145. Stereochemistry of the *Robinson* Anellation: Studies on the Mode of Formation of the Intermediate Hydroxy Ketones

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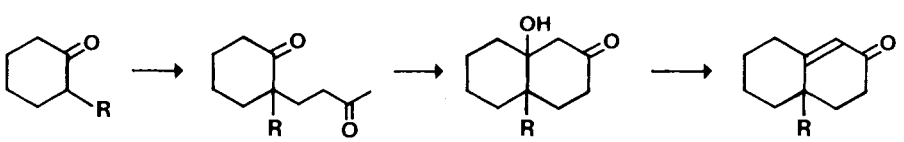
The stereochemical outcome of the base-catalyzed cyclization of diketones **5–8** has been investigated under protic conditions (*Scheme 3*). The more stable *trans*-fused ketols are preferentially formed in kinetically controlled aldol reactions, when the incipient angular substituent R = H (**6**→**10a**) or CN (**7**→**11a**, **8a**→**12a**). For R = Me (as in **5**), axial attack of the side-chain enolate double bond on the ring C=O group results in the rather selective formation of *cis*-**9b**. It is assumed that these cyclizations are controlled by relative product stabilities (product-like transition state) and steric effects. The competition between fused (*e.g.* **9**) and bridged ketol (*e.g.* **13**) formation in these cyclizations is discussed. The *cis*-fused ('steroid') ketols were readily equilibrated with their *trans*-counterparts (**9b** ⇄ **9a**, **10b** ⇄ **10a**, **11b** ⇄ **11a**) under aprotic conditions (5 mol-% of LDA, THF, 0°), thus, allowing assessments of relative stabilities.

1. Introduction. – The *Robinson* anellation is a convenient method for conversion of cyclohexanones **1** to hexahydronaphthalenones **4** and related ring systems (*Scheme 1*). Since the original report by *Rapson* and *Robinson* in 1935 [1], a variety of modifications have been developed for this venerable reaction [2], which has found widespread use in the synthesis of terpenes and steroids [3]. A modern innovation involves *Lewis*-acid-catalyzed conjugate addition of (kinetic or thermodynamic) silyl-enoles derived from **1** to α,β-unsaturated enones to give diketones **2**, which on acid- or base-catalyzed cyclization afford hexahydronaphthalenones **4** [4].

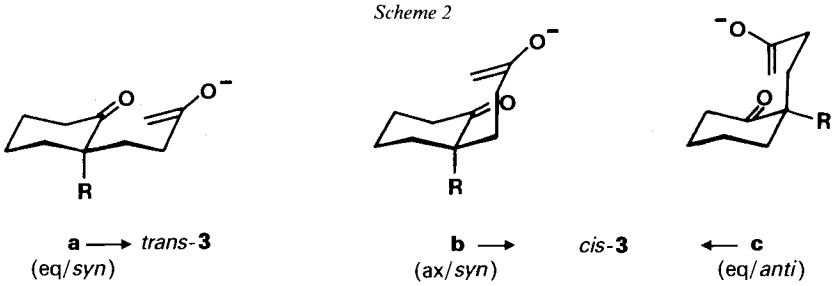
Scheme 1



When the anellation sequence is carried out under moderate basic conditions, the intermediate hydroxy ketones **3** can often be isolated, starting from either **1** [5] or **2** [6]. Since substituted cyclohexanones **1** can give rise to regioisomeric and/or diastereoisomeric diketones **2** by the initial *Michael* reaction, the crystalline nature of **3** provides a convenient feature for separation of isomers (see, *e.g.*, [5a]).

In principle, cyclization of **2** to **3** can follow three stereochemical pathways, if one assumes chair-like transition states (*Scheme 2*). These pathways differ in the direction of attack of the side-chain enolate double bond on the C=O group of the cyclohexanone moiety (axial or equatorial), and the orientation of the donor and acceptor groups (synclinal/antiperiplanar [7]).

Scheme 2



Marshall and *Fanta* [5c] and *Spencer et al.* [8] have shown more than 20 years ago, that the stereochemical outcome of the base-catalyzed cyclization of **2** to **3** is governed by the nature of the incipient angular substituent R. Ring closure of **2** (R = H) leads to *trans*-**3**, while the corresponding *cis*-fused compounds **3** are obtained for R = Me or AcO in kinetically controlled aldol reactions.

Interestingly, two closely related questions have never received an answer: i) *Which is the preferred mode of formation – if at all – of* cis*-hydroxy ketones* **3** *from conformationally flexible diketones* **2**? ii) *Which factors are responsible for reversal of the configuration of the ring fusion of* **3**, *when going from R = H to R = Me, AcO?*

Information about *i* should be inferable from the cyclization of diketone **5**, since cyclization modes **a**–**c** (*Scheme 2*) give rise to diastereoisomeric ketols **9a**–**c**[1]), which are conformationally locked in the *cis*-series by virtue of the Me group at C(1) (*Scheme 3*).

Scheme 3

Diketone	R^1	R^2	R	R^3	Hydroxy ketone[1])
5	H	H	CH_3	CH_3	**9a–c**
6	CH_3	CH_3	H	H	**10a,b**
7	H	H	CN	CH_3	**11a–c**
8a	H	CH_3	CN	H	**12a**
8b	CH_3	H	CN	H	**12c**

Inspection of the literature revealed that compounds with structure **9** had been frequently described [9], but only one of the two possible *cis*-hydroxy ketones **9b**/**9c** had been characterized. *Marshall* and *Hochstetler* [9b] established the *cis*-ring fusion of a crystalline hydroxy ketone (m.p. 103°), obtained by condensation of 2-methylcyclohexanone with ethyl vinyl ketone under protic conditions, but the configuration at C(1) could not be assigned unambiguously. *Stothers et al.* [9c] came to the conclusion that *Marshall*'s hydroxy ketone is the (all-*cis*)-isomer **9b**, based on correlation of ^{13}C-NMR-shift data.

Recently, *Ziegler* [9d] reported on the aprotic *Robinson* anellation of 2-methylcyclohexanone with ethyl vinyl ketone (LDA, THF) to give approximately equal amounts of *trans*-**9a**, which had already been prepared by *Ayer et al.* [9e] by an indirect route, and a structurally not defined *cis*-hydroxy ketone.

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[1]) In the following, the letters **a**–**c** behind the compound number refer to the mode of formation according to *Scheme 2*.

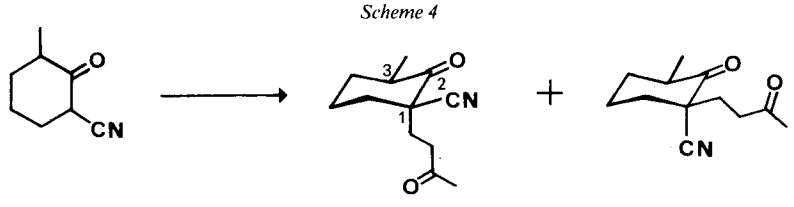
Clearly, for unambiguous structure assignments, both *cis*-fused compounds **9b** and **9c** should be at hand, and to answer question *i*, it should be known, whether the isolated aldol compounds correspond to kinetic products. We, therefore, investigated the cyclization of **5** under various conditions. In addition, the cyclization of diketones **6–8** was studied under protic conditions, in order to gain insight into the factors, which control the configuration of the ring fusion (question *ii*).

2. Results. – 2.1. *Synthesis of Diketones* **5–8**. Diketone **5** [4] [9d] was prepared by alkylation of cyclohexyl(2-methylcyclohexylidene)amine with ethyl vinyl ketone in THF, followed by hydrolysis, according to the method of *Pfau et al.* [10].

Diketone **6** was synthesized from 2-(hydroxymethylidene)-6,6-dimethylcyclohexanone in two steps, involving Et_3N-catalyzed *Michael* addition to methyl vinyl ketone in THF, and subsequent treatment of the intermediate diketoaldehyde with K_2CO_3/EtOH/H_2O, using a procedure of *Corey* and *Nozoe* [11] (yield 85%).

Dioxo-carbonitriles **7**, **8a**, and **8b** were obtained, in high yield, by Et_3N-catalyzed *Michael* addition of 2-cyanocyclohexanone to ethyl vinyl ketone, and 3-methyl-2-oxocyclohexanecarbonitrile to methyl vinyl ketone in THF (r.t., 4–5 days), respectively (*Scheme 4*). The latter reaction afforded a diastereoisomeric mixture **8a**/**8b** 1:5[2]), which could be separated by chromatography on silica gel.

Scheme 4



8b **8a**

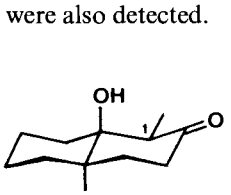
The assignment of configurations is based on the following observations: *a*) the large difference in the polarity of **8a** and **8b** on silica gel (R_f (pentane/Et_2O 1:1) 0.28 and 0.13, respectively) can be rationalized as consequence of the orientation of the C(2)=O and C(1)–CN dipoles, which show into the same direction in case of the more polar **8b**. *b*) In the ^{1}H-NMR spectrum, H–C(3) of **8a** is considerably deshielded (0.34 ppm) compared to **8b** by the *syn*-axial CN group at C(1). *c*) Treatment of **8a** as well as **8b** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF (r.t., 5 h) gave a 3:1 equilibrium ratio in favor of **8a**. The thermodynamically more stable isomer is expected to have the substituent at C(1) with the higher *A* value[3]) in an equatorial position.

2.2. *Cyclization of (±)-2-Methyl-2-(3-oxopentyl)cyclohexanone* (**5**). Reaction of **5** with a 0.022M soln. of NaOMe (6 mol-%) in THF/MeOH 8:1 (0°, 80 min) afforded the *cis*-fused hydroxy ketones **9b** and **9c** in a ratio of 5:1 (yield *ca.* 90%) as the principal cyclization products. The melting point of the major **9b** (102–103°), which was easily

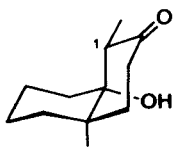
[2]) This corresponds roughly to the kinetic product ratio, since **8a** and **8b** were interconverted rather slowly under the reaction conditions.

[3]) The *A* value of the CN group is *ca.* 0.24 kcal/mol [12a], of an unbranched alkyl group (Et) *ca.* 1.8 kcal/mol [12b].

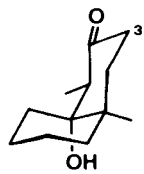
isolated in pure form by crystallization, corresponded to the value given in [9b]. Chromatography of the mother liquor on silica gel afforded the diastereoisomeric *cis*-**9c** as an oil and the bridged **13** (yield 5%). Trace amounts of *trans*-**9a** [9e] (*ca.* 1%) and **14** [13] (*ca.* 1%) were also detected.



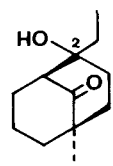
9a



9b



9c



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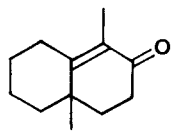

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The relative amounts of **9b** and **9c** formed in the cyclization of **5** were dependent on the reaction time (*Table 1, Entries 1–4*). After *ca.* 50% conversion, the ratio of **9b**/**9c** was 20:1, whereas prolonged standing of the reaction mixture afforded a 47:53 equilibrium ratio for **9b**/**9c** with considerable amounts of **14** produced (*Entry 4*).

When **9b**, **9c**, and **13** were separately subjected to the above reaction conditions (0°, 15 h), nearly the same ratio of products was obtained as from **5** (*Entry 4*), thus, allowing equilibration of **9b**, **9c**, **13**, and **5** – but not of **9a** – prior to complete dehydration to **14**. Since these equilibrations required some hours, it can be concluded that **9b** is formed mainly from **5** and not *via* **13**. Thus, **9b** corresponds to the kinetic cyclization product of **5** under protic conditions. The slow formation of **9a** from **9b** and **9c** shows that aldolization of **5** is somewhat reversible, and that interconversion of **9b** and **9c** may not only occur by epimerization at C(1), but also by the *retro*-aldol/aldol process.

Table 1. *Cyclization of 2-Methyl-2-(3-oxopentyl)cyclohexanone* (**5**). The ratio of products was determined by GLC. The results of *Entries 4* and *7* were confirmed by ^{1}H-NMR. The total recovery of material (*Entries 2* and *7*) was > 95%.

Entry	Conditions	Time	Ratio of products					
			5	**9a**	**9b**	**9c**	**13**	**14**
1	protic[a])	10 min	52	< 1	42	2	3	< 1
2	protic[a])	80 min	4	1	74	15	5	1
3	protic[a])	3 h	3	2	60	28	4	3
4	protic[a])	16 h	2	4	35	40	3	16
5	*Knoevenagel*[b])	30 min	81	0	9.5	0.5	0	9
6	*Knoevenagel*[b])	60 min	67	0	14	1	0	18
7	*Knoevenagel*[b])	2 h	39	0	20	2	0	39
8	aprotic[c])	c)	19	20	15	6	39	1

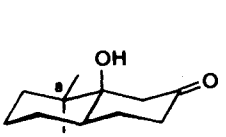
[a]) 6 mol-% of 0.022M NaOMe in THF/MeOH 8:1 (*v*/*v*) at 0°.
[b]) 1.5 equiv. of 0.2M pyrrolidine/AcOH in THF at reflux.
[c]) 0.8 equiv. of LDA in THF, −60 to +4° during 2 h, then H_3O^+.

The *cis*-configuration of the ring fusion of **9b** (which had already been established by *Marshall* and *Hochstetler* [9b]) and **9c** followed readily from their ^{1}H-NMR spectra, since they were different from the known [9e] *trans*-compound **9a**[4]). The structures of **9b** and **9c** could unambiguously be assigned by NOE-difference spectroscopy. On irradiation of the angular Me group, H_{ax}–C(1) and H_{ax}–C(3) of the minor (liquid) hydroxy ketone **9c** showed 15% and 7% enhancement, respectively, whereas the same protons were unaffected in the case of the major (crystalline) compound **9b**. Thus, in **9c** the angular Me group has to be axial, in **9b** equatorial with respect to the cyclohexanone ring. This difference also gives rise to diagnostic chemical shift values of the angular Me groups: 1.07 ppm for **9b**, 1.22 ppm for **9c**[5]).

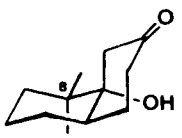
Next, the cyclization of **5** under *Knoevenagel* conditions (pyrrolidine/AcOH, THF, reflux) was examined (*Table 1, Entries 5–7*). Again, a high preference for formation of **9b** was observed. Control experiments (*cf. Table 4* in *Exper. Part*) showed that **9b** dehydrates more rapidly than **9c** under the reaction conditions (→**14**), and that slow interconversion of **9b** and **9c** occurred, most likely by epimerization at C(1). Thus, the ratios of *Entries 5–7* reflect the faster rate of formation of **9b** rather than the faster rate of dehydration of **9c**.

Cyclization of **5** under aprotic conditions (0.8 mol-equiv. of LDA, THF, −60°→+4°) was least selective (*Table 1, Entry 8*), giving rise to **13** as the main product [6]). Interestingly, also considerable amounts of *trans*-compound **9a** were formed. The formation of **9a** and **9b** is probably not kinetically controlled, since treatment of either isomer with LDA (5 mol-%; THF, 0°) rapidly established a 5:4 (equilibrium) ratio of **9a**/**9b** (only trace amounts of **9c** and **13** were observed). The reversibility of aldol reactions using preformed Li-enolates in aprotic solvents is often encountered [17].

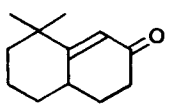
2.3. *Cyclization of (±)-2,2-Dimethyl-6-(3-oxobutyl)cyclohexanone* (**6**). Treatment of the conformationally biased **6** with a 0.022M soln. of NaOMe (5.5 mol-%) in THF/MeOH 8:1 (0°, 5 h) afforded *trans*-compound **10a** (m.p. 85–86°) and *cis*-compound **10b** (m.p. 116°) in a ratio of 13:1 (yield *ca.* 80%). The reaction was followed by GLC (*cf. Table 2*) and the products easily separated by chromatography on silica gel.



10a



10b



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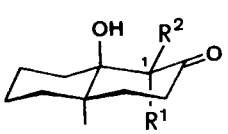
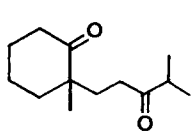
[4]) The formation of **9d** (either by cyclization of **5** or epimerization of **9a** at C(1)) can be ruled out, since the Me groups would be in an energetically unfavorable 1,3-*syn*-diaxial arrangment. For the same reason, one can assume that the cyclization of **5** proceeds *via* the corresponding (*Z*)-enolate of the side chain. This is supported by the fact that diketone **15** resists cyclization when exposed to base as shown by *Baisted* and *Whitehurst* [14], as well as *Haynes* and *Timmons* [15]. In agreement with this is our finding, that hydroxy ketone **16** (for the preparation, see *Exper. Part*) is completely transformed to **15** on heating with NaOMe by a *retro*-aldol process.



9d $R^1 = CH_3$, $R^2 = H$
16 R^1, $R^2 = CH_3$



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[5]) The corresponding 2-deoxy compounds of **9b** and **9c** resonate at 0.96 and 0.95 ppm (CCl_4), respectively [9b]. The up-field shift of axial Me groups at C(4) of cyclohexanones is well documented, see, *e.g.* [16].

[6]) The configuration at C(2) of **13** could not be established.

Table 2. *Cyclization of 6,6-Dimethyl-2-(3-oxobutyl)cyclohexanone* (**6**) *with 5.5 mol-% of 0.022M NaOMe in THF/MeOH 8:1 (v/v) at 0°*

Entry	Time	Ratio of products[a])			
		6	**10a**	**10b**	**17**
1	15 min	71	26	2	1
2	2 h	24	69	4	3
3	5 h	7	79	6	8
4	27 h	4	64	5	27

[a]) Determined by GLC. The recovery of material (*Entry 3*) after chromatography was > 95%.

The ratio of **10a**/**10b** was not altered with reaction time, and it was found that the cyclization of **6** is kinetically controlled, since the aldol products **10a** and **10b** were interconverted rather slowly. Eventually, these control experiments (*Table 5* in *Exper. Part*) showed that **10b** dehydrates more rapidly than **10a** (→**17**), and that **6** and **10a** (equilibrium ratio *ca.* 1:16) – but not **10b** – are equilibrated prior to complete transformation to enone **17**.

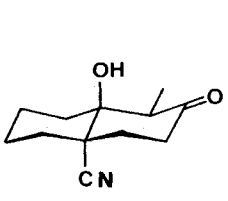
The assignment of configurations for **10a** and **10b** is based on the fact, that equilibration of either isomer with LDA (5 mol-%, THF, 0°, 5 h) afforded a 9:1 ratio in favor of **10a**[7]). The isomer with a *trans*-ring fusion is expected to be thermodynamically more stable.

Calculations by *Agami et al.* [18] have revealed that the unsubstituted *trans*-hydroxy ketone **3** (R = H) is energetically favored over the corresponding 'steroid' and 'non-steroid' *cis*-ketols **3** (R = H) by 1.7 and 1.8 kcal/mol, respectively. This enthalpy difference should be reduced by *ca.* 0.9 kcal/mol in the present case, since the additional Me groups at C(8) have four (in **10a**) and three (in **10b**) *gauche*-butane-like interactions with the decalin system (assuming chair-like conformations).

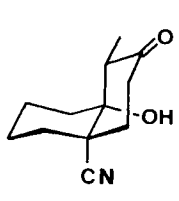
This assignment is supported by TLC (see below) and correlation of ^{13}C-NMR-shift values (*Table 3*).

2.4. *Cyclization of Dioxo-carbonitriles* **7**, **8a**, *and* **8b**. The cyclization of structurally similar compounds had been described earlier [19], but in no case, the configuration of the ring fusion of the product hydroxy ketones has been elucidated.

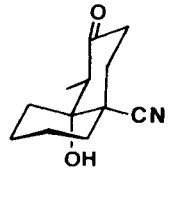
Reaction of **7** with a 0.022M soln. of NaOMe (5.5 mol-%) in THF/MeOH 8:1 (0°, 2 h), gave rise to *trans*-compound **11a**, *cis*-compounds **11b** and **11c**, and **18** in a ratio of 65:19:11:5, as determined by GLC and ^{1}H-NMR analysis. Chromatography of the crude product on silica gel enabled the isolation of the individual isomers.



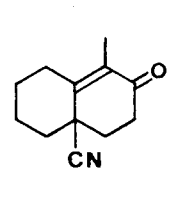
11a



11b



11c



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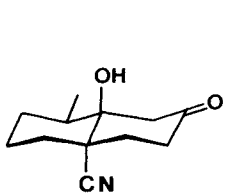
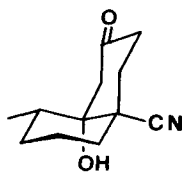
[7]) This corresponds to an enthalpy difference of $\Delta\Delta G° = 1.3$ kcal/mol between **10a**/**10b**.

The *cis*-isomers **11b** and **11c** were rapidly interconverted (equilibrium ratio *ca.* 5:4) and slowly transformed to *trans*-isomer **11a** under the reaction conditions (*cf. Table 6* in *Exper. Part*), whereas the major cyclization product **11a** was largely unaffected, keeping with the greater thermodynamic stability of the *trans*-decalin system with an angular CN group[8]). Since **11b**/**11c** are much less stable than **11a** (treatment of either **11a** or **11b** with 5 mol-% of LDA in THF (0°, 5 h) afforded a *ca.* 15:1 equilibrium ratio for **11a**/**11b**), the *trans*/*cis* ratio of 2:1 observed in the cyclization of **7** must be mostly of kinetic origin.

Finally, the cyclization of the conformationally biased **8a** and **8b** was examined. Treatment of **8a** with a 0.022M soln. of NaOMe (5 mol-%) in THF/MeOH 8:1 (0°, 75 min) afforded *trans*-compound **12a** (m.p. 168–169°) and *cis*-isomer **12c** (m.p. 118–119°)



12a



12c

in a ratio of 7:1, while **8b** yielded the same products in a 2:5 ratio. The different product ratios show that cyclization is somewhat faster than epimerization at C(3), which leads to interconversion of **8a** and **8b**. Thus, the major hydroxy ketone obtained from **8b** must possess structure **12c**, since the axial disposition of the 3-oxobutyl chain allows only equatorial attack.

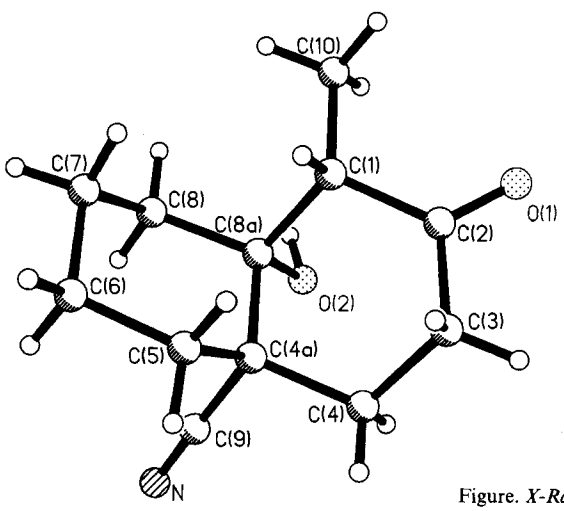


Figure. *X-Ray structure of (±)*-**11b**

[8]) It can be estimated, that **11a** should be *ca.* 1.3 kcal/mol more stable than the *cis*-isomers **11b**/**11c** by subtracting twice the *A* value of the CN group (0.24 kcal/mol)[3]) from the *Agami*'s value of 1.7–1.8 kcal/mol (see above), since the *trans*-isomer **11a** has four, the *cis*-isomers **11b**/**11c** only two 1,3-*syn* interactions of the angular CN group with axial H-atoms of the decalin system.

Interestingly, neither *cis*-hydroxy ketone, deriving from axial attack (mode **b**), nor bridged hydroxy ketones could be detected among the crude cyclization products of **8a**/**8b** by 400-MHz ^{1}H-NMR analysis. The cyclization of **8a**/**8b** must be under kinetic control, since *trans*-compound **12a** and *cis*-isomer **12c** were not interconverted when subjected to the conditions of their formation.

The configuration of **11a** and **12a** was proven by their conversion to **9a** and geosmin, respectively, as published previously [20] for the latter ketol. The structure of **11b** was determined by X-ray analysis (see *Fig.* and *Exper. Part*)[9]).

On TLC (silica gel, hexane/AcOEt 4:1), the *trans*-isomers **9a**–**12a** have greater mobility than their *cis*-counterparts. Within the *cis*-series, the 'non-steroid' hydroxy ketones **9c** and **11c** have higher R_f values (silica gel, CH_2Cl_2/AcOEt 12:1[10])) than the 'steroid' isomers **9b** and **11b**. There is also good correlation of ^{13}C-NMR chemical shift values for C(1), C(4a), and C(8a) (*Table 3*).

Table 3. *Selected ^{13}C-NMR Chemical Shifts* (100 MHz, $CDCl_3$) *of* **9**–**12**. δ(C) in ppm with TMS as internal standard.

Compound[a])	δ(C)			Compound[a])	δ(C)		
	C(1)	C(4a)	C(8a)		C(1)	C(4a)	C(8a)
9a[b])	49.6	37.4	78.7	**11a**	51.7	44.6	76.5
9b	46.5	38.3	80.7	**11b**[c])	46.1	45.8	78.0
9c	51.6	37.9	77.3	**11c**	54.1	45.4	75.5
10a	48.0	37.8	78.8	**12a**	49.3	44.1	76.2
10b	45.2	36.6	80.8	**12c**	50.1	45.2	74.9

[a]) For numbering of C-atoms, see *Scheme 3*.
[b]) Values taken from [35].
[c]) in $CDCl_3$/DMSO 10:1 (*v*/*v*).

3. Discussion. – The investigation of the stereochemistry of nucleophilic addition reactions to cyclohexanones has resulted in the conception of many models[11]), which make an analysis *a priori* a delicate task.

Nevertheless, the stereochemical outcome of the cyclization of diketones **5**–**8** can be rationalized to some extent by considering steric factors. When the incipient angular substituent R has a low *A* value as for **6** (R = H), and **7**, **8** (R = CN)[3]), the transition state leading to the *trans*-fused hydroxy ketones contains less developing *gauche*-butane-like interactions than the corresponding transition state leading to the *cis*-compounds, as can be judged from relative product stabilities.

Since these cyclizations are only slightly exothermic, and $\Delta\Delta G°$ between the *trans*- and *cis*-isomers of **10**–**12** is > 1 kcal/mol, product stability may be important for the relative rate of formation of different isomers. For a discussion of this point, see [22]. However, other factors than steric ones must be involved, since cyclization of **7** affords a higher proportion or *cis*-hydroxy ketones, when compared to **6**, although the *trans*-hydroxy ketone (**11a**) is thermodynamically more favored in the former case.

[9]) We are indebted to Dr. *J. Daly* and Mr. *P. Schönholzer* (*F. Hoffmann-La-Roche AG*, Basel) for X-ray structure analysis.
[10]) This solvent combination proved to be unique to separate the *cis*-isomers **9b**/**9c** and **11b**/**11c** from each other.
[11]) Conformational, (stereo)electronic, and steric effects have been offered among others to rationalize the experimental data. For recent work in this area, see, *e.g.* [21].

In the cyclization of **5** (R = Me), the transition states corresponding to modes **a–c** (*Scheme 2*) must be closer in steric energies (compare relative stabilities of **9a–c** as discussed in *2.2*). The diminished stability of the transition state leading to the *trans*-compound **9a** is due to the fact that the angular Me group is axial to both rings. Two factors may explain the preferred formation of **9b**: *a*) equatorial attack of the enolate double bond leading to **9a** and **9c** is impeded by the axial alkyl group at C(2)[12]); *b*) since steric energies are more balanced (see above), the formation of **9b** may be the result of the intrinsic bias for C-nucleophiles to add to cyclohexanones in an axial fashion [21d] [24].

Cyclization of **6** seems to be in disagreement with *a*) mentioned above, since it leads preferably to the *trans*-compound **10a**, despite the presence of an axial Me group at the α-position of the cyclohexanone moiety[12]). However, the additional equatorial Me group[12]) present in **6**, and the higher steric energy disfavor the transition state leading to the *cis*-isomer **10b** (*cf.* relative stabilities of **10a**/**10b** as discussed in *2.3*, the latter being only by *ca.* 0.4 kcal/mol more stable than **6** as judged from the equilibration experiments with NaOMe and LDA). Cyclization of **6** may be actually more complex, since it may not involve chair-like transition states as is assumed in the present discussion[13]).

One might argue that stereoelectronic effects could be responsible for the preferred formation of **9b** in the cyclization of **5** (on axial attack C–C bond formation occurs *anti* to the C(2)–Me bond), but this effect should be even more pronounced for the more electronegative CN group[14]). However, mode **b** is neither preferred exceedingly (**7** → **11**) nor even observed (**8a** → **12a**/**12c**) for R = CN.

Interestingly, the cyclizations of **5–8** under protic conditions proceed mainly with *synclinal* orientation of the reactant centers[15]), although the *antiperiplanar* mode is usually preferred in intramolecular aldol reactions using protic solvents [7b] or in aprotic solvents without a coordinating cation [28]. The preference for the *syn*-pathway (mode **b**) in the cyclization of **5** under *Knoevenagel* conditions is expected, and is related to the proline-catalyzed *Hajos-Wiechert* reaction [6a].

Finally, we address the formation of bridged hydroxy ketones in the cyclization of **5**, **7**, and **8**. Under protic conditions, diketone **5** was the only one to afford *ca.* 5% of a bridged aldol product (**13**). Equilibration experiments (see *2.2*) have revealed that **13** is thermodynamically disfavored by *ca.* 1.5 kcal/mol over **9a–c**, the former having nearly the same stability as **5**.

Interestingly, cyclization of the unsaturated diketone **19** under protic conditions (6 mol-% of 0.022M NaOMe in THF/MeOH 8:1, 0°, 45 min) exclusively furnished a diastereoisomeric mixture (*ca.* 5:1) of bridged compounds **20** (*Scheme 5*) [29]. In fact, cyclization of related diketones with an unsaturation in the ring (oxo group, double bond) are known to yield preferentially bridged aldol products [30][16]).

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[12]) It is well known that an axial Me group at C(2) of a cyclohexanone impedes equatorial attack, but has no (steric) effect on axial attack. On the other hand, an equatorial Me group at the same position reinforces equatorial attack [21c] [23].

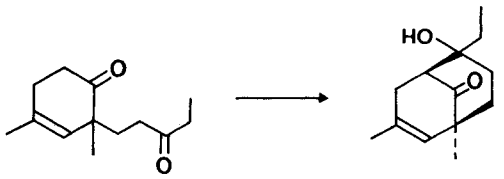
[13]) For instance, **10a** contains the structural characteristics of *trans*-3-(*tert*-butyl)-4-methoxycyclohexanone which is known to exist in appreciable proportions of non-chair forms [25].

[14]) There is much controversy in the literature about the order of *antiperiplanar* effects. For relevant discussions, see [23c] [26].

[15]) For a thorough treatment of transition-state structures for aldol reactions, see [27].

[16]) Thus, the statements found in the literature [30b] [31] that bridged ketols are the kinetically preferred products in the base-catalyzed *Robinson* anellation are not valid for the cyclization of saturated diketones as **5**, **7**, and **8**.

Scheme 5



19 **20**

Under aprotic conditions (LDA, THF), however, cyclization of **5** afforded **13** as the main product. Under these conditions (see *2.2*), **5** is first converted to a mixture of enolates prior to cyclization. The ratio of **13**/**9a–c** must be largely determined by the initial rate of proton abstraction at C(4′) and C(6), respectively.

I thank Prof. *J. Baldwin*, Dr. *G. Fráter*, Dr. *P. Naegeli* for many valuable hints and discussions, Dr. *E. Billeter*, Mr. *J. Märki*, and Dr. *J. Schmid* (*Givaudan Forschungsgesellschaft AG*, Dübendorf) for NMR and MS measurements, Dr. *A. Dirscherl* (*F. Hoffmann-La Roche AG*, Basel) for performing the elemental analysis, and Miss *R. Imhof* and Mr. *H. Jenal* for experimental assistance.

Experimental Part

General. See [32]. GLC: *Carlo Erba GC 6000 Vega Series* instrument equipped with a *SE-30* glass cap. column (28 m × 0.3 mm), He as carrier gas (70 kPa); temp. program: samples were injected at 90°; after 2 min, 8°/min→200°, then 20°/min →240°. ^{1}H-NMR (200 MHz): *Bruker AC-F 200* spectrometer. X-Ray analysis: data collection on a *Nicolet R3m* four-circle diffractometer fitted with a graphite monochromator and *LT1* cooling apparatus.

1. Synthesis of Diketones. – 1.1. *(±)-2-Methyl-2-(3-oxopentyl)cyclohexanone* (**5**) [4] [9d]. According to the method of *Pfau et al.* [10], 33.7 g (0.30 mol) of 2-methylcyclohexanone, 33.0 g (0.33 mol) of cyclohexylamine, and 30 mg of TsOH were refluxed in 100 ml of toluene for 6 h with azeotropic removal of H_2O. The solvent was evaporated under reduced pressure, and the crude cyclohexyl(2-methylcyclohexylidene)amine dissolved in 60 ml of dry THF. Ethyl vinyl ketone (31 ml, 0.31 mol) was added during 10 min and the resulting soln. kept at r.t. for 4 days under N_2. A soln. of 39 g of AcOH and 13 g of AcONa in 400 ml of H_2O was added and the mixture vigorously stirred at r.t. for 1 h. The soln. was neutralized with $NaHCO_3$ and then extracted with Et_2O (2 × 700 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Bulb-to-bulb distillation of the crude product (130°/0.1 Torr) afforded 48.1 g (82%) of a colorless liquid. GLC showed two peaks at t_R 10.2 and 10.4 min in a ratio of 15:85. Repeated chromatography on SiO_2 with hexane/AcOEt 7:1 afforded pure **5**. TLC: R_f (hexane/AcOEt 2:1) 0.44. GLC: t_R 10.4 min. IR ($CHCl_3$): 1701*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.045 (*t*, *J* = 7, CH_3); 1.05 (*s*, CH_3); 1.54–2.48 (*m*, 14 H). MS: 196 (5, M^+), 112 (100), 57 (76).

1.2. *(±)-2,2-Dimethyl-6-(3-oxobutyl)cyclohexanone* (**6**). To a soln. of 1.632 g (10.6 mmol) of 2-(hydroxymethylidene)-6,6-dimethylcyclohexanone [33] in 11 ml of dry THF were added successively 1.58 g (22.5 mmol) of methyl vinyl ketone (*Fluka, purum*) and 0.68 g (6.7 mmol) of Et_3N. The resulting mixture was stirred at r.t. for 24 h under N_2 and then evaporated to give 2.372 g (100%) of a yellow oil. The crude material (1.783 g) was heated under reflux in a mixture of 25 ml of EtOH and 8 ml of 0.25M aq. K_2CO_3 for 2 h. Then, 1.5 ml of 1M aq. K_2CO_3 were added, and reflux was continued for 2 h. The mixture was poured into ice/H_2O and extracted with Et_2O (2 × 250 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Chromatography (SiO_2 (30 g), hexane/AcOEt 7:1) of the residual oil, followed by bulb-to-bulb distillation (120°/0.2 Torr), afforded 1.327 g (85%) of **6** as a colorless liquid (single peak on GLC). TLC: R_f (hexane/AcOEt 2:1) 0.41. GLC: t_R 9.3 min. IR ($CHCl_3$): 1705*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.04 (*s*, CH_3); 1.17 (*s*, CH_3); 1.20–2.16 (*m*, 11H), overlapped by 2.13 (*s*, CH_3CO); 2.30–2.68 (*m*, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.23 (*t*); 23.67 (*t*); 24.75 (*q*); 25.23 (*q*); 29.53 (*q*); 34.64 (*t*); 41.20 (*t*); 41.59 (*t*); 44.89 (*d*); 45.20 (*s*); 208.64 (*s*); 216.26 (*s*). MS: 196 (14, M^+), 43 (100). Anal. calc. for $C_{12}H_{20}O_2$ (196.29): C 73.43, H 10.27; found: C 73.29, H 10.40.

1.3. *(±)-2-Oxo-1-(3-oxopentyl)cyclohexanecarbonitrile* (**7**). To a soln. of 1.259 g (10.22 mmol) of 2-oxocyclohexanecarbonitrile [34] in 10 ml of dry THF were added 1.3 ml (*ca.* 13 mmol) of ethyl vinyl ketone (*Fluka, purum*),

followed by 0.5 ml of Et_3N. The yellow soln. was kept at r.t. for 5 d under N_2 and then evaporated. The residue was chromatographed (SiO_2 (12 g), pentane/Et_2O 1:1) to give 1.876 g (89%) of **7** as a faint yellow liquid. TLC: R_f (pentane/Et_2O 1:1) 0.27. GLC: t_R 12.4 min. IR ($CHCl_3$): 2240*w*, 1722*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.07 (*t*, J = 7.5, CH_3); 1.70–2.84 (*m*, 14H), overlapped by 2.46 (*q*, J = 7.5). ^{13}C-NMR (100 MHz, $CDCl_3$): 7.77 (*q*); 21.87 (*t*); 27.56 (*t*); 27.71 (*t*); 35.99 (*t*); 37.75 (*t*); 38.95 (*t*); 39.03 (*t*); 51.04 (*s*); 119.55 (*s*); 203.13 (*s*); 209.30 (*s*). MS: 207 (26, M^+), 178 (23), 150 (13), 123 (7), 57 (100), 55 (86).

1.4 *(±)-*trans- *and (±)-*cis-*3-Methyl-2-oxo-1-(3-oxobutyl)cyclohexanecarbonitrile* (**8a** and **8b**, resp.). To a soln. of 2.306 g (16.8 mmol) of 3-methyl-2-oxocyclohexanecarbonitrile [34] in 15 ml of dry THF were added successively 2 ml (*ca.* 24 mmol) of methyl vinyl ketone (*Fluka, purum*) and 0.6 ml of Et_3N. The resulting mixture was kept at r.t. for 100 h under N_2 and then evaporated. GLC indicated a 1:5 ratio for **8a**/**8b**. Bulb-to-bulb distillation (160°/0.08 Torr) yielded 3.267 g (94%) of **8a**/**8b** 47:53 as a yellow liquid. This mixture (1.922 g) was chromatographed (SiO_2 (30g), pentane/Et_2O 1:1) leading to 888 mg of **8a**. Further elution with pentane/Et_2O 1:3 afforded 979 mg of **8b**. Both diastereoisomers crystallized on standing.

Equilibration of **8a** *and* **8b**. Compounds **8a** and **8b** (8 mg) were separately dissolved in 0.6 ml of dry THF and then treated with 1 drop (*ca.* 12 mg) of DBU. The resulting soln. was stirred at r.t. for 5 h under N_2 and then quenched with 2 drops of AcOH. GLC of both equilibration experiments indicated a 3:1 ratio for **8a**/**8b** (minor amounts of hydroxy ketones were also formed).

Data of **8a**. M.p. 43–44°. TLC: R_f(pentane/Et_2O 1:1) 0.28. GLC: t_R 11.3 min. IR ($CHCl_3$): 2235*w*, 1725*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.07 (*d*, J = 6.5, CH_3–C(3)); 1.32–1.46 (*m*, 1 H); 1.63 (*td*, J = 13.5, 4, 1 H); 1.77–1.92 (*m*, 2 H); 2.10–2.25 (*m*, 6 H), overlapped by 2.18 (*s*, CH_3CO); 2.30–2.38 (*m*, 1 H); 2.59 (*ddd*, J = 5, 11, 18, 1 H); 2.79 (*ddd*, J = 5, 11, 18, 1 H); 3.01–3.11 (*m*, H–C(3)); irradiation of the *d* at 1.07→*dd* at 3.06 (J = 5.5, 12.5).^{13}C-NMR (100 MHz, $CDCl_3$): 14.44 (*q*); 22.63 (*t*); 27.39 (*t*); 29.93 (*q*); 37.27 (*t*); 39.29 (*t*); 40.24 (*t*); 43.15 (*d*); 50.54 (*s*); 119.87 (*s*); 204.71 (*s*); 206.64 (*s*). MS: 207 (17, M^+), 124 (49), 122 (36), 58 (63), 43 (100). Anal. calc. for $C_{12}H_{17}NO_2$ (207.27): C 69.54, H 8.27, N 6.76; found: C 69.57, H 8.15, N 6.71.

Data of **8b**. M.p. 54–55°. TLC: R_f (pentane/Et_2O 1:1) 0.13. GLC: t_R 12.1 min. IR ($CHCl_3$): 2245*w*, 1715*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.07 (*d*, J = 6.5, CH_3–C(3)); 1.45 (*qd*, J = 13, 4, 1 H); 1.75–2.35 (*m*, 9 H), overlapped by 2.18 (*s*, CH_3CO); 2.44–2.58 (*m*, 2 H); 2.66–2.78 (*m*, 2 H); irradiation of the *d* at 1.07→dd at 2.72 (J = 6, 12.5). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.73 (*q*); 20.10 (*t*); 28.33 (*t*); 30.04 (*q*); 35.21 (*t*); 37.56 (*t*); 38.82 (*t*); 40.93 (*d*); 52.78 (*s*); 119.75 (*s*); 205.63 (*s*); 206.16 (*s*). MS: 207 (8, M^+), 124 (30), 122 (23), 58 (69), 43 (100). Anal. calc. for $C_{12}H_{17}NO_2$ (207.27): C 69.54, H 8.27, N 6.76; found: C 69.50, H 8.28, N 6.76.

2. Cyclization of 5. – 2.1. *Protic Conditions*. To 383 mg (1.95 mmol) of **5** were added 5 ml of cold (0°) 0.022M NaOMe (0.11 mmol) in THF/MeOH 8:1 (*v*/*v*)[17]. The resulting soln. was stirred at 0° for 80 min under N_2. AcOH (20 mg) was added and the solvent evaporated. The residue was distributed between Et_2O (200 ml) and H_2O, the org. extract dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Crystallization from Et_2O/hexane at 0° afforded 143 mg (37%) of **9b** (98% pure by GLC), m.p. 98–99°. Two further crystallizations raised the m.p. to 102–103°. The mother liquor (237 mg) contained 59% of **9b**, 24% of **9c**, 8% of **13**, 6% of **5**, 1–2% of **9a**, and 1–2% of **14**, as determined by GLC. The presence of the minor constituents **5**, **9a**, **13**, and **14** was confirmed by ^{1}H-NMR. Chromatography (SiO_2 (10 g), hexane/AcOEt 4:1) of the mother liquor allowed separation of **14**, **5**, **9a**, and **13**, but not of **9b** and **9c** (see R_f values given below). The *cis*-fused **9b** and **9c** could, however, be easily separated by chromatography (SiO_2, CH_2Cl_2/AcOEt 12:1; R_f 0.16 and 0.21, resp.). The total recovery of material was > 95%. In another experiment, 154 mg (0.78 mmol) of **5** were stirred in 2 ml of 0.022M NaOMe (0.044 mmol) in THF/MeOH 8:1 (*v*/*v*)[17]) at 0° under N_2. After 10 min, 80 min, 3 h, and 16 h, aliquot samples were removed, quenched with excess AcOH/AcONa/H_2O pH 4.1, and then analyzed by GLC. The results are given in *Table 1*.

(±)-3,4,4aα,5,6,7,8,8aα-Octahydro-8aα-hydroxy-1α,4aα-dimethyl-2(1 H)-naphthalenone (**9b**). M.p. 102–103°. TLC: R_f (hexane/AcOEt 2:1) 0.31. GLC: t_R 11.7 min. IR ($CHCl_3$): 3600*w*, 3500*w* (br.), 1710*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.00 (*d*, J = 6.5, CH_3–C(1)); 1.07 (*d*, J < 1, CH_3–C(4a)); 1.22 (*s*, OH, exchangeable with D_2O); 1.28–1.42 (*m*, 2 H); 1.49–1.59 (*m*, 2 H); 1.61–1.77 (*m*, 4 H); 2.11 (*td*, J = 14, 5, 1 H), overlapped by *m*, 1 H; 2.28 (*ddd*, J = 2, 5, 14, 1 H); 2.54 (*tdd*, J = 14, 6.5, < 1, 1 H); 3.00 (*qd*, J = 6.5, < 1, H–C(1)).^{13}C-NMR (100 MHz, $CDCl_3$): 6.68 (*q*); 21.01 (*t*); 21.62 (*q*); 23.42 (*t*); 32.52 (*t*); 33.60 (*t*); 36.95 (*t*); 37.94 (*t*); 38.25 (*s*); 46.47 (*d*); 80.72 (*s*); 212.89 (*s*). MS: 196 (13, M^+), 125 (11), 112 (100), 97 (34), 83 (22), 55 (33), 43 (34). Anal. calc. for $C_{12}H_{20}O_2$ (196.29): C 73.43, H 10.27; found: C 73.37, H 10.45.

(±)-3,4,4aα,5,6,7,8,8aα-Octahydro-8aα-hydroxy-1β,4aα-dimethyl-2(1 H)-naphthalenone (**9c**). Liquid. TLC: R_f (hexane/AcOEt 2:1) 0.31. GLC: t_R 11.4 min. IR ($CHCl_3$): 3605*w*, 3500*w* (br.), 1708*s*. ^{1}H-NMR (400 MHz,

[17]) Prepared by dissolving 212 mg of Na in 46 ml of MeOH, followed by addition of 368 ml of dry THF.

$CDCl_3$): 1.02 (*d*, *J* = 6.5, CH_3–C(1)); 1.05–1.19 (*m*, 1 H); 1.22 (*s*, CH_3–C(4a)); 1.28–1.36 (*m*, 1 H); 1.40 (*ddd*, *J* = 2, 7, 14, 1 H); 1.45–1.61 (*m*, 6 H); 1.73–1.83 (*m*, 1 H); 2.13 (*td*, *J* = 14, 5, 1 H); 2.32 (*ddd*, *J* = 2, 5, 14, 1 H); 2.57 (*tdd*, *J* = 14, 7, 1, 1 H); 2.87 (*qd*, *J* = 6.5, 1, H–C(1)). ^{13}C-NMR (100 MHz, $CDCl_3$): 6.53 (*q*); 20.48 (*t*); 21.04 (*t*); 22.03 (*q*); 28.35 (*t*); 31.54 (*t*); 35.31 (*t*); 37.72 (*t*); 37.90 (*s*); 51.62 (*d*); 77.34 (*s*); 211.08 (*s*). MS: 196 (7, M^+), 112 (100), 97 (15), 83 (10), 55 (13), 43 (10), 41 (11).

(±)-2-Ethyl-2-hydroxy-5-methylbicyclo[3.3.1]nonan-9-one (**13**). M.p. 100–102°. TLC: R_f (hexane/AcOEt 2:1) 0.26. GLC: t_R 10.65 min. IR ($CHCl_3$): 3582*w*, 3420*w* (br.), 1710*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.91 (*t*, *J* = 7.5, CH_3); 0.99 (*s*, CH_3); 1.38 (*d*, *J* ≈ 1, OH); 1.46–2.22 (*m*, 12 H); 2.34–2.40 (*m*, 1 H). MS: 196 (10, M^+), 112 (100).

(±)-4,4a,5,6,7,8-Hexahydro-1,4a-dimethyl-2(3H)-naphthalenone (**14**) [13]. Liquid. TLC: R_f (hexane/AcOEt 2:1) 0.53. GLC: t_R 10.2 min. IR and ^{1}H-NMR: in agreement with the values reported in [13].

2.2. Knoevenagel *Conditions*. Compound **5** (25 mg, 0.13 mmol) was heated in 1 ml of a 0.2M soln. of pyrrolidine and AcOH in THF[18]) at reflux under N_2. After 30 min, 60 min, and 120 min, aliquot samples were withdrawn, quenched with excess AcOH/AcONa/H_2O pH 4.1, and then analyzed by GLC. The results are listed in *Table 1, Entries 5–7*. The control experiments are summarized in *Table 4*.

Table 4. *Reaction of* **9a–c** (12 mg) *with 1 ml of 0.2M Pyrrolidine/AcOH in THF*[18]) *under Reflux for 2 h*

Compound	Ratio of products[a])				
	5	**9a**	**9b**	**9c**	**14**
9a	0	85	0	0	15
9b	16	0	60	4	20
9c	1	0	4	90	5

[a]) Determined by GLC.

2.3. *Aprotic Conditions*. To a soln. of 0.3 ml (2.1 mmol) of $(i\text{-}Pr)_2NH$ in 3 ml of dry THF were added, at 0° under N_2, 0.55 ml of 1.4M BuLi (*ca.* 0.8 mmol) in hexane within 1 min. The mixture was stirred at 0° for 12 min and then cooled to −60°. A soln. of 203 mg (1.03 mmol) of **5** in 2 ml of dry THF was added with a syringe over 1 min and the resulting soln. warmed to 4° during 2 h. After addition of 0.5 ml of AcOH, the mixture was poured into ice/H_2O, and extracted with Et_2O (2 × 100 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Chromatography (SiO_2 (18 g), hexane/AcOEt 4:1) afforded 36 mg (18%) of **5**, 32 mg (16%) of **9a**, 32 mg (16%) of a 5:2 mixture **9b**/**9c**, and 64 mg (32%) of **13** (m.p. 100–102°).

(±)-3,4,4aα,5,6,7,8,8aβ-Octahydro-8aβ-hydroxy-1β,4aα-dimethyl-2(1H)-naphthalenone (**9a**) [9e]. M.p. 109–110° (from Et_2O/hexane). TLC: R_f (hexane/AcOEt 2:1) 0.39. GLC: t_R 11.7 min. IR ($CHCl_3$): 3600*w*, 3490*w* (br.), 1707*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.99 (*d*, *J* = 6.5, CH_3–C(1)); 1.27 (*s*, CH_3–C(4a)), overlapped by 1.21–1.30 (*m*, 1 H); 1.32 (*s*, OH); 1.41 (*ddd*, *J* = 2, 7, 13, 1 H); 1.45–1.71 (*m*, 7 H); 2.06 (*tdd*, *J* = 13, 5.5, < 1, 1 H); 2.37 (*ddd*, *J* = 1.5, 5.5, 14, 1 H); 2.50 (*tdd*, *J* = 14, 7, < 1, 1 H); 2.61 (*q*, *J* = 6.5, H–C(1)). ^{13}C-NMR: see [35]. MS: 196 (14, M^+), 125 (14), 112 (100), 55 (56).

Equilibration of **9a** *and* **9b**. To a soln. of 7.85 g (40 mmol) of **9b** in 100 ml of dry THF at 0° were added 20 ml of 0.1M LDA (2 mmol) in THF/hexane 13:1 (*v*/*v*) over 3 min. The resulting soln. was stirred at 0° for 4 h under N_2, then quenched with 1 ml of AcOH, and evaporated. The residue was distributed between Et_2O (500 ml) and H_2O, the org. extract dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 7.77 g of faint yellow crystals. GLC showed the presence of 95% of a mixture **9a**/**9b** (same t_R on *SE-30*), 3% of **9c**, and 0.5–1% of each **5**, **13**, and **14**. ^{1}H-NMR showed a 5:4 ratio for **9a**/**9b**. GLC on a *OV-1701* cap. column revealed the same ratio. Exactly the same result was obtained, when pure **9a** was equilibrated under these conditions.

3. Cyclization of 6. – To 788 mg (4.01 mmol) of **6** were added 10 ml of cold (0°) 0.022M NaOMe (0.22 mmol) in THF/MeOH 8:1 (*v*/*v*)[17]). The soln. was stirred at 0° for 5 h under N_2 and then worked up as described in *2.1* to give a mixture **6**/**10a**/**10b**/**17** in a ratio of 7:79:6:8, as determined by GLC. Chromatography (SiO_2 (30 g), hexane/AcOEt 4:1) afforded the pure compounds. The recovery of material was > 95%.

[18]) Prepared by adding AcOH to a 0.2M soln. of pyrrolidine in dry THF, until the soln. showed a pH of 7, when diluted with 10 volumes of H_2O.

(±)-3,4,4aα,5,6,7,8,8aβ-Octahydro-8aβ-hydroxy-8,8-dimethyl-2(1H)-naphthalenone (**10a**). M.p. 85–86° (from Et_2O/hexane). TLC: R_f (hexane/AcOEt 2:1) 0.34. GLC: t_R 11.6 min. IR ($CHCl_3$): 3605*w*, 3480*w* (br.), 1712*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.91 (*s*, CH_3); 1.04 (*s*, CH_3); 1.10–2.48 (*m*, 14 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.19 (*t*); 23.61 (*q*); 24.20 (*q*); 28.25 (*t*); 29.33 (*t*); 35.63 (*t*); 37.75 (*d*); 37.94 (*s*); 41.23 (*t*); 48.00 (*t*); 78.78 (*s*); 212.03 (*s*). MS: 196 (44, M^+), 178 (8), 125 (52), 82 (100). Anal. calc. for $C_{12}H_{20}O_2$ (196.29): C 73.43, H 10.27; found: C 73.55, H 10.31.

(±)-3,4,4aα,5,6,7,8,8aα-Octahydro-8aα-hydroxy-8,8-dimethyl-2(1H)-naphthalenone (**10b**). M.p. 116° (from Et_2O/hexane). TLC: R_f (hexane/AcOEt 2:1) 0.23. GLC: t_R 12.0 min. IR ($CHCl_3$): 3600*w*, 3470*w* (br.), 1706*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.87 (*s*, CH_3); 1.05 (*s*, CH_3); 1.30–2.52 (*m*, 13 H), overlapped by 1.52 (*d*, J = < 1, OH); 2.71 (*d*, J = 14.5, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.33 (*t*); 21.81 (*q*); 24.47 (*q*); 27.23 (*t*); 29.04 (*t*); 36.58 (*t*); 36.58 (*d*); 38.34 (*t*); 38.61 (*s*); 45.24 (*t*); 80.81 (*s*); 212.42 (*s*). MS: 196 (31, M^+), 178 (7), 125 (41), 82 (100). Anal. calc. for $C_{12}H_{20}O_2$ (196.29): C 73.43, H 10.27; found: C 73.46, H 10.47.

(±)-4,4a,5,6,7,8-Hexahydro-8,8-dimethyl-2(3H)-naphthalenone (**17**) [36]. M.p. 72–73° (from hexane). TLC: R_f (hexane/AcOEt 2:1) 0.43. GLC: t_R 10.4 min. IR ($CHCl_3$): 1662*s*, 1608*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.07–2.62 (*m*, 17 H), overlapped by 1.14 (*s*, 2 CH_3); 5.96 (*d*, J = 2, H–C(1)). MS: 178 (56, M^+), 163 (17), 150 (31), 135 (53), 122 (70), 107 (100). Anal. calc. for $C_{12}H_{18}O$ (178.28): C 80.85, H 10.18; found: C 80.68, H 10.45.

In another experiment, 32 mg (0.16 mmol) of **6** were stirred in 0.4 ml of 0.022M NaOMe (0.0088 mmol) in THF/MeOH 8:1 (*v*/*v*)[17]) at 0° under N_2. After 15 min, 2 h, 5 h, and 27 h, aliquot samples were removed, quenched with excess AcOH/AcONa/H_2O pH 4.1, and analyzed by GLC. The results are given in *Table 2*.

The control experiments are summarized in *Table 5*.

Table 5. *Reaction of* **10a** *and* **10b** *with 0.4 ml of 0.022M NaOMe in THF/MeOH 8:1 (v/v)*[17]) *at 0°*

Compound		Time	Ratio of products[a])			
			6	**10a**	**10b**	**17**
10a	(20 mg)	2 h	5	89	1	5
10a	(20 mg)	27 h	4	64	5	27
10b	(4 mg)	2 h	2	4	82	12
10b	(4 mg)	27 h	2	24	12	62

[a]) Determined by GLC.

Equilibration of **10a** *and* **10b** *under Aprotic Conditions.* Reaction of pure samples of **10a** and **10b** with 5 mol-% of LDA in THF at 0° for 5 h, as described in *2.3*, afforded **6**/**10a**/**10b**/**17** in a ratio of 5:82:9:4 (GLC).

4. Cyclization of 7. – Compound **7** (642 mg, 3.10 mmol) was treated with 7 ml of cold (0°) 0.022M NaOMe (0.154 mmol) in THF/MeOH 8:1 (*v*/*v*)[17]) at 0° for 2 h under N_2, and then worked up as described in *2.1*. GLC of the crude product showed 4 peaks at t_R 12.0, 12.9, 13.1, and 14.0 min in a ratio of 5:65:11:19, corresponding to **18**, **11a**, **11c**, and **11b**, resp. Only trace amounts (< 1%) of **7** could be detected. Chromatography (SiO_2 (26 g), CH_2Cl_2/AcOEt 12:1) afforded the pure compounds. The total recovery of material was > 95%.

(±)-3,4,4aα,5,6,7,8,8aβ-Octahydro-8aβ-hydroxy-1β-methyl-2-oxo-1H-naphthalene-4aα-carbonitrile (**11a**). M.p. 123–124° (from CH_2Cl_2/hexane). TLC: R_f (CH_2Cl_2/AcOEt 12:1) 0.23. GLC: t_R 12.9 min. IR ($CHCl_3$): 3600*w*, 3475*w* (br.), 2230*w*, 1712*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.05 (*d*, J = 6.5, CH_3–C(1)); 1.44–1.92 (*m*, 9 H); 1.99 (*ddd*, J = 2, 6.5, 14, 1 H); 2.19 (*td*, J = 14, 4.5, 1 H); 2.49 (*ddd*, J = 2, 4.5, 14, 1 H); 2.76 (*tdd*, J = 14, 7, 1, 1 H); 2.92 (*qd*, J = 6.5, 1, H–C(1)). ^{13}C-NMR (100 MHz, $CDCl_3$): 6.53 (*q*); 19.79 (*t*); 22.12 (*t*); 31.30 (*t*); 31.99 (*t*); 32.74 (*t*); 38.51 (*t*); 44.59 (*s*); 51.74 (*d*); 76.50 (*s*); 122.72 (*s*); 208.99 (*s*). MS: 207 (13, M^+), 180 (13), 84 (100). Anal. calc. for $C_{12}H_{17}NO_2$ (207.27): C 69.54, H 8.27, N 6.76; found: C 69.63, H 8.33, N 6.77.

Reduction of **11a** according to the procedure that has been described for **12a** [20], followed by *Jones* oxidation of the resulting diol, afforded **9a** (overall yield 30%).

(±)-3,4,4aα,5,6,7,8,8aα-Octahydro-8aα-hydroxy-1α-methyl-2-oxo-1H-naphthalene-4aα-carbonitrile (**11b**). M.p. 176–177° (from AcOEt/hexane). TLC: R_f (CH_2Cl_2/AcOEt 12:1) 0.13. GLC: t_R 14.0 min. IR ($CHCl_3$): 3590*w*, 2235*w*, 1720*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.07 (*d*, J = 6.5, CH_3–C(1)); 1.30–1.44 (*m*, 1 H); 1.74 (*td*, J = 13.5, 3.5, 1 H); 1.78–2.24 (*m*, 8 H); 2.40–2.46 (*m*, 2 H); 2.67–2.77 (*m*, 1 H); 2.81 (*q*, J = 6.5, H–C(1)). ^{13}C-NMR (100 MHz, $CDCl_3$/DMSO 10:1): 6.45 (*q*); 22.48 (*t*); 30.97 (*t*); 31.36 (*t*); 34.27 (*t*); 36.28 (*t*); 45.84 (*s*); 46.11 (*d*); 77.96 (*s*); 123.07 (*s*); 209.02 (*s*). MS: 207 (13, M^+), 180 (29), 84 (100). Anal. calc. for $C_{12}H_{17}NO_2$ (207.27): C 69.54, H 8.27, N 6.76; found: C 69. 65, H 7.83, N 6.76.

X-Ray Analysis[9]) *of* **11b**. *Crystal Data*: orthorhombic *Pbca*; $a = 7.971$ (2), $b = 11.320$ (2), $c = 23.527$ (4) Å; density: $D = 1.297$ Mg/m^3, $Z = 8$. *Data Collection*: crystal size not measured, temp. 180 K; wavelength: 0.71069 Å; $\theta_{min}/\theta_{max}$: 0/28°; peak/background ratio 5:1; total data measured 2958 excluding standards; total data observed 1644; rejection criterion: $I > 2.5 \times \sigma(I)$; number of parameters 139. The refinement was performed using the *SHELXTL* package of the *R3m* system[19]) $R = 0.0488$.

(±)-3,4,4aα,5,6,7,8,8aα-Octahydro-8aα-hydroxy-1β-methyl-2-oxo-1 H*-naphthalene-4aα-carbonitrile* (**11c**). M.p. 145–147° (from CH_2Cl_2/hexane). TLC: R_f (CH_2Cl_2/AcOEt 12:1) 0.18. GLC: t_R 13.1 min. IR ($CHCl_3$): 3600*w*, 3565*w*, 3460*w* (br.), 2235*w*, 1716*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.09 (*d*, $J = 6.5$, CH_3–C(1)), overlapped by 0.98–1.14 (*m*, 1 H); 1.32–1.72 (*m*, 5 H); 1.83–1.92 (*m*, 1 H); 2.04 (*ddd*, $J = 2, 6.5, 14$, 1 H); 2.16 (*d*, $J = 1$, OH); 2.22 (*td*, $J = 14, 4.5$, 1 H); 2.42 (*td*, $J = 14, 4$, 1 H); 2.49 (*ddd*, $J = 2, 4.5, 14$, 1 H); 2.81 (*tdd*, $J = 14, 7, 1$, 1 H); 3.00 (*qd*, $J = 6.5$, 1, H–C(1)). ^{13}C-NMR (100 MHz, $CDCl_3$): 6.42 (*q*); 19.41 (*t*); 19.75 (*t*); 26.46 (*t*); 28.41 (*t*); 30.97 (*t*); 37.96 (*t*); 45.38 (*s*); 54.05 (*d*); 75.52 (*s*); 122.87 (*s*); 207.66 (*s*). MS: 207 (14, M^+), 180 (6), 124 (27), 84 (100). Anal. calc. for $C_{12}H_{17}NO_2$ (207.27): C 69.54, H 8.27, N 6.76; found: C 69.70, H 8.38, N 6.79.

(±)-4,4a,5,6,7,8-Hexahydro-1-methyl-2-oxo-3 H*-naphthalene-4a-carbonitrile* (**18**). Liquid. TLC: R_f 0.52 (CH_2Cl_2/AcOEt 12:1). GLC: t_R 12.0 min. IR ($CHCl_3$): 2235*w*, 1677*s*, 1622*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.32–1.54 (*m*, 2 H); 1.80–2.06 (*m*, 7 H), overlapped by 1.84 (*d*, $J = 1.5$, CH_3–C(1)); 2.19–2.41 (*m*, 3 H); 2.55 (*td*, $J = 16, 4$, 1 H); 2.69 (*ddd*, $J = 4.5, 14.5, 16$, 1 H); 2.86–2.94 (*m*, 1 H). MS: 189 (61, M^+), 161 (100).

Table 6. *Reaction of* **11a–c** *with 0.2 ml of 0.022* M *NaOMe in THF/MeOH 8:1 (v/v)*[17]) *at 0° for 2 h*

Compound		Ratio of products[a])[b])			
		11a	**11b**	**11c**	**18**
11a	(10 mg)	96	1	1	2
11b	(10 mg)	15	27	21	37
11c	(10 mg)	15	27	21	37

[a]) Determined by GLC.

[b]) Only trace amounts (< 1%) of **7** were detected.

The control experiments are shown in *Table 6*.

Equilibration of **11a** *and* **11b** *under Aprotic Conditions*. Treatment of **11a** and **11b** separately with 5 mol-% of LDA in THF at 0° for 5 h, as described in *2.3*, afforded **11a**/**11b** *ca.* 15:1 (GLC). Minor amounts of **11c** and **18** were also detected.

5. Cyclization of 8a and 8b. – To 136 mg (0.66 mmol) of **8a** were added 1.5 ml of cold (0°) 0.022M NaOMe (0.033 mmol) in THF/MeOH 8:1 (*v/v*)[17]). The soln. was stirred at 0° for 75 min under N_2 and then worked up as described in *2.1* to give 137 mg of a crystalline product. ^{1}H-NMR (400 MHz) and GLC (*OV-1701*) revealed a 7:1 ratio for **12a**/**12c**. Two crystallizations from AcOEt/hexane afforded pure **12a**, m.p. 168–169°.

Cyclization of 193 mg (0.93 mmol) of **8b** in 2 ml of 0.022M NaOMe (0.044 mmol) in THF/MeOH 8:1 (*v/v*)[17]) at 0° for 75 min, as described above, afforded 194 mg of a crystalline product. ^{1}H-NMR (400 MHz) and GLC (*OV-1701*) showed a 2:5 ratio for **12a**/**12c**. Chromatography on SiO_2 (10 g) with CH_2Cl_2/AcOEt 12:1 and crystallization from CH_2Cl_2/hexane afforded pure **12c**, m.p. 118–119°.

There was no significant difference in rate of cyclization of **8a** and **8b**. No signals attributable to bridged ketols, enones, or *cis*-hydroxy ketone **12b** (derived from axial attack, mode **b** in *Scheme 2*) could be detected by ^{1}H-NMR in the crude mixture.

Control Experiment. Compounds **12a** and **12c** (9 mg of each) were separately treated with 0.1 ml of 0.022M NaOMe in THF/MeOH 8:1 (*v/v*)[17]) at 0° for 75 min under N_2. The starting compounds were recovered unchanged after workup (no interconversion of **12a** and **12c** was observed by TLC).

(±)-3,4,4aα,5,6,7,8,8aβ-Octahydro-8aβ-hydroxy-8β-methyl-2-oxo-1 H*-naphthalene-4aα-carbonitrile* (**12a**). M.p. 168–169° (from AcOEt/hexane). TLC: R_f (CH_2Cl_2/AcOEt 12:1) 0.21. GLC: t_R 12.7 min. IR ($CHCl_3$): 3600*w*, 3475*w* (br.), 2232*w*, 1713*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.91 (*d*, $J = 6.5$, CH_3–C(8)); 1.28–1.42 (*m*, 1 H); 1.52–1.60 (*m*, 1 H); 1.70–1.90 (*m*, 4 H); 1.96 (*d*, $J = 2$, OH); 2.00–2.12 (*m*, H–C(8)); 2.01 (*ddd*, $J = 2, 6.5, 13.5$, 1 H); 2.24 (*td*, $J = 13.5, 4.5$, 1 H); 2.48 (*ddt*, $J = 15, 4.5, 2$, 1 H); 2.62 (*dd*, $J = 2, 15$, 1 H); 2.71 (*dd*, $J = < 1, 15$, 1 H);

[19]) Atomic coordinates and thermal parameters are deposited at the *Cambridge Crystallographic Data Centre*.

2.76 (*tdd*, J = 15, 6.5, < 1, 1 H); irradiation at 0.91 (*d*)→2.06 (*dd*, J = 4, 12, H_{ax}–C(8)). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.34 (*q*); 22.29 (*t*); 28.67 (*t*); 30.90 (*t*); 31.73 (*t*); 37.48 (*d*); 38.52 (*t*); 44.14 (*s*); 49.26 (*t*); 76.23 (*s*); 122.30 (*s*); 208.05 (*s*). MS: 207 (60, M^+), 150 (44), 138 (64), 122 (100). Anal. calc. for $C_{12}H_{17}NO_2$ (207.27): C 69.54, H 8.27, N 6.76; found: C 69.30, H 8.14, N 6.72.

The assignment of configuration for **12a** follows from the conversion to geosmin as described in [20].

(±)-3,4,4aα,5,6,7,8,8aα-Octahydro-8aα-hydroxy-8α-methyl-2-oxo-1 H*-naphthalene-4aα-carbonitrile* (**12c**). M.p. 118–119° (from CH_2Cl_2/hexane). TLC: R_f (CH_2Cl_2/AcOEt 12:1) 0.14. GLC: t_R 12.7 min. IR ($CHCl_3$): 3595*w*, 3455*w* (br.), 2235*w*, 1713*s*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.96 (*d*, J = 6, CH_3–C(8)); 1.40–1.70 (*m*, 5 H); 1.83–1.91 (*m*, 1 H); 2.04 (*ddd*, J = 2, 7, 14, 1 H), overlapped by *s*, OH; 2.29 (*td*, J = 14, 5, 1 H); 2.34–2.50 (*m*, 2 H); 2.76 (*d*, J = 14, 1 H); 2.76 (*tdd*, J = 14, 7.5, < 1, 1 H); 2.84 (*ddd*, J = 14, 2, < 1, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.83 (*q*); 19.77 (*t*); 28.35 (*t*); 28.92 (*t*); 30.39 (*t*); 33.08 (*d*); 37.76 (*t*); 45.21 (*s*); 50.08 (*t*); 74.85 (*s*); 122.86 (*s*); 206.41 (*s*). MS: 207 (43, M^+), 150 (41), 138 (93), 122 (97), 43 (100). Anal. calc. for $C_{12}H_{17}NO_2$ (207.27): C 69.54, H 8.27, N 6.76; found: C 69.63, H 8.32, N 6.77.

6. *Retro*-Aldol Cleavage of (±)-3,4,4a*α*,5,6,7,8,8a*β*-Octahydro-8a*β*-hydroxy-1,1,4a*α*-trimethyl-2(1*H*)-naphthalenone (16). – A soln. of 179 mg (0.85 mmol) of (±)-1,1,10α-trimethyl-2α-hydroxy-8,9-octalin β-oxide [37] in 3 ml of dry THF was slowly added to a suspension of 81 mg (2.13 mmol) of $LiAlH_4$ in 2 ml of THF. The mixture was heated at reflux for 15 h under N_2, poured onto ice/H_2O and acidified with 5 ml of aq. 5N H_2SO_4. Extraction with AcOEt (2 × 80 ml) afforded 182 mg of crystalline (±)-perhydro-1,1,4aα-trimethylnaphthalene-2α,8aβ-diol (*ca.* 90% pure). An anal. sample was prepared by recrystallization from hexane at 0°. M.p. 74–75°. TLC: R_f (hexane/AcOEt 2:1) 0.17. IR ($CHCl_3$): 3615*m*, 3460*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.86–1.88 (*m*, 23 H), overlapped by 3*s* at 0.91, 1.04, 1.13; 3.80–3.94 (*m*, 1 H). MS: 212 (< 1, M^+), 112 (100).

To a chilled soln. of 20 mg (0.09 mmol) of the above diol in 1 ml of AcOH/acetone 1:1 (*v*/*v*) was added 0.1 ml (*ca.* 0.2 mmol) of cold (0°) *Jones* reagent [38][20]). The resulting mixture was stirred at 0° for 20 min, and then 0.2 ml of i-PrOH was added. The mixture was stirred for another 2 min, then poured onto 20 ml of ice/H_2O and extracted with Et_2O (2 × 50 ml). The combined org. extracts were washed with sat. $NaHCO_3$ soln. (1 × 50 ml), dried ($MgSO_4$), and evaporated to give 20 mg of **16** as a colorless liquid (91% pure by GLC). TLC: R_f (hexane/AcOEt 2:1) 0.44. GLC: t_R 12.8 min.

Crude **16** was dissolved in 3 ml of 0.1M NaOMe (0.3 mmol) in THF/MeOH 1:1 (*v*/*v*) and the soln. stirred at r.t. for 2 h[21]). The solvent was evaporated *in vacuo* at 50° (bath temp.) and the residue distributed between Et_2O (50 ml) and ice/H_2O. The org. extract was dried ($MgSO_4$), filtered, and concentrated to give 20 mg of a colorless oil (88% pure by GLC; no **16** could be detected anymore by GLC and TLC). The anal. data of this compound were identical with a sample prepared from cyclohexyl(2-methylcyclohexylidene)amine and isopropyl vinyl ketone following the procedure given in *1.1*.

(±)-2-Methyl-2-(4-methyl-3-oxopentyl)cyclohexanone (**15**) [14] [15] [39]. TLC: R_f (hexane/AcOEt 2:1) 0.49. GLC: t_R 11.3 min. IR ($CHCl_3$): 1705*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.06 (*s*, CH_3); 1.08 (*d*, J = 7, CH_3); 1.09 (*d*, J = 7, CH_3); 1.50–2.72 (*m*, 13 H). MS: 210 (1, M^+), 167 (25), 139 (29), 112 (22), 55 (66), 43 (100).

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