Monatshefte für Chemie 130, 1257–1268 (1999)

Monatshefte für Chemie
Chemical Monthly

A Synthetic Approach to Perhydro-3-isoquinolinones Bearing an Angular Methyl Group *via* Organocuprate Addition

Peter Stanetty[1,*], **M. Hassan Bahardoust**[1], **Marko D. Mihovilovic**[1], and **Kurt Mereiter**[2]

[1] Institute of Organic Chemistry, Vienna University of Technology, A-1060 Vienna, Austria
[2] Institute of Mineralogy, Crystallography, and Structural Chemistry, Vienna University of Technology, A-1060 Vienna, Austria

Summary. The addition of organocuprates to the activated C–C double bond in 2*H*-3,3a,4,5,6,7-hexahydro-2-indenone followed by trapping of the anionic intermediate with MeI as electrophile is reported. Structural assignment of the resulting product was carried out *via* its oxime using X-ray diffraction. A subsequent *Beckmann* rearrangement gave the desired title compound.

Keywords. Organocuprate addition; *Michael*-type addition; *Beckmann* rearrangement; Ergosterol biosynthesis inhibitors; X-Ray diffraction.

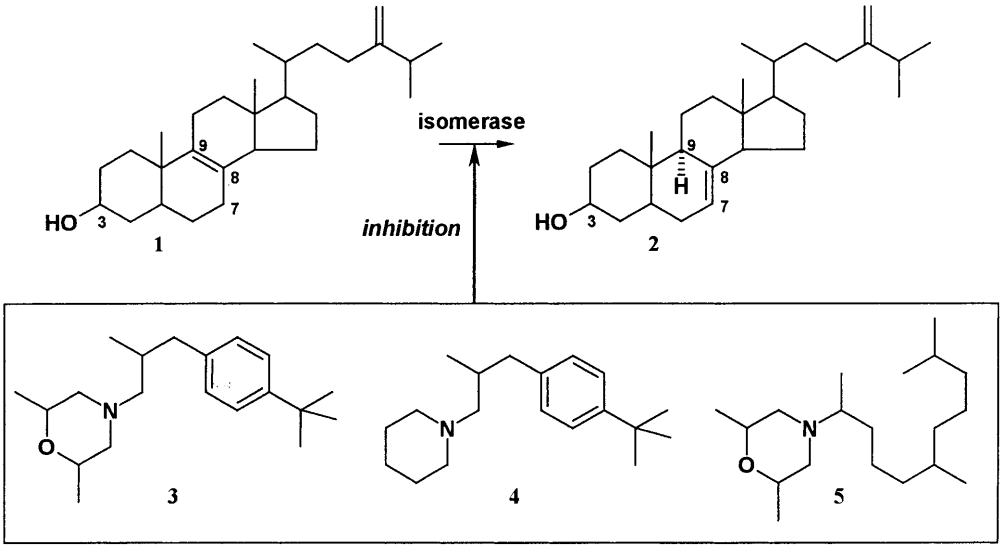
Ein Syntheseweg zu Perhydro-3-isochinolinonen mit angulärer Methylgruppe über Organocuprat-Addition

Zusammenfassung. Die Addition von Organocupraten an die aktivierte C–C Doppelbindung in 2*H*-3,3a,4,5,6,7-Hexahydro-2-indenon, gefolgt von einer Abfangreaktion des anionischen Zwischenprodukts mit MeI als Elektrophil, wurde untersucht. Die Strukturaufklärung des erhaltenen Produktes erfolgte mittels Röntgendiffraktion seines Oxims. Eine anschließende *Beckmann*-Umlagerung lieferte die gewünschte Titelverbindung.

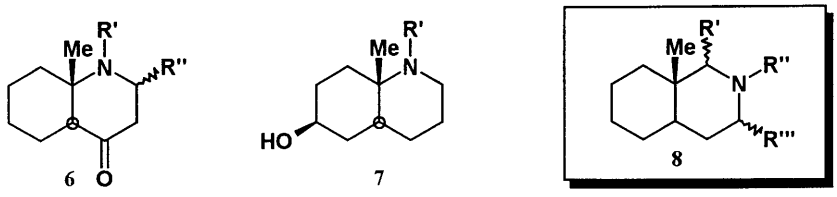
Introduction

A major target for highly selective fungicides in agrochemical disease control is represented by the biosynthesis of ergosterol [1]. The generally accepted mode of action of these compounds is the inhibition of the enzyme Δ^8-Δ^7-isomerase which is responsible for the isomerization reaction from fecosterol (**1**) to episterol (**2**) (Scheme 1) [2]. Especially perhydrated heterocyclic molecules with lipophilic side chains such as phenpropimorph (**3**), fenpropidine (**4**), or tridemorph (**5**) exhibit high biological activity and have been successfully introduced as commercial products [3].

* Corresponding author



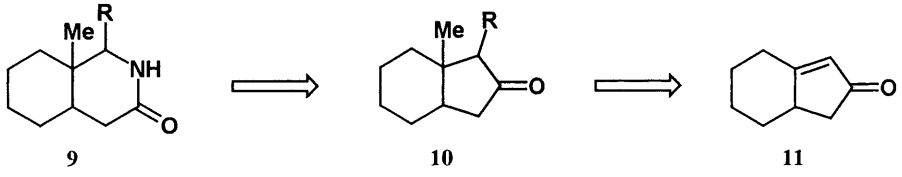
Scheme 1



Scheme 2

Compared to the monocyclic series, the field for potential bicyclic inhibitors is by far not as well investigated [4]. In an effort to close this gap we have recently started to develop synthetic routes to perhydro-quinolinones **6** and perhydro-quinolinoles **7** using hetero-*Diels-Alder* methodology [5] and reductive cyclization techniques [6] (Scheme 2). We have expected to improve the affinity of the inhibitor for the active site of the target enzyme by introducing an angular methyl group as a general structural feature. Hence, these products act as a heterocyclic mimic for parts of the steroidal skeleton.

Expanding our research in this field on isoquinolines of type **8** with an angular methyl group, we now present our first approach towards the key intermediate **9**. Retrosynthetic analysis of the system suggested access by a ring expansion reaction of the *Beckmann* type (Scheme 3). For the synthesis of the precursor **10** we envisioned a double addition technique starting from enone **11** as acceptor for a



Scheme 3

conjugate 1,4-addition and introducing the angular group *via* an organocuprate. Quenching of the intermediate anion with a suitable electrophile would then enable access to the system substituted in position 1 in one step.

Results and Discussion

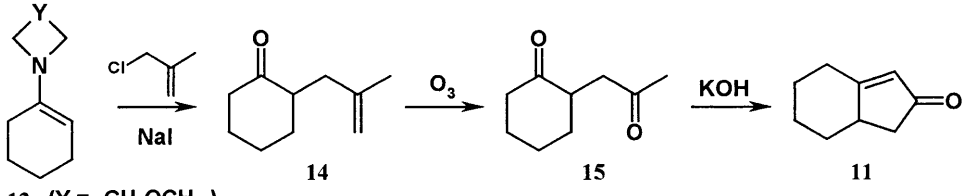
Synthetic aspects

The synthesis of the *Michael* acceptor **11** was initiated by *Stork* alkylation of cyclohexanonenamine **12** or **13** with 3-chloro-2-methylpropene to give **14** (Scheme 4) [7]. Best results were obtained in the presence of one equivalent of NaI. The optimized procedure reported for this conversion minimizes troublesome side reactions such as double alkylation. Ozonolysis of **14** gave the diketone **15** in excellent yield. This two-step procedure allows substantially improved access to **15** avoiding alternative routes using readily decomposing iodides [8] or expensive reagents [9]. Subsequent condensation of precursor **15** under basic reaction conditions led to the *Michael* acceptor **11** [10].

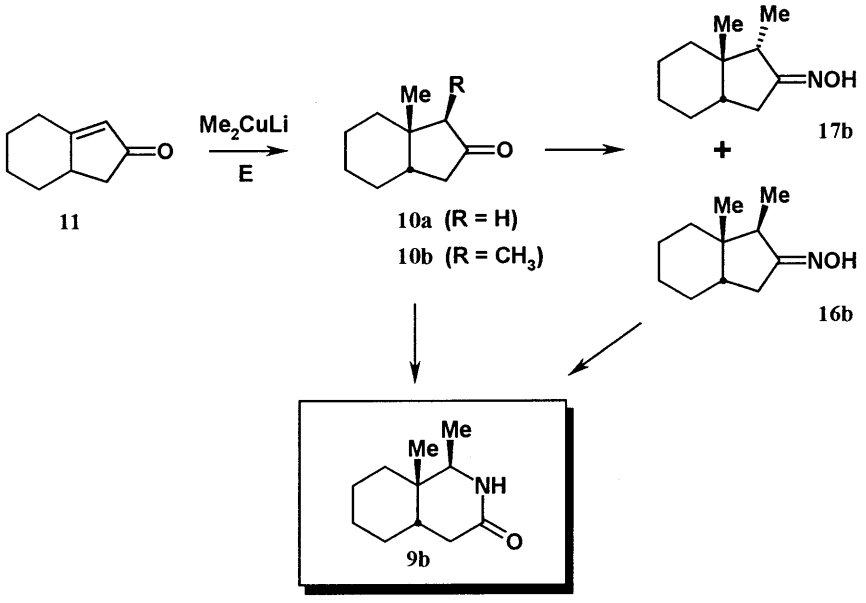
Michael type addition with Me_2CuLi prepared *in situ* followed by hydrolysis ($E = H^+$, $R = H$) gave ketone **10a** with *cis*-annelation of the cyclic system as expected from similar results in the literature [11] (Scheme 5). Since we encountered some problems when we tried to trap the intermediate anion with an alkyliodide ($E = MeI$, $R = Me$), *HMPA* was added to the reaction mixture after the initial addition of Me_2CuLi in order to enhance the reactivity of the intermediate species. With this modification the conversion to one single compound **10b** [12] was improved significantly.

The stereochemistry of **10b** was established after conversion to the corresponding oxime **16b**. X-Ray diffraction of a crystal (Fig. 2) confirmed that the initial attack of the organometallic species occurs *cis* to the proton at the annelation site. In contrast to our expectations, the position of the second methyl group was found to be *cis* to the angular substituent. This result is remarkable since in similar reactions the effect of steric hindrance usually directs the attack of the electrophile into the *trans* position [13].

Conversion of the ketone **10b** to the corresponding oxime proved to be very sensitive to the reaction conditions. Depending on the base used, substantial amounts of the epimeric compound **17b** were isolated (Table 1, entry 2). In an optimization process (entries 1, 3–5) this undesired side reaction could be suppressed completely, maximizing the yield of **16b** (entry 6). According to the



Scheme 4



Scheme 5

Table 1. Product ratio for the oxime formation from ketone **11b**

Entry	Conditions	**16b**	**17b**
1	$H_2NOH \cdot HCl/HCl/EtOH$	15%	0%
2	$H_2NOH \cdot HCl/NaOAc$	45%	13%
3	$H_2NOH \cdot HCl/MeOH$	47%	0%
4	$H_2NOH \cdot HCl/NaOH$	38%	0%
5	$H_2NOH \cdot HCl/NaOH/MeOH$	55%	0%
6	$H_2NOH \cdot HCl/pyridine/MeOH$	97%	0%

crystal structure determination, the OH-group of the oxime **16b** is in *anti*-position to C9 (labeling according to Fig. 2). Hence, both electronic and steric aspects favor migration of this center, leading to the desired 1,8a-dimethyl-3-isoquinolinone **9b**. However, the ring expansion reaction under standard *Beckmann* rearrangement conditions using strong mineral (Table 2, entry 1) or organic (entry 2) acids gave only small amounts of the desired target compound **9b**. The yield of heterocyclic material was successfully increased by improving the leaving group quality of the

Table 2. Optimization of the *Beckmann* ring expansion reaction depending on the starting material (SM)

Entry	Condition	SM	Yield
1	*conc.* H_2SO_4	**16b**	13%
2	$MeSO_3H$	**16b**	32%
3	TsCl/pyridine	**16b**	96%
4	*one-pot:* $H_2NOTs/HCOOH$	**11b**	55%
5	*one-pot:* $H_2NOH \cdot HCl/TsCl/pyridine$	**11b**	77%

OH-moiety *via* tosylation in the presence of a base (entry 3). X-Ray diffraction of the obtained product **9b** confirmed that the rearrangement proceeded as expected with the sterically more demanding group to migrate giving a single isomer (Fig. 3).

Expanding the above methodology to a one-pot procedure for the direct conversion of ketone **10b** to the isoquinolinone system, we used *Ts*ONH$_2$ in the presence of concentrated formic acid. Although the reaction gave the expected compound after refluxing for several hours, the yield of **9b** was only fair (entry 4). Much better results were obtained when hydroxylamine was used to prepare the oxime, followed by *in situ* tosylation with *Ts*Cl in the presence of pyridine (entry 5). These conditions gave clean conversion to **9b** without formation of any other isomer.

Comparison of the molecular and crystal structures of **17b**, **16b**, *and* **9b**

Atomic coordinates of the non-hydrogen atoms of **17b**, **16b**, and **9b** are compiled in Table 3. The molecular structures as encountered in the crystalline state and the adopted crystallographic atom numberings are shown in Figs. 1, 2, and 3. In the three compounds, the six-membered rings C(3) through C(8) adopt normal chair-conformations. The five-membered rings in **17b** and **16b** as well as the six-membered lactam ring in **9b** display envelope or half-chair conformations with essentially planar parts formed by C(1), C(2), C(3), C(9), N, and O, from which the ring atom C(8) deviates by about 0.60–0.64 Å. This envelope conformation is stabilized by the presence of sp^2-hybridized C(1) atoms in the five-membered rings and by two sp^2-hybridized atoms C(1) and N in the six-membered ring.

Although the two oximes **17b** and **16b** differ formally only in the *cis*- and *trans*-disposition of their methyl groups C(10)H$_3$ and C(11)H$_3$, the molecular structures of the two compounds show marked stereochemical differences in their bicyclic ring systems (Figs. 1 and 2). Despite the *cis*/*trans*-isomerism, the methyl groups C(11)H$_3$ adopt equatorial positions at the five-membered rings of both compounds with the result that the torsion angles C(11)–C(9)–C(8)–C(10) are of comparable size, measuring $-73°$ in **17b** and $-50°$C in **16b**. This is achieved by a reversal in the conformation of the bicyclic system. In **17b** the angular methyl group C(10)H$_3$ is oriented axially relative to the six-membered ring and equatorially relative to the five-membered ring, whereas in **16b** the situation is reversed. Hence, the annelation of the five-membered to the six-membered ring is axial for C(2) and equatorial for C(9) in **17b**, whereas in **16b** it is equatorial and axial. In that context, the envelope-shaped 5-ring is *exo*-oriented in **17b** and *endo*-oriented in **16b**.

The lactam **9b** retains the main conformational features of **16b** (Fig. 3). Surprisingly, this analogy between **16b** and **9b** is not limited to the molecular structure, but holds also for the arrangement and interaction of the molecules in their crystal structures despite the significant differences between the functional groups >C=NOH (**16b**) and -HN-(C=O)- (**9b**). This is achieved in both compounds by the formation of cyclically hydrogen-bonded dimers of symmetry C$_i$: in the oxime **16b** by molecular dimers linked *via* a six-membered ring $\cdots$N–O–H$\cdots$N′–O′–H′$\cdots$ (primed atoms are inversion related to unprimed ones, dots indicate hydrogen bonds), in the lactam **9b** by molecular dimers linked *via* an eight-membered ring $\cdots$O–C(1)-N–H$\cdots$O′–C(1)′-N′–H′$\cdots$. The hydrogen bond

Table 3. Atomic coordinates of *cis*-lactam $C_{11}H_{19}NO$ (**9b**), *cis*-oxime $C_{11}H_{19}NO$ (**16b**), and *trans*-oxime $C_{11}H_{19}NO$ (**17b**)

	x	*y*	*z*
cis-lactam $C_{11}H_{19}NO$ (**9b**)			
N	0.4351(7)	0.1509(5)	0.3852(3)
O	0.7657(5)	0.1670(5)	0.4951(3)
C(1)	0.6563(9)	0.2213(6)	0.4133(4)
C(2)	0.7660(7)	0.3589(7)	0.3385(4)
C(3)	0.6234(7)	0.4430(6)	0.2580(4)
C(4)	0.6153(8)	0.6133(6)	0.3331(4)
C(5)	0.4847(9)	0.7014(7)	0.2516(5)
C(6)	0.2530(8)	0.5599(7)	0.1846(4)
C(7)	0.2541(8)	0.3849(6)	0.1142(4)
C(8)	0.3910(7)	0.2912(6)	0.1924(3)
C(9)	0.2826(7)	0.2040(6)	0.2933(4)
C(10)	0.4079(9)	0.1401(7)	0.1035(4)
C(11)	0.0667(7)	0.0328(7)	0.2458(4)
cis-oxime $C_{11}H_{19}NO$ (**16b**)			
O	0.7386(2)	0.1655(2)	0.4951(1)
N	0.5131(2)	0.1443(2)	0.4328(1)
C(1)	0.5221(2)	0.2538(2)	0.3680(1)
C(2)	0.7342(2)	0.3852(2)	0.3469(2)
C(3)	0.6358(2)	0.4647(2)	0.2516(1)
C(4)	0.6395(3)	0.6534(2)	0.3110(2)
C(5)	0.4983(3)	0.7189(2)	0.2259(2)
C(6)	0.2469(3)	0.5779(2)	0.1782(2)
C(7)	0.2327(2)	0.3892(2)	0.1127(1)
C(8)	0.3874(2)	0.3142(2)	0.1852(1)
C(9)	0.3038(2)	0.2532(2)	0.2910(1)
C(10)	0.4004(5)	0.1494(3)	0.0992(2)
C(11)	0.0874(3)	0.0740(2)	0.2602(2)
trans-oxime $C_{11}H_{19}NO$ (**17b**)			
N	0.0573(1)	0.1813(2)	0.4548(1)
O	0.0075(1)	0.0377(2)	0.3883(1)
C(1)	0.1094(1)	0.3299(2)	0.4169(1)
C(2)	0.1273(2)	0.3603(3)	0.3167(1)
C(3)	0.2051(1)	0.5541(3)	0.3149(1)
C(4)	0.2847(2)	0.5558(3)	0.2365(2)
C(5)	0.3780(2)	0.3936(4)	0.2500(2)
C(6)	0.4412(2)	0.4152(4)	0.3431(2)
C(7)	0.3613(1)	0.4008(3)	0.4209(1)
C(8)	0.2654(1)	0.5639(2)	0.4128(1)
C(9)	0.1690(1)	0.5002(3)	0.4739(1)
C(10)	0.3102(2)	0.7852(3)	0.4380(2)
C(11)	0.1995(2)	0.4434(4)	0.5738(1)

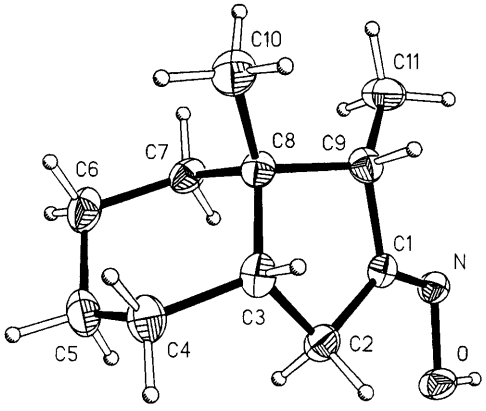


Fig. 1. Molecular structure of **17b** in the crystalline state with crystallographic atom numbering (20% ellipsoids)

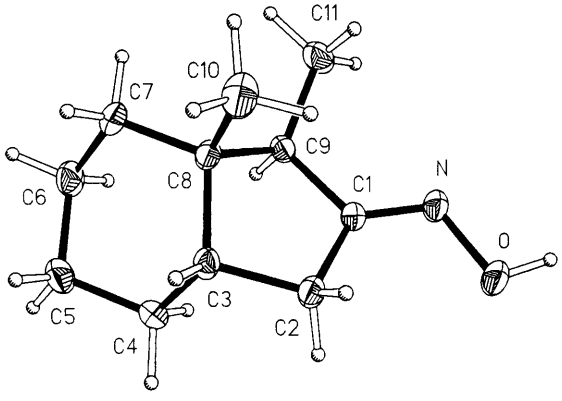


Fig. 2. Molecular structure of **16b** in the crystalline state with crystallographic atom numbering (20% ellipsoids)

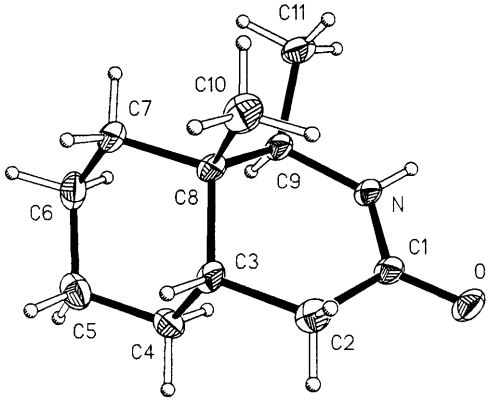


Fig. 3. Molecular structure of **9b** in the crystalline state with crystallographic atom numbering (20% ellipsoids)

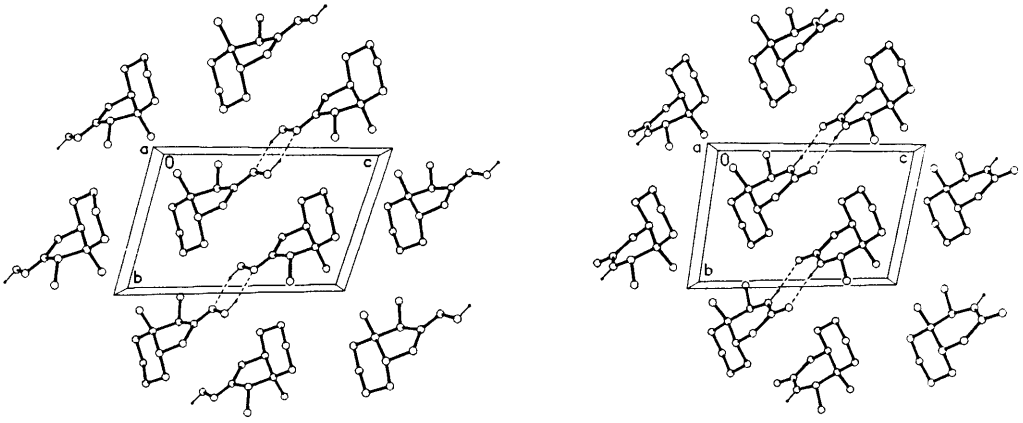


Fig. 4. Packing plots of the crystal structures of **16b** (left) and **9b** (right) viewed along the *a* axes; C-bonded H-atoms omitted for clarity, H-bonds as broken line; the comparison shows the hydrogen bonded dimers and visualizes that the two compounds are *pseudo*-isostructural

distances N···O′ are 2.833 Å in **16b** and 2.920 Å in **9b**. As shown in Fig. 4, the H-bonded dimers of **16b** and **9b** are analogous in shape and spatial arrangement and, hence, also in the triclinic unit cells, space group P $\bar{1}$. Consequently, the compounds can be regarded as *pseudo*-isostructural.

A generally accepted crystallographic proof for this view is the fact that both crystal structures can be successfully refined with the atomic parameters of its congener as the starting values. The largest shifts in these refinements concern C(1), N, and O. In comparison to **9b** and **16b**, oxime **17b** likewise forms hydrogen bonded dimers of inversion symmetry with O···N′ = 2.814 Å, but the spatial arrangement is different and leads to a unit cell with monoclinic symmetry, space group $P2_1/c$, and a doubled unit cell content.

Experimental

General

All solvents were distilled prior to use. Dry CH_2Cl_2 was prepared by distillation from P_2O_5, dry MeOH by distillation from Mg, dry diethyl ether by distillation from Na/benzophenone, dry acetone and dry acetonitrile by distillation from dry K_2CO_3. Dry pyridine (Aldrich) was stored over molecular sieves (4Å). Methyllithium was obtained from Aldrich as 1.5 *M* solution in diethyl ether. TLC was performed on Merck precoated silica gel plates (5554) and flash column chromatography on silica gel 60 from E. Merck (40–63 μm, 9385).

Melting points were determined using a Kofler hot stage microscope and are uncorrected. Elemental analyses of all new compounds were carried out in the Microanalytical Laboratory, University of Vienna, and gave good agreement with the calculated values. The NMR spectra were recorded with a Bruker AC 200 (200 MHz) spectrometer from $CDCl_3$ solution; chemical shifts are reported in ppm relative to internal *TMS*.

2-(2-Methyl-2-propenyl)cyclohexanone (**14**; $C_{10}H_{16}O$)

To a 10% solution of enamine **12/13** (120 mmol, 1.2 eq) in a 4:1 mixture of dry acetone/dry acetonitrile, dried NaI (1.0 eq) was added under nitrogen. This suspension was treated dropwise with

freshly distilled 3-chloro-2-methylpropene (1 eq) at room temperature and then refluxed for 24 h. After concentration of the reaction mixture, the residue was taken up with H_2O and refluxed for 2 h. The product was isolated by extraction with diethyl ether. The combined organic layers were washed with 1 *N* HCl, satd. $NaHCO_3$ solution, and brine, dried over Na_2SO_4, and concentrated to give **14** after distillation *in vacuo*. Enamine **12** yielded 66% and compound **13** 68% of pure **14** as a colorless liquid. B.p.: 44–45°C/1 mbar; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 1.15–2.57 (m, 11H), 1.68 (s, 3H, CH_3), 4.7 and 4.65 (2s, 2H, $=CH_2$) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 22.0 (q, CH_3), 24.5 (t, C-4), 27.7 (t, C-5), 33.0 (t, C-3), 37.1 (t, CH_2), 41.7 t, C-6), 48.0 (d, C-2) 111.5 (t, $=CH_2$), 142.9 (s, =C), 212.1 (s, C-1)ppm.

2-(2-Oxopropyl)cyclohexanone (**15**; $C_9H_{14}O_2$)

A solution of 3.00 g **14** (19.7 mmol) in 40 cm^3 dry CH_2Cl_2 under nitrogen was cooled to −70°C and gently treated with ozone generated by an ozonizer (Sander Labor Ozonisator) at a flow of approx. 140×10^3 $cm^3\cdot h^{-1}$ and in a concentration of approx. 20 g O_3/m^3 until the color of the mixture changed to blue. The O_3 flow was stopped and the solution stirred at reaction temperature until the color faded. The treatment with ozone was repeated until the blue color remained and TLC indicated complete conversion (usually 20–30 min). The reaction mixture was warmed to room temperature, dimethylsulfide (10 eq) in 10 cm^3 of methanol was added, and the solution was stirred for 5 h. Concentration and distillation *in vacuo* gave 2.58 g (85%) of pure **15** as a colorless liquid. B.p.: 63–65°C/0.5 mbar; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 1.22–2.38 (m, 9H), 2.15 (s, 3H, CH_3), 2.84–3.02 (m, 2H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 25.0 (d, C-4), 27.6 (d, C-5), 30.1 (q, CH_3) 33.7 (d, C-3), 41.5 (d, C-6), 42.9 (d, CH_2), 46.1 (d, C-2), 206.8 (s, C=O), 210.9 (s, C-1)ppm.

2H-3,3a,4,5,6,7-Hexahydro-2-indenone (**11**; $C_9H_{12}O$)

To remove oxygen, a mixture of 400 cm^3 5% KOH and 10 cm^3 EtOH was treated with N_2. To this 9.90 g **15** (64.2 mmol) were added, and the solution was refluxed for 6 h. After cooling to room temperature the mixture was neutralized with dilute H_2SO_4 and extracted with diethyl ether. The combined organic layers were washed with water, dried over Na_2SO_4, concentrated, and distilled to give 8.00 g (92%) of pure **11** as a colorless liquid B.p.: 38°C/0.23 mbar; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 0.96–2.78 (m, 11H), 5.80 (s, 1H, C–1) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 25.0, 26.8, 30.7, and 34.8 (4t, C-4, C-5, C-6 and C-7), 41.5 (d, C-3a), 42.1 (t, C-3), 126.4 (d, C-1), 184.6 (s, C-7a) 208.6 (s, C-2) ppm.

cis-2H-1,3,3a,4,5,6,7,7a-Octahydro-7a-methyl-2-indenone (**10a**; $C_{10}H_{16}O$)

Dimethylcopperlithium was prepared by treating a suspension of dry CuI (1 eq) in dry diethyl ether (1:20 dilution) with methyllithium solution (2 eq) at −15°C under nitrogen. The mixture gave a yellow precipitate with the first equivalent of MeLi and turned homogenous after complete addition. This solution (1.3 eq Me_2CuLi) was cooled to −40°C, 1.00 g **11** (7.34 mmol, 1 eq) was added dropwise, the mixture was warmed to −25°C, and stirred for 6 h. After hydrolysis with satd. NH_4Cl solution and extraction with diethyl ether, the combined organic layers were washed with water, dried over Na_2SO_4, and concentrated. *Kugelrohr* distillation gave 1.01 g (91%) of pure **10a** as colorless oil B.p.: 45°C/0.7 mbar; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 1.12 (s, 3H, CH_3), 1.20–2.45 (m, 13 H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 21.6 and 21.8 (2t, C-5 and C-6), 26.3 (t, C-4), 26.4 (q, CH_3), 33.9 (t, C-7), 37.8 (s, C-7a), 41.5 (d, C-3a), 42.4 (t, C-3), 51.4 (t, C-1), 219.6 (s, C-2) ppm.

(1α,3aα,7aα)-2H-1,3,3a,4,5,6,7,7a-Octahydro-1,7a-dimethyl-2-indenone (**10b**; $C_{11}H_{18}O$)

The initial addition of Me_2CuLi was carried out according to the procedure for the conversion of **11** (2.00 g, 14.69 mmol) to **10a**. After 6 h at −25°C the reaction mixture was cooled to −40°C again,

and *HMPA* (20 vol%) and MeI (3.5 eq) were added subsequently. The solution was warmed to −25°C and stirred for 6 h. General workup according to **10a** gave 1.94 g (87%) of pure **10b** as a colorless oil after *Kugelrohr* distillation B.p.: 75°C/0.7 mbar; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 0.83 (s, 3H, CH_3), 0.90 (d, $J = 7$ Hz, 3H, CH_3), 1.10–2.50 (m, 12H) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 7.7 and 24.1 (2q, 2×CH_3), 21.5 and 24.7 (t, C-5 and C-6), 29.3 (t, C-4), 33.8 (t, C-7) 40.2 (s and d, C-7a and C-3a), 42.8 (t, C-3), 47.1 (d, C-1), 221.4 (s, C-2) ppm.

(1α,3aα,7aα)-2H-1,3,3a,4,5,6,7,7a-Octahydro-1,7a-dimethyl-2-indenone oxime (**16b**; $C_{11}H_{19}NO$)

Ketone **10b** (3.06 g, 18.42 mmol) and hydroxylamine hydrochloride (3 eq) were dissolved in 30 cm^3 of a 1:1 mixture of dry MeOH and pyridine and heated to 60°C for 5 h. After evaporation of the solvents *in vacuo* the residue was taken up with CH_2Cl_2 and 2 *N* HCl. The organic layer was washed with water, dried over Na_2SO_4, and concentrated. Recrystallization from MeOH gave 3.27 g (97%) of pure **16b** as colorless crystals.

M.p.: 126–128°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 0.80 (s, 3H, CH_3), 0.99 (d, $J = 7$ Hz, 3H, CH_3), 1.02–2.60 (m, 12H), 8.9 (bs, 1H, OH) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 10.8 and 23.2 (2q, 2×CH_3), 21.7 and 24.5 (2t, C-5 and C-6), 28.8 (t, C-4), 31.9 and 33.0 (2t, C-3 and C-7), 41.0 and 41.6 (2d, C-1 and C-3a), 41.7 (s, C7a), 169.0 (s, C-2) ppm.

(1α,3aβ,7aβ)-2H-1,3,3a,4,5,6,7,7a-Octahydro-1,7a-dimethyl-2-indenone oxime (**17b**; $C_{11}H_{19}NO$)

Ketone **10b** (1.94 g, 11.67 mmol) was added to a solution of hydroxylamine hydrochloride (3 eq) and sodium acetate (5 eq) in 60 cm^3 of a 1:1 mixture of MeOH and H_2O and refluxed for 4 h. After cooling to room temperature the precipitated crystals were collected by filtration to give pure **16b**. The remaining solution was concentrated and taken up with water and diethyl ether. The organic layer was dried over Na_2SO_4 and evaporated. Separation from remaining **16b** could be achieved by repeated recrystallization from petroleum ether and MeOH. A total of 1.19 g (45%) of **16b** and 0.35 g (13%) of pure **17b** were isolated as colorless crystals.

M.p.: 120–126°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 0.99 (d, $J = 7$ Hz, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.10–2.50 (m, 12H), 8.4 (bs, 1H, OH) ppm; ^{13}C NMR (50 MHz, δ, $CDCl_3$): 8.7 and 22.0 (2q, 2×CH_3), 20.1, 21.4, and 23.1 (3t, C-4, C-5, and C-6), 27.2 and 28.7 (2t, C-3 and C-7), 41.3 (s, C-7a), 41.4 and 41.6 (2d, C-1 and C-3a), 168.0 (s, C-2) ppm.

(1α,3aα,7aα)-3H-1,2,4a,5,6,7,8,8a-Octahydro-1,8a-dimethyl-3(4H)-isoquinolinone (**9b**; $C_{11}H_{19}NO$)

Method A: From oxime **16b**

Oxime **16b** (0.45 g, 2.48 mmol) was dissolved in 20 cm^3 of dry pyridine, cooled to −10°C, and treated with 4-toluenesulfonyl chloride (1 eq). The mixture was slowly warmed to room temperature and stirred until TLC indicated complete conversion (approx. 4 h), After hydrolysis with 2 *N* HCl and extraction with CH_2Cl_2 the combined organic layers were washed with water, dried over Na_2SO_4, and concentrated. Recrystallization from diisopropyl ether gave 0.43 g (96%) of pure **9b**.

Method B: One-pot reaction from ketone **10b**

Hydroxylamine (1 eq) in 5 cm^3 of dry pyridine was added to a solution of 1.00 g ketone **10b** (6.02 mmol) in 15 cm^3 of dry pyridine, and the mixture was heated to 60°C for 2 h. After the reaction was cooled to −10°C, 4-toluenesulfonyl chloride (1 eq) was added, and the solution was slowly warmed to room temperature. General workup according to *Method A* gave 1.02 g (77%) of pure **9b** as colorless crystals after recrystallization.

M.p.: 139–140°C; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 0.83 (s, 3H, CH_3), 1.05 (d, $J = 7$ Hz, 3H, CH_3), 1.10–1.83 (m, 9H), 2.00 (d, $J = 19$ Hz, 1H, H-3a), 2.68 (dd, $J_1 = 19$ Hz, $J_2 = 6$ Hz, 1H, H-3b), 3.85 (q, $J = 7$ Hz, 1H, H-1), 5.6 (bs, 1H, NH) ppm; ^{13}C NMR(50 MHz, δ, $CDCl_3$): 15.7 and 21.9 (2q, 2×CH_3), 21.3, 25.9, and 29.1 (3t, C-5, C-6, and C-7), 33.8 (s, C-8a), 35.0 and 35.2 (2t, C-4 and C-8), 41.2 (d, C-4a), 47.9 (d, C-1), 171.9 (s, C-3) ppm.

Crystal structure of **9b**

A colorless crystal of **9b** ($C_{11}H_{19}NO$, $Fw = 181.27$, triclinic, space group $P\bar{1}$, $a = 6.756(3)$ Å, $b = 7.745(4)$ Å, $c = 11.075(6)$ Å, $\alpha = 94.65(3)°$, $\beta = 103.00(3)°$, $\gamma = 111.68(3)°$, $V = 516.0(4)$ Å^3, $Z = 2$, d(calcd) = 1.167 g/cm^3, $T = 295$ K) was used for data collection with Philips PW 1100 four-circle diffractometer (MoK_α radiation, ω-scans, $\theta = 2$–$18°$, $-5 \le h \le 5$, $0 \le k \le 6$, $-9 \le l \le 9$, 710 reflections collected, 699 independent, no correction for absorption). All available crystals gave distinctly broadened X-ray reflections, and therefore data collection covered only a limited θ-range. The structure was solved with direct methods and was refined on F^2 with anisotropic displacement factors for non-hydrogen atoms. Hydrogen atoms were located from a difference *Fourier* map and refined riding with the atoms to which they were bonded. Final refinement gave $R_1 = 0.096$ and $wR_2 = 0.247$ for all 699 reflections and 119 parameters. $R_1 = 0.094$ for the 646 data with $F_o^2 > 2\sigma(F_o^2)$. Excursions in final difference *Fourier* map; between -0.35 and 0.29 e · Å^{-3} [15].

Crystal structure of **16b**

A yellow rounded crystal (0.4×0.4×0.8 mm) of **17b** $C_{11}H_{19}NO$, $Fw = 181.27$, triclinic space group $P\bar{1}$, $a = 6.376(3)$ Å, $b = 7.988(3)$ Å, $c = 11.776(4)$ Å, $\alpha = 101.61(1)°$, $\beta = 101.13(1)°$, $\gamma = 110.34(1)°$, $V = 527.8(3)$ Å^3, $Z = 2$, d(calcd) = 1.141 g/cm^3, $T = 303$ K) was used for data collection with a Siemens/Bruker SMATR CCD diffractometer (sealed X-ray tube, MoK_α radiation, $\lambda = 0.71073$ Å, graphite monochromator, 0.3° ω-scan frames, $\theta = 2$–$25°$, $-7 \le h \le 7$, $-9 \le k \le 9$, $0 \le l \le 13$, 2946 reflections collected, 1781 independent, correction for absorption by multi-scan method and program SADABS, $R_{int} = 0.026$). The structure was solved with direct methods and was refined on F^2 using anisotropic displacement factors for all non-hydrogen atoms. Hydrogen atoms were located from a difference *Fourier* map and were refined in x, y, z, and U_{iso} without restraints. Final refinement gave $R_1 = 0.044$ and $wR_2 = 0.106$ for all 1781 reflections and 195 parameters. $R_1 = 0.040$ for the 1600 data with $F_o^2 > 2\sigma(F_o^2)$. Excursions in final difference *Fourier* map: between -0.13 and 0.15 e · Å^{-3} [15].

Crystal structure of **17b**

A colorless rounded crystal (0.3×0.5×0.8 mm) of **16b** ($C_{11}H_{19}NO$, $Fw = 181.27$, monoclinic, space group $P2_1/c$, $a = 11.847(2)$ Å, $b = 6.325(1)$ Å, $c = 14.485(3)$ Å, $\beta = 93.87(1)°$, $V = 1082.9(3)$ Å^3, $Z = 4$, d(calcd) = 1.112 g/cm^3, $T = 295$ K) was used for data collection with a Philips PW1100 four-circle diffractometer (MoK_α radiation, $\lambda = 0.71073$ Å, graphite monochromator, ω–2θ scans, $\theta = 2$–$25°$, $0 \le h \le 14$, $0 \le k \le 7$, $-17 \le l \le 17$, 1993 reflections collected, 1903 independent, no correction for absorption, $R_{int} = 0.012$). The structure was solved with direct methods (program SHELXS) and refined on F^2 (program SHELXL97) [14] using anisotropic displacement factors for all non-hydrogen atoms. Hydrogen atoms were located from a difference *Fourier* map and were refined in *x,y,z,* and U_{iso} without restraints. Final refinement gave $R_1 = 0.058$ and $wR_2 = 0.112$ for all 1903 reflections and 195 parameters. $R_1 = 0.041$ for the 1439 data with $F_o^2 > 2\sigma(F_o^2)$. Excursions in final difference *Fourier* map: between -0.12 and 0.15 e · Å^{-3} [15].

Acknowledgements

Financial support of this project by *Novartis Crop Protection AG*, Basel, Switzerland, is highly appreciated.

References

[1] For a review on the ergosterol biosynthesis see: Mercer EI (1984) Pestic Sci **15**: 133
[2] For a review about inhibitors of the ergosterol biosynthesis see: Burden RS, Cooke DT, Carter GA (1989) Phytochemistry **28**: 1791
[3] Isenring HP (1987) Antifungal Morpholine Derivatives: Chemistry and Structure-Activity Relationships. In: Fromtling RA (ed) Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents. JR Prous Science Publishers, SA, p 543
[4] Taton M, Benveniste P, Rahier A (1987) Phytochemistry **26**: 385; Schmitt P, Gonzales R, Benveniste P, Ceruti M, Cattel L (1987) Phytochemistry **26**: 2709
[5] Stanetty P, Mihovilovic MD (1997) Chem Lett 849; Stanetty P, Mihovilovic MD, Mereiter K, Völlenkle H, Renz F (1998) Tetrahedron **54**: 875
[6] Kremslehner, M (1997) PhD Thesis. Vienna University of Technology
[7] Letsinger RL, Tranham JG (1948) J Am Chem Soc **70**: 2818
[8] Cantor SE, Tarbell DS (1964) J Am Chem Soc **86**: 2902; Corey EJ, Bass JD, LeMahieu R, Mitra RB (1964) J Am Chem Soc **86**: 5570; Murase N, Marouka K, Ooi T, Yamamoto H (1997) Bull Chem Soc Jpn **70**: 700
[9] Tsuda T, Chujo Y, Nishi S-I, Tawara K, Saegusa T (1980) J Am Chem Soc **102**: 6384; Hirao T, Fujii T, Ohshiro Y (1994) Tetrahedron **50**: 10207
[10] Islam AM, Rapheal RA (1952) J Am Chem Soc **74**: 4086
[11] Beth A, Pelletier J, Russo R, Soucy M, Brunell RH (1975) Can J Chem **53**: 1504; Nagumo S, Suemune H, Sakai K (1988) Tetrahedron Lett **29**: 6927
[12] Elliott GH, Listead RP (1938) J Chem Soc 660
[13] Posner GH, Lentz CM (1977) Tetrahedron Lett **37**: 3215
[14] Sheldrick GM (1997) SHELX-97: Programs for the Solution and Refinement of Crystal Structures. University of Göttingen, Germany
[15] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC 115821 (**17b**), CCDC 115822 (**16b**), and CCDC 115823 (**9b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk)

Received March 15, 1999. Accepted May 3, 1999