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Unfolding the frontalin chemistry: a facile selective hydrogenation of 7-methylidene-6,8-dioxabicyclo[3.2.1]octanes, 2:2 ensembles of ketones and acetylene

Elena Yu. Schmidt,[a,b] Ivan A. Bidusenko,[a] Igor A. Ushakov[a] and Boris A. Trofimov*[a]

[a] *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 664033 Irkutsk, Russian Federation. Fax: +7 3952 419 346; e-mail: boris_trofimov@irioch.irk.ru*
[b] *Angarsk State Technical University, 665835 Angarsk, Russian Federation*

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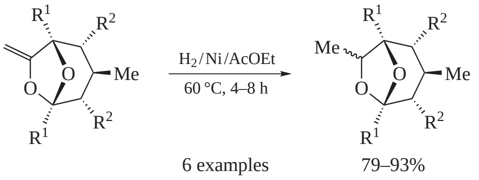
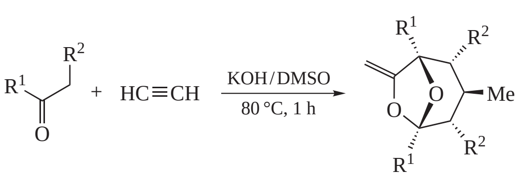
Nickel-catalyzed low pressure hydrogenation of 1,5-diaryl-7-methylidene-6,8-dioxabicyclo[3.2.1]octanes proceeds chemospecifically at the double bond and brings about mostly 1*R,3*R**,5*S**,7*R** diastereomers.**



The 6,8-dioxabicyclo[3.2.1]octanes are frequently encountered in the living nature as structural moieties of insect pheromones of frontalin family,[1] mammal hormones[2] and marine toxins.[3] They are often used as building blocks in fine organic synthesis for the preparation of δ,ε-unsaturated ketones,[4] cyclopentane-1,2-diols,[5] substituted pyridines,[6] and dihydropyrans.[7] Consequently, a great deal of efforts is now being spent to develop rational approaches to construct these scaffolds.[8] However, most of the proposed strategies are either multistep or require difficult-to-access starting materials.[8]

Recently, we have discovered a one-pot diastereoselective synthesis of 7-methylidene-6,8-dioxabicyclo[3.2.1]octanes **1** *via* superbase-catalyzed 2:2 self-organization of ketones and acetylene, inexpensive and widespread starting materials (Scheme 1).[9] A cardinal highlight of this method is the introduction of the enol double bond into 6,8-dioxabicyclo[3.2.1]octane scaffold. The systematic investigations of synthetic potential of these molecules have given a new impetus to extension of the frontalin chemistry that, in particular, led to extraordinary short routes to substituted 3,4-dihydropyrans,[7,10] acylated cyclopentadienes,[11] and 1,6-dioximes.[12]



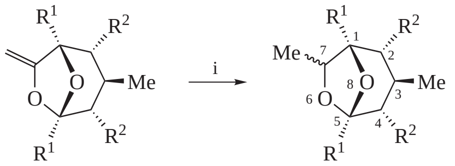
1, up to 86%

Scheme 1

Here we report a facile selective hydrogenation of the exocyclic double bond in compounds **1** with the complete avoiding of possible hydrogenolysis of the acetal moiety (*cf.* refs. 13, 14).

After a series of experiments we have found that the selective hydrogenation (without the acetal C–O bond cleavage) of the double bond of bicyclooctanes **1a**–**f** is implemented under the following conditions: Raney nickel (5 mol%), bubbling of hydrogen gas at 1 atm, ethyl acetate, 60 °C (Scheme 2). The isolated yields of products **2a**–**f** reached 65–93%.[†]

The outcome of the reaction does not directly depend on the steric and electronic effects of the substituents in the bicyclooctane framework. Bicyclooctanes **1e**,**f** with additional Me groups at the 2- and 4-positions provide 85 and 79% yields of the



1a–**f** **2a**–**f**

	R^1	R^2	t/h	Yield of **2** (%)	*dr*
a	Ph	H	4	84	2:1
b	4-PhC_6H_4	H	4	93	2:1
c	3-$MeOC_6H_4$	H	8	65	2:1
d	2-naphthyl	H	4	87	3:1
e	Ph	Me	6	85	1:0
f	4-MeC_6H_4	Me	4	79	1:0

Scheme 2 *Reagents and conditions*: H_2 (1 bar), Ni (Raney), EtOAc, 60 °C, 4–8 h.

[†] The IR spectra were recorded on a Bruker IFS25 spectrophotometer. NMR spectra were recorded on Bruker DPX-400 and AV-400 spectrometers (400.1 MHz for ^{1}H and 100.6 MHz for ^{13}C) in $CDCl_3$ using HMDSO as internal standard. 7-Methylene-6,8-dioxabicyclo[3.2.1]octanes **1a**–**f** were synthesized by published procedures from ketones and acetylene.[9]

Hydrogenation of 7-methylidene-6,8-dioxabicyclo[3.2.1]octanes **1a**–**f** *(typical procedure)*. Raney nickel (5 mol%) in ethyl acetate (1 ml) was added to a solution of bicyclooctane **1** (2 mmol) in ethyl acetate (20 ml). Bubbling hydrogen was passed (~1.5 ml min^{-1}) through this mixture heated to 60 °C until the consumption of starting bicyclooctane **1** (monitored by TLC). The catalyst was filtered off, and ethyl acetate was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, ethyl acetate) to give a mixture of the diastereomers. Separation of the diastereomers, if required, was implemented by column chromatography (silica gel, hexane–ethyl acetate, 9:1).

corresponding hydrogenated derivatives **2e**,**f** which are formed exclusively as single diastereomers. At the same time, bicyclooctanes **1a–d** are hydrogenated with formation of a mixture of two diastereomers in ~2 : 1 ratio, predominantly as $1R^*,3R^*,5S^*,7R^*$ ones. We succeded in separating them by column chromatography (SiO$_2$, hexane–diethyl ether, 9 : 1).

The observed stereoselectivity breach is obviously due to the steric effects though more exact understanding of this result is difficult because of heterogeneous nature of the catalysis. Since the stereoselective reaction proceeds for sterically encumbered substrates **1e**,**f**, it can be assumed that they interact with catalytically active centers more specifically.

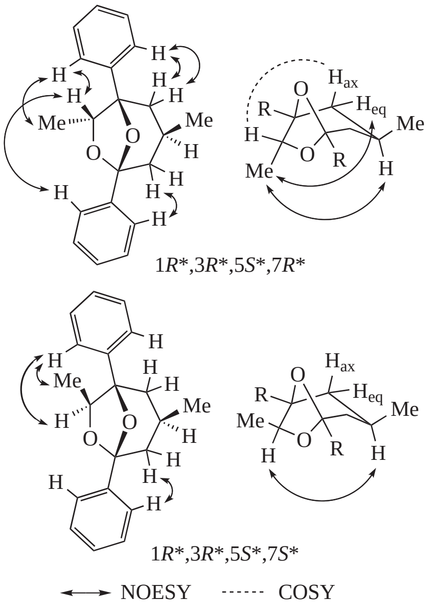


Figure 1 H–H interactions in 2D NMR spectra of compound **2a**.

The structure of compounds **2a–f** was established by ^{1}H and ^{13}C NMR spectroscopy (for details, see Online Supplementary Materials). Assignment of the diastereomers was made using 2D COSY and NOESY spectra (Figure 1).

In conclusion, a simple, highly effective low pressure procedure for the selective hydrogenation of 1,5-diaryl-7-methylidene-6,8-dioxabicyclo[3.2.1]octanes under mild conditions using Raney nickel as a catalyst has been developed. In view of the one-pot synthesis of the starting compounds from ketones and acetylene, this reaction represents substantial contribution to the frontalin-tailored chemistry. A new family of 6,8-dioxabicyclo[3.2.1]-octanes thus synthesized can be employed for the preparation of 1,6-dioximes,[12] di-[7] and tetrahydropyrans,[15] analogues of polysaccharides[16] as well as in total synthesis of natural products.[17]

In overall, this is another evidence that transition metal-free self-organization of ketones and acetylene represents a robust platform for unfolding novel branches of nature-related synthesis.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.09.021.

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($1R^*,3R^*,5S^*$)-3,7-Dimethyl-1,5-diphenyl-6,8-dioxabicyclo[3.2.1]-octane **2a** (a mixture of two diastereomers in a 2 : 1 molar ratio): yield 495 mg (84%), colorless oil. Found (%): C, 81.46; H, 7.40. Calc. for C$_{20}$H$_{22}$O$_2$ (%): C, 81.60; H, 7.53.

($1R^*,3R^*,5S^*,7R^*$)-3,7-Dimethyl-1,5-diphenyl-6,8-dioxabicyclo-[3.2.1]octane (major isomer): yield 288 mg (49%), colorless oil. IR (film, ν/cm^{-1}): 3062, 3030, 2953, 2926, 2869, 1605, 1495, 1449, 1378, 1369, 1349, 1320, 1263, 1240, 1162, 1144, 1132, 1118, 1093, 1081, 1068, 1016, 995, 978, 949, 938, 896, 849, 818, 761, 747, 698, 671, 662, 650, 579, 553. ^{1}H NMR, δ: 7.67–7.63 (m, 2H), 7.52–7.47 (m, 2H), 7.41–7.24 (m, 6H) [Ph], 3.99 (qd, 1H, H-7, ^{3}J 6.6 Hz, ^{4}J 1.3 Hz), 2.58–2.47 (m, 1H, H-3), 2.42 (dd, 1H, H-2$_{eq}$, ^{2}J 13.8 Hz, ^{3}J 5.7 Hz), 2.18 (dd, 1H, H-4$_{eq}$, ^{2}J 13.3 Hz, ^{3}J 5.8 Hz), 1.57 (dd, 1H, H-4$_{ax}$, ^{2}J 13.3 Hz, ^{3}J 10.8 Hz), 1.50 (dd, 1H, H-2$_{ax}$, ^{2}J 13.8 Hz, ^{3}J 12.0 Hz), 1.42 (d, 3H, C^{7}Me, ^{3}J 6.6 Hz), 1.03 (d, 3H, C^{3}Me, ^{3}J 6.6 Hz). ^{13}C NMR, δ: 142.1, 141.2, 128.5, 128.3, 128.4, 127.7, 125.4, 124.8 (12C) [Ph], 107.1 (C^{5}), 85.1 (C^{1}), 82.2 (C^{7}), 43.6 (C^{4}), 38.0 (C^{2}), 25.3 (C^{3}), 22.1 (C^{3}*Me*), 13.3 (C^{7}*Me*).

($1R^*,3R^*,5S^*,7S^*$)-3,7-Dimethyl-1,5-diphenyl-6,8-dioxabicyclo-[3.2.1]octane (minor isomer): yield: 165 mg (28%), colorless oil. IR (film, ν/cm^{-1}): 3061, 3030, 2953, 2928, 2869, 1605, 1494, 1449, 1377, 1366, 1345, 1329, 1308, 1241, 1180, 1142, 1127, 1100, 1070, 1063, 1040, 1011, 996, 983, 948, 937, 908, 900, 850, 760, 752, 699, 672, 664, 625, 552, 522. ^{1}H NMR, δ: 7.67–7.63 (m, 2H), 7.38–7.34 (m, 2H), 7.41–7.30 (m, 5H), 7.25–7.22 (m, 1H) [Ph], 4.54 (q, 1H, H-7, ^{3}J 6.3 Hz), 2.49–2.37 (m, 1H, H-3), 2.23 (dd, 1H, H-2$_{eq}$, ^{2}J 13.7 Hz, ^{3}J 5.2 Hz), 2.14 (dd, 1H, H-4$_{eq}$, ^{2}J 13.3 Hz, ^{3}J 5.4 Hz), 1.60 (dd, 1H, H-4$_{ax}$, ^{2}J 13.3 Hz, ^{3}J 11.3 Hz), 1.49 (dd, 1H, H-2$_{ax}$, ^{2}J 13.7 Hz, ^{3}J 12.5 Hz), 1.01 (d, 3H, C^{3}Me, ^{3}J 6.2 Hz), 0.75 (d, 3H, C^{7}Me, ^{3}J 6.2 Hz). ^{13}C NMR, δ: 142.0, 141.7, 128.3, 128.2, 127.1, 125.5, 125.1 (12C) [Ph], 107.5 (C^{5}), 86.0 (C^{1}), 79.3 (C^{7}), 44.7 (C^{2}), 43.9 (C^{4}), 25.3 (C^{3}), 21.6 (C^{3}*Me*), 20.5 (C^{7}*Me*).

For characteristics of compounds **2b–f**, see Online Supplementary Materials.