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Cleavage of the oxygen bridge in 8-oxabicyclo[3.2.1]octanes by reductive elimination

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Abstract—Several 2(4)-bromo- or chloro-8-oxabicyclo[3.2.1]oct-6-en-3-ones (**2**), available by [4+3] cycloaddition of monohalogeno-oxyallyl intermediates with furans, were reduced to halogenated 8-oxabicyclo[3.2.1]oct-6-en-3*endo*-ols (**6**) and saturated analogues (**7**). Cycloheptene-1,3*trans*-diols (**8**,**11**) were formed preferentially by reductive elimination. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

A host of [4+3] cycloadducts have been prepared from furans and oxyallyl intermediates, generated from α-halogenoketones by various methods. The resulting 8-oxabicyclo[3.2.1]oct-6-en-3-ones were useful and continue serving as building blocks for synthesis of cyclic and acyclic targets.[1,2] In most cases, the oxa-bridge, i.e. the ether linkage, has to be cleaved at an appropriate stage of the synthetic route. Various efforts have been made to solve this problem, but no general methodology emerged. A major breakthrough was achieved by Lautens et al., who introduced organometals that attack the C6–C7 double bond and simultaneously assist cleavage of the C–O bond.[2]

We envisaged another methodology based on the reductive cleavage of β-halogenoethers (Boord reaction).[3] The prerequisite for this type of cleavage is an oxa[3.2.1]bicyclic skeleton with a halogeno-substituent vicinal to the oxygen atom of the bridge.[4] 2(4)-Monohalogeno-8-oxabicyclo-[3.2.1]oct-6-en-3-ones (**2**), available by various [4+3] cycloaddition techniques,[5] should allow introduction of the halogen atom needed for the Boord reaction as early as possible.

2. [4+3] Cycloadditions

Though some oxabicycles (**2a**,**b**,**d**,**f**) had been already synthesised,[6–9] we investigated on this occasion cycloadditions by reaction of representative α,α′-dihalogeno-ketones (**1a**–**d**) with furan and 2-methylfuran in the presence of 2,2,2-trifluoroethanol/sodium 2,2,2-trifluoroethoxide (TFE/NaTFE), paying attention to the improved procedure given in Ref. 10. The *endo* diastereomer of oxabicycle **2d** was available from an earlier preparation by the lithium perchlorate/triethylamine method.[9]

A priori, cycloaddition of substituted oxyallyl intermediates to furan is anticipated to give *endo*/*exo* stereoisomers. Indeed, reaction of furan with (*R**, *R**)-2,4-dichloro- or dibromopentan-3-one (**1a**,**c**), provided a mixture of diastereomeric oxabicycles with *endo*- and *exo*-oriented halogen atoms (**2a***n*+**2a***x* and **2e***n*+**2e***x*, respectively), where the *endo* isomers predominate. The isomers with *exo*-methyl groups at C-4 were not formed in appreciable amount (Scheme 1).

The *endo*-selectivity of the cyclocondensation of 1,3-dichloro-3-methylbutan-2-one (**1b**) and furan seemed to be higher: the *exo*-chloride **2b***x* could not be detected (however, traces of bicyclic by-products remained unidentified, see Section 5). But, apart from the bicycle **2b***n*, a trace of the substituted furan **4** (1%) was isolated. This may indicate that the cycloaddition occurs by a stepwise mechanism (Hoffmann's Class B[11]).

For the bicycle **2c**, 2,4-dichloro-2-methylpentan-3-one would be needed. Since preparation of the latter in a high purity seemed to be cumbersome, and the *endo*/*exo* selectivity of the cycloaddition anticipated as uncertain, we prepared the crowded bicycle **2c** by methylation of the lithium enolate obtained from **2b** with LDA in THF; only one of the possible two diastereomers was found. Alkylations of oxabicyclic enolates are favoured to occur from the *exo*-face,[12] and therefore, the *endo*-chloro bicycle **2c***n* should result. This assignment of the configuration is supported by the ^{1}H NMR spectrum, comparing the methyl resonances with those of **2a***n*, **2a***x* and **2b***n* (Table 1). The bromo analogue **2h***n* was prepared by methylation of **2f***n*.

Keywords: cycloadditions; halohydrins; haloketones; cycloheptenes; oxyallyl intermediates; furans; diols.

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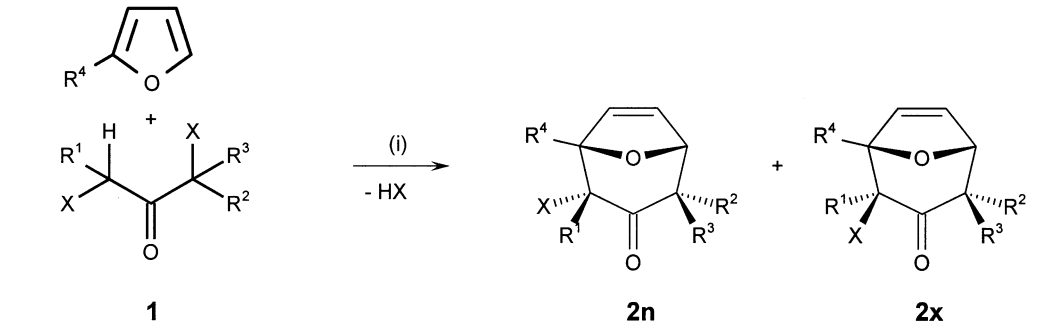
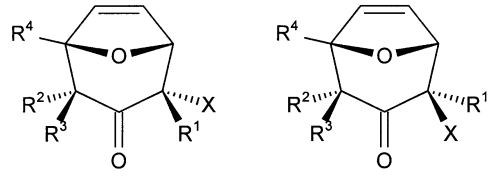


1	R^1	R^2	R^3	X
a	CH_3	CH_3	H	Cl
b	H	CH_3	CH_3	Cl
c	CH_3	CH_3	H	Br
d	H	CH_3	CH_3	Br

2, 3	R^1	R^2	R^3	R^4	X
a	CH_3	CH_3	H	H	Cl
b	H	CH_3	CH_3	H	Cl
c	CH_3	CH_3	CH_3	H	Cl
d	H	CH_3	CH_3	CH_3	Cl
e	CH_3	CH_3	H	H	Br
f	H	CH_3	CH_3	H	Br
g	H	CH_3	CH_3	CH_3	Br
h	CH_3	CH_3	CH_3	H	Br

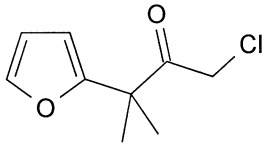


(i) CF_3CH_2ONa / CF_3CH_2OH

Scheme 1. [4+3] Cycloaddition of oxyallyls generated from dihaloketones **1a**–**d**. The letters *n* and *x* denote *endo* and *exo* configuration of the cycloadducts.

The oxabicyclic bromoketone **2f***n* is known to be formed from 1,1,3-tribromo-3-methylbutan-2-one and furan by the Noyori methods, i.e. under reductive conditions.[7] We tried to prepare it by dehydrobromination of the dibromoketone **1d** with NaTFE/TFE in the presence of furan. The cycloadduct **2f***n* thus obtained was accompanied by minor amounts of the *exo*-isomer **2f***x* (ca. 11%) that could be separated by chromatography.

Volatile by-products arose from reactions of the dibromoketones **1c** and **d**. They could be easily removed by evaporation and turned out to be trifluoroethyl esters of unsaturated butanoic acids (**5a**,**b**), with yields of ca. 7 and 14%, respectively. Undoubtedly, these esters are formed by way of a Favorskii rearrangement via bromocyclopropanones.



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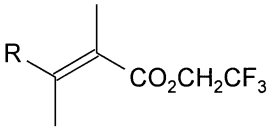


5a: R = H
5b: R = CH_3

2-Methylfuran and **1d** gave the expected four diastereomeric oxabicycles. Regioselectivity was considerable, i.e. the cycloadducts **2g**, with the halogen atom *vicinal* to the bridgehead methyl group, dominated over the cycloadducts **3g**. The main *endo*-product (**2g***n*) could be separated easily by crystallisation in 59% yield.

The assignment of the *endo*/*exo* isomers is based on the characteristic differences in the vicinal coupling constants of the *endo*- and *exo*-protons at C-2/C-4 with the bridgehead proton ($^3J_{4x,5}$=4–5 Hz, $^3J_{4n,5}\leq$1 Hz), and on the deshielding effect observed for these *exo*-protons and also *exo*-methyl groups in many oxabicycles.[11]

The ^{13}C NMR spectra show characteristic differences too (Table 2): the chemical shifts of *endo* methyl groups occur at higher field than those of the *exo* methyls. Substitution of the 2(4)-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-ones by chloro or bromo atoms causes an upfield shift of the carbonyl resonance (C-3) ($\Delta\delta$ ca. 4–8 ppm) in comparison with the corresponding dehalogenated oxabicycles.

To summarise, the cyclocondensation of α,α′-dihalogenoketones (**1**) with furan and 2-methylfuran in the presence of NaTFE/TFE proceeds with good yields (56–87%). Those oxabicycles with the halogeno substituent in the *endo* position predominate in all cases, and can be obtained in pure form by crystallisation with yields of 49–80%.

3. Reduction and catalytic hydrogenation

In order to circumvent dehalogenation of the bicyclic

Table 1. ^{1}H NMR data of 2(4)-halogeno 8-oxabicyclo[3.2.1]oct-6-en-3-ones (**2**,**3**) ($CDCl_3$, TMS as internal standard, δ-scale, coupling constants J in Hz)

	1-H	2-H	4-H	5-H	6-H	7-H	CH_3
2a*n*	4.79 d, *J*=1.7	–	3.08 dq, *J*=7.0, 4.6	4.84 dd, *J*=4.6, 1.6	6.51[a], *J*=6.1, 1.7	6.40[a], *J*=6.1, 1.7	1.04 d [4*endo*], *J*=7.0, 1.86 s [2*exo*]
2a*x*[b]	[c]	–	3.39 dq, *J*=7.1, 4.5	[c]	6.40[a], *J*=6.1, 1.8	6.30[a], *J*=6.1, 1.8	1.01 d [4*endo*], *J*=7.1, 1.50 s [2*endo*]
2b*n*	5.05 dd, *J*=4.7, 1.7	4.76 d, *J*=4.7	–	4.49 d, *J*=1.7	6.47[a], *J*=6.1, 1.7	6.42[a], *J*=6.1, 1.7	1.05 s [4*endo*], 1.38 s [4*exo*]
2c*n*	4.77 *J=1.7*	–	–	4.47 d, *J*=1.7	6.50[a], *J*=6.0, 1.7	6.43[a], *J*=6.0, 1.7	1.03 s [4*endo*], 1.40 s [4*exo*], 1.89 s [2*exo*]
2d*n*	–	4.53 s	–	4.49 d, *J*=1.8	6.36, *J*=6.0, 1.8	6.19, *J*=6.0	1.05 s [4*endo*], 1.37 s [4*exo*], 1.65 s [1-CH_3]
2e*n*	4.88 d, *J*=1.7	–	3.13 dq, *J*=7.0, 4.7	4.79 dd, *J*=4.7, 1.7	6.57[a], *J*=6.1, 1.7	6.39[a], *J*=6.1, 1.7	1.05 d [4*endo*], *J*=7.0, 2.04 s [2*exo*]
2e*x*	4.92 d, *J*=1.7	–	3.51 dq, *J*=7.1, 4.5	4.84 dd, *J*=4.5, 1.7	6.49[a], *J*=6.0, 1.7	6.33[a], *J*=6.0, 1.7	1.02 d [4*endo*], *J*=7.1, 1.67 s [2*endo*]
2f*n*	5.10[d], *J*=4.7, 1.3	4.89[d], *J*=4.7	–	4.47 d, *J*=1.3	6.48[a], *J*=6.2, 1.3	6.46[a], *J*=6.2, 1.3	1.05 s [4*endo*], 1.38 s [4*exo*]
2f*x*	5.04 dd, *J*=1.7, 0.7	3.89 d, *J*=0.7	–	4.49 d, *J*=1.7	6.40[a], *J*=6.0, 1.7	6.26[a], *J*=6.0, 1.7	1.00 s [4*endo*], 1.62 s [4*exo*]
2g*n*	–	4.66 s	–	4.44 d, *J*=1.7	6.34, *J*=6.0, 1.7	6.25, *J*=6.0	1.05 s [4*endo*], 1.35 s [4*exo*], 1.68 s [1-CH_3]
2g*x*[b]	–	3.93 s	–	4.50 d, *J*=1.8	6.43, *J*=5.8, 1.8	6.05, *J*=5.8	0.99 s [4*endo*], 1.58 s [4*exo*], 1.58 s [1-CH_3]
2h*n*	4.84 d, *J*=1.8	–	–	4.42 d, *J*=1.8	6.57[a], *J*=6.1, 1.8	6.40[a], *J*=6.1, 1.8	1.04 s [4*endo*], 1.40 s [4*exo*], 2.06 s [2*exo*]
3g*n*[b]	–	–	4.91[d], *J*=4.6	5.07[d], *J*=4.6, 5.9	6.38, *J*=5.9, 1.7	6.28, *J*=5.9	1.10 s [2*endo*], 1.29 s [2*exo*], 1.40 s [1-CH_3]
3g*x*[b]	–	–	ca. 3.93[e]	5.01[f]	6.16, *J*=5.9, 1.9	6.37, *J*=5.9	1.04 s [2*endo*], 1.42 s [1-CH_3], 1.52 s [2*exo*]

[a] AB sub-spectrum with double lines; the assignments for 6-H and 7-H may be reversed.
[b] The data were picked out from the spectrum of a mixture of isomers (Section 5).
[c] Masked by signals of isomer(s) (Section 5).
[d] AB sub-spectrum.
[e] The signal is superimposed by the resonance of 4-H from **2g***x*.
[f] Multiplet centre, three lines with ca. 0.9 Hz separation (X-part from ABX sub-spectrum).

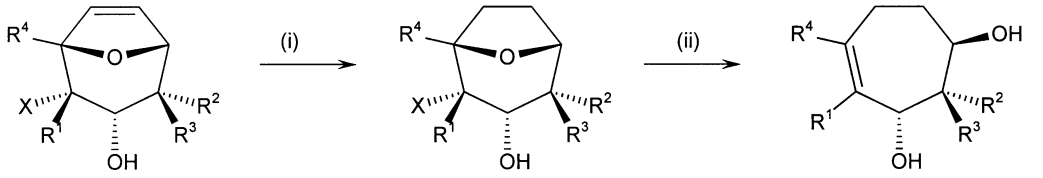
α-halogenoketones under reductive conditions, we transformed at first the carbonyl group. The unsaturated oxabicycles **2** were subjected to standard reduction with $LiAlH_4$ in THF. With the exception of the crowded **2c***n*, that gave a 78:22 mixture of the *endo*/*exo* diastereomers **6c** and 3*exo*-**6c**, only the 8-oxabicyclo[3.2.1]oct-6-en-3*endo*-ols (**6**) were isolated. An analogous behaviour has been observed reducing α,α′-dichloro-8-oxabicyclo-[3.2.1]octan-3-ones.[10]

For the alcohols **6a**,**b** and **6d**–**g**, the *endo* configuration at C-3 was deduced from the vicinal coupling constant (^{1}H NMR) between the 3-H and its neighbour protons, $^3J_{2,3}$ or $^3J_{3,4}$ which is found to be 4.5–4.9 Hz. This value is consistent with a *cis* relationship of the halogeno and hydroxy substituents, leading to *gauche* coupling of the vicinal protons, as observed with oxabicyclic *endo*-3-ols.[13,14] This argument cannot be applied for the tetrasubstituted chlorohydrins **6c**. However, the major isomer showed a doublet of triplets at δ=3.39 with a line distance of 5.1 and 1.5 Hz, consistent with the coupling constants $^3J_{3,OH}$ and $^4J_{1,3}=^4J_{3,5}$, respectively. Apparently, the smaller J is due to a W coupling pathway of 3*exo*-H with the bridgehead protons, and therefore the major isomer should be **6c** (3-*endo*). For the minor isomer remains 3-*exo*-**6c**; in this case no W-coupling is observed.[15]

Table 2. ^{13}C NMR chemical shifts ($CDCl_3$, δ, ppm) of 2(4)-halogeno 8-oxabicyclo[3.2.1]oct-6-en-3-ones (**2**,**3**)

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	2-CH_3	4-CH_3
2a*n*	86.4	74.7	203.3	50.0	83.0	134.1[a]	133.7[a]	26.7 [*exo*]	10.45 [*endo*]
2a*x*[b]	86.1	–[c]	–[c]	46.4	82.7	135.5[a]	131.8[a]	21.5 [*endo*]	10.0 [*endo*]
2b*n*	82.3	62.3	203.1	54.6	87.0	131.9[a]	135.6[a]	–	20.2 [*endo*], 24.4 [*exo*]
2c*n*	86.1[a]	73.3	208.4	54.3	86.7[a]	134.3[a]	133.4[a]	28.7 [*exo*]	21.3 [*endo*], 26.4 [*exo*]
2d*n*	86.8	68.4	203.3	53.3	88.5	134.9	134.9	–, 21.3 [1-CH_3]	20.3 [*endo*], 24.5 [*exo*]
2e*n*	86.9	70.6	202.8	51.1	82.9	134.8[a]	133.5[a]	28.0 [*exo*]	10.6 [*endo*]
2e*x*	86.2	63.3	201.9	46.4	82.7	135.1[a]	131.8[a]	22.6 [*endo*]	10.0 [*endo*]
2f*n*	82.6	54.5	202.5	55.9	86.9	132.3[a]	135.5[a]	–	20.3 [*endo*], 24.6 [*exo*]
2f*x*	82.9	45.3	205.7	53.9	85.9	131.3[a]	136.4[a]	–	20.6 [*endo*], 28.0 [*exo*]
2g*n*	86.6	61.6	203.0	54.2	88.4	134.7[a]	135.4[a]	–, 22.3 [1-CH_3]	20.45 [*endo*], 24.7 [*exo*]
2g*x*[b]	84.7	52.5	206.1	52.0	86.7	134.1[a]	136.2[a]	–, 21.7 [1-CH_3]	20.7 [*endo*], 27.9 [*exo*]
2h*n*	86.7	68.9	208.0	55.7	86.7	134.3[a]	134.1[a]	30.0 [*exo*]	21.4 [*endo*], 26.8 [*exo*]
3g*n*[b]	89.5	58.6	203.0	54.9	82.5	131.5[a]	139.5[a]	16.6 [*endo*], 20.2 [*exo*]	–, 21.45 [1-CH_3]
3g*x*[b]	–[c]	–[c]	–[c]	45.4	82.7	130.4[a]	140.6[a]	16.9 [*endo*], 20.2 [*exo*]	–, 25.0 [1-CH_3]

[a] The assignments may be reversed.
[b] The data were picked out from the spectrum of a mixture of isomers (see Section 5).
[c] The signal was too weak to be detected.



6 - 7	R^1	R^2	R^3	R^4	X
a	CH_3	CH_3	H	H	Cl
b	H	CH_3	CH_3	H	Cl
c	CH_3	CH_3	CH_3	H	Cl
d	H	CH_3	CH_3	CH_3	Cl
e	CH_3	CH_3	H	H	Br
f	H	CH_3	CH_3	H	Br
g	H	CH_3	CH_3	CH_3	Br

8	R^1	R^2	R^3	R^4
a	CH_3	CH_3	H	H
b	H	CH_3	CH_3	H
c	CH_3	CH_3	CH_3	H
d	H	CH_3	CH_3	CH_3

(i) H_2, Pd/C, CH_3OH

(ii) 1. BuLi, THF, 2. $Na[C_{10}H_8]$, THF

Scheme 2.

The C═C double bond of the 3-*endo*-alcohols **6** was saturated by catalytic hydrogenation over palladium on charcoal in methanol; the carbon–halogen bonds were not affected and thus the halogen substituents of the oxabicycles **7** (and **6**) are adjusted in different stereochemical relationship to the two oxygen atoms, i.e. antiperiplanar (*ap*) and synclinal (*sc*) (Scheme 2).

4. Reductive cleavage

In order to prevent unwanted side reactions, especially the competing elimination in 2,3-position (see e.g. compounds **9a**,**b**,**d**), the alcohols **7** were first deprotonated with 1 equiv. of BuLi (in THF, at −78°C). For the cleavage of the oxygen bridge, THF solutions of the radical anions prepared from naphthalene and sodium,[16] and 4,4′-di-*tert*-butylbiphenyl and lithium (LiDBB, Freeman's reagent)[17] were examined. Thus, the reductive elimination was achieved under mild conditions and at low temperatures (Table 3).

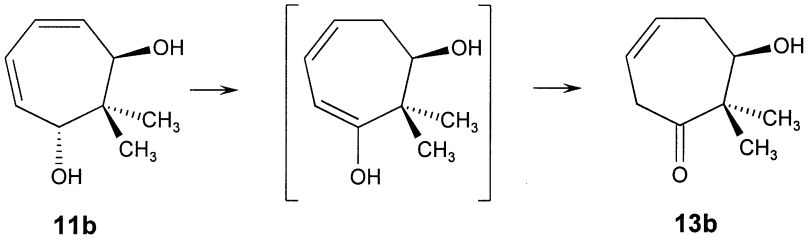
LiDBB in THF proved to be most effective, as demonstrated with **7a** and **c** (Table 3, entries 1 and 2). On reaction at −78°C, hydrolytic work-up and chromatography on silica, the cycloheptenediols **8a** and **c**, respectively, could be isolated in >95% yield.

Sodium naphthalenide in THF (ca. 0.5 M solution), a less expensive and more stable reagent, gave lower yields with **7a** and **c** (60–61%, entries 3 and 5). A somewhat higher reaction temperature and a slightly longer reaction time had to be applied with these chlorides. By-products were formed, appearing on the TLC as spots with strong UV absorption. Presumably, they arise from coupling of the naphthalenide radical anion with the radical intermediates derived from the oxabicycles **7** (see, e.g. compound **10**). Fortunately, the unwanted products could easily be removed by simple chromatography on a silica column.

For the reductive elimination of the bromobicycles **7e**–**g**, treatment with zinc/copper-couple in aqueous methanol, at room temperature, was sufficient. However, apart from the anticipated cycloheptenediols (**8a**,**b**,**d**), the oxabicyclooctenes **9a**,**b**,**d** were formed as minor products. These bicyclic olefins proved to be labile and volatile, and thus could be removed easily by evaporation under reduced

Table 3. Cycloheptene-1,3-diols (**8**) by reductive elimination of 2-halogeno-8-oxabicyclo[3.2.1]octan-3-ols (**7**)

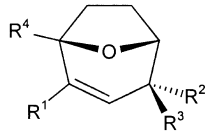
Entry	Educt	Reagent, solvent	Temp./time	Product	Yield (%)
1	**7a**	BuLi/LiDBB, THF	−78°C/15 min	**8a**	97
2	**7c**	BuLi/LiDBB, THF	−78°C/15 min	**8c**	95
3	**7a**	BuLi/$Na[C_{10}H_8]$, THF	−35→−30°C/30 min	**8a**	61
4	**7b**	BuLi/$Na[C_{10}H_8]$, THF	−35→−30°C/30 min	**8b**	81
5	**7c**	BuLi/$Na[C_{10}H_8]$, THF	−35→−30°C/30 min	**8c**	60
6	**7d**	BuLi/$Na[C_{10}H_8]$, THF	−35→−30°C/30 min	**8d**	93
7	**7e**	BuLi/$Na[C_{10}H_8]$, THF	−78°C/20 min	**8a**	53
8	**7f**	BuLi/$Na[C_{10}H_8]$, THF	−78°C/20 min	**8b**	77
9	**7g**	BuLi/$Na[C_{10}H_8]$, THF	−78°C/20 min	**8d**	87
10	**7e**	Zn/Cu, CH_3OH/H_2O (9:1)	Room temp./3 h	**8a**	32
11	**7f**	Zn/Cu, CH_3OH/H_2O (9:1)	Room temp./3 h	**8b**	69
12	**7g**	Zn/Cu, CH_3OH/H_2O (9:1)	Room temp./3 h	**8d**	69



Scheme 3.

pressure. In contrast, the chloride **7b** gave no reaction with zinc/copper-couple, even after several hours reflux. The low yield with **7e** (entry 10) is partly due to further side-reactions; two by-products could be isolated, presumably (2*endo*,3*endo*,4*endo*)-2,4-dimethyl-8-oxabicyclo[3.2.1]octan-3-ol (9%) and (2*endo*,3*endo*)-2-methyl,4-methylidene-8-oxabicyclo[3.2.1]octan-3-ol (7%), as indicated by the spectra.

With sodium naphthalenide in THF, the bromobicycles **7e**–**g** were smoothly cleaved too, even at −78°C. The reduced yield with **7e** is partially also due to by-products, that could be separated from **8a** by chromatography. GC/MS analysis and spectroscopy established a dihydronaphthalene constitution **10**, suggesting formation by coupling of the oxabicyclohept-2-yl radical intermediate derived from **7e**, with the naphthalenide radical anion at different positions.



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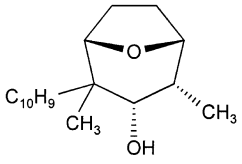


10

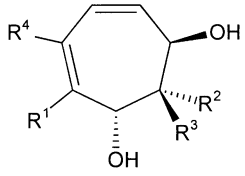
9	R^1	R^2	R^3	R^4
a	CH_3	CH_3	H	H
b	H	CH_3	CH_3	H
c	CH_3	CH_3	CH_3	H
d	H	CH_3	CH_3	CH_3

In order to examine dehalogenations by sodium/liquid ammonia, and lithium in THF, the bromo-alcohol **7f** was selected as a model. The lithium alkoxide, prepared from **7f** and BuLi in THF was treated with dispersed lithium at room temperature. To our surprise, no cleavage was observed. Aqueous work-up, followed by liquid chromatography gave 2,2-dimethyl-8-oxabicyclo[3.2.1]octan-3-*exo*-ol (56%) and 2,2-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (32% isolated yield). The former product, i.e. the *exo* alcohol, is expected to arise from a one-electron reduction (dissolving alkali metal reduction) of the corresponding ketone.[18] The latter, presumably, results from a rearrangement of the lithium alkoxide derived from the bicyclic *cis*-1,2-dihalogenohydrin.[19]

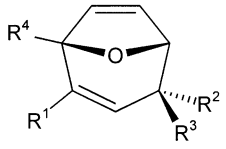
With sodium in liquid ammonia/THF at −78°C, the lithium alkoxide of **7f** underwent debromination, but showed only partial cleavage; apart from **8b** (36%) 2,2-dimethyl-8-oxabicyclo[3.2.1]octan-3*endo*-ol (32%) was isolated.

The trimethylsilyl ether, obtained from the alcohol **7f** (TMSOTf, CH_2Cl_2, 2,6-lutidine) was dissolved in liquid ammonia/diethyl ether (ca. 6:1, v/v) and treated with sodium at −78°C. A complex mixture resulted from which the olefin **9b** and the diol **8b**, i.e. the cleavage product, could be isolated with 32 and 6% yield, respectively.

Reductive cleavage of *unsaturated* oxabicycles was examined with the bromohydrins **6a**,**b**,**d** that were prepared by $LiAlH_4$ reduction of the bromoketones **2e**–**g**. Indeed, treatment with zinc/copper-couple led to the expected cycloheptadienediols **11a**,**b**,**d** in reasonable yields (38, 58, 52% isolated), but here, the oxabicyclic dienes **12a**,**b**,**d** were formed in larger amounts (28, 6, 20%) compared with the reaction of the saturated educts **7e**–**g**. The dienes **12** could be easily removed from the diols **11** by kugelrohr distillation.



11



12

11, 12	R^1	R^2	R^3	R^4
a	CH_3	CH_3	H	H
b	H	CH_3	CH_3	H
d	H	CH_3	CH_3	CH_3

Both cleavage products **11** and **12** are very labile compounds. As for **11a**, a sample could be obtained in impure form with ca. 38% yield. Chromatography led to high losses and, therefore, the isolated yield was only 8%.

On distillation (kugelrohr, 130°C/0.001 Torr), **11b** rearranged partially to the hydroxyketone **13b**, as revealed by NMR spectroscopy. Even at 6°C, chromatographically purified **11b** in $CDCl_3$ solution underwent this rearrangement. One may be tempted to postulate a 1,5-hydrogen shift to a dienol intermediate (Scheme 3). Hoffmann et al.[20] reported that 6-hydroxy-7,7-dialkylcyclohepta-2,4-dienones behave similarly, and the isomerisation rate

depends on the solvent. Dimethylsulfoxide accelerates the reaction,[20] an effect we observed with **11b** too.

To sum up, the cleavage of 8-oxabicyclo[3.2.1]octan-3-ols and -oct-6-en-3-ols, chloro- or bromo-substituted at the 2(4) position, by reductive elimination is a highly stereoselective transformation leading to unsaturated *trans*-1,3-diols of the seven-membered ring. Anyway, bromo or chloro substituents are often needed as auxiliary groups for assembling oxabicyclics by [4+3] cycloaddition. Hence, *endo*cyclic reductive elimination extends the usage of the oxyallyl cycloaddition in organic synthesis. An application of this protocol in sesquiterpene synthesis has been described recently.[14,21] Further research should focus on the control of the two competing elimination reactions by modification of the substituents.

5. Experimental

5.1. General

NMR spectra were recorded on Bruker AC 250, CXP 300 and ARX 500 spectrometers, usually in $CDCl_3$ solutions. The chemical shifts δ are reported in ppm (TMS as internal standard, $\delta=0$). IR spectra were recorded on a Perkin Elmer 457 instrument and are reported in terms of frequency of absorption ν, cm^{-1}; listed are only absorptions that are characteristic of functional groups and unsaturation.

Reactions were monitored by gas chromatography (GLC) and/or thin layer chromatography (TLC). For GLC, a Carlo-Erba-Fractovap 4160 GI instrument with integrator was used; analyses were made with programmed oven temperature (40°C→300°C, heating rate 10 K/min) on a 20 m glass capillary column coated with PS 086. Injection was 'on-column'. Hydrogen (0.4 bar) was used as carrier gas. The percent values give the relative peak areas obtained by integration of the FID signals. TLC was carried out on precoated silica sheets, Polygram Sil G/UV_{254}, distributed by Macherey and Nagel, Düren, Germany; the spots were visualised by spraying with vanilline/H_2SO_4 solution,[22] followed by warming, or by UV extinction. For preparative column chromatography and adsorptive filtrations, silica 60 (Macherey and Nagel, 63–200 μm) was used. For elution and TLC developing, predried petroleum ether (PE) was distilled (bp 40–65°C). Ethyl acetate (EA) was dried over calcium chloride, distilled, and kept dry over molecular sieve 4 Å.

Kugelrohr distillations were carried out with a Büchi apparatus GKR-50, Büchi Laboratoriumstechnik AG, Flawil/Switzerland. Melting points were determined with a Büchi 510 apparatus, and are not corrected. Elemental analyses were performed by the service of the Institut für Organische Chemie, University of Stuttgart.

(R^*,R^*)-2,4-Dichloropentan-3-one (**1a**) and 1,3-dichloro-3-methylbutan-2-one (**1b**) were prepared by reaction of pentan-3-one and 3-methylbutan-2-one, respectively, with sulfuryl chloride, according to the procedure of Wyman and Kaufman.[23] (R^*,R^*)-2,4-dibromopentan-3-one (**1c**) and 1,3-bromo-3-methylbutan-2-one (**1d**) were prepared after literature procedures.[24,25]

2,2,2-Trifluoroethanol (TFE) was commercially available in high purity (GLC>99%, Fluka, *puriss*., or ABCR, Karlsruhe, Germany) and was used directly, without further purification. For sodium trifluoroethoxide/trifluoroethanol (NaTFE/TFE) reagent see Ref. 10. Furan and 2-methylfuran was purchased from Fluka, Neu-Ulm, Germany. In order to remove phenolic stabilisers it was shaken with 5% aqueous potassium hydroxide solution until the aqueous layer remained colourless, dried over calcium chloride and distilled before use from potassium hydroxide pellets. THF was distilled from sodium/benzophenone. Methanol was dried by refluxing with magnesium turnings and distillation. Diisopropylamine was freshly distilled from calcium hydride before use. Zinc/copper-couple was prepared by the procedure of Jäger and Häfele.[26]

The following reagents were purchased and used directly: palladium on activated charcoal (10%) hydrogenation catalyst (Fluka); *n*-Butyllithium (BuLi) (Merck, 1.6 M solution in hexane); 4,4′-di-*tert*-butylbiphenyl (Fluka, purum, >98%); ethylenediaminetetraacetic acid disodium salt dihydrate (EDTA) (Merck, Titriplex III, *pro analysi*).

5.1.1. Reaction of (R^*,R^*)-2,4-dichloropentan-3-one (1a) with furan: (2*endo*, 4*endo*)-2-chloro-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (2a*n*) and (2*exo*, 4*endo*)-2-chloro-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (2a*x*). Dichloroketone **1a** (3.10 g, 20 mmol) and furan (5.45 g, 80 mmol) were mixed and chilled in an ice bath. A 1 M solution of NaTFE in TFE (22 mL) was added dropwise with magnetic stirring over 2 h. Stirring was continued at room temperature for 2 h. Water (20 mL) and dichloromethane (10 mL) was added, and the layers separated. The aqueous layer was extracted with dichloromethane (2×10 mL). The combined dichloromethane solutions were washed with brine (20 mL), dried with sodium sulfate and concentrated in a rotary evaporator. The residue was sublimed at 50–60°C/0.005 Torr. The ^{1}H NMR spectrum of the resulting colourless solid (3.19 g, 86% yield) showed the signals reported for the diastereomers **2a***n* and **2a***x*;[6] from the integrals a ratio of 88:12 was derived. The solid was recrystallised from heptane (7 mL) to give isomer **2a***n* (2.52 g, 68%) with mp 69–70°C. A second crystallisation gave 2.26 g (61% yield) with mp 70–72°C. For ^{1}H NMR and ^{13}C NMR spectra see Tables 1 and 2.

5.1.2. Reaction of 1,3-dichloro-3-methylbutan-2-one (1b) with furan: (4*endo*)-4-chloro-2,2-dimethyl-8-oxabicyclo-[3.2.1]oct-6-en-3-one (2b*n*) and 1-chloro-3-furyl-3-methylbutan-2-one (4). Prepared from **1b** (3.10 g, 20 mmol), furan (5.45 g, 80 mmol) and 1 M NaTFE solution (22 mL); protocol and work-up as described before. The residue was sublimed at 60°C/0.01 Torr. The colourless sublimate (3.23 g, 87%) had mp 83–84°C. The IR and ^{1}H NMR spectra were in agreement with the data reported for **2b***n*.[6] Upon recrystallisation from *n*-heptane (7 mL) the mp rose to 84–85°C (Ref. 6: mp 85–86°C); yield 3.00 g (80%). For ^{1}H NMR and ^{13}C NMR spectra see Tables 1 and 2. The mother-liquor from the crystallisation was concentrated and

subjected to chromatography on silica (20 g), eluting with PE/EA (8:1). The first fractions, after a fore-run (30 mL), contained 22 mg (1%) of **4**, a colourless oil. The ^{1}H NMR spectrum was in agreement with the reported data.[6] From the following fractions, 81 mg (2%) of **2b***n* was isolated, and at last 36 mg of a colourless viscous oil. According to the NMR spectra, the latter substance was a mixture of several bicyclic compounds, whose structure could not be rigorously identified.

5.1.3. (2*endo*)-2-Chloro-2,4,4-trimethyl-8-oxabicyclo-[3.2.1]oct-6-en-3-one (2c*n*). A 100 mL two-necked flask, equipped with a gas inlet and septum was thoroughly dried (heat gun) and charged with a solution of dry diisopropylamine (1.21 g, 12 mmol) in THF (20 mL) under an argon atmosphere, and chilled in an ice bath. BuLi solution (7.5 mL, 12 mmol) was added by means of a syringe with magnetic stirring. After 30 min at 0°C, a solution of **2b***n* (1.87 g, 10 mmol) in THF (10 mL) was added dropwise and stirred for further 30 min in the ice bath. Iodomethane (1.70 g, 12 mmol) was added by syringe, the ice bath removed, and the mixture stirred for 24 h at room temperature. 2 M hydrochloric acid (30 mL) was added, and the mixture extracted with diethyl ether (3×20 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ and NaCl solutions (30 mL each) and dried with sodium sulfate. After filtration and evaporation of the solvent, the remaining liquid was chromatographed on silica (180 g), eluting with PE/EA (20:1), to give 1.84 g of a pale yellow liquid that was distilled in a kugelrohr at 70°C/0.001 Torr. A nearly colourless oil (1.78 g, 89% yield) was obtained which solidified in the refrigerator (mp 21–22°C). For ^{1}H NMR and ^{13}C NMR spectra see Tables 1 and 2. IR (film): 3420 (overtone of C=O), 3080 (=C–H), 1725 (C=O), 1595 (C=C). Anal. calcd for $C_{10}H_{13}ClO_2$ (200.7): C 59.86, H 6.53, Cl 17.67; found C 59.78, H 6.58, Cl 17.73.

5.1.4. Reaction of (*R,*R**)-2,4-dibromopentan-3-one (1c) with furan: (2*endo*,4*endo*)-, (2*exo*,4*endo*)-2-bromo-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (2e*n*, 2e*x*) and 2,2,2-trifluoroethyl (*Z*)-2-methylbut-2-enoate (5a).** Dibromoketone **1c** (4.88 g, 20 mmol) and furan (5.45 g, 80 mmol) were mixed and cooled in an ice bath. A 1 M solution of NaTFE in TFE (25 mL) was added dropwise with magnetic stirring over 3.5 h. Stirring was continued at 0°C for 4 h, then overnight, allowing the ice bath to thaw. Progress of the reaction was monitored by GLC. Since ca. 5% of educt **1e** was still left, more NaTFE solution (2 mL) was added dropwise (ice bath, 30 min). After stirring at 0°C for 2 h, water (20 mL) was added, and the layers separated. The aqueous layer was extracted with dichloromethane (3×10 mL). The combined dichloromethane solutions were washed with water (20 mL), brine (20 mL), and dried with sodium sulfate. The GLC of an extract sample showed three peaks with t_R=2.4 (**5a**), 11.3 (**2e***n*) and 11.6 min (**2e***x*) with relative peak areas of 23 (**5a**):77 (**2e***n* and **2e***x*, two signals, no base-line separation). The solution was filtered and concentrated at atmospheric pressure. Remaining volatile components (inter alia **5a**) were condensed in a trap cooled by liquid nitrogen, using oil-pump vacuum. The residue, a yellowish oil (3.37 g) solidified slowly, but darkened on standing. Purification by filtration over silica (30 g), eluting with 350 mL of PE/EA (10:1), gave 2.58 g of a pale yellow oil which solidified in the refrigerator. A ^{1}H NMR spectrum indicated bicycles **2e***n* and **2e***x* in the ratio of ca. 10:1. The solid was dissolved in 20 mL of boiling *n*-hexane; on cooling the main product crystallised to give 2.25 g (49%) **2e***n* with mp 75–76°C. The mother-liquor was concentrated and subjected to chromatography on silica (35 g), eluting with PE/EA (8:1). The first fractions gave 85 mg of **2e***n*; 196 mg of **2e***x* with mp 78–79°C were isolated from the following fractions. The combined yield of cycloadducts **2e***n*+**2e***x* was 55%.

2e*n*: TLC (PE/EA 3:1): red spot with R_f=0.55. For ^{1}H NMR and ^{13}C NMR spectra see Tables 1 and 2. IR (KBr): 3070 (=C–H), 1710 (C=O), 1585 (C=C). Anal. calcd for $C_9H_{11}BrO_2$ (231.1): C 46.78, H 4.80, Br 34.58; found C 46.69, H 4.77, Br 34.73.

2e*x*: TLC (PE/EA 3:1): red spot with R_f=0.45. For ^{1}H NMR and ^{13}C NMR spectra see Tables 1 and 2. IR (KBr): 3395 (overtone of C=O), 3070 (=C–H), 1710 (C=O), 1585 (C=C). Anal. calcd for $C_9H_{11}BrO_2$ (231.1): C 46.78, H 4.80, Br 34.58; found C 46.87, H 4.74, Br 34.74.

The liquid condensed in the cold trap was distilled in a 15 cm Vigreux column. The distillate (0.26 g), a colourless liquid with bp 125°C, had a sweet smell. The spectra were in agreement with **5a** (see below). Yield 7%. Further weak ^{1}H NMR signals at δ=1.8–1.9, 4.52 and 6.99 may be assigned to the (*E*)-isomer.

5.1.5. 2,2,2-Trifluoroethyl (*Z*)-2-methylbut-2-enoate (5a) by Favorskii rearrangement of 1c. (*R**,*R**)-2,4-dibromopentan-3-one (**1c**) (1.22 g, 5 mmol) was cooled in an ice bath. 2 M NaTFE solution (5 mL) was added dropwise with magnetic stirring within 1 h. The ice bath was removed and stirring continued for 3 h. Water (10 mL) was added and the layers separated. The aqueous layer was extracted with dichloromethane (2×5 mL). The combined organic layers were dried with sodium sulfate and concentrated in a rotary evaporator. The residue was distilled in a kugelrohr at 60°C/10 Torr to give 0.51 g (56%) of colourless liquid **5a**. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.93 (dq, J=1.5 Hz, 3H, 2-CH_3), 2.02 (dq, J=7.3, 1.5 Hz, 3H, 4-H), 4.53 (q, $J_{H,F}$=8.5 Hz, 2H, CH_2CF$_3$), 6.23 (qq, J=7.3, 1.5 Hz, 1H, 3-H). ^{13}C NMR (63 MHz, $CDCl_3$): δ=15.9 (2-CH_3), 20.9 (C-4), 60.1 (q, $J_{C,F}$=36.4 Hz, *C*H$_2$CF$_3$), 123.2 (q, $J_{C,F}$=277.2 Hz, CH$_2$*C*F$_3$), 126.4 (C-2), 141.1 (C-3), 166.0 (C-1). IR ($CDCl_3$): 3010 (=C–H), 1730 (C=O), 1640 (C=C). Anal. calcd for $C_7H_9F_3O_2$ (182.1): C 46.16, H 4.98; found C 45.99, H 4.71.

5.1.6. Reaction of 1,3-dibromo-3-methylbutan-2-one (1d) with furan: *endo*- and *exo*-4-bromo-2,2-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (2f*n*, 2f*x*) and 2,2,2-trifluoroethyl 3-methylbut-2-enoate (5b). Prepared from 12.20 g (50 mmol) of **1d**, 13.62 g (200 mmol) of furan and 75 mL of 1 M NaTFE solution as described for the foregoing compound; for details see Ref. 14. The combined yield of cycloadducts **2f***n*+**2f***x* was 84%; 7.74 g (67%) of **2f***n*, 1.29 g of **2f***x*, and 1.23 g (14%) of **5b** were isolated.

5.1.7. Reaction of 1,3-dibromo-3-methylbutan-2-one (1d)

with 2-methylfuran: *endo*- and *exo*-2-bromo-1,4,4-trimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (2g*n*, 2g*x*), *endo*- and *exo*-4-bromo-1,2,2-trimethyl-8-oxabicyclo-[3.2.1]oct-6-en-3-one (3g*n*, 3g*x*)Prepared from 12.20 g (50 mmol) of **1d**, 16.42 g (200 mmol) of 2-methylfuran and 58 mL, 1 M NaTFE solution as described for **2e**; for details see Ref. 14. Yield of **2g***n*: 7.28 g (59%); **2g***x* (ca. 5%), **3g***n* (ca. 2%), and **3g***x* (ca. 1%) were obtained as mixtures.

5.1.8. *endo*-2-Bromo-2,4,4-trimethyl-8-oxabicyclo[3.2.1]-oct-6-en-3-one (2h*n*). A solution of **2f***n* (2.31 g, 10 mmol) in THF (15 mL) was added dropwise to a solution of LDA, prepared from diisopropylamine (1.11 g, 11 mmol) in THF (10 mL), and BuLi solution (7 mL, 11 mmol), as described for **2c***n*; for details see Ref. 14. Yield: 1.91 g (78%).

5.2. General procedure for reduction of halogeno-oxabicycles 2 with lithiumaluminium hydride (LAH)

To a stirred suspension of LAH (0.19 g, 5 mmol) in THF (10 mL) a solution of halogeno-ketone **2** (10 mmol) in THF (10 mL) was added dropwise and with cooling in an ice bath. The ice bath was removed and stirring was continued at room temperature for 2 h. Then water (10 mL) was added dropwise (*caution*) with ice cooling and vigorous stirring. The precipitate was dissolved by adding dilute sulfuric acid (10%, ca. 8 mL). The two layers were separated, and the aqueous phase extracted with diethyl ether (3×10 mL). The combined organic solutions were washed with saturated $NaHCO_3$ solution (25 mL) and brine (25 mL) and dried with sodium sulfate. After filtration, the solvent was removed in a rotary evaporator.

5.2.1. (2*endo*,3*endo*,4*endo*)-2-Chloro-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (6a). Prepared from **2a***n* (2.31 g, 10 mmol) in THF (10 mL) with 0.19 g (5 mmol) of LAH in THF (10 mL). The remaining colourless solid was purified by chromatography on silica (100 g), eluting with PE/EA (10:1). A colourless solid with mp 66–67°C was obtained. Yield 1.71 g (91%). ^{1}H NMR (250 MHz, $CDCl_3$) δ=1.01 (d, J=7.3 Hz, 3H, 4*n*-CH_3), 1.83 (s, 3H, 2*x*-CH_3), 2.15 (bs, 1H, OH), 2.45 (ddq, J=7.3, 4.5, 3.4 Hz, 1H, 4-H), 3.64 (d, J=4.5 Hz, 1H, 3-H), 4.48 (m, 1H, 5-H), 4.51 (t, J=1.7 Hz, 1H, 1-H); AB sub-spectrum with δ_B=6.43, δ_A=6.49, J_{AB}=6.1 Hz; the lines are split into doublets with 1.7 Hz (6-H and 7-H). ^{13}C NMR (63 MHz, $CDCl_3$) δ=13.1 (4*n*-CH_3), 29.1 (2*x*-CH_3), 36.9 (C-4), 71.7 (C-2), 75.7 (C-3), 82.9 (C-5), 84.8 (C-1), 133.1 (C-7), 135.6 (C-6). IR (KBr) 3455, 3075, 1590. Anal. calcd for $C_9H_{13}ClO_2$ (189.65): C 57.30, H 6.95, Cl 18.79; found C 46.50, H 6.96, Cl 18.86.

5.2.2. (2*endo*,3*endo*)-2-Chloro-4,4-dimethyl-8-oxabicyclo-[3.2.1]oct-6-en-3-ol (6b). Prepared from 1.87 g (10 mmol) of **2b***n* in 12 mL of THF with 0.19 g (5 mmol) of LAH. The remaining colourless solid (1.87 g) was recrystallised from diethyl ether/*n*-hexane (1:1). Colourless needles (1.34 g, 72%) with mp 96–97°C were obtained. TLC (PE/EA 3:1): green spot with R_f=0.39. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.02 (s, 3H, 4*n*-CH_3), 1.22 (s, 3H, 4*x*-CH_3), 2.06 (bs, 1H, OH), 3.60 (broadened d, $J_{2,3}$=4.8 Hz, 1H, 3-H), 4.22 (m, appearing as a t, line distance 1.6 Hz, 1H, 5-H), 4.49 (dd, J=4.8, 3.7 Hz, 1H, 2-H), 4.68 (d, split into a t with ca. 1.6 Hz, J=3.7 Hz, 1H, 1-H); AB sub-spectrum with δ_B=6.42 and δ_A=6.52, J_{AB}=6.0 Hz (6-H and 7-H), the A and B-part is split into doublets with J=1.7 Hz each. ^{13}C NMR (63 MHz, $CDCl_3$): δ=22.3 (4*n*-CH_3), 26.8 (4*x*-CH_3), 40.1 (C-4), 58.6 (C-2), 75.1 (C-3), 80.9 (C-1), 86.3 (C-5), 131.9 (C-6), 136.8 (C-7). IR (KBr): 3430 (O–H), 3080 (=C–H), 1590 (C=C). Anal. calcd for $C_9H_{13}ClO_2$ (188.65): C 57.30, H 6.95, Cl 18.79; found C 57.41, H 6.93, Cl 18.80.

5.2.3. (2*endo*,3*endo*)-2-Chloro-2,4,4-trimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (3-*endo*-6c) and (2*endo*,3*exo*)-2-chloro-2,4,4-trimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (3-*exo*-6c). Prepared from 2.01 g (10 mmol) of **2c***n* with 0.19 g (5 mmol) of LAH, following the general procedure. The colourless residue was subjected to chromatography on silica (100 g). Elution with PE/EA (10:1) gave no separation of the diastereomers. The isolated colourless solid which melted at 63–65°C (1.81 g, 89%) proved to be a 78:22 mixture of 3*endo*-**6c** and 3*exo*-**6c** (^{1}H NMR). Recrystallisation from diethyl ether (5 mL) gave 1.07 g (53%) of the main isomer 3*endo*-**6c** with mp 79–80°C.

5.2.4. 3-*endo*-6c. ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.99 (s, 3H, 4*n*-CH_3), 1.28 (s, 3H, 4*x*-CH_3), 1.93 (s, 3H, 2*x*-CH_3), 2.24 (d, J=5.1 Hz, 1H, OH), 3.39 (dt, J=5.1, 1.5 Hz, 1H, 3-H), 4.24 (s, 1H, 5-H), 4.55 (t, J=1.5 Hz, 1H, 1-H), AB sub-spectrum with δ_B=6.37, δ_A=6.44, J_{AB}=6.2 Hz (6-H and 7-H), the A and B part is split to doublets with J=1.5 Hz each. ^{13}C NMR (63 MHz, $CDCl_3$): δ=23.2 (4*n*-CH_3), 28.8 (4*x*-CH_3), 31.7 (2*x*-CH_3), 39.8 (C-4), 73.1 (C-2), 80.0 (C-3), 85.0 (C-1), 86.7 (C-5), 131.8 (C-6), 135.1 (C-7).

The NMR data of 3*exo*-**6c** were picked out from the spectra of the 78:22 mixture: ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.92 (s, 3H, 4*n*-CH_3), 1.12 (s, 3H, 4*x*-CH_3), 1.75 (s, 3H, 2*x*-CH_3), 2.05 (d, J=5.4 Hz, 1H, OH), 3.78 (d, J=5.4 Hz, 1H, 3-H), 4.28 (d, J=1.5 Hz, 1H, 5-H), 4.62 (d, J=1.6 Hz, 1H, 1-H). Two doublets at δ=6.33 and 6.40, with line distance of 1.7 and 1.6 Hz, respectively, may be attributed to the AB sub-spectrum from 6-H and 7-H; the remaining AB lines were masked by those of 3*endo*-**6c**. ^{13}C NMR (63 MHz, $CDCl_3$): δ=20.1 (4*n*-CH_3), 24.3, 24.6 (2*x*-CH_3 and 4*x*-CH_3), 41.0 (C-4), 72.2 (C-2), 79.7 (C-3), 86.0 (C-1), 87.6 (C-5), 131.0 (C-6), 132.1 (C-7). Anal. calcd for $C_{10}H_{15}ClO_2$ (202.7): C 59.26, H 7.46, Cl 17.49; found C 59.26, H 7.45, Cl 17.46.

5.2.5. (2*endo*,3*endo*)-2-Chloro-1,4,4-trimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (6d). Prepared from 4.01 g (20 mmol) of **2d***n* in 25 mL of dry THF with 0.38 g (10 mmol) of LAH in 20 mL of dry THF (45 min at 0°C, then 3 h at room temperature). The remaining solid was sublimed at 70°C/0.001 Torr and recrystallised from *n*-hexane (20 mL) to yield 3.44 g (85%) of colourless solid **6d** with mp 76–77°C. TLC (PE/EA 4:1): violet spot with R_f=0.60. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.02 (s, 3H, 4*n*-CH_3), 1.21 (s, 3H, 4*x*-CH_3), 1.49 (s, 3H, 1-CH_3), 2.14 (bs, 1H, OH), 3.61 (broadened d, line distance 4 Hz, 1H, 3-H), 4.23 (t, line distance ca. 1.5 Hz, 1H, 5-H), 4.28 (d, $^3J_{2,3}$=4.9 Hz, 1H, 2-H), 6.16 (d, $^3J_{6,7}$=5.9 Hz, 1H, 7-H), 6.44 (dd, $^3J_{6,7}$=5.9 Hz, $^3J_{5,6}$=1.8 Hz, 1H, 6-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=21.3 (1-CH_3), 22.2 (4*n*-CH_3), 26.7 (4*x*-CH_3), 40.3 (C-4), 65.0 (C-2), 75.6 (C-3), 86.0 (C-1),

87.2 (C-5), 134.9 (C-6), 136.1 (C-7). IR (KBr): 3455, 3360 (O-H), 3065 (=C-H), 2970, 2940, 2925, 2885, 2855 (C-H), 1590 (C=C). Anal. calcd. for $C_{10}H_{15}ClO_2$ (202.7): C 59.26, H 7.46, Cl 17.49; found C 59.09, H 7.47, Cl 17.39.

5.2.6. (2*endo*,3*endo*,4*endo*)-2-Bromo-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (6e). Prepared from 2.31 g (10 mmol) of **2e***n* in 12 mL of dry THF with 0.19 g (5 mmol) of LAH in 10 mL of dry THF at 0°C (20 min), then at room temperature for 2 h. The remaining yellow oil (2.18 g) solidified in the refrigerator. It was purified by chromatography on silica (220 g), eluting with PE/EA (4:1), to give 1.78 g (76%) of a colourless solid with mp 91°C. TLC (PE/EA 4:1): red spot with R_f=0.31. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.02 (d, $^3J_{4,4\text{-Me}}$=7.3 Hz, 3H, 4*n*-CH_3), 2.06 (s, 3H, 2*x*-CH_3), 2.15 (d, disappeared after shaking with D_2O, $^3J_{3,OH}$=6.4 Hz, 1H, OH), 2.56 (m, 12 lines, 1H, 4-H), 3.64 (m, 6 lines, 1H, 3-H), 4.46 (m, 4 lines, 1H, 5-H), 4.63 (m, appearing as a t, line distance 1.4 Hz, 1H, 1-H); AB sub-spectrum with δ_B=6.49 and δ_A=6.51, J_{AB}=6.2 Hz, the A and B part is split into doublets with 1.3 Hz each (6-H and 7-H). After shaking with D_2O the multiplet at 3.64 changed to a dt with $^3J_{3,4}$=4.7 Hz and $^4J_{1,3}$=$^4J_{1,5}$=1.3 Hz. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=13.3 (4*n*-CH_3), 30.3 (2*x*-CH_3), 37.9 (C-4), 71.3 (C-2), 75.9 (C-3), 82.8 (C-5), 85.3 (C-1), 133.8 (C-7), 135.6 (C-6). IR (KBr): 3440 (O-H), 3090, 3070 (=C-H), 2955, 2940, 2930, 2905, 2885, 2850, 2800 (C-H), 1590 (C=C). Anal. calcd. for $C_9H_{13}BrO_2$ (233.1): C 46.37, H 5.62, Br 34.28; found C 46.50, H 5.70, Br 34.37.

5.2.7. (2*endo*,3*endo*)-2-Bromo-4,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (6f). Prepared from 11.56 g (50 mmol) of **2f***n* in 55 mL of dry THF with LAH (1.0 g, 26.5 mmol) at 0°C (1 h), then 2 h at room temperature. The remaining colourless solid (11.13 g) was recrystallised from ether (110 mL) to give 8.94 g (77%) of colourless needles with mp 111–112°C. TLC (PE/EA 3:1): red spot with R_f=0.40. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.03 (s, 3H, 4*n*-CH_3), 1.24 (s, 3H, 4*x*-CH_3), 2.04 (broadened d, disappeared after shaking with D_2O, $^3J_{3,OH}$=4.7 Hz, 1H, OH), 3.57 (bs, 1H, 3-H), 4.23 (m, appearing as a t, line distance 1.5 Hz, 1H, 5-H), 4.63 (dd, $^3J_{2,3}$=4.8 Hz, $^3J_{1,2}$=3.5 Hz, 1H, 2-H), 4.74 (d, split into triplets with ca. 1.6 Hz, $^3J_{1,2}$=3.5 Hz, 1H, 1-H); AB sub-spectrum with δ_B=6.47 and δ_A=6.54, J_{AB}=6.1 Hz, the A part is split into doublets with 1.8 Hz, the B part with 1.6 Hz (6-H and 7-H). After shaking with D_2O the multiplet at 3.57 changed to a broad d with a line distance of 4.6 Hz. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=22.6 (4*n*-CH_3), 26.8 (4*x*-CH_3), 41.4 (C-4), 53.4 (C-2), 75.2 (C-3), 81.3 (C-1), 86.3 (C-5), 132.3 (C-6), 136.7 (C-7). IR (KBr): 3460 (O-H), 3085 (=C-H), 2965, 2940, 2910, 2870, 2850 (C-H), 1590 (C=C). Anal. calcd. for $C_9H_{13}BrO_2$ (233.1): C 46.37, H 5.62, Br 34.28; found C 46.60, H 5.67, Br 34.03.

5.2.8. (2*endo*,3*endo*)-2-Bromo-1,4,4-trimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (6g). Prepared from 2.45 g (10 mmol) of **2g***n* in 12 mL of dry THF with 0.19 g (5 mmol) of LAH in 10 mL of dry THF at 20 min, then 2 h at room temperature. The remaining colourless solid (2.41 g) was filtrated over silica (100 g) with PE/EA (4:1) to give 2.01 g (81%) of **6g** as a colourless solid with mp 96–97°C. TLC (PE/EA 4:1): red spot with R_f=0.57. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.03 (s, 3H, 4*n*-CH_3), 1.22 (s, 3H, 4*x*-CH_3), 1.53 (s, 3H, 1-CH_3), 2.15 (bs, 1H, OH), 3.58 (dd, $^3J_{2,3}$=4.8 Hz, $^4J_{3,5}$=1.5 Hz, 1H, 3-H), 4.23 (m, appearing as a t, line distance 1.5 Hz, 1H, 5-H), 4.46 (d, $^3J_{2,3}$=4.8 Hz, 1H, 2-H), AB sub-spectrum with δ_B=6.20 (7-H) and δ_A=6.45 (6-H), J_{AB}=5.9 Hz, the A part is split into doublets with $^3J_{5,6}$=1.8 Hz. ^{13}C NMR (62.90 MHz, $CDCl_3$): δ=22.4, 22.5 (1-CH_3, 4*n*-CH_3), 26.7 (4*x*-CH_3), 41.3 (C-4), 60.9 (C-2), 75.8 (C-3), 86.1 (C-1), 87.3 (C-5), 135.2 (C-6), 136.1 (C-7). IR (KBr): 3450, 3350 (O-H), 3085, 3070 (=C-H), 2970, 2940, 2915, 2890, 2850 (C-H), 1595 (C=C). Anal. calcd. for $C_{10}H_{15}BrO_2$ (247.1): C 48.60, H 6.12, Br 32.33; found C 48.47, H 5.99, Br 32.49.

5.3. Catalytic hydrogenation of halogeno-8-oxabicyclo-[3.2.1]oct-6-en-3-ols (6)

5.3.1. (2*endo*,3*endo*,4*endo*)-2-Chloro-2,4-dimethyl-8-oxabicyclo[3.2.1]octan-3-ol (7a). A solution of **6a** (755 mg, 4 mmol) in methanol (30 mL) was shaken with palladium on carbon catalyst (10% Pd) (40 mg) in an atmosphere of hydrogen gas, at normal pressure and room temperature. When the uptake of hydrogen had stopped, the catalyst was removed by filtration and washed with methanol. The filtrates were concentrated in a rotary evaporator and the remaining solid purified by sublimation at 60°C/0.01 Torr. The colourless solid (748 mg, 98%) showed mp 95–96°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.01 (d, J=7.3 Hz, 3H, 4*n*-CH_3), 1.66–1.75 (m, 1H), 1.75 (s, 3H, 2*x*-CH_3), 1.85 (m, 1H), 2.19–2.37 (m, 2H), 2.38 (s, 1H, OH), 2.47 (m, 1H), 3.58 (split s, 1H, 3-H), 4.07 (m, 2H, 5-H). ^{13}C NMR (126 MHz, $CDCl_3$) δ=13.4 (4*n*-CH_3), 24.2 (C-7), 25.8 (C-6), 28.6 (2*x*-CH_3), 37.2 (C-4), 75.40, 75.44 (C-2 and C-3), 79.1 (C-5), 81.5 (C-1). IR (KBr): 3450 (OH). Anal. calcd for $C_9H_{15}ClO_2$ (190.7): C 56.69, H 7.93, Cl 18.59: found C 56.65, H 7.95, Cl 18.59.

5.3.2. (2*endo*,3*endo*)-2-Chloro-4,4-dimethyl-8-oxabicyclo-[3.2.1]octan-3-ol (7b). Prepared from 1.89 g (10 mmol) of **6b** in 75 mL of methanol with 0.10 g of 10% Pd/C catalyst. Sublimation at 60°C/0.01 Torr gave 1.85 g (97%) of a colourless solid with mp 71–72°C. TLC (PE/EA 5:1): orange-coloured spot with R_f=0.70. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.05 (s, 3H, 4*n*-CH_3), 1.12 (s, 3H, 4*x*-CH_3), 1.78 (m, 2H, 6-H or 7-H), 2.24 (d, J=1.5 Hz, 1H, OH), 2.32 (m, 2H, 6-H or 7-H), 3.53 (m, 5 lines, 1H, 3-H), 3.76 (m, appearing as a d, line distance 7 Hz, 1H, 5-H), 4.28 (m, 6 lines, 1H, 2-H), 4.42 (m, appearing as a t, line distance 4 Hz, 1H, 1-H). ^{13}C NMR/DEPT (63 MHz, $CDCl_3$): δ=22.5 (4*n*-CH_3), 24.5, 24.7 (CH_2, C-6 and C-7), 26.5 (4*x*-CH_3), 40.5 (C-4), 61.4 (CH, C-2), 74.6 (CH, C-3), 77.5 (CH, C-1), 82.6 (CH, C-5). IR (KBr): 3400 (OH). Anal. calcd for $C_9H_{15}ClO_2$ (190.7): C 56.69, H 7.93, Cl 18.59; found C 56.57, H 7.89, Cl 18.82.

5.3.3. (2*endo*,3*endo*)-2-Chloro-2,4,4-trimethyl-8-oxabicyclo[3.2.1]octan-3-ol (7c). Prepared from 811 mg (4 mmol) of 3*endo*-**6c** with 40 mg of 10% Pd/C catalyst in 30 mL of methanol. Sublimation at 60°C/0.05 Torr gave 794 mg (97%) with mp 74–75°C. ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.05 (s, 3H, 4*n*-CH_3), 1.20 (s, 3H, 4*x*-CH_3), 1.69–1.95 (m, surmounted by a s at 1.89 from 2*x*-CH_3,

5H, *exo*-6-H and 7-H), 2.25–2.49 (m, 2H, 4-H and *endo*-6- and 7-H), 2.53 (d, J=1.0 Hz, 1H, OH), 3.32 (d, J=1.0 Hz, 1H, 3-H), 3.79 (broadened d, J=7.9 Hz, 1H, 5-H), 4.12 (m, appearing as a d, 1H, 1-H). ^{13}C NMR/DEPT (63 MHz, $CDCl_3$): δ=24.0 (4*n*-CH_3), 24.9 (CH_2, C-6), 26.0 (CH_2, C-7), 28.2 (4*x*-CH_3), 30.9 (2*x*-CH_3), 40.4 (C-4), 79.3 (CH, C-3), 81.8 (CH, C-1), 83.1 (CH, C-5). The signal for C-2 was too weak to be detected. IR (KBr): 3465 (O-H). Anal. calcd for $C_{10}H_{17}ClO_2$ (204.7): C 58.68, H 8.37, Cl 17.32; found C 58.70, H 8.40, Cl 17.26.

Preparation and spectra of compounds **7d**–**g** are described in Ref. 14.

5.4. Reductive cleavages

5.4.1. (1α,2β,3β)-2,4-Dimethylcyclohept-4-en-1,3-diol (8a). (a) LiDBB solution.[17] A 25 mL two-necked flask, equipped with a gas inlet and septum was thoroughly dried (heat gun) and charged with 4,4′-di-*tert*-butylbiphenyl (959 mg, 3.6 mmol). Under an argon atmosphere THF (18 mL) was added. The solution was cooled in an ice bath. With vigorous magnetic stirring, small pieces of clean lithium (40 mg, 5.8 mmol) were added, maintaining an argon stream. Stirring was continued for 3 h in the ice bath.

(b) Chloroalcohol **7a** (see above) (191 mg, 1 mmol) was dissolved under argon in THF (5 mL) using a thoroughly dried 25 mL two-necked flask, equipped with a gas inlet, septum and magnetic stirring bar. The solution was cooled with an acetone/dry ice bath under argon. BuLi solution (0.63 mL, 1 mmol) was added dropwise by syringe with magnetic stirring. After 30 min stirring at −78°C, 15 mL of the LiDBB solution (3 mmol, see section (a)) was added dropwise by syringe. Stirring was continued for 15 min at −78°C. The reaction mixture was quenched by adding water (10 mL), and the layers separated. The aqueous layer was extracted with diethyl ether (3×10 mL), the combined organic solutions washed with brine (15 mL) and dried with sodium sulfate. After filtration and rotary evaporation of the solvent the remaining solid was purified by chromatography on silica (20 g), eluting with PE/EA (1:1). Yield 151 mg (97%) of a colourless solid (**6a**). A sample for analysis was recrystallised from diethyl ether and gave mp 94–95°C. ^{1}H NMR (500 MHz, CD_3CN) δ=0.94 (d, J=7.1 Hz, 3H), 1.47–1.53 (m, 1H), 1.64–1.71 (m, surmounted by a triplet at 1.69, J=1.6 Hz, 4H), 1.74–1.93 (m, 2H), 2.26–2.34 (m, 1H), 2.76 (d, J=3.9 Hz, 1H), 2.79 (d, J=5.0 Hz, 1H), 3.68 (m, 1H), 4.54 (d, J=3.9 Hz, 1H), 5.56 (m, 1H). ^{13}C NMR (126 MHz, CD_3CN) δ=12.6, 20.2, 21.2, 30.5, 43.8, 71.1, 72.5, 124.4, 141.2. IR (KBr): 3320, 3010. Anal. calcd for $C_9H_{16}O_2$ (156.2): C 69.20, H 10.32; found C 69.04, H 10.19.

5.4.2. (1α,3β)-2,2,4-Trimethylcyclohept-4-en-1,3-diol (8c). Following the general procedure 205 mg of **7c** were made to react. After chromatography, 102 mg (60%) of **8c** with mp 89–90°C were obtained. ^{1}H NMR (500 MHz, CD_3CN): δ=0.83 (s, 3H, 2-CH_3), 1.01 (s, 3H, 2-CH_3), 1.47–1.54 (m, 1H, 7-H), 1.62–1.68 (m, 1H, 7-H), 1.71 (d, J=0.7 Hz, 3H, 4-CH_3), 1.96–2.13 (m, 2H, 6-H), 2.53 (d, J=5.3 Hz, 1H, 1-OH), 2.66 (d, J=4.6 Hz, 1H, 3-OH), 3.68 (ddd, J=9.1, 5.3, 3.5 Hz, 1H, 1-H), 3.92 (d, J=4.6 Hz, 1H, 3-H), 5.58 (m, 1H, 5-H). ^{13}C NMR/DEPT (126 MHz, CD_3CN): δ=20.2 (2-CH_3), 22.6 (CH_2, C-7), 24.9 (4-CH_3), 32.6 (CH_2, C-6), 41.2 (C-2), 76.5, 79.0 (CH, C-1, C-3), 126.0 (CH, C-5), 142.4 (C-4). IR (KBr): 3400 (OH), 3000 (=C–H). Anal. calcd for $C_{10}H_{18}O_2$ (170.25): C 70.55, H 10.66; found C 70.56, H 10.67.

5.5. General procedure for reductive cleavage by sodium naphthalenide

(a) Sodium naphthalenide solution in THF (c=0.5 mol/L). A 100 mL two-necked flask, equipped with a gas inlet and septum was thoroughly dried (heat gun) and charged with naphthalene (641 mg, 5 mmol). Under a nitrogen atmosphere, THF (10 mL) was added. With magnetic stirring small pieces of clean sodium (140 mg, 6 mmol) were added, maintaining a nitrogen stream. Stirring was continued for 3 h at room temperature.

(b) Chloroalcohol **7** (see above) (1 mmol) was dissolved under nitrogen in THF (5 mL) using a thoroughly dried 25 mL two-necked flask, equipped with a gas inlet, septum and magnetic stirring bar. BuLi solution (0.63 mL, 1 mmol) was added dropwise by syringe with magnetic stirring at −40°C. After 30 min stirring at −40→35°C, 6 mL of the sodium naphthalenide solution (3 mmol, see section (a)) was added dropwise by syringe. Stirring was continued for 30 min at −35→−30°C. The reaction mixture was quenched by adding water (10 mL), and the layers separated (at room temperature). The aqueous layer was extracted with diethyl ether, and the combined organic solutions dried with sodium sulfate.

5.5.1. (1α,2β,3β)-2,4-Dimethylcyclohept-4-en-1,3-diol (8a). Treatment of chloroalcohol **7a** (191 mg, 1 mmol) following the general procedure gave a solid that was purified by chromatography on silica (20 g), eluting with PE/EA (1:1). Yield 95 mg (61%). For physical properties see above. A preparation from **7e** is described in Ref. 14.

5.5.2. *trans*-2,2-Dimethylcyclohept-4-en-1,3-diol (8b). (a) Treatment of **7b** (191 mg, 1 mmol) with BuLi solution (0.63 mL, 1 mmol) and sodium naphthalenide solution (6 mL of a 0.5 M solution in THF, 3 mmol) following the general procedure, afforded a colourless solid that was purified by chromatography on silica (20 g), eluting with PE/EA (1:1). One obtained 127 mg of **8b** (81%), a colourless solid with mp 107°C.

(b) Treatment of **7f** (235 mg, 1 mmol) in 5 mL of THF with BuLi solution (0.63 mL, 1 mmol) and sodium naphthalenide solution (6 mL of 0.5 M solution, 3 mmol) according to the general procedure, but at −78°C (dry ice/acetone bath), gave after chromatography 120 mg (77%) of **8b**. ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.99 (s, 3H, 2-CH_3), 1.05 (s, 3H, 2-CH_3), 1.60–2.08 (m, 6H, 6-H, 7-H, 1-OH and 3-OH), 3.75 (dd, J=6.9, 2 Hz, 1H, 1-H), 4.44 (d, J=4.5 Hz, 1H, 3-H), 5.57–5.65 (m, 1H, 5-H), 5.75–5.88 (m, 1H, 4-H). ^{13}C NMR/DEPT (63 MHz, DMSO-D_6): δ=20.5 (2-CH_3), 20.7 (CH_2, C-7), 24.1 (2-CH_3), 29.5 (CH_2, C-6), 40.6 (C-2), 70.7 (CH, C-1), 75.6 (CH, C-3), 127.4 (CH, C-5), 138.5 (CH, C-4). IR (KBr): 3370 (OH), 3000 (=C–H),

1645 (C=C). Anal. calcd for $C_9H_{16}O_2$ (156.2): C 69.20, H 10.32; found C 69.05, H 10.47.

5.5.3. *trans*-2,2,5-Trimethylcyclohept-4-en-1,3-diol (8d). (a) Treatment of **7d** (205 mg, 1 mmol) following the general procedure gave after chromatography on silica (20 g), eluting with PE/EA (1:1), 158 mg (93%) of **8d**, a colourless solid with mp 109–110°C.

(b) Treatment of **7g***n* (249 mg, 1 mmol) in THF (5 mL) with BuLi solution (0.63 mL,1 mmol) following the general procedure, but at −78°C (dry ice/acetone bath) gave after chromatography with PE/EA (1:1) 148 mg of **8d** (87%). ^{1}H NMR (250 MHz, CD_3CN): δ=0.85 (s, 3H, 2-CH_3), 0.91 (s, 3H, 2-CH_3), 1.48–1.85 (m, surmounted by a finely split s at 1.71, 6H, 5-CH_3, 6-H, 7-H), 2.30–2.44 (m, 1H, 6-H), 2.60 (d, J=5.1 Hz, 1H, 1-OH or 3-OH), 2.67 (d, J=4.7 Hz, 1H, 1-OH or 3-OH), 3.55 (m, 1H, 1-H), 4.22 (m appearing as a t, line distance 4.8 Hz, 1H, 3-H), 5.25 (m, 1H, 4-H). ^{13}C NMR/DEPT (63 MHz, CD_3CN): δ=21.6 (2-CH_3), 23.6 (2-CH_3), 25.8 (5-CH_3), 27.6, 30.2 (CH_2, C-6 and C-7), 41.9 (C-2), 72.9 (CH, C-1), 77.7 (CH, C-3), 131.3 (CH, C-4), 138.3 (C-5). IR (KBr): 3360 (OH). Anal. calcd for $C_{10}H_{18}O_2$ (170.25): C 70.55, H 10.66; found C 70.62, H 10.56.

5.6. General procedure for reductive cleavage by zinc/copper-couple

To a stirred solution of bromohydrin **7** or **6**, respectively, (4–5 mmol) in methanol/water (9:1, v/v, 20–30 mL) freshly prepared zinc/copper-couple (4–5 g)[26] was added in small portions, and the progress of the reaction monitored by TLC. When educt **7** had disappeared (3 h), the mixture was filtered by suction with a sintered glass frit. The inorganic residue was thoroughly washed with methanol. The combined filtrate and washings were concentrated in a rotary evaporator at 50°C/300 mbar by half and mixed with aqueous EDTA solution (1.86 g ethylenediaminetetraacetic acid disodium salt dihydrate in 30 mL of water). A colourless precipitate, appearing after a few minutes, was dissolved by adding 15% aqueous NaOH (2–4 mL). The mixture was extracted with dichloromethane (5×20 mL). The combined dichloromethane phases were dried with sodium sulfate, filtrated and concentrated in a rotary evaporator at 50°C/300 mbar to a few mL. Remaining volatile components were condensed in a trap cooled by liquid nitrogen, using oil-pump vacuum. The residue was NMR pure in many cases; otherwise it was purified by chromatography. Preparative details and spectra for compounds **8**–**12** are described in Ref. 14.

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