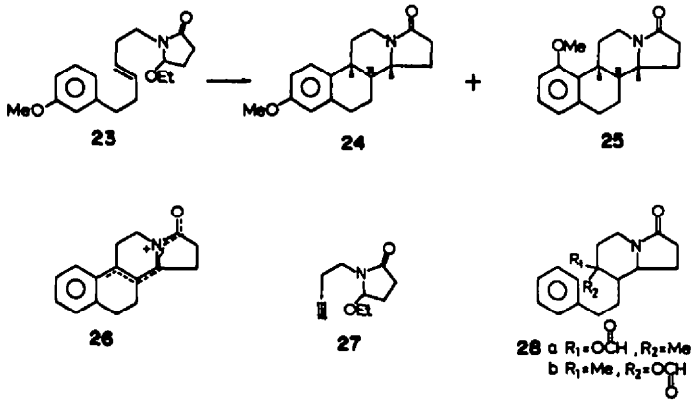


Fig. 1. Comparison of 100 MHz ^1H NMR spectra of cyclisation products. Solvent $CDCl_3$.



Scheme 4.

100%), which is ascribed to ion **26**. This again points to a facile loss of hydrogen from C_{14}.

Interestingly, when a comparison was made between the cyclisation rates of **27** and **3** the latter reaction was observed to proceed considerably faster. Although kinetic measurements have not been carried out, it may be tempting to speculate on the origin of this effect, particularly since other alkylsubstituted acetylenic substrates do not show this behaviour.[14] At first sight it seems, that the aromatic ring possesses a propensity to enhance the formation of the first C–C bond because of its active participation[15] in the construction of the second C–C bond. Definitive conclusions, however, have to await further investigation.

Treatment of the methylsubstituted E-olefin **8** with formic acid affords a mixture of mono- and dicyclisation products. GLC analyses of the crude reaction product shows one main peak (40%), corresponding to **12**. The PMR spectra ($CDCl_3$) of the crude cyclisation product show two singlets at δ 7.96 and δ 8.04 (O$\overset{O}{\overset{\|}{C}}$H) in a 1:1 ratio; together with two singlets at δ 1.55 and δ 1.59 which are attributed to the presence of monocyclisation products **28a** and **28b**. Besides the Me signal of **12** at δ 1.16 another small singlet at δ 1.21 accounting for less than 5% of material can be obserbed. The presence, therefore, of an isomer of **12** cannot be excluded.

In view of the observed sensitivity of polyolefin cyclisations towards the acidity and nucleophilic character of the cyclisation medium, a number of additional cyclisations of **8** were carried out.

Table 1 shows the percentages of **12** present in the crude reaction product, as measured by GLC analyses.

As can be seen from the CF_3COOH result the cyclisation of **8** → **12** is promoted considerably upon using a strong acid in a solvent of low nucleophilicity.

The CF_3COOH cyclisation (10% CF_3COOH/CH_2Cl_2 at

Table 1. Cyclisation reactions of **8** affording **12**

Time	Temp.	Acid used	Yield†
18 hr	r.t.	HCOOH	40%
30 min	5°C	$CHCl_2COOH$	75%
20 hr	r.t.	Ac_2O–AcOH	≈70%
2 hr	0–10°C	HCl–EtOH‡	49%
70 hr	r.t.	pTsOH–C_6H_6	29%
30 min	5°C	CF_3COOH–CH_2Cl_2	89%

†Determined via GLC analysis.

‡During the conversion **4**→**8** under similar conditions none of **12** is formed, presumably because of the presence of borate esters.

5°) also allows isolation of **12** by crystallisation from the crude reaction mixture in 84% yield. Its structure was evidenced from the ^{1}H NMR data and could be proven by NOE measurements. Irradiation of the singlet at δ 1.10 (C_9–Me) shows an increase of the H_{14}-signal at δ 3.46 (12–16%). This result establishes a 1–3 diaxial interaction between H_{14} and the axial C_9-methyl group which is in accordance with a *trans-anti* structure for **12**.

Discussion and mechanistic aspects. So far much of the discussion on biomimetic olefin cyclisations has been centered towards the question whether cyclisation reactions of this type proceed via a synchronous or a step-wise bond formation process. Although the outcome of this work does not solve this problem unambiguously, leaving undecided the question whether one straightforward answer can be given for all of the different olefin cyclisations, some observations in the present work are of general interest.

When comparing the results of the cyclisation of ethoxylactams possessing a single internal olefinic bond with the experimental outcome on analogous models possessing an additional aromatic ring, a few remarkable facts are noteworthy. First of all the relative mildness and efficacy of the ring closure are remarkable in addition to its stereospecific character. Although this may seem an obvious outcome for the reaction of **5** one has to keep in mind that the cyclisation of **6** has to proceed from an unnatural geometry. Particularly in view of the lack of reference material in carbocyclisation studies and considering the necessary chairlike transition state for a synchronous process possessing several unfavorable non-bonded interactions the results are not self-evident. In reverse the exclusive formation of the *cis-syn* derivative **10** can be best explained via a synchronous process since in the stepwise reaction an intermediate **A** is expected to be formed (Fig. 2).

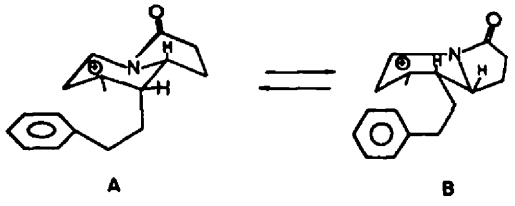
The latter may rapidly convert into the boat-like form **B** via conformational inversion, especially since **A** suffers from steric interactions with the pyrrolidone ring. Moreover, one of the destabilizing 1,4 flagpole interactions is missing in the heterocyclic ring. Thus it may be anticipated that in the event of partial cyclisation to **A** isomerisation to **B** is energetically possible, which would result in the formation of a second *trans-syn* isomer. Since none of the latter compound could be detected in the crude cyclisation mixture a synchronous pathway for the formation of two C–C bonds in one step seems likely. Similar arguments may be derived from the ring closure of **8**. Although the yield of **12** in HCOOH is comparatively low its formation is most probably not accompanied by significant amounts of other stereoisomers. In view of the fact that the reaction of the corresponding monoolefin affords two stereoisomers in almost equal ratio[6] the present result is remarkable. Virtually there is no obvious reason why in a stepwise process the formation of a *cis-anti* isomer would be completely prohibited. Furthermore, the concurrent formation of the formates **28a** and **28b** which do not undergo cyclisation upon additional exposure to HCOOH points to the existence of a second closely related pathway in which the intermediate carbenium character is more dominant.

Therefore the cyclisation of **8** to **12** may also be regarded as a synchronous process.

Finally the CF_3COOH result in which bond formation over two C–C linkages of **8** is found to occur almost exclusively under formation of the *trans-anti* isomer **12** also supports the idea of two possible cyclisation routes, which can be visualized as extremes on the reaction scale.

In conclusion the results on the acylimmonium cyclisations seem to indicate that in case of a competition between a synchronous and a stepwise process the C–C bond formations proceed "the most optimal concerted" in a medium of low nucleophilicity. Furthermore the degree of concertedness may also depend on the order of increasing nucleophilicity of the participating π-bonds. Lastly the result on the cyclisation of the Z-isomer **6** shows the concept of biomimetic olefin cyclisation also to be applicable with olefins of unnatural geometry.

Finally, the method gives promising results from a synthetic point of view with regard to the structural variations possible in different parts of the molecule. Further work in this area is therefore actively pursued.



A B

Fig. 2. Possible transition states for stepwise ringclosure.

EXPERIMENTAL

M.ps and b.ps are uncorrected. Analyses were carried out by Messr. H. Pieters of this laboratory. IR spectra were recorded on Unicam SP 200 or Perkin–Elmer 125. Absorptions are given in cm^{-1}. ^{1}H NMR spectra were measured on a Varian A-60 or a HA-100 instrument. Chemical shifts are reported as δ values in ppm relative to TMS (δ TMS = 0.0 ppm).

4 - Phenyl - 1 - butyn **13**. A soln of freshly distilled propargyl bromide (119 g; 1 mole) in anh. ether (200 ml) was added dropwise to 28 g Mg in ether (150 ml) with stirring at 5–10° (75 min). After additional stirring for 1 hr at 10°, benzyl bromide (95 ml; 0.8 mole) in ether (100 ml) was added dropwise to this soln. The mixture was kept for 2 hr at 5° and 20 hr at r.t. THF (500 ml) was added meanwhile removing ether by distillation after which was refluxed for 3 hr. After standing overnight the mixture was poured into sat NH_4Cl aq (300 ml) and water (300 ml) and extracted with ether (7x). The combined extracts were washed with sat NaCl aq, dried over $MgSO_4$ and evaporated. Distillation of the residue afforded 60.99 g of **13**, b.p. 81–96°/15 mm. N_{D25} 1.5219 (Lit.[16] N_{D25} 1.5210). Yield: 59%. IR ($CHCl_3$): 3300 (C≡CH), 2100 (C≡C). ^{1}H NMR (CCl_4): 1.78 (t, 1H, C≡CH), 2.1–3.0 (m, 4H, Ph–CH_2–CH_2–C≡C), 6.9–7.4 (5H, aromatic H).

6 - Phenyl - 3 - hexynol - 1 **14**. To a cooled (−70°) soln of Li-amide (prepared from 1.38 g Li and 200 ml ammonia) **13** (26 g; 0.2 mole) was added (10 min) with stirring. The acetone/CO_2 bath was removed and DMSO (100 ml) was added dropwise. Ammonia was allowed to evaporate until temp. reached 15°. With ice-cooling ethyleneoxyde (15 ml, 0.3 mole) added. After stirring for 0.5 hr at

r.t. the mixture was poured into 600 ml ice-water and extracted with ether (6×). The combined extracts were washed successively with sat NH_4Cl aq and sat NaCl aq, dried over $MgSO_4$ and evaporated. Distillation of the residue gave 3.52 g of **13** and 20.98 g of **14** (b.p. 120–125°/0.2 mm). Yield: 60%. IR ($CHCl_3$): 3500 (OH). ^1H NMR (CCl_4): 2.1–3.0 (7H, Ph–CH_2–CH_2–C≡C–CH_2–C–OH), 3.51 (t, 2H, –CH_2OH), 6.7–7.4 (5H, aromatic H). (Found: C, 82.7; H, 8.1. $C_{12}H_{14}O$ M = 174.23. Calc.: C, 82.72; H. 8.10%).

6 - *Phenyl* - 3 - (*E*) - *hexenol* - 1 **15**. **14** (5.22; 30 mmole) was added dropwise (10 min) to a refluxing soln of Na (2.07 g, 3 eq) in ammonia. After refluxing for 2 hr ammonia was allowed to evaporate, while subsequently ether and sat NH_4Cl aq was added. The aqueous layer was extracted with $CHCl_3$ (3×). Washing of the combined organic layers with sat $NaHCO_3$ aq, drying over Na_2SO_4 and evaporate afforded 5.16 g of oily **15**. Yield: 97%. An analytical sample was purified by distillation, b.p. 95°/0.1 mm. IR ($CHCl_3$): 3500 (OH). ^1H NMR (CCl_4): 1.9–2.9 (7H, Ph–CH_2–CH_2–C≡C–CH_2–C–OH), 3.44 (t, 2H, CH_2OH), 5.40 (m, 2H, –CH=CH), 6.9–7.4 (5H, aromatic H). (Found: C, 81.9; H, 9.2. $C_{12}H_{16}O$ M = 176.23. Calc.: C, 81.77; H, 9.15%).

1 - N - *Succinimide* - 6 - *phenyl* - 3 - *hexyn* **3**. To an ice-cooled soln of succinimide (3.81 g; 39 mmole), alcohol **14** (5.22 g; 30 mmole) and Ph_3P (7.86 g; 30 mmole) in freshly distilled THF (50 ml) dimethylazodicarboxylate (4.38 g; 30 mmole) in THF (20 ml) was added with stirring. The mixture was stirred for 18 hr at r.t. The solvent was evaporated, the residue dissolved in $CHCl_3$ and washed successively with 1 N NaOH, sat NaCl aq, 2 N HCl (2×) and sat $NaHCO_3$ aq. The $CHCl_3$ soln was dried over $MgSO_4$ and evaporated. From the residue Ph_3PO was crystallized with EtOAc. **3** Could be crystallized from the evaporated filtrate with EtOH: 3.45 g, m.p. 83–85°; second fraction: 1.40 g, m.p. 82–85°. Column chromatography (SiO_2/$CHCl_3$ acetone 4:1) of the mother liquor afforded another crop: 0.47 g, m.p. 82–85°, yield: 69%. IR ($CHCl_3$): 1770 and 1700 (imide). ^1H NMR ($CDCl_3$): 2.2–3.0 (10H), 3.62 (t, 2H, N–CH_2), 7.0–7.4 (5H, aromatic H). (Found: C, 75.3; H, 6.7; N, 5.5. $C_{16}H_{17}NO_2$. M = 255.30. Calc.: C, 75.27; H, 6.71; N, 5.49%).

1 - N - *Succinimide* - 6 - *phenyl* - 3 - (*E*) - *hexene* **1**. In the way as described for **3**, alcohol **15** was converted to **1**. By fractionated crystallization from EtOAc and EtOH **1** was obtained in 48% yield. Recrystallization of an analytical sample afforded m.p. 53–55°. IR ($CHCl_3$): 1770 and 1700 (imide). ^1H NMR ($CDCl_3$): 2.0–2.9 (10H), 3.50 (t, 2H, N–CH_2), 5.42 (m, 2H, CH=CH), 7.0–7.4 (5H, aromatic H). (Found: C, 74.8; H, 7.5; N, 5.4. $C_{16}H_{19}NO_2$, M = 257.32. Calc.: C, 74.68; H, 7.44; N, 5.44%).

1 - N - *Succinimide* - 6 - *phenyl* - 3 - (*Z*) - *hexene* **2**. 2.00 g of imide **3** was hydrogenated in EtOH with 30 mg of Lindlar catalyst at r.t. (1 atm) for 16 hr. After filtration and evaporation 2.06 g of **2** was obtained as a colourless oil. An analytical sample was purified by bulb-to-bulb distillation (200°/0.05 mm). IR ($CHCl_3$): 1770 and 1700 (imide). ^1H NMR (CCl_4): 2.0–2.8 (10H), 3.40 (t, 2H, N–CH_2), 5.39 (m, 2H, CH=CH), 7.0–7.4 (5H, aromatic H). (Found: C, 74.8; H, 7.4. $C_{16}H_{19}NO_2$, M = 257.32. Calc.: C, 74.68; H, 7.44%).

3 - *Phenyl* - 1 - (1' - *methylcyclopropyl*) - *butan* - 1 - *ol* **18**. NaH 60% disp. (4.12 g; 0.103 mole) was washed under N_2 with light petroleum. Freshly distilled THF (25 ml) was added. With ice-cooling the suspension was stirred while a soln of keto ester **16** (17.0 g; 0.1 mole) in THF (25 ml) was added over a period of 45 min. After stirring for 0.5 hr at r.t. benzyl bromide (17.1 g; 0.1 mole) was added gradually. The mixture was stirred for 20 hr at r.t. and 1 hr at reflux. Water was added until the ppt had dissolved and the aqueous layer was extracted with ether (4×). The combined org. layers were washed with sat NaCl aq, dried over $MgSO_4$ and evaporated. The obtained yellowish liquid (26.04 g **17**) was employed in the next step without purification. IR ($CHCl_3$): 1730 (ester C=O), 1690 (ketone C=O). ^1H NMR (CCl_4): 0.3–1.4 (10H), 3.05 (d, 2H, Ph–CH_2), 3.77 (t, 1H, CH–CO_2Et), 4.08 (q, 2H, OCH_2), 6.9–7.4 (5H, aromatic H).

A mixture of crude **17** (26.0 g; 0.1 mole), 200 ml EtOH, 75 ml H_2O and 94.5 g $Ba(OH)_2$ 8 aq was heated at reflux for 16 hr. The mixture was cooled and poured into an ice/HCl mixture and extracted with $CHCl_3$ (3×). The $CHCl_3$ layers were washed with sat $NaHCO_3$ aq and dried over $MgSO_4$. After evaporation of the solvent, the residue was submitted to distillation. 15.13 g of 3 - Phenyl - 1(1' - methylcyclopropyl) - butan - 1 - one was obtained with b.p. 85–90°/0.1 mm, yield 82%. IR ($CHCl_3$): 1600 (ketone C=O). ^1H NMR (CCl_4): 0.2–1.5 (7H), 2.4–3.1 (m, 4H, Ph–CH_2–CH_2–CO–), 6.8–7.4 (5H, aromatic H).

A soln of the ketone (13.16 g; 71.5 mmole) in anhyd ether (50 ml) was added over a period of 15 min to a stirred mixture of LAH (2.66 g) in ether (25 ml). During addition the mixture was cooled in an ice bath. After stirring for 3 hr at r.t., with water saturated ether and subsequently sat $NaSO_4$ aq and Na_2SO_4 were added. After standing overnight the white ppt was filtered off and washed with ether. Evaporation of the filtrate afforded a colourless oily residue (13.26 g). An analytical sample was purified by distillation, b.p. 110°/1 mm. IR ($CHCl_3$): 3500 (OH). ^1H NMR (CCl_4): 0.0–0.8 (4H), 0.98 (s, 3H, Me), 1.4–3.0 (5H), 6.9–7.3 (5H, aromatic H). (Found: C, 82.1; H, 9.6. $C_{13}H_{18}O$, M = 190.27. Calc.: C, 82.06; H, 9.54%).

1 - N - *Succinimide* - 6 - *phenyl* - 3 - *methyl* - 3 - (*E*) - *hexene* **4**. A soln of **18** (9.50 g; 50 mmole) in anhyd ether (50 ml) was added to a cooled (ice bath) mixture of *o*-phenylene phosphorochloridite (9.50 g; 55 mmole), dry pyridine (10 ml) and ether (75 ml). The resulting suspension was stirred for 2 hr at r.t. Then it was extracted with water, 5% aq lactic acid until washings were acid (3×), sat NaCl aq and sat $NaHCO_3$ aq. The ether soln was dried over $MgSO_4$ and concentrated to give the crude phosphite ester. The crude phosphite ester, dissolved in ether (25 ml) was added to a soln of 0.1 mole $ZnBr_2$ in anhyd ether (200 ml) and the mixture stirred for 20 hr at r.t. 200 ml H_2O and 200 ml light petroleum were added. The organic phase was washed with water (2×) and sat $NaHCO_3$ aq, dried over $MgSO_4$ and evaporated. The oily residue contained phosphate impurities and was used without purification.

The crude bromide **19** (12.40 g) was heated at 100° for 20 hr with anhyd KOAc (36 g) and anhyd DMF (200 ml). The dark-brownish reaction mixture was poured into water (1 ltr) and extracted with light petroleum, ether (2×) and EtOAc (2×). The combined org. layers were washed with water and sat $NaHCO_3$ aq, dried over $MgSO_4$ and evaporated. The residue was dissolved in anhyd ether (100 ml) and added with ice-cooling to a stirred mixture of LAH (9.12 g) and ether (50 ml). After stirring for 1 hr at r.t. aqueous ether was added, followed by sat Na_2SO_4 aq and Na_2SO_4. After standing overnight the resulting mixture was filtered. The residue obtained on evaporation of the filtrate was submitted to distillation. 5.75 g of **20** was obtained with b.p. 98–102°/0.05 mm, yield (from cyclopropylcarbinol **18**): 61%. IR ($CHCl_3$): 3300 (OH). ^1H NMR (CCl_4): 1.48 (s, 3H, Me), 3.49 (t, 2H, CH_2OH), 5.20 (m, 1H, C=CH), 6.9–7.4 (5H, aromatic H).

In the way as described for **3**, alcohol **20** (30 mmole) was converted to **4**. Column chromatography (SiO_2/$CHCl_3$ aceton 4:1) and crystallization from EtOH afforded 3.39 g of **4**, m.p. 68–70°, yield: 42%. IR ($CHCl_3$): 1780 and 1700 (imide). ^1H NMR ($CDCl_3$): 1.65 (s, 3H, Me), 2.1–2.8 (10H), 3.60 (s, 2H, N–CH_2), 5.18 (t, 1H, C=CH), 7.0–7.5 (5H, aromatic H). (Found: C, 75.4; H, 7.7; N, 5.1. $C_{17}H_{21}NO_2$. M = 271–35. Calc.: C, 75.24; H, 7.80; N, 5.16%).

Desoxy - 13 - *aza* - 18 - *norestrone* (trans-anti) **9**. To a stirred soln of 2.0 g of **1** in EtOH (150 ml) at 5° 2.0 g of $NaBH_4$ was added. While temp. was kept at 0–5°, 2 N HCl in EtOH (3 drops) was added at regular intervals (15 min) during 4 hr. The excess of $NaBH_4$ was destroyed by adding HCl in EtOH at 0–5° till Ph 2 or 3. After stirring for 1 additional hr at 0–5° the mixture was poured into dil $NaHCO_3$ aq and extracted with $CHCl_3$ (4×). The $CHCl_3$ layers were washed with sat NaCl aq, dried over $MgSO_4$ and evaporated. The oily residue was purified by column chromatography (SiO_2/$CHCl_3$ aceton 4:1) giving 1.96 g of **5**, yield: 87%. IR ($CHCl_3$): 1680 (lactam C=O). ^1H NMR: 1.17 (t, 3H, O–C–CH_3), 1.7–2.8 (10H), 2.8–3.7 (4H, N–CH_2 and O–CH_2), 4.89 (m, 1H, N–CH–OEt), 5.43 (m, 2H, CH=CH), 7.0–7.4 5H, aromatic H).

Ethoxy lactam **5** (200 mg) was stirred in HCOOH (3 ml) for 18 hr at r.t. The solvent was evaporated at reduced pressure; the residue, dissolved in $CHCl_3$, was washed with sat $NaHCO_3$ aq and dried over $MgSO_4$. After evaporation **9** was obtained as a solid (171 mg). Recrystallization from diisopropylether afforded 149 mg, m.p. 108–110°, yield: 89%. IR ($CHCl_3$): 1670 (lactam C=O); ^1H NMR ($CDCl_3$): 1.0–3.1 (13H), 3.33 (m, 1H, H_{14}), 4.31 (m, 1H, H_{12}-eq. 7.0–7.3 (4H, aromatic H). See Fig. 1. (Found: C, 79.4; H, 8.0; N, 5.8. $C_{16}H_{19}NO$, M = 241.32. Calc.: C, 79.63; H, 7.94; N, 5.80%).

Desoxy - 13 - *aza* - 18 - *norestrone* (cis-syn) **10**. In the way as

described for 1, 2 was reduced to 6, yield: 77% after column chromatography. IR ($CHCl_3$): 1690 (lactam C=O). ^1H NMR ($CDCl_3$): 1.19 (t, 3H, O–C–CH_3), 1.7–2.8 (10H), 2.8–3.7 (4H, OCH_2 and N–CH_2), 4.90 (m, 1H, N–CH_2–OEt), 5.42 (m, 2H, CH=CH), 7.0–7.4 (4H, aromatic H).

In the way as described for 9, 6 was cyclized to 10. The solid residue, obtained after work-up, was recrystallized from EtOAc and diisopropylether, m.p. 140–142°, yield: 85%. IR ($CHCl_3$): 1670 (lactam C=O). ^1H NMR ($CDCl_3$): 1.5–3.0 (13H), 3.80 (m, 1H, H_{14}), 4.15 (m, 1H, H_{12}-eq, 6.9–7.3 (4H, aromatic H). See Fig. 1. (Found: C, 79.6; H, 8.0; N, 5.7. $C_{16}H_{19}NO$, M = 241.32. Calc.: C, 79.63; H, 7.94; N, 5.80%).

Desoxy - 8,9 - dehydro - 13 - aza - 18 - norestrone 11. In the way as described for 1, 3 was reduced to 7, yield: 85% after column chromatography. IR ($CHCl_3$): 1685 (lactam C=O). ^1H NMR ($CDCl_3$): 1.21 (t, 3H, O–C–CH_3), 1.7–2.4 (10H), 3.0–3.8 (4H, N–CH_2 and O–CH_2), 5.01 (m, 1H, N–CH–OEt), 7.1–7.4 (4H, aromatic H).

In the way as described for 9, 7 was cyclized to 11. The oily residue, obtained after work-up was crystallized from ether 90 mg, m.p. 112–117°, yield: 54%. Recrystallization of an analytical sample from EtOAc afforded m.p. 117–119°. IR ($CHCl_3$): 1675 (lactam C=O). ^1H NMR ($CDCl_3$): 1.3–3.1 (11H), 4.29 (m, 1H, H_{14}), 4.40 (m, 1H, H_{12}-eq, 7.0–7.3 (4H, aromatic H). (Found: C, 80.3; H, 7.2; N, 5.9. $C_{16}H_{17}NO$, M = 239.30. Calc.: C, 80.30; H, 7.16; N, 5.85%).

Desoxy - 13 - aza - 9 - methyl - 18 - norestrone 12. In the way as described for 1, 4 was reduced to 8, yield: 81% after column chromatography. IR ($CHCl_3$): 1690 (lactam C=O). ^1H NMR ($CDCl_3$): 1.23 (t, 3H, O–C–CH_3), 1.63 (s, 3H, Me), 1.7–2.8 (10H), 3.0–3.7 (4H, N–CH_2 and O–CH_2), 4.90 (m, 1H, N–CH–OEt), 5.22 (t, 1H, C=CH), 7.0–7.4 (5H, aromatic H).

To a stirred soln of 8 (300 mg) in CH_2Cl_2 (4 ml) at 5° 0.4 ml of CF_3COOH was added. After stirring for 0.5 hr at 5°, the mixture was poured into an ice/K_2CO_3 mixture. The water phase was extracted with $CHCl_3$ (2×). The combined organic layers were dried over $MgSO_4$ and evaporated. Crystallization of the residue from diisopropylether gave 212 mg of 12, m.p. 89–94°, yield: 84%. Recrystallization of an analytical sample gave m.p. 92–94°. IR ($CHCl_3$): 1660 (lactam C=O). ^1H NMR ($CDCl_3$): 1.22 (s, 3H, C_9-Me), 1.3–3.3 (12H), 3.46 (m, 1H, H_{14}), 4.16 (m, 1H, H_{12}-eq), 7.0–7.4 (4H, aromatic H). (Found: C, 79.9; H, 8.2; N, 5.5. $C_{17}H_{21}NO$, M = 255.35. Calc.: C, 79.96; H, 8.29; N, 5.49%).

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