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TRANSFORMATION OF HYDROXYCYCLOALKANONES TO OXABICYCLOALKENES

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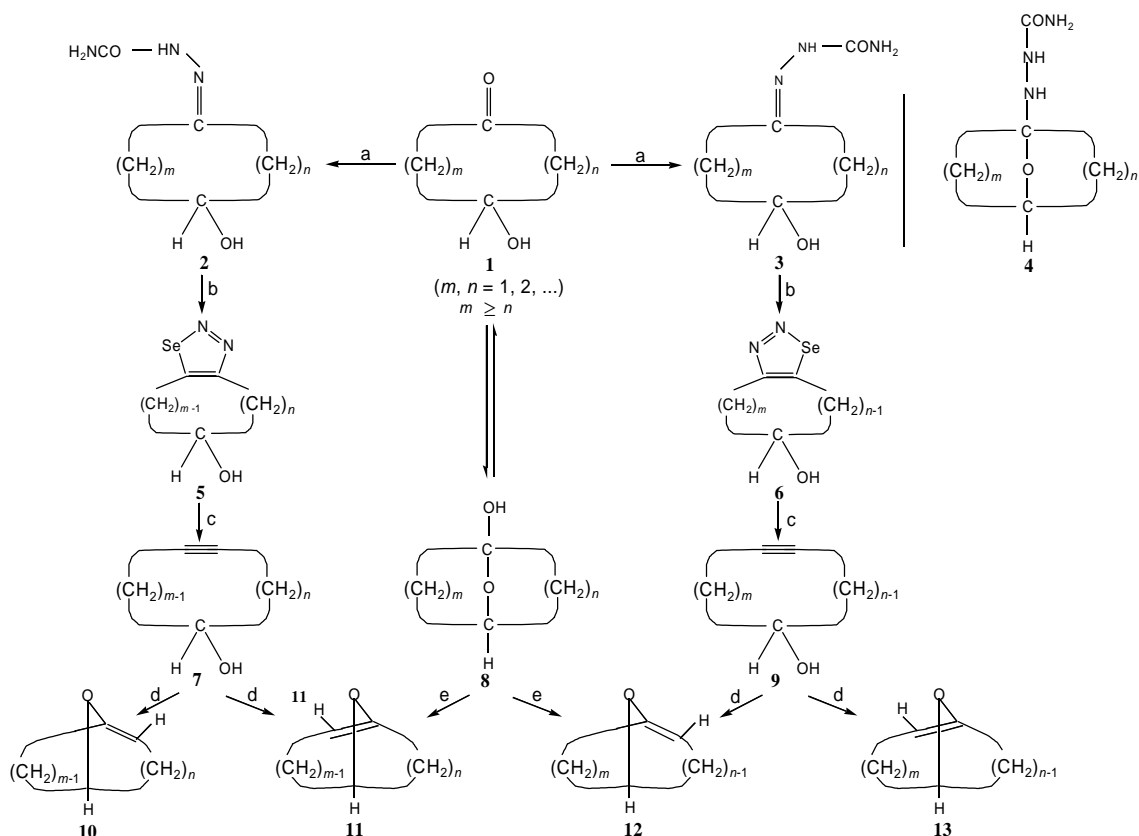
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Abstract – Oxabicycloalkenes, which represent *anti*-Bredt enol ethers, can be generated by catalytic dehydration of the hemiacetals of hydroxycycloalkanones (Method I). Another option is provided by the transformation of hydroxycycloalkanones to the corresponding 1,2,3-selenadiazoles and their thermal fragmentation on Cu powder (Method II). The intermediate hydroxycycloalkynes show a transannular addition of the OH group to the triple bond. Altogether seven new oxabicycloalk-1-enes were obtained by this methods.

In recent years an increasing number of natural products and closely related synthetic analogues, which have the structures of oxabicycloalk-1-enes with an *anti*-Bredt enol ether functionality, have been studied.¹ The majority of them has the scaffold of 10-oxabicyclo [4.3.1]dec-1(9)-enes^{1a,e,f,i,j,k,p} or 11-oxabicyclo[6.2.1]undec-1(10)-enes.^{1c,d,l,m,n,r,t,u,v,w} Another interesting realization of such enol ether structures was achieved in the series of fullerenes.² The preparation of these compounds requires multi-step syntheses in which the formation of a strained enol ether double bond is a special challenge. Bridgehead olefins with this substructure can have pyramidalized and/or twisted double bonds.

Hydroxycycloalkanones **1** provide an easy access to *anti*-Bredt enol ethers. Scheme 1 summarizes the possible reaction routes. The cyclic hemiacetals **8**, tautomers of **1**, can be catalytically dehydrated to **11** and/or **12** (route I). Alternatively, **1** can be transformed to the stereoisomeric semicarbazones **2/3**, for which cyclic tautomers **4** exist as well. The subsequent ring closure reaction with SeO₂ yields the 1,2,3-selenadiazoles **5/6**. The regioselectivity of the ring closure does not depend on the preferred isomer **2**, **3** or **4**. Thermal cleavage of **5/6** on copper powder gives the hydroxycycloalkynes **7/9**, which perform transannular addition reactions: **7** → **10**, **11** and **9** → **12**, **13** (route II). Symmetric ketones **1** (*m* = *n*) yield only one enol ether **11**≡**12** and only one semicarbazone **2**≡**3**, selenadiazole **5**≡**6** and hydroxycycloalkyne

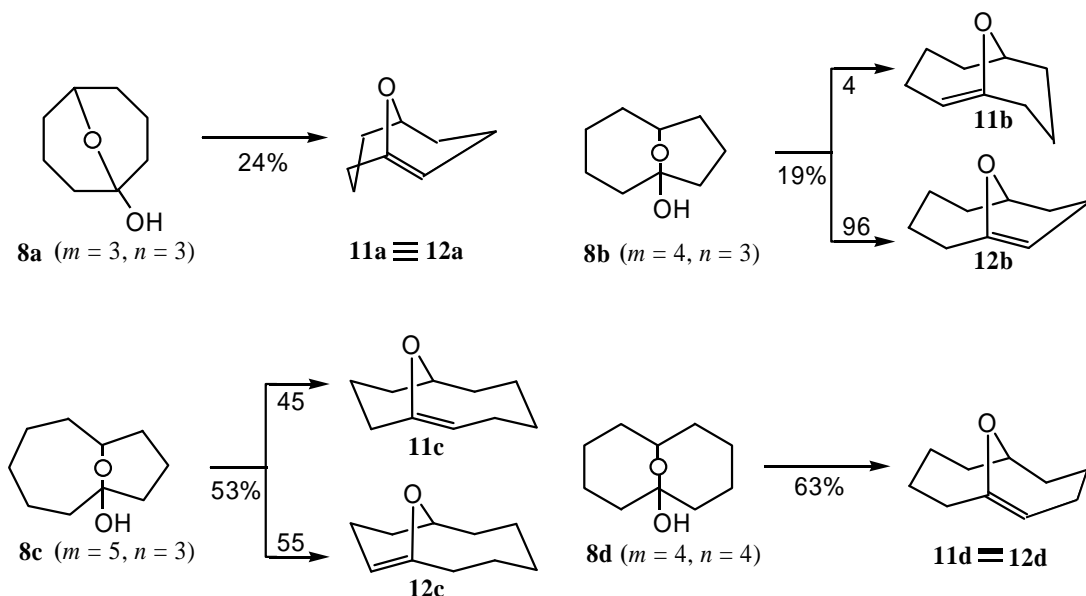
7⇌**9**, but then two transannular addition products **10**⇌**13** and **11**⇌**12** can be formed. Two enol ethers can result in the case $n = m-1$ (**7** → **10**⇌**11**) and (**9** → **12**⇌**13**). In all other cases ($m-n > 1$), the ketones **1** can serve for the generation of four isomeric oxabicycloalkenes **10**–**13**. Of course, steric and/or electronic effects can influence the regioselectivity in all unsymmetrical cases, and can lead to uniform products.



Scheme 1. Generation of oxabicycloalkenes **10**–**13** from hydroxycycloalkanones **1** by route I: **1** ⇌ **8** → **11**, **12** or route II: **1** ⇌ **8** → **2/3** ⇌ **4** → **5/6** → **7/9** → **10**–**13**: (a) $\text{H}_2\text{N}-\text{NH}-\text{CONH}_2$, H^+ ; (b) SeO_2 ; (c) 160–180 °C; (d) 180–200 °C; (e) 90–120 °C, cat.

The β -elimination of H_2O can be performed by heating **1a-d** ⇌ **8a-d**⁴⁻⁹ in the presence of catalytic amounts of *p*-toluenesulfonic acid to 90–120 °C at 1 kPa (Scheme 2). In a typical procedure, 5–6 mmol of starting compound was treated with 10 mg (0.05 mmol) *p*-toluenesulfonic acid monohydrate. The generated water was removed under reduced pressure, so that the reverse reaction, the addition of water to the reactive double bond of the *anti*-Bredt enol ether, can not take place. The *anti*-Bredt enol ethers were then condensed in a cold trap. The residue contains bimolecular condensation products, derived from two molecules **1** or from **1** and **8**.³ These competing reactions decrease the yields - in particular for the smaller and therefore more strained enol ethers. Due to symmetry reasons, the reactions of **8a** and **8d** are leading to single enol ethers, whereas **8b** and **8c** generate the mixtures **11b/12b** and **11c/12c**, respectively.

However, the dehydration of **8b** is highly regioselective in favor of **8b** → **12b**. Such a strong selectivity can not be found in the case **8c** → **11c**, **12c**.

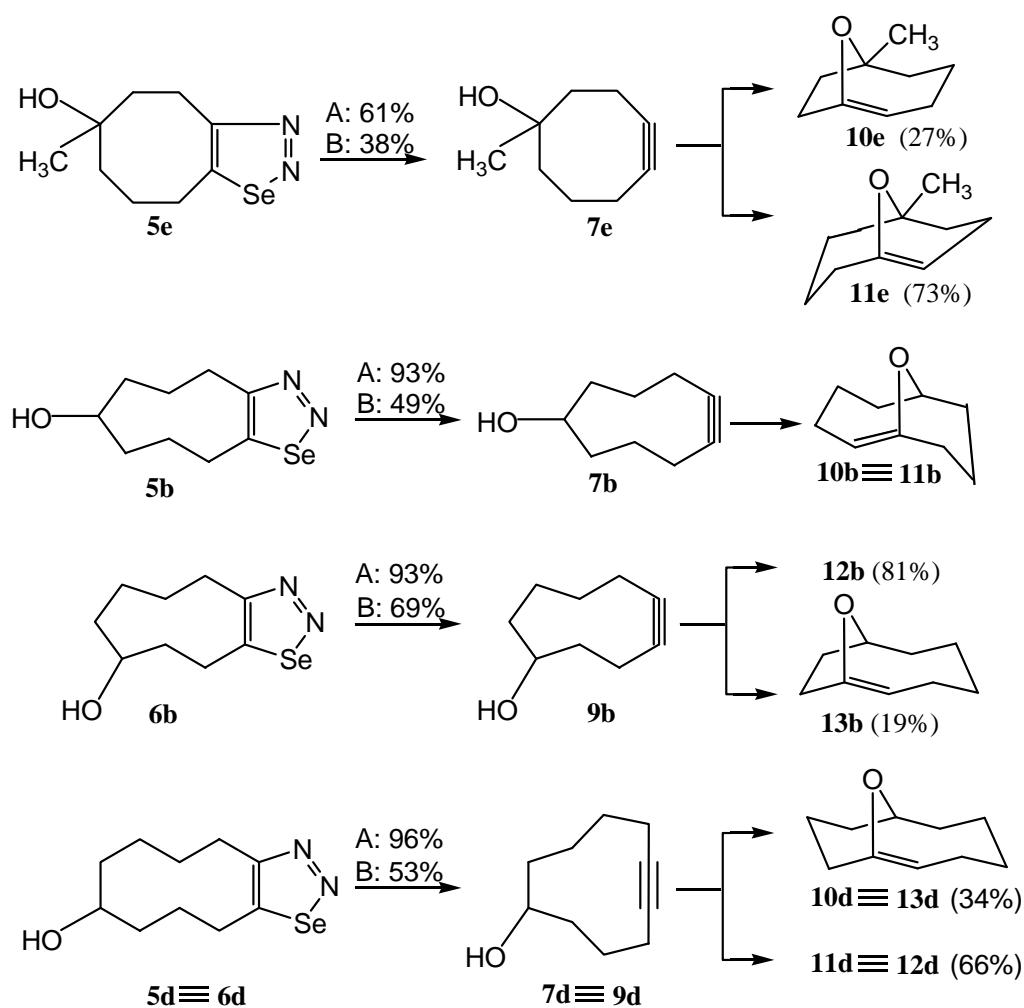


Scheme 2. Monomolecular elimination (method I) of H₂O from the hemiacetals **8**, which are in equilibrium with the corresponding hydroxycycloalkanones **1**: **8a** ⇌ **1a**⁴, **8b** ⇌ **1b**⁵, **8c** ⇌ **1c**^{6,7}, **8d** ⇌ **1d**⁸ (Method A: 90-120 °C, 1-3 kPa, 0.01 equivalent of *p*-toluene-sulfonic acid)

Method II in Scheme 1 makes use of the transannular addition of hydroxy groups to triple bonds in cycloalkynes.¹⁰ Scheme 3 summarizes the generation of **10b**, **10d**, **10e**, **11d**, **11e**, **12b** and **13b**. The corresponding hydroxycycloalkanones **1** are transformed via the (*Z/E*)-semicarbazones **2/3** and their bicyclic isomers **4** to the 1,2,3-selenediazoles **5** and/or **6**. Thermal cleavage of **5** and/or **6** on Cu powder yields at 160-180 °C the hydroxycycloalkynes **7** and/or **9**. At 180-200 °C, the resulting *anti*-Bredt enol ethers are formed *in situ* by the quantitative isomerization **7/9** → **10-13**. It is not necessary to isolate the hydroxycycloalkynes. The copper powder enhances the yields of the alkynes. It has no influence on the transannular cyclization.

1,2,3-Selenediazole **5e**¹¹ was obtained in a yield of 90% by reaction of the corresponding oxo-compound¹² and H₃CMgCl. 5-Hydroxycyclononanone **1b** yielded via its semicarbazone **2b/3b/4b** 44% of a 80:20 mixture of the 1,2,3-selenediazoles **5b** and **6b**.¹³ Accordingly, 6-hydroxycyclodecanone **1d** furnishes 47% of 1,2,3-selenediazole **5d**.¹⁴

The hydroxycycloalkynes (**7b,d,e**; **9b**) and the oxabicycloalkenes (**10b,d,e**; **11a,c,d,e**; **12b,c**; **13b**) are colorless oils. To our best knowledge, **7b**, **7e**, **9b**, and **10b**, **10e**, **11c**, **11e**, **12b**, **12c** and **13b** are new compounds. The separation of enol ether mixtures by GC or HPLC seems to be feasible. We succeeded in the separation of **11c** and **12c** by column chromatography on SiO₂. However, a contact of pure **11c** or **12c** with SiO₂ in CDCl₃ over several days led again to a catalytic equilibration (**11c** : **12c** = 45 : 55).



Scheme 3. Thermal fragmentation of the 1,2,3-selenediazoles on Cu powder. Method A (160-180 °C, 10⁻²-10⁻¹ kPa) leads to the hydroxycycloalkynes. Method B (180-200 °C, 10⁻²-10⁻¹ kPa) leads directly to the oxabicycloalkenes

Table 1 summarizes the characteristic NMR data of the hydroxycycloalkynes and the oxabicycloalkenes. The $\delta(^{13}\text{C})$ values of the olefinic double bonds in the *anti*-Bredt compounds show a significant variation. High δ values for both olefinic carbon atoms were found for the systems **11a** and **11e**,

which have the highest strain. The double bond has therein *trans* configuration related to the 8-membered ring and *cis* configuration related to the 6-membered ring. The column RS in Table 1 contains the size of the rings in which the double bonds have *trans* configuration. Compared to normal enol ethers, such as (*Z*)-2-methoxy-2-butene¹⁵, β -C has in **11a,e** a δ value of 120.0 ± 0.3 ppm, which is about 17 ppm down-field shifted. We attribute this effect to a low interaction of the p(O) orbital with the olefinic π bond, that means to a low electron density on β -C. A complete correlation of the ¹H and ¹³C chemical shifts is given for **12b** in Figure 1.

Table 1. Characteristic ¹H and ¹³C NMR data of the hydroxycycloalkynes **7, 9** and the oxabicycloalkenes **10-13** (δ values in CDCl₃, TMS as internal standard)

Compd.	RS	C≡C	CHO	Compd.	RS	=CH	=CO	CHO
11a	8	5.70	4.65					
	120.3	159.0 79.5						
7e	8		–	10e	8	4.84		–
	95.5, 96.3	73.4			111.8	157.0 74.9		
11e	8	5.65	–					
	119.8	160.6 84.9						
7b	9		4.11	10b	9	4.98		4.07
	88.8, 88.8	74.7			111.3	154.0 76.1		
9b	9		3.94	12b	9	5.17		4.14
	87.6, 88.0	71.8			109.7	155.3 72.6		
13b	9	4.48	4.10					
	109.3	154.9 75.6						
11c	10	5.02	4.12					
	111.9	151.9 80.4						
12c	10	4.72	4.02					
	102.2	151.7 72.7						
7d	10		4.25	10d	10	5.02		4.12
	84.4, 84.9	69.6			111.9	151.9 80.4		
11d	10	5.10	4.00					
	113.2	156.3 74.5						

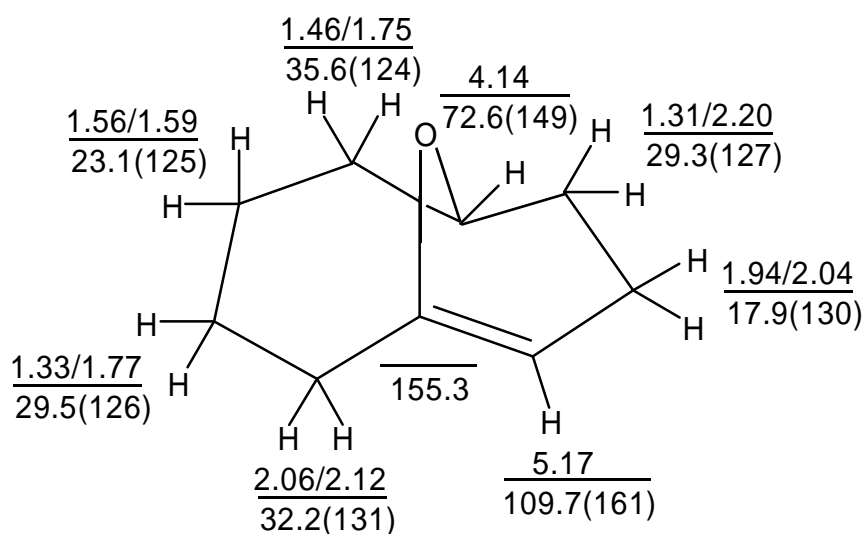


Figure 1. ^1H and ^{13}C NMR data of 10-oxabicyclo[4.3.1]dec-1(9)ene (**12b**); $\delta(^1\text{H})/\delta(^{13}\text{C})$ values in CDCl_3 , TMS as internal standard. The numbers in parentheses indicate the $^1J(\text{C,H})$ coupling constants in Hz. The assignment of the signals is based on homo- and heteronuclear shift correlations and on NOE measurements

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 11. **5e**: Viscous oil; ¹H NMR (CDCl₃): δ = 3.55-3.00, m, 4H/2.20-1.85, m, 3H/1.85-1.28, m, 5H (CH₂), 1.27 (s, 3H, CH₃). ¹³C NMR (CDCl₃): δ = 160.6, 157.0 (heteroaromat. C), 73.0 (C_qO), 40.9, 35.4, 25.3, 24.3, 23.9 (CH₂), 31.6 (CH₃). ⁷⁷Se NMR (CDCl₃): δ = 219.7. MS (FD): *m/z* (%) = 247 [M + H⁺, Se isotope pattern].
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 13. **5b**: Viscous oil; ¹H NMR (CDCl₃): δ = 3.69 (m, 1H, CH), 3.22 (m, 2H, CH₂), 3.05 (m, 2H, CH₂), 2.26 (br. s, 1H, OH), 2.00-1.30 (m, 8H, 4CH₂). ¹³C NMR (CDCl₃): δ = 161.2, 160.2 (heteroaromat. C), 70.7 (CHO), 33.7, 32.1, 27.8, 26.4, 24.4, 22.5 (CH₂). MS (EI): *m/z* (%) = 246 (2, M⁺, Se pattern), 137

- (44), 116 (100); **6b**: viscous oil; ^1H NMR (CDCl_3): $\delta = 3.74$ (m, 1H, CH), 3.17 (m, 2H, CH_2), 3.05 (m, 2H, CH_2), 2.48 (br. s, 1H, OH), 2.00-1.20 (m, 8H, 4 CH_2). ^{13}C NMR (CDCl_3): 161.2, 159.4 (heteroaromat. C), 70.4 (CHO), 37.1, 32.5, 27.0, 25.4, 21.2, 20.6 (CH_2).
14. **5d**: mp 101-103 °C. ^1H NMR (CDCl_3): $\delta = 3.91$ (m, 1H, CH), 3.20 (m, 3H), 3.05 (m, 1H), 1.95 (m, 1H), 1.89 (m, 2H), 1.63 (m, 2H), 1.48 (m, 2H), 1.38 (m, 1H), 1.33 (m, 1H), 1.15 (m, 1H), 1.02 (m, 1H) [7 CH_2]. ^{13}C NMR (CDCl_3): $\delta = 160.1$, 159.5 (heteroaromat. C), 69.8 (CHO), 33.7, 28.3, 27.2, 27.0, 26.1, 24.9, 19.5 (CH_2). ^{77}Se NMR (CDCl_3): $\delta = 204.7$ (SeO_2 in H_2O : $\delta = 0$). ^{15}N NMR (CDCl_3): $\delta = 88.8$, 80.5 (CH_3NO_2 : $\delta = 0$). MS (EI): m/z (%) = 261 (1) [$\text{M} + \text{H}^+$, Se isotope pattern], 151 (19), 133 (33), 91 (82), 81 (64), 67 (100).
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