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2-TOSYLOXYMETHYLCYCLANONES: RING SIZE DEPENDENCE OF FRAGMENTATION VERSUS INTRAMOLECULAR ALKYLATION[1]

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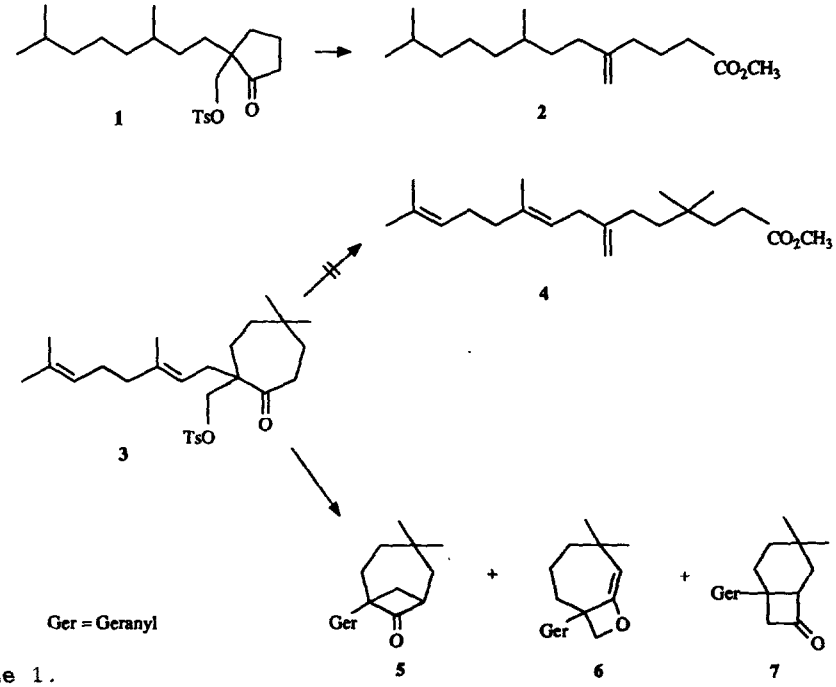
Abstract - The results reported seem to indicate, that in the presence of a nucleophilic base intramolecular alkylation is the normal reaction mode of tosyloxymethylcyclanones of type **14** and that the fragmentation reaction of five-membered compounds is the exception, probably because of the high steric energy of the alkylation transition states, e.g. of type **E**.

Introduction

Cyclopentanones carrying a CH_2-X substituent (X = leaving group) in the 2-position react on exposure to hydroxide or alkoxide mainly by a Grob fragmentation process. On the contrary, very little fragmentation occurs in the cyclohexanone and none in the cycloheptanone series.[2-6]



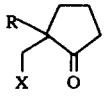
Scheme 1.

For example (Scheme 1), on reaction with sodium methoxide in methanol, **1** furnished fragmentation product **2** in 61% yield, whereas under the same conditions seven-membered ring compound **3** yielded only the intramolecular alkylation products **5**, **6**, and **7**.[3] These and related findings are summarized in Table 1.

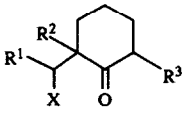
What are the factors that determine the different reactivity of these compounds as a function of ring-size? The present paper describes results bearing on this question.[1]

Table 1. Reactions of some 2-CH_2X-substituted cyclanones with nucleophilic bases

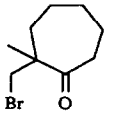
Entry	Starting material	Nucleophile/ Base	Fragmentation %	C-Alkylation %	O-Alkylation %	Ref.
1	**8a**	HO^-	82	--	--	2
2	**1**	CH_3O^-	61	--	--	3
3	**8b**	HO^-	43	6	--	4
4	**9a**	HO^-	4	78	--	5
5	**9b**	HO^-	1	90	--	5
6	**9c**	HO^-	3	89	--	5
7	**3**	CH_3O^-	--	39	35	3
8	**10**	HO^-	--	22	--	6



8	R	X
a	CH_3	OMs
b	CH_2-OCH_3	OTs



9	R^1	R^2	R^3	X
a	H	CH_3	H	OTs
b	H	CH_3	CH_3	OTs
c	CH_3	CH_3	H	OTs



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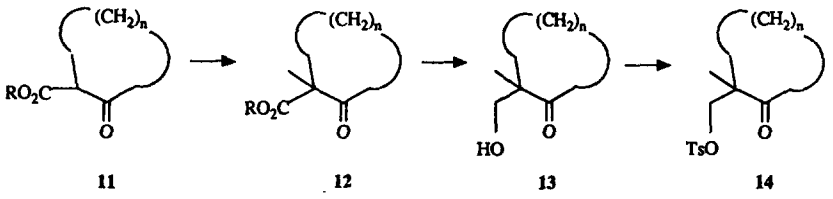
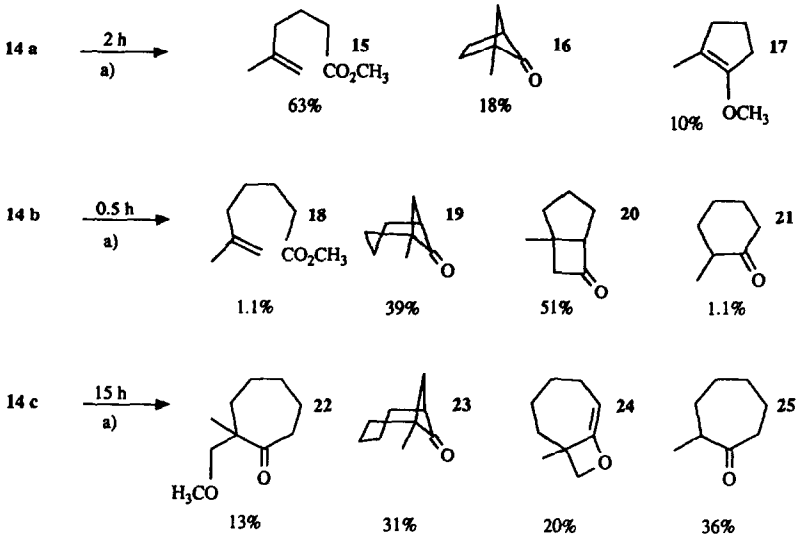
Reaction of **14a**, **14b**, and **14c** with CH_3ONa in CH_3OH

Since the results collected in Table 1 have been obtained under rather different experimental conditions we have studied the product formation of 2-tosyloxymethyl-cyclanones **14a**, **14b**, and **14c** under identical conditions (CH_3ONa in CH_3OH).

14a-14c were prepared using standard chemistry (**11**-->**12**-->**13**-->**14**, see Scheme 2 and Experimental). For the selective reduction of ß-keto esters **12** to give keto alcohols **13**, the methodology introduced by Barton[7,8] was used.



11 - 14	n
a	1
b	2
c	3



a) 0.35 mol l^{-1} CH_3ONa in CH_3OH, 90 °C

Scheme 2.

In Scheme 2 the product analysis results for the reactions of **14a**, **14b**, and **14c** with CH_3ONa in CH_3OH are compiled. Yields were determined by GC. Our results agree well with those summarized in Table 1: Fragmentation is the main reaction only of the 5-membered compound **14a**. Note should be taken of the fact that even in the five-membered ring system the C-alkylation product **16** is formed to a considerable extent. The only previous example of such a process we are aware of has been reported by Gerdes et

al.[4] (see entry 3 in Table 1). Side product **22** is a direct substitution product, and **21** and **25** are formed by retro-aldol fragmentation.

Mechanistic considerations

Our working basis for studying the factors that govern the differences in product formation (fragmentation versus intramolecular alkylation), depending on ring-size, is summarized in Scheme 3.

Fragmentation product **G** arises from **B**, most probably via transition state **D**,[9] whereas the alkylation products **H** and **I** are derived from **C**. Whether transition states **E** and **F** are involved is unknown at present. In principle, the precursor of all intramolecular alkylation products, such as **5**, **6**, and **7**, could be a zwitterionic intermediate such as **J**,[10] formed from **C** by tosylate loss (see Scheme 3, cf. the Favorskii rearrangement[11]). Compound **20** is most likely formed via such an intermediate.[10]

Experimentally, our work has focussed on the formation of the anionic intermediates **B** and **C** from **A**. Two extreme cases may be considered:

(i) Preequilibria between **A**/**B** and **A**/**C**, respectively, are maintained.

(ii) Formation of **B** and **C** is irreversible.[12] The ratio k_1/k_2 (see Scheme 3) would then directly determine the extent to which fragmentation and alkylation products are formed,[13]

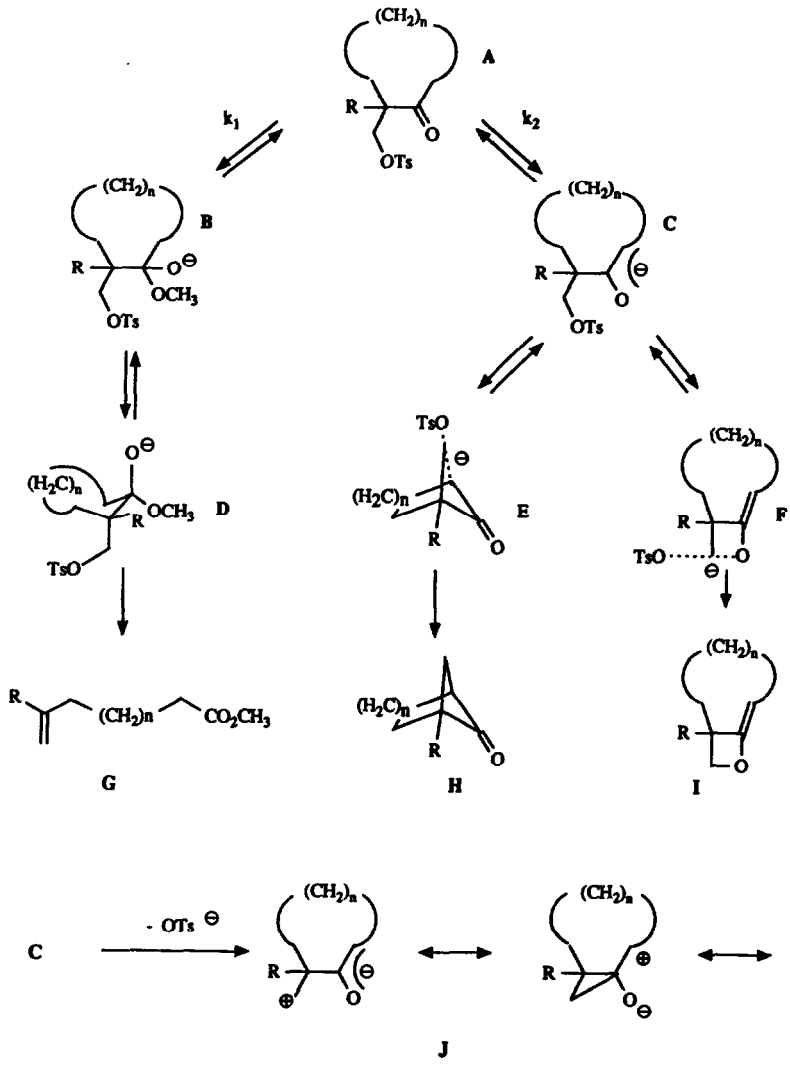
$$\frac{k_1}{k_2} = \frac{[G]}{[H] + [I]} \qquad (1)$$

and, from the results summarized in Scheme 2, relation (2) would follow (n as in Scheme 3).

$$(k_1/k_2)_{n=1} > (k_1/k_2)_{n=2} > (k_1/k_2)_{n=3} \qquad (2)$$

Rates of $NaBH_4$ reduction and silyl enol ether formation of some model cyclanones

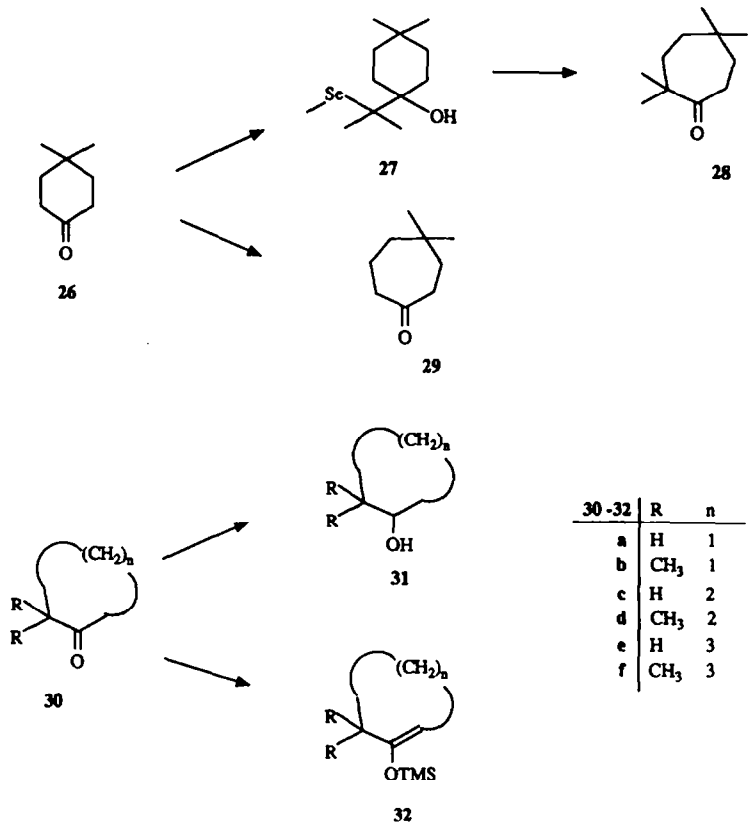
As a measure of k_1 (cf. Scheme 3 and eqns. (1) and (2)), the (relative) rates of sodium borohydride reduction of cyclanones **28**-**30** (cf. **30**-->**31**, reactivity towards nucleophiles) were determined and as a measure of k_2, the rates of silyl enol ether formation (cf. **30**-->**32**, kinetic acidity). **30d** was prepared from 2-methylcyclohexanone using the Ireland-Marshall procedure,[14] and **29** from **26** as described by Taguchi et al.[15,16] For the synthesis of **28**, **30b**, and **30f** advantage was taken of Krief's recently introduced ring expansion of cyclic ketones via ß-hydroxy selenides (cf. **26**-->**27**-->**28**).[17]



Scheme 3.

From the results compiled in Table 2 it is obvious, that cyclic ketone reduction with $NaBH_4$ is considerably retarded by 2,2-disubstitution. The reactivity order (as a function of ring size) in the 2,2-substituted cyclanones is, however, the same as published by Brown and Ichikawa[18] for the unsubstituted compounds: cyclohexanone > cyclopentanone > cycloheptanone.[19,20]

For silyl enol ether formation[21] the following reactivity order was determined (Table 3): 2,2-dimethylcyclopentanone > 2,2-dimethylcyclo-



30-32	R	n
a	H	1
b	CH_3	1
c	H	2
d	CH_3	2
e	H	3
f	CH_3	3

Scheme 4.

Table 2. Relative rates of $NaBH_4$ reduction of some cyclic ketones in isopropanol at 25°C

30a	30b	30c	30d	30e	30f	29	28
6.5[18]	0.09	80.6[18]	4.5	1.0	0.08	1.4	0.12

heptanone > 2,2-dimethylcyclohexanone. At least in the cycloheptanone series the rate of trimethylsilyl enol ether formation is not very much influenced by 2,2-disubstitution as compared with the parent ketone (cf. **30e** vs. **30f** and **29** vs. **28**).

Table 3. Relative rates of trimethylsilyl ether formation of some cyclic ketones

30b	30d	30e	30f	29	28
2.0	0.47	1.0	1.25	1.43	1.14

The results collected in Table 2 and 3 seem to rule out that the extent to which fragmentation and alkylation products are formed from **A** (see Scheme 3) is determined by the ratio k_1/k_2. If it is assumed, that (a) mechanism (ii, vide supra) operates for the formation of the fragmentation and intramolecular alkylation products, respectively, (b) that the relative rates in Tables 2 and 3 are measures of k_1 and k_2, respectively, and (c) that $(k_1/k_2)_{n=2}$ = [**18**]/[**19**]+[**20**] = 1.1:90 (see Scheme 2), the following ratios are calculated from the results in Tables 2 and 3: $(k_1/k_2)_{n=1}$ = 1/17400 and $(k_1/k_2)_{n=3}$ = 1/12200. This order of the k_1/k_2 values is totally in disagreement with relation (2).

Exchange Experiments

Treatment of **14c** with CD_3ONa (0.16 mol l^{-1}) in CD_3OD for 4 d at 4°C led to complete hydrogen-deuterium exchange at the free α-position of the CO group (see Experimental). **14c** was otherwise completely stable under these conditions: the formation of **22**, **23**, **24**, or **25** was not observed. The same results have been obtained for **14a** and **14b**.

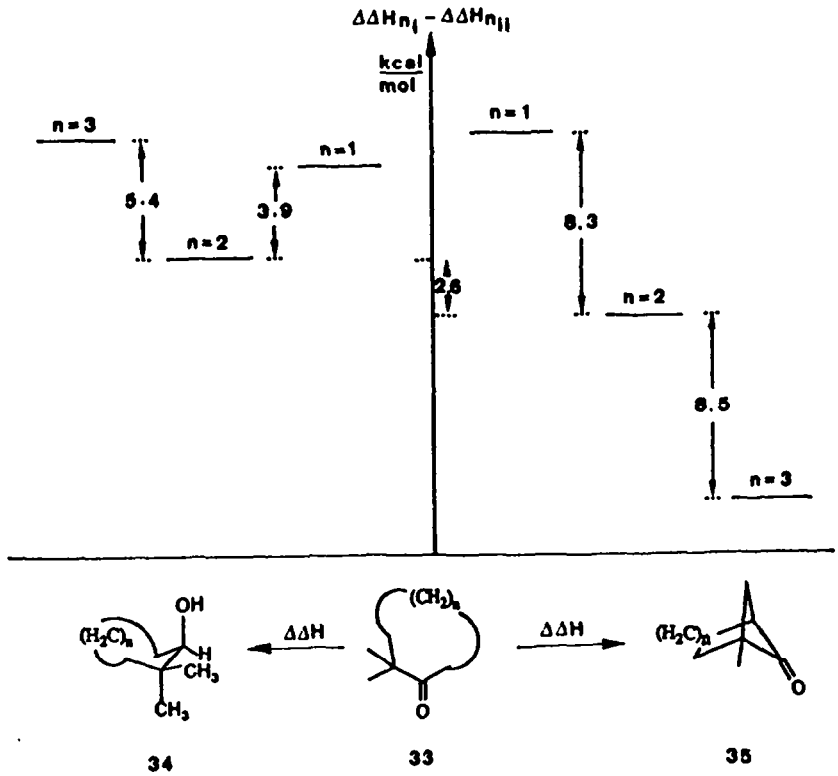
When **14c** was treated with 0.3 % NaOH in CD_3OD - $H_2{}^{16}O$ - $H_2{}^{18}O$ = 4:1:1 for 4 d at 4°C, oxygen exchange at the carbonyl group occurred, as was evident from the appearance of two carbonyl carbon signals in the ^{13}C NMR spectrum (1:1 ratio), the shift separation being 5 Hz (caused by the well-known ^{18}O isotope shift[22,23]). No other changes were observed in the spectrum. After work-up the IR-spectrum showed two carbonyl absorptions ($\Delta\nu$ ca. 35 cm^{-1} 1:1 ratio), also demonstrating the exchange reaction. Exactly the same results were obtained for **14a** and **14b**.

Conclusions

The results reported above demonstrate that preequilibria between **A** and **B**, and **A** and **C** (Scheme 3) are maintained.

The product studies seem to indicate, that intramolecular alkylation is the normal reaction mode of 2-tosyloxymethylcyclanones and that the fragmentation reaction of the 5-membered compounds is the exception. We believe, that the high steric energy of transition state geometries such as **E** is the reason that in the 5-membered series alkylation is the minor reaction. This view is supported by some estimations based on force field calculations. The heats of formation have been calculated[24] (Scheme 5),

a) for cyclic ketones **33** (n = 1,2,3) as models for **A** in Scheme 3
b) for the corresponding alcohols adopting conformation **34** (n = 1,2,3) with the OH and one of the methyl groups in antiperiplanar position, as models for **D** in Scheme 3
c) for bicyclic ketones **35** (n = 1,2,3), as models for **E** in Scheme 3.



Scheme 5.

The differences between the calculated ΔH_f values of ketones **33** and the transition states models **34** and **35**, respectively, are depicted in Scheme 5. Since the absolute values are certainly of no significance, only the difference between them are shown in Scheme 5. These values are a measure of the change in steric energy in going from **33** to **34** and **35**, respectively, depending on ring size. The two sets of calculated numbers have been correlated assuming a Gibbs energy difference of 2.6 kcal/mol between the two n = 2 states. The 2.6 kcal/mol value corresponds to the

experimentally established 35:1 ratio (at 90°C) of **19** and **18** in the reaction of **14b** with CH_3ONa (see Scheme 2). From Scheme 5 it may then be concluded that in the 7-membered series relative to the starting ketone the "transition state" **E** (for C-alkylation) is so much lower in energy than "transition state" **D** (for fragmentation) that no fragmentation would be expected whereas in the 5-membered series the two "transition states" are rather close in energy (1.8 kcal/mol). In this series both fragmentation (preferred) and C-alkylation would be expected on the basis of this argumentation, which is in good agreement with the experimental result (see Scheme 2). This reasoning hinges, however, upon the assumption that the A-values of the two sets of reactions are equal.

Experimental

Materials and methods

All reactions were performed in oven-dried glassware under a positive pressure of argon. Liquids and solutions were transferred by syringe, and were introduced into reaction flasks through rubber septa. Usual work-up means partioning the reaction mixture between an aqueous phase and an organic solvent (given in parenthesis), drying the combined organic solutions over $MgSO_4$ and removal of solvent by distillation in vacuo using a rotatory evaporator. The instrumentation used: ^{1}H-NMR: WP 80 (Bruker), AM 400 (Bruker), LRC means long range couplings ; ^{13}C NMR: AM 400 (Bruker); IR: Perkin Elmer 257 and 1310; MS: MAT-731 and MAT-CH-5 (Varian); analytical GC: Sichromat 3 (Siemens), preparative GC: PYE-104 (Philips, FID) and Aerograph 920 (Varian, WLD); LC: Medium pressure chromatography (MPLC) using 31.0 cm x 2.5 cm (column B, 60 g SiO_2), 40.0 cm x 4.5 cm (column C, 220 g SiO_2), and 37.0 x 1.5 (column A, 17 g SiO_2) glass tubes, silica gel 50 µm (Grace), Duramat pump (CfG), UV detector Chromatochord III (Serva).

ß-Keto esters **12a**, **12b**, **12c**.

12a,[25] **12b**,[26] **12c**[27] (prepared from **11a**, **11b**, **11c** by anion formation with sodium hydride in THF and subsequent reaction with methyl iodide) are known compounds, for spectral data, see.[28]

Preparation of 2-hydroxymethyl-cyclanones **13a**, **13b**, **13c**.

Reduction of ß-ketoesters **12a**, **12b**, and **12c** was performed as described by Barton et al. (method (2), LDA[29] was used as base, after reduction of **12a** excess of $LiAlH_4$ was destroyed with anhydrous ammonia). Yields after SC (hexanes-ethyl acetate 1:2): **13a** (68%), **13b** (34%), **13c** (38%). **13a** and **13b** are known compounds, for spectral data, see.[28]

2-Hydroxymethyl-2-methyl-cycloheptan-1-one (**13c**).

Oil.- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.15 (s, 3H, CH_3); 1.26-1.27 (8H, CH_2-3 - CH_2-6); 2.20-2.88 (3H, CH_2-7, OH); 3.39 and 3.72 (AB system, |J| = 11 Hz, 2H, CH_2-OH). - IR (CCl_4): 3630, 3480 (broad, O-H), 1690 (CO).- $C_9H_{16}O_2$ (156.2), MS: m/z (%) = 138 (38, $[M-H_2O]^+$); 126 (12); 71 (52); 69 (78); 56 (100).

Preparation of tosyloxymethyl-cyclanones **14a**, **14b**, **14c**.

A solution of **13b** (224 mg, 1.57 mmol), NEt_3 (444 µl, 3.2 mmol), DMAP (40 mg, 0.16 mmol) and tosyl chloride (330 mg, 1.7 mmol) in dry CH_2Cl_2 (10 ml) was stirred for 24 h at 20°C. Usual work-up (5% NH_4Cl-CH_2Cl_2) and MPLC

(hexanes-ethyl acetate 10:1) gave **14b** (400 mg, 1.35 mmol, 86%). **14a** and **14c** were prepared using the same procedure.

2-Methyl-2-[p-toluenesulfonyloxymethyl]-cyclopentanone (**14a**).[30]
M.p.: 66-67°C (from hexanes-ethyl acetate, ref.[30] 65-67°C).- ^{1}H NMR (400 MHz, CD_3OD): δ = 0.95 (s, 3H, 2-CH_3); 1.75-1.82 (1H), 1.82-1.96 (2H), and 2.03-2.10 (1H, CH_2-3 - CH_2-4); 2.11-2.19 (1H, 5-H); 2.25-2.34 (1H, 5-H'); 2.45 (s, 3H, Ar-CH_3); 3.84 and 3.95 (AB system, |J| = 9.2 Hz, 2H, CH_2-OTs); 7.43-7.75 (4H, Ar-H). - ^{13}C NMR (100 MHz, CD_3OD): δ = 19.5 (2-CH_3 and C-4); 21.6 (Ar-CH_3); 33.8 (C-3); 38.5 (C-5); 49.6 (C-2); 74.5 (CH_2-OTs); 129.0, 131.1, 133.9, 146.7 (Ar-C's); 221.4 (C-1). - IR (CCl_4): 1740 (C=O); 1605 (C=C, aromat); 1370 (ν_{as} SO_2); 1185, 1175 cm^{-1} (ν_s SO_2).

2-Methyl-2-[p-toluenesulfonyloxymethyl]-cyclohexanone (**14b**).[4,31]
^{1}H NMR (400 MHz, CD_3OD): δ = 1.08 (s, 3H, 2-CH_3); 1.63-1.77 (5H) and 1.87-1.93 (1H, CH_2-2 - CH_2-5); 2.17-2.23 (1H, 6-H); 2.43-2.48 (1H, 6-H'); 2.45 (s, 3H, Ar-CH_3); 3.97 and 4.01 (AB system, |J| = 9.5 Hz, 2H, CH_2-OTs); 7.44-7.76 (4H, Ar-H). - ^{13}C NMR (100 MHz, CD_3OD): δ = 20.6 (2- CH_3); 21.6 (Ar-CH_3 and C-4); 28.0 (C-5); 36.6 (C-3); 39.4 (C-6); 49.7 (C-2); 75.7 (CH_2-OTs); 129.0, 131.1, 134.0, 146.6 (Ar-C's); 214.0 (C-1). - IR (CCl_4): 1705 (C=O); 1595 (C=C, aromat); 1370 (ν_{as} SO_2); 1185, 1175 cm^{-1} (ν_s SO_2) .

2-Methyl-2-[p-toluenesulfonyloxymethyl]-cycloheptanone (**14c**).
^{1}H NMR (400 MHz, CD_3OD): δ = 1.05 (s, 3H, CH_3); 1.43-1.68 (7H) and 1.87 (ddd, $|J_1|$ = 15 Hz, J_2 = 10 Hz, J_3 = 1 Hz, 1H, CH_2-3 - CH_2-6); 2.38-2.45 (1H, 7-H), 2.47 (s, 3H, Ar-CH_3), 2.51-2.60 (1H, 7-H'); 3.95 and 4.00 (AB system, |J| = 10 Hz, 2H, CH_2-OTs); 7.44-7.77 (4H, Ar-H). - ^{13}C NMR (100 MHz, CD_3OD): δ = 21.4 (Ar-CH_3, 2-CH_3); 25.1; 27.2; 31.2; 33.9 (C-3 - C-6); 41.6 (C-7); 51.9 (C-2); 75.3 (CH_2-OTs); 128.9, 131.0, 133.8, 146.5 (Ar-C's), 216.4 (C-1).- IR (CCl_4): 1695 (C=O); 1370 (ν_{as} SO_2); 1190, 1180 cm^{-1} (ν_s SO_2) . - MS: m/z (%) = 155 (21); 138 (60); 123 (12); 109 (100). - (Found: C, 61.98; H, 7.10). $C_{16}H_{22}O_4S$ (310.4) requires C, 61.91; H, 7.14).

Reactions of **14a**, **14b**, **14c** with CH_3ONa in CH_3OH.
a) Reaction of **14b**: A solution of CH_3ONa in CH_3OH (0.7 mol/l, 6.6 ml) was added to a solution of **14b** (390 mg, 1.3 mmol) in CH_3OH (6.5 ml). The mixture was heated to 90°C (glass autoclave) for 30 min. After cooling to 20°C Et_2O (100 ml) and 5% NH_4Cl (100 ml) were added. The organic layer was washed with 5 % NH_4Cl solution (2 x) and dried over $MgSO_4$. The product ratios were determined by GC (40 m x 0.28 mm glass capillary column (OV 17), 100°C, carrier gas: H_2). Five compounds were identified: 6.6 min (unidentified, 8%); 7.3 min (1.1%, 2-methyl-cyclohexanone (**21**), identical (GC) with an authentic sample), 8.1 min (51%, **20**), 10.0 min (39%, **19**) and 13.5 min (1.1%, **18**). After very careful solvent evaporation the residue was separated by prep. GC (20% carbowax on chromsorb P-NAW, 60/80 mesh, 2.4 m x 7 mm, 80 °C, WLD detector, carrier gas: He).
b) Reaction of **14a**: Procedure as described for **14b**, heating to 90°C: 2h. Analytical GC as described in a). Three compounds were identified: 4.6 min (10%, **17**), 5.2 min (18%, **16**), and 7.8 min (63%, **15**). Preparative separation was performed by LC (pentane-Et_2O 20:1) followed by prep. GC (2 m x 7 mm, 3% OV 101 on Chromosorb W-HP 60/80 mesh, 60°C, FID detector , carrier gas: N_2).
c) Reaction of **14c**: Procedure as described for **14b**, heating to 90°: 15h. Analytical GC as described in a), however a temperature program was used: 50°C-->200°C, 5°/min. Four compounds were identified: 6.1 min (36%, 2-methylcycloheptanone (**25**), identical (GC) with an authentic sample[32]), 8.6 min (20%, **24**), 8.9 min (31%, **23**), 13.3 min (13%, **22**). Preparative separation as described in b).

Methyl 5-methyl-5-hexenoate (15).[33]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (narrow m (LRC), 3H, 5-CH_3); 1.74 (quint + LRC J = 7.5 Hz, 2H, CH_2-3); 2.01 (t, J = 7.5 Hz, 2H, CH_2-4); 2.27 (t, J = 7.5 Hz, 2H, CH_2-2); 3.62 (s, 3H, OCH_3); 4.62 (1H) and 4.69 (1H, LRC, CH_2-6). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 22.7 (5-CH_3 and C-3); 33.4 (C-2); 37.0 (C-4); 51.4 (OCH_3); 110.6 (C-6); 144.7 (C-5); 174.1 (C-1). - IR ($CDCl_3$): 1740 (C=O); 1645 (>C=CH_2); 890 cm^{-1} (>C=CH_2) . - MS m/z (%) = 142 (12, M^+); 127 (2); 111 (22); 110 (13); 82 (81); 74 (95); 43 (100).

1-Methyl-bicyclo[2.1.1]hexan-5-one (16).
NMR ($CDCl_3$) results from 400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR, DEPT,[34] COSY,[35] ^{13}C/^{1}H 2D shift correlation using large $^1J_{CH}$ couplings[36]):

C	δ (^{1}H)	δ (^{13}C)	COSY crosspeaks
1		61.55	
2	1.59-1.73 m	27.15	3-H, 3-H', 2-H', and 6-H
3	1.73-1.90 m	22.43	4-H, 2-H, 2-H', 3-H', and 6-H
4	2.80-2.84 m	53.10	3-H, 3-H', 6-H and 6-H'
5		201.92	
6	1.38-1.47 m	33.00	4-H, 2-H and 3-H
7	1.21 s	11.85	

IR ($CDCl_3$): 1775 cm^{-1} (C=O). - $C_7H_{10}O$ (110.2), MS: m/z (%) = 110 (10, M^+); 82 (51); 69 (45); 67 (99); 55 (96); 41 (100). The 2,4-dinitrophenylhydrazone was prepared using a standard procedure.[37] M.p. 153-154°C (from ethanol). (Found: C, 53.83 ; H, 4.90. $C_{13}H_{14}N_4O_4$ (290.3) requires C, 53.78; H, 4.86).

1-Methoxy-2-methyl-cyclopent-1-ene (17).
^{1}H NMR (400 MHz, C_6D_6): δ = 1.62-1.68 (2H, CH_2); 1.71 (narrow m (LRC), 3H, CH_3-2); 2.12-2.26 (4H, CH_2-3 and CH_2-5); 3.38 (s, 3H, OCH_3). - IR ($CHCl_3$): 1690 cm^{-1} (C=C-O). - $C_7H_{12}O$ (112.2), MS (from GC-MS): m/z (%) = 112 (56, M^+); 111 (65); 97 (96); 81 (44); 79 (46); 41 (100). On treatment of 17 with 2,4-dinitrophenylhydrazine/sulfuric acid in ethanol[37] the 2,4-dinitrophenylhydrazone of 2-methylcyclopentanone was formed, m.p. 151-153°C (from ethanol, ref.[38] 153-154°C).

Methyl 6-methyl-6-heptenoate (18).[5]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (quint, J = 7.5 Hz + LRC, 2H, CH_2); 1.61 (quint, J = 7.5 Hz + LRC, 2H, CH_2); 1.68 (s, 3H, 6-CH_3); 2.01 (t, J = 7.5 Hz + LRC, 2H, CH_2-5); 2.32 (t, J = 7.5 Hz, 2H, CH_2-2); 3.65 (s, 3H, OCH_3); 4.65 and 4.68 (LRC, 2H, CH_2-7).- IR ($CDCl_3$): 1730 cm^{-1} (C=O) . - MS (from GC-MS): m/z (%) = 156 (4, M^+); 125 (10); 124 (18); 82 (100).

1-Methyl-bicyclo[3.1.1]heptan-6-one (19).[5]
^{1}H NMR (400 MHz, COSY, $CDCl_3$): δ = 1.05 (s, 3H, 1-CH_3): 1.50-1.66 (2H, 4-H and 2-H); 1.68-1.81 (2H, 2-H' and 4-H'); 1.95-2.05 (1H, 3-H'); 2.10-2.24 (3H, 3-H and CH_2-7); 2.97-3.03 (1H, 5-H). - IR ($CDCl_3$): 1755 cm^{-1} (C=O). - MS (from GC-MS): m/z (%) = 124 (2.3, M^+); 109 (0.6, $[M-CH_3]^+$); 96 (28); 82 (30); 81 (100); 67 (52).

1-Methyl-bicyclo[3.2.0]heptan-6-one (20).[5]
^{1}H NMR (400 MHz, COSY, $CDCl_3$): δ = 1.42 (s, 3H, 1-CH_3); 1.47-1.60 (1H); 1.60-1.72 (2H, CH_2-4); 1.76-1.92 (2H); 1.92-2.00 (1H), 2.68 (1H, 7-H); 2.82 (1H, 7-H'); 2.97-3.02 (1H, 5-H). $|J_{7,7'}|$ = 20 Hz, $J_{5,7}$ = 1.9 Hz, $J_{5,7'}$ = 6.1 Hz.- IR ($CDCl_3$): 1760 cm^{-1} (C=O). - MS (from GC-MS): m/z (%) = 124 (1.8, M^+); 109 (1.0); 96 (14); 82 (81); 81 (82); 67 (100).

2-Methoxymethyl-2-methyl-cycloheptan-1-one (22).
^{1}H NMR(80 MHz, $CDCl_3$): δ = 1.04 (s, 3H,2-CH_3); 1.16-2.69 (8H, CH_2 signals); 2.30-2.69 (2H, CH_2-7); 3.28 (s, 3H, OCH_3); 3.32 and 3.33 (2H,-CH_2-O-). - IR ($CDCl_3$): 1690 cm^{-1} (C=O). - $C_{10}H_{18}O_2$ (170.2), MS (from GC-MS): m/z (%): 170 (26, M^+); 155 (5); 138 (57), 127 (40); 45 (100).

1-Methyl-bicyclo[4.1.1]octan-7-one (23).[6]
^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.15 (s, 3H, 1-CH_3); 1.37-2.04 (10H, CH_2 signals); 3.08-3.39 (1H, 6-H). - IR ($CDCl_3$): 1760 cm^{-1} (C=O) . - MS (from GC-MS): m/z (%) = 138 (19); 123 (3); 110 (35); 96 (47); 95 (79); 82 (44); 81 (100).

1-Methyl-8-oxa-bicyclo[5.2.0]non-6-ene (24).
^{1}H NMR (80 MHz, $CDCl_3$): δ = 1.50 (s, 3H, 1-CH_3); 1.13-2.18 (CH_2 signals); 4.21 and 4.39 (AB system, |J| = 4.5 Hz, 2H, CH_2-9); 4.74 (dd, J_1 = 8 Hz, J_2 = 5 Hz, 1H, 6-H). - IR ($CDCl_3$): 1715 (C=C-O); 1150, 1080 cm^{-1} (C-O-C) . - $C_9H_{14}O$ (138.2), MS (from GC-MS): m/z (%) = 138 (65, M^+); 123 (12); 93 (100).

1-(1-Methyl-1-methylseleno-ethyl)-4,4-dimethylcyclohexan-1-ol (27).
To a solution of 2,2-[bis(methylseleno)]propane (300 µl) in THF (2 ml) n-butyllithium (1.6 M in hexane, 1.0 ml, 1.6 mmol) was added at -78°C. The mixture was stirred at -78°C for 40 min, then a solution of **26** (200 mg, 1.58 mmol) in THF (1 ml) was added. The reaction mixture was stirred at -78 °C for 2.5 h, then 5% aqueous NH_4Cl (2 ml) was added. Usual work-up (ether) and SC (hexanes-ethyl acetate 15:1) gave **27** (325 mg, 78%). - ^{1}H NMR (80 MHz, $CDCl_3$): δ = 0.85 (s, 3H) and 0.93 (s, 3H, $C(CH_3)_2$); 1.08-1.30 (2H, ring protons); 1.48 (s, 6H, Se-$C(CH_3)_2$); 1.52-1.69 (6H, ring protons); 1.88 (s, 1H, OH); 2.03 (s, 3H, Se-CH_3). - IR (CCl_4): 3600, 3500 cm^{-1} (OH) . - MS: m/z (%) = 264 (7.4, M^+)[39] ; 169 (18); 151 (22); 138 (83); 127 (44); 109 (54); 95 (50); 41 (100). - (Found: C, 54.80; H, 9.20. $C_{12}H_{24}OSe$ (263.3) requires C, 54.74; H, 9.19).

2,2,5,5-Tetramethylcycloheptanone (28).
To a solution of **27** (315 mg, 1.2 mmol) in $CHCl_3$ (5 ml) thallous ethoxide (475 µl, 6.7 mmol) was added and the mixture was stirred at 20°C for 2.5 h. Work-up (ether-water) and LC (40 g SiO_2, pentane-ether 40:1) gave **28** (143 mg, 69%).- ^{1}H NMR (80 MHz, $CDCl_3$): δ = 0.95 (s, 6H, 5-CH_3 and 5-CH_3'); 1.05 (s, 6H, 2-CH_3 and 2-CH_3'); 1.14-1.75 (6H, CH_2 signals); 2.35-2.58 (2H, CH_2-7). - IR (CCl_4): 1700 cm^{-1} (C=O) . - MS: m/z (%) = 168 (27, M^+); 153 (10); 150 (9); 140 (8); 99 (56); 81 (98); 43 (100); 41 (100). (Found: C, 78.48; H, 11.87. $C_{11}H_{20}O$ (168.3) requires C, 78.51; H, 11.98).

Determination of the relative reduction rates of ketones **28**, **29**, and **30** with $NaBH_4$.
To a solution of cycloheptanone (**30e**, 0.1 mmol), one of the ketones to be reduced (see Table 2) (0.1 mmol), and a suitable hydrocarbon standard (5 mg) in isopropanol (1 ml) 0.5 equiv of a 0.1 molar solution[40] of $NaBH_4$ (recrystallized from diglyme[41]) was added. The mixture was stirred at 25°C for 20 h. After addition of 0.1 N HCl (1 ml) the products were isolated by extractive work-up (ether). Product analysis was performed by GC (10 m x 0.28 mm glass capillary column (OV 17), 50°C --> 115°C, 5°C/min, carrier gas: H_2). Both the starting mixture and the product mixture were analyzed, and the relative rates were determined by normation of the areas of the ketone peaks before and after the reaction, relative to the standard. For both cycloheptanone and the ketone to be studied (see Table 2) the expression A = 1 - $(\text{peak area})_{t=0}$ / $(\text{peak area})_{t=20h}$ was determined. The ratio A_{Keton} / $A_{\text{Cycloheptanon}}$ corresponds then to the reduction rate of the ketone under investigation relative to cycloheptanone. Each value in Table 2 is the average of three experimental results. The following GC retention times have been observed: **30b**: 5 4 min, **30d**: 5.4 min, **30e**: 6.8

min, **30f**: 7.8 min, **29**: 9.9 min, **28**: 10.5 min, decane: 3.1 min, undecane: 5.0 min, dodecane: 7.7 min.

Relative rate constant for silyl enol ether formation from some cyclanones.
To a solution of cycloheptanone (**30e**, 0.1 mmol), one of the ketones **28**, **29**, **30b**, **30d**, **30f**, a suitable hydrocarbon standard (5 mg), and trimethylsilyl chloride (140 µl, 1 mmol) in dry THF (1 ml) at -78°C a 0.16 M LDA solution[29] (0.6 ml, 0.1 mmol) was added and the mixture was stirred at -78°C for 5 min. Then triethylamine (0.4 ml) was added and (after removal of the cooling bath) saturated $NaHCO_3$ solution (1 ml). After extractive work-up (ether) the relative rates were determined as described above. In the case of **29** the A value was divided by 2 to correct for the presence of four acidic hydrogens. Each value in Table 3 is the average of three experimental results.

Hydrogen-deuterium exchange experiments with **14a**, **14b**, and **14c**.
A solution of one of the ketones **14a**, **14b**, and **14c** (9.8 mg) in 0.16 M CD_3ONa in CD_3OD (0.5 ml) was left at 4°C for 4 d. Then the mixture was directly analyzed by 400 MHz ^1H NMR. The following signals were absent after the exchange reactions: **14a**: δ = 2.14 and 2.30, **14b**: δ = 2.17-2.23 and 2.43 - 2.48, **14c**: δ = 2.38-2.45 and 2.51-2.60.

^{16}O --> ^{18}O exchange experiments with **14a**, **14b**, and **14c**.
To a solution of one of the ketones **14a**, **14b**, or **14c** (45 mg) in CD_3OH (0.4 ml) were added 2% NaOH in $H_2{}^{16}O$ (0.4 ml) and $H_2{}^{18}O$ (0.4 ml). The mixture was left at 4°C for 4 d and was then directly analyzed by ^{13}C NMR. Then the products were isolated by extractive work-up (ether) and analyzed by IR. Results: **14a**: two signals in the CO region ($\Delta\delta$ = 0.052 ppm), IR bands at 1750 and 1715 cm^{-1}; **14b**: two signals in the CO region ($\Delta\delta$ = 0.050 ppm), IR bands at 1710 and 1675 cm^{-1} ; **14c**: two signals in the CO region ($\Delta\delta$ = 0.052 ppm), IR bands at 1705 and 1670 cm^{-1}.

Force field calculations.[24]
The following H_f values were calculated (kcal/mol):

33, n = 1: -61.12	n = 2: -69.10	n = 3:	-70.34
34, n = 1: -71.89	n = 2: -83.17	n = 3:	-79.68
35, n = 1: - 9.52	n = 2: -25.81	n = 3:	-35.59

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References and notes

1 Preliminary Communication: Welzel,P.;Böttger,D.;Heinz,U.; Said,A.H.;Fischer,A.;Adams,E.*Pure App.Chem.***1987**,*59*,385-392.
2 Eschenmoser,A.;Frey,A.*Helv.Chim.Acta* **1952**,*35*,1660-1666.
3 Böttger,D.;Welzel,P.*Liebigs Ann.Chem.***1985**,837-852.
4 Gerdes,H.;Marschall,H.;Weyerstahl,P.*Chem.Ber.***1975**,*108*,3448-3460.
5 Nerdel,F.;Frank,D.;Marschall,H.*Chem.Ber.***1967**,*100*,720-735.
6 Julia,S.;Gueremy,C.*Bull.Soc.Chim.Fr.***1965**,2994-3001.
7 Barton,D.H.R.;Hesse,R.H.;Wilshire,C.;Pechet,M.M.*J.Chem.Soc., Perkin Trans.I* **1977**,1075-1079.
8 Kraus,G.A.;Frazier,K.*J.Org.Chem.***1980**,*45*,4262-4263.
9 Grob,C.A.*Angew.Chem.***1969**,*81*,543-554, *Angew.Chem., Int.Ed.Engl.* **1969**,*8*,535.

[10] cf.Tsuda, Y.; Tanno,T.; Ukai, A.; Isobe,K. *Tetrahedron Lett.* **1971**, 2009-2012; Kirmse,W.;Alberti,J.*Chem.Ber.***1973**,*106*,236-245; Wolff,S.; Agosta,W.C.*J.Chem.Soc.,Chem.Commun.***1973**,771, and references therein.
[11] Review: Hunter,D.H.;Stothers,B.;Warnhoff,E.W. in "Rearrangement in Ground and Excites States", ed. De Mayo,P. Academic Press, New York, 1980, vol.1,p.392.
[12] For examples of this type in the Favorskii rearrangement, see ref.[11]
[13] Frost,A.A.;Pearson,R.G. "Kinetik und Mechanismen homogener chemischer Reaktionen", Verlag Chemie, Weinheim, 1964, p. 148.
[14] Ireland,R.E.;Marshall,J.A.*J.Org.Chem.***1962**,*27*,1615-1619; Ainsworth,C.*Org.Synth.*,Coll.Vol.IV,536-539(1963).
[15] Taguchi,H.;Yamamoto,H.;Nozaki,H.*J.Am.Chem.Soc.***1974**,*96*,6510-6511; *J.Am.Chem.Soc.***1974**,*96*,3010-3011.
[16] St-Jacques,M.;Vaziri,C.;Frenette,D.A.;Goursot,A.;Flizár,S. *J.Am.Chem.Soc.***1976**,*98*,5759-5765.
[17] Krief,A.;Laboureur,J.L.*Tetrahedron Lett.***1987**,*28*,1545-1548, and references therein.
[18] Brown,H.C.;Ichikawa,K.*Tetrahedron* **1957**,*1*,221-230.
[19] Rate constants for the reaction of simple cyclic ketones with perbenzoic acid: Friess,S.L.*J.Am.Chem.Soc.* **1949**, *71*, 2571-2575.
[20] Rate constants for the addition of hydroxylamine to (inter alia) cyclic ketones: Lamaty,G.;Petitjean,A.;Roque,J.P.; Natat,A.*Rec.Trav.Chem. Pays-Bas* **1979**,*98*,400-405;Geneste,P.;Lamaty,G.;Roque,J.P. *Tetrahedron* **1971**,*27*,5561-5578.
[21] Corey,E.J.;Gross,A.W.*Tetrahedron Lett.***1985**,*25*,495-498.
[22] Risley,J.M.;van Etten,R.L.*J.Am.Chem.Soc.***1979**,*101*,252-253.
[23] Vederas,J.C.*J.Am.Chem.Soc.***1980**,*102*,374-376.
[24] cf.Doering,W.v.E.;Roth,W.R.;Breuckmann,R.;Figge,L.;Lennartz, H.-W.;Fessner,W.-D.;Prinzbach,H.*Chem.Ber.***1988**,*121*,1-9.
[25] Mayer,R.*Angew.Chem.***1956**,*68*,169-174.
[26] Karpf,M.*Helv.Chim.Acta* **1984**,*67*,73-85, and references therein.
[27] Buchta,E., Kranz,J. *Liebigs Ann.Chem.***1956**,*601*,170-181.
[28] Heinz,U. Dissertation, Universität Bochum, 1987
[29] Lithiumdisopropylamid, prepared as described by Seebach,D.; Enders,D.*Chem.Ber.***1975**,*108*,1293-1320.
[30] Matsumoto,T.;Shirahima,H.;Ichihara,A.;Shin,H.;Kagawa,S.;Sakan,F.; Nishida,S.;Matsumoto,S.;Saito,K.;Hashimoto,H.*Bull.Chem.Soc.Jap.***1972**,*45*, 1140-1144.
[31] Gerdes,H.;Javeri,S.;Marschall,H.*Chem.Ber.***1980**,*113*,1907-1920.
[32] Baldwin S.W.;Landmesser,N.G.*Synth.Commun.***1978**,8,413-419.
[33] Wolff,S.;Agosta,W.C.*J.Am.Chem.Soc.***1983**,*105*,1292-1299.
[34] Bendall,M.R.;Doddrell,D.M.;Pegg,D.T.*J.Am.Chem.Soc.***1981**,*103*,4603-4605; Doddrell,D.M.;Pegg,D.T.;Bendall,M.R.*J.Magn.Reson.***1982**,*48*,323-327.
[35] Bax,A.;Freeman,R.;Morris,G.*J.Magn.Reson.***1981**,*42*,164-168;Bax,A. Freeman,R. ibid.**1981**,*44*,542-561.
[36] Maudsley,A.A.;Müller,L.;Ernst,R.R.*J.Magn.Reson.***1977**,*28*,463-469; Bodenhausen,G.;Freeman,R. ibid.**1977**,*28*,471-476;Bax,A.; Morris,G.A. ibid.**1981**,*42*,501-505.
[37] Organikum, 15th ed.,VEB Deutscher Verlag der Wissenschaften, Berlin, 1977, p. 484.
[38] Lutz,G.A.;Bearse,A.E.;Leonard,J.E.;Croxton,F.C.*J.Am.Chem.Soc.* **1948**,*70*,4139-4142.
[39] Calculated for ^{80}Se. All Se containing ions gave the correct isotope pattern.
[40] Concentration determined exactly by measuring the H_2 volume after addition of 2 N HCl.
[41] Brown,H.C.;Mead,E.J.;Subba Rao,B.C.*J.Am.Chem.Soc.***1955**,*77*,6209-6213.