Expedient nonclassical reaction of acetylenes with ketones: controlling the switch between bicyclic ketal and cyclopentenol formation

Elena Yu. Schmidt, Ivan A. Bidusenko, Natalia A. Cherimichkina, and Boris A. Trofimov*

Laboratory of Unsaturated Heteroatomic Compounds,
A.E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences
1 Favorsky Str., 664033 Irkutsk, Russia
E-mail: boris_trofimov@irioch.irk.ru

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Abstract

The condition-controlled switch between the bicyclic ketals, 7-methylene-6,8-dioxabicyclo[3.2.1]octanes and 3-acyl-2-cyclopenten-1-ols formation during the 2:2 self-assembly of acetylenes with ketones in the presence of the KOH/DMSO suspension at 30-70 ^{o}C has been developed. The selectivity reaches ca. 100% for bicyclic ketals and 67% for cyclopentenols. Both reactions are diastereoselective.

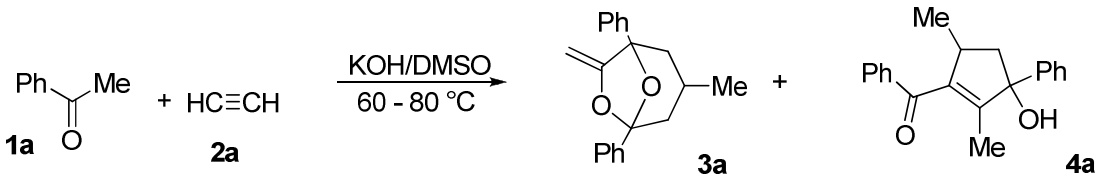
Keywords: Acetylenes, ketones, 6,8-dioxabicyclo[3.2.1]octanes, cyclopentenols, C-C bond formation

Introduction

The development of new reactions leading to the formation of C-C and C-O bonds, constructing biologically and pharmaceutically important structures via a single-reactor methodology, represents a long-standing challenge of fine organic synthesis. Acetylene and other alkynes, owing to their high and diverse reactivity, are frequently used to respond to this challenge. Now this trend[1-4] gains strength due to the depletion of fossil hydrocarbons. Consequently, new methods (including those based on coal)[1,5] for acetylene production arise. Over many years, fundamental organic synthesis has revealed a diversity of reactions of alkynes, which provide new C-C, C-N, and C-O bond formation, *e.g.* in important biomolecules as pyrroles,[6,7] pyridines,[2,8-10] vitamins A and E,[1,11] β-carotene,[11] linalool,[11] citral,[12] steroids,[13,14] etc. In this area of organic synthesis, the application of superbasic media such as alkaline metal hydroxide or alkoxide/DMSO[15] to promote the reactions of alkynes with nucleophiles is a comparatively underestimated approach. However, some impressive results have already been reported

including one-pot alkyne-based syntheses of azulenones,[16] pyrroles,[15,17] 7-methylene-6,8-dioxabicyclo[3.2.1]octanes,[18,19] Δ^2-isoxazolines,[20] and 4-methylene-3-oxa-1-azabicyclo[3.1.0]hexanes.[21] An intriguing feature of the superbasic medium KOH/DMSO is its tunability, *i.e.* the ability to change considerably the character of its catalytic activity.[15,22,23] This stems from the limited solubility of KOH in DMSO which forms a suspension consisting of microcrystals, nanoparticles, diverse associates and a true molecular solution. These are in temperature-, concentration- and solvent-dependent dynamic equilibrium, thus mimicking a kind of living system.[23]

We have recently shown that the one-pot assembly of 3-methyl-7-methylene-1,5-diphenyl-6,8-dioxabicyclo[3.2.1]octane (having the pheromone frontaline scaffold)[24-27] from acetophenone **1a** and acetylene **2a** promoted by a KOH/DMSO suspension (Scheme 1) is accompanied by the formation of a minor product (yield < 1%), 3-benzoyl-2,4-dimethyl-1-phenyl-2-cyclopenten-1-ol (**4a**), a structural isomer of the bicyclic ketal **3a**.



Scheme 1. The reaction of acetophenone **1a** with acetylene **2a** in the KOH/DMSO system.

Like the bicyclic ketal **3a**, the cyclopentenol **4a** is also built up from two molecules of ketone **1a** and two of the acetylene **2a**. A fascinating feature of this four-molecular self-organization is the regio- and stereoselectivity: both structural isomers **3a** and **4a** are formed exclusively as single diastereomers despite the presence of several asymmetric carbons. Later, we succeeded in turning this negligible side reaction into the major one.[28]

Since both 6,8-dioxabicyclo[3.2.1]octanes and cyclopentenols are closely related to valuable naturally occurring compounds[24-27] and known drugs,[29-34] the improvement of their accessibility deserves additional endeavor. Herein we summarize the results of our systematic study to elaborate a practical and scalable synthesis of both 6,8-dioxabicyclo[3.2.1]octanes and cyclopentenols in one synthetic operation.

Results and Discussion

Table 1 contains selected data giving an insight into the effect of the conditions on the products yield and ratio for the reaction between acetophenone **1a** and acetylene **2a** in the KOH/DMSO suspension.

Table 1. The reaction of acetophenone **1a** with acetylene **2a** in the presence of the KOH/DMSO suspension (Scheme 1): tuning the yield and ratio of the products by changing the reaction conditions[a]

Entry	KOH:**1a** Molar ratio	Temp (°C)	Time (min)	Conversion of **1a** (%)	**3a**:**4a** Molar ratio [b]	**3a**+**4a** Total yield (%) [c]
1	1:1	70	15	100	99:1	94
2	1:1	50	15	100	89:11	84
3	1:1	40	15	78	77:23	63
4	1:1	30	15	46	50:50	41
5	1:2	70	15	100	91:9	90
6	1:4	70	15	100	91:9	92
7	1:8	70	15	100	83:17	93
8	1:15	70	15	88	38:62	87
9	1:15	70	60	93	38:62	75
10	1:15	70	180	94	37:63	82
11	1:15	70	240	96	36:64	85
12	1:15	70	480	100	38:62	98

[a] Reagents and conditions: initial pressure of acetylene **2a** at ambient temperature was 12-14 atm, acetophenone **1a** (17 mmol, 2.00 g), DMSO (50 mL). [b] Determined from ^{1}H NMR data of the reaction mixtures. [c] Isolated yields after column chromatography (basic Al_2O_3, hexane, $CHCl_3$).

As can be seen from Table 1, the tuning of the catalytic system by the decrease of KOH:ketone **1a** molar ratio from 1:1 to 1:15 leads to a drastic inversion of the products ratio, virtually to the switch from the preferable formation of bicyclic ketal **3a** to cyclopentenol **4a** (from 99:1 to 36-38:62-64, *cf.* entries 1 and 8-12). A similar change of the products ratio up to 50:50 occurs by affecting the catalytic activity of the KOH/DMSO system via the reaction temperature decrease from 70 to 30 °C (entries 1-4), although the conversion of acetophenone **1a** expectedly drops from 100 to 46%.

The switchable nature of the reaction is clearly demonstrated by the experiments in which the reaction mixture basicity is lowered by the addition of water. Even the addition of 1% of water to the reaction mixture (1:1 KOH:ketone **1a** molar ratio, 70 °C, 15 min) dramatically alters the **3a:4a** molar ratio (from 99:1 to 58:42). At higher water content in the reaction mixtures (5 and 10% of water), the **3a:4a** molar ratio is retained, while the conversion and the yield diminish (for 5% to 61 and 43%, for 10% to 59 and 34%).

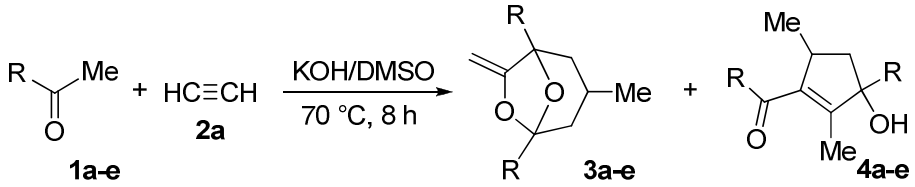
The reaction products **3a** and **4a** are easily and cleanly separated by column chromatography (basic Al_2O_3, first dioxabicyclooctane **3a** is washed off with *n*-hexane, and then cyclopentenol **4a** is washed with $CHCl_3$). A surprising feature of the cyclopentenol **4a** assembly is the unusually

small amount of basic species needed for its optimum formation, while to attain the highest yield of dioxabicyclooctane **3a**, a 15-fold higher concentration of base is crucial.

Until now the true scope of this double-faced reaction remained obscure. In accordance with the best conditions for the simultaneous synthesis of compounds **3a** and **4a** (Table 1), the relation between the substrate structure and the products yield and ratio was studied and the reactions were carried out with a 1:15 KOH:ketone **1** molar ratio.

Table 2 shows that the assembly of bicyclic ketals **3** and cyclopentenols **4** from ketones and acetylene tolerates both acetylarenes **1a-c** and acetylhetarenes **1d**,**e**. For all the ketones, the total yields (**3**+**4**) range 72-98%. Under these conditions, the conversion of the starting ketones **1** is close to 100%. An unexpected result is that in the case of 4-acetylpyridine **1d**, the assembly proceeds with complete loss of the pyridyl carbonyl function to deliver cyclopentenol **4d′**.

Table 2. Substrate scope and the products yield and ratio for the reaction of ketones **1a-e** with acetylene **2a** in the presence of the KOH/DMSO system [a]



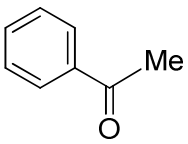
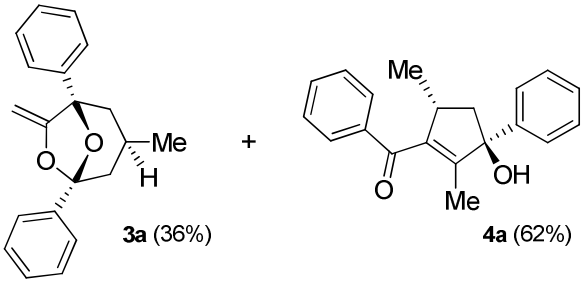
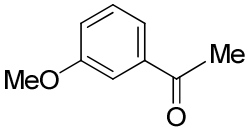
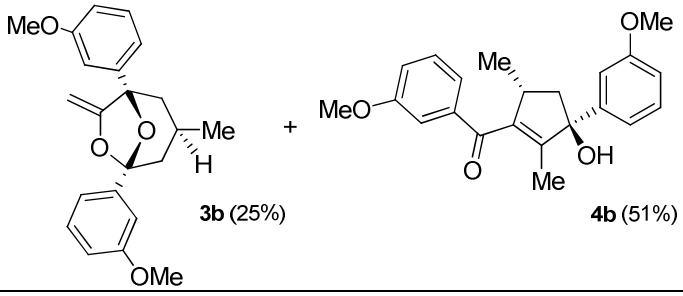
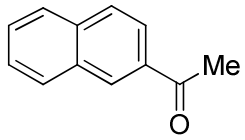
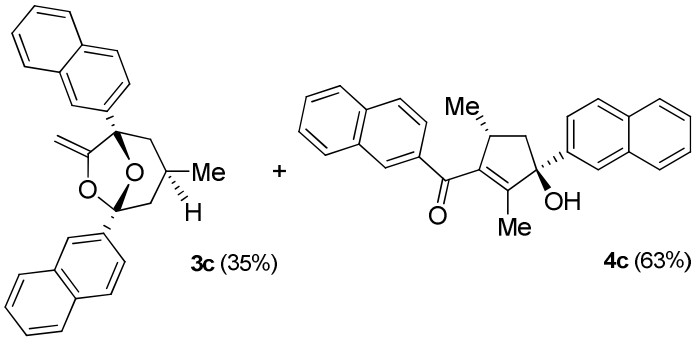
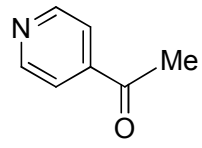
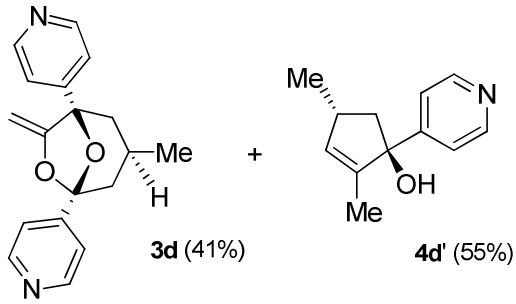
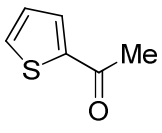
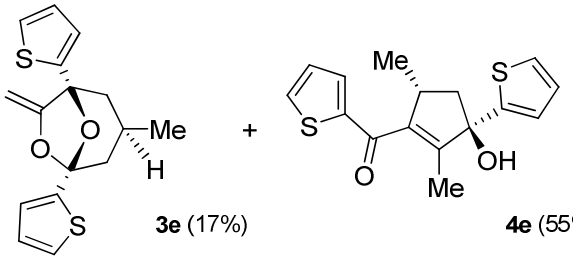
Ketone (R)	Products (yield, %) [b]	**3**:**4** Molar ratio [c]
 **1a**	 **3a** (36%) + **4a** (62%)	38:62
 **1b**	 **3b** (25%) + **4b** (51%)	48:52

Table 2 (continued)

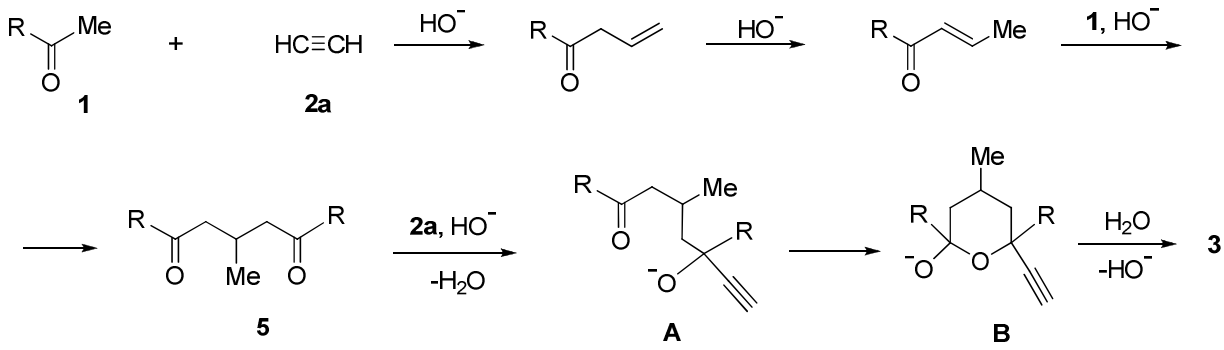
Ketone (R)	Products (yield, %) [b]	**3**:**4** Molar ratio [c]
 **1c**	 **3c** (35%) + **4c** (63%)	35:65
 **1d**	 **3d** (41%) + **4d'** (55%)	43:57[d]
 **1e** [e]	 **3e** (17%) + **4e** (55%)	33:67

[a] Reagents and conditions: ketone **1** (17.0 mmol), KOH·0.5H_2O (0.07 g, 1.1 mmol), DMSO (50 mL), initial pressure of acetylene **2a** at ambient temperature was 12-14 atm (stirred reactor). [b] Isolated yield after column chromatography (basic Al_2O_3, hexane, $CHCl_3$). [c] Determined from ^{1}H NMR data of the reaction mixtures. [d] **3d**:**4d'** Molar ratio. [e] The reaction was carried out at 80 °C using KOH:ketone **1e** molar ratio = 1:2.

Some decrease of the cyclopentenol **4b** content in the crude product in case of ketone **1b,** as compared to the unsubstituted acetophenone **1a** (38:62 *vs.* 48:52, Table 2), may be explained by a lower nucleophilicity of the corresponding carbanion due to the electron-accepting effect of the *meta*-methoxy substituent.

The key intermediates of this switchable reaction are 1,5-diketones **5**, which further undergo the Favorsky ethynylation and subsequent ring closure in the acetylenic ketoalcoholate **A** to give ketals **3** (Scheme 2). The intermediates **5** themselves result from the nucleophilic addition of two molecules of a ketone **1** to acetylene **2a** (first, C-vinylation of the ketone **1**, then prototropic

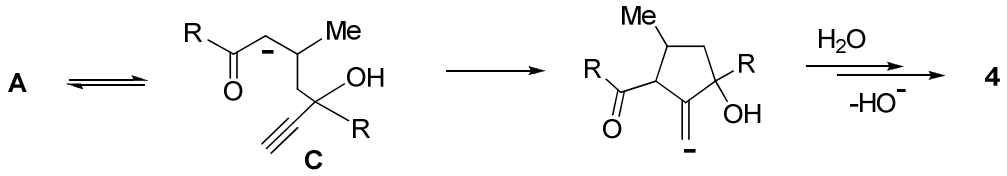
rearrangement of the adduct and Michael addition of the second molecule of deprotonated ketone to the α,β-unsaturated ketone).



Scheme 2. The assembly of 7-methylene-6,8-dioxabicyclo[3.2.1]octanes **3**.

The diastereoselectivity of this assembly (Scheme 2) is secured by the final ring closure that can occur only when the hydroxy and ethynyl groups are in a *cis*-orientation relative to the distorted tetrahydropyrane plane of hemi-ketal **B**.

Obviously, the cyclopentane ring closure originates from the addition of carbon-centered anion **C** to the triple bond (Scheme 3) that should precede and compete with the formation of hemiacetal intermediate **B** (Scheme 2).



Scheme 3. A tentative mechanism for the formation of 3-acyl-2-cyclopenten-1-ols **4**.

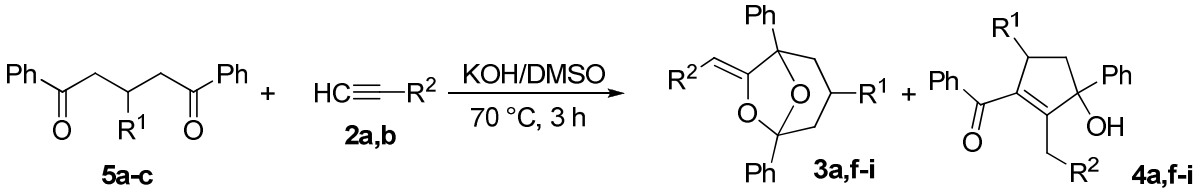
A likely model of the diastereoselectivity of the cyclopentenol **4** assembly (Scheme 3) is the template effect of the potassium cation which retains an enolizable carbonyl function and a hydroxyl group on one side of the closing ring.

Now it is understandable how the decrease in KOH content slows down the rate of hemiacetal **B** formation and the nucleophilic addition of the O-centered anionic site to the triple bond (i.e. the assembly of bicyclic ketals **3**, Scheme 2), and why, in this case, the competitive formation of cyclopentenols **4** is favored. It follows that the intramolecular C-vinylation (assembly of cyclopentenols **4**, Scheme 3) is not so sensitive to the basicity of the medium. Apparently, at a lower concentration of KOH, the conformations with *anti*-orientation of the C=O and OH groups become less populated, and hence the C-vinylation gains the competition.

Notably, the assembly of cyclopentenols **4** is limited to methylaryl(hetaryl)ketones only. When ethyl or other alkyl aromatic or heteroaromatic ketones are employed, exclusively bicyclic ketals **3** are regio- and stereoselectively assembled, obviously due to the sterically hindered access of a branched carbanionic center to the acetylenic moiety in the intermediate **C** (Scheme 3).

In the light of the proposed mechanism, 7-methylene-6,8-dioxabicyclo[3.2.1]octanes **3** and 3-acyl-2-cyclopenten-1-ols **4** might also be assembled from acetylenes and 1,5-diketones **5**, readily available via the aldol condensation of aldehydes with two molecules of ketone.[35-37] The reaction of 1,5-diketones **5a-c** with acetylenes **2a**,**b** has been conducted under the best conditions selected from numerous experiments, in which the major reaction parameters (the catalyst and reactants molar ratio, reaction temperature and time) were varied (Table 3). These conditions allow the complete conversion of 1,5-diketones **5**.

Table 3. The product yields and ratios for the reaction of 1,5-diketones **5a-c** with acetylenes **2a**,**b** in the presence of the KOH/DMSO system (KOH:diketone **5** molar ratio = 1:2)



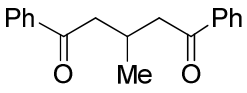
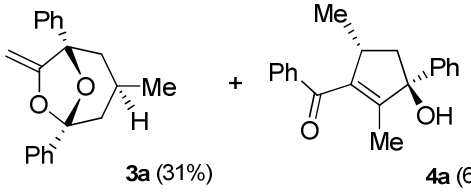
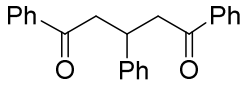
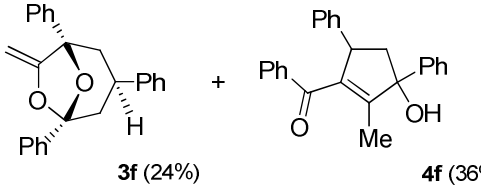
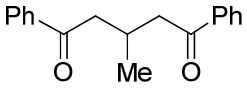
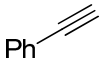
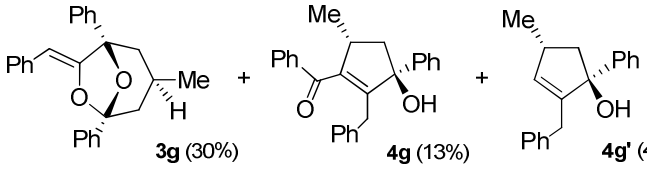
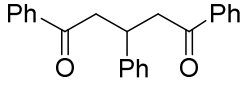
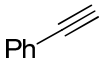
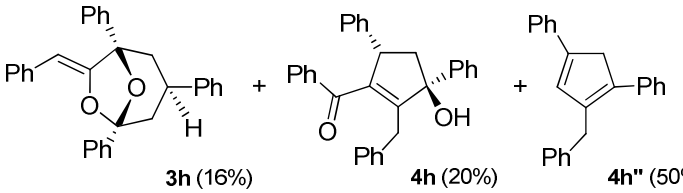
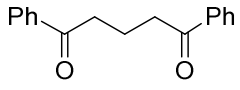
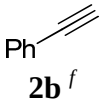
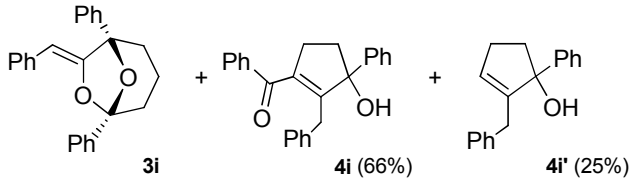
1,5-Diketone (R^1)	Acetylene (R^2)	Products (yield, %) [a]	**3**:**4** Molar ratio [b]
 **5a**	HC≡CH **2a** [c,d]	 **3a** (31%) + **4a** (65%)	30:70
 **5b**	HC≡CH **2a** [c]	 **3f** (24%) + **4f** (36%)[e]	45:55
 **5a**	 **2b** [f]	 **3g** (30%) + **4g** (13%) + **4g'** (40%)	43:57
 **5b**	 **2b** [f]	 **3h** (16%) + **4h** (20%) + **4h"** (50%)	20:77

Table 3 (continued)

1,5-Diketone (R^1)	Acetylene (R^2)	Products (yield, %) [a]	**3**:**4** Molar ratio [b]
 **5c**	 **2b** [f]	 **3i** + **4i** (66%) + **4i'** (25%)	5:95

[a] Isolated yield after column chromatography (basic Al_2O_3, hexane, $CHCl_3$). [b] Determined from ^{1}H NMR data of the reaction mixtures. [c] The reactions were carried out with acetylene **2a** [initial pressure at ambient temperature was 12-14 atm (stirred reactor)], 1,5-diketone **5** (6 mmol), KOH·0.5H_2O (0.2 g, 3 mmol), DMSO (50 mL). [d] The reaction time was 0.5 h. [e] Diastereomers ratio = 3:1. [f] Phenylacetylene **2b** (7.7 mmol).

From Table 3 it is seen that the synthesis of bicyclic ketals **3** and cyclopentenols **4** can be realized from both substituted acetylenes (such as phenylacetylene **2b**) and diverse 1,5-diketones **5**. As anticipated, yields of the products and their ratios (as well as sometimes their structure) are controlled considerably by the substituents in 1,5-diketones **5**. Similar to the direct reaction of ketones **1** with acetylene **2a** (Table 2), in some cases, deacylation of cyclopentenols **4** occurs (formation of cyclopentenols **4′**). In the reaction of 1,5-diketone **5b** with phenylacetylene **2b**, the formed cyclopentenol **4h** is subjected to both deacylation and dehydration to the corresponding cyclopentadiene **4h″** (Table 3).

Conclusions

In conclusion, it has been shown for the first time that self-organization of two molecules of acetylenes and two molecules of ketones in the KOH/DMSO superbasic suspension delivering 7-methylene-6,8-dioxabicyclo[3.2.1]octanes and 3-acyl-2-cyclopenten-1-ols can be efficiently controlled by changing the catalyst content, temperature and basicity of the reaction mixture. The selectivity of 7-methylene-6,8-dioxabicyclo[3.2.1]octanes and 3-acyl-2-cyclopenten-1-ols formation is up to 100% and 67%, respectively. Both products are easily separated and purified by column chromatography. Independent practical synthesis of bicyclic ketals and cyclopentenols has been developed from available 1,5-diketones, which have proven to be common key intermediates for both self-assemblies. Particularly important is that all the syntheses are strictly diastereoselective: only a single diastereomer is formed in all the cases, despite the presence of a number of stereogenic centers in all the molecules.

Experimental Section

General. KOH·0.5H_2O, DMSO (with content of water 0.2-0.3%) and all other chemicals and solvents are commercially available and were used without further purification. The elaborated procedure does not require degassing of DMSO and use of inert atmosphere. The 1,5-diketones were synthesized by using published procedure.[38,39] ^{1}H and ^{13}C NMR spectra were recorded at 400.13 and 100.61 MHz, respectively, on an instrument equipped with an inverse gradient 5 mm probe in $CDCl_3$ with hexamethyldisiloxane (HMDS) as an internal standard. All 2D NMR spectra were recorded by using a standard gradient Bruker pulse program. Standard COSY spectra with a 90°, 45° pulse sequence were recorded.[40] The NOESY spectra were recorded in the phase-sensitive TPPI mode with mixing time of 1-1.4 s.[41] HSQC spectra via double INEPT transfer in the phase sensitive TPPI mode with GARP decoupling during acquisition were recorded.[42] HMBC spectra were obtained with the inverse technique and processed in the magnitude mode.[43]

Typical procedure for the reaction of ketones 1a-e with acetylene 2a. A suspension of ketone **1a-e** (17.0 mmol) and KOH·0.5H_2O (0.07 g, 1.1 mmol) in DMSO (50 mL) was placed into a 0.25-L stirred reactor. The latter was fed with acetylene under pressure (initial pressure at ambient temperature was 12-14 atm and then decompressed to atmospheric pressure to remove air). The reactor was fed with acetylene again and heated (70 °C) for 8 h. The reaction mixture, after cooling to room temperature, was diluted with cool (5-7 °C) water (50 mL) and extracted with diethyl ether (15 mL×5). The extract was washed with water (20 mL×3) and dried (K_2CO_3) for 3 h. After removal of the solvent, a crude residue was separated by column chromatography (basic Al_2O_3): first dioxabicyclooctane **3** was washed off with hexane, and then cyclopentenol **4** was washed off with $CHCl_3$.

Bicyclooctane **3a** (0.89 g, 36%, yellow oil) and cyclopentenol **4a** (1.54 g, 62%, colorless crystals; mp =132-133 °C, lit.[28] 132-134 °C) were obtained from 2.00 g of ketone **1a**.

Bicyclooctane **3a** (4.6 g, 38%) and cyclopentenol **4a** (5.5 g, 45%) were obtained from 10.0 g of ketone **1a** and 0.54 g KOH·0.5H_2O.

Bicyclooctane **3b** (0.75 g, 25%, yellow oil) and cyclopentenol **4b** (1.53 g, 51%, yellow oil) were obtained from 2.55 g of ketone **1b**.

Bicyclooctane **3c** (0.98 g, 35%, yellow crystals; mp = 134-137 °C, lit.[18] 136-138 °C) and cyclopentenol **4c** (1.76 g, 63%, colorless crystals; mp =212-213 °C, lit.[28] 211-214 °C) were obtained from 2.89 g of ketone **1c**.

Bicyclooctane **3d** (1.03 g, 41%, white crystals, mp = 119-120 °C, lit.[44] 116-120 °C) and cyclopentenol **4d′** (0.88 g, 55%, yellow crystals; mp =101-102 °C, lit.[28] 101-102 °C) were obtained from 2.06 g of ketone **1d**.

Bicyclooctane **3e** (0.44 g, 17%, white crystals; mp = 112-113 °C, lit.[18] 110-112 °C) and cyclopentenol **4e** (1.42 g, 55%, brown oil) were obtained from 2.15 g of ketone **1e**.

Typical procedure for the reaction of diketones 5a,b with acetylene 2a.
The reaction of 1,5-diketones **5a,b** with acetylene **2a** was carried out analogously to the described above procedure with 6 mmol of 1,5-diketone **5a,b**, 3 mmol (0.2 g) of $KOH \cdot 0.5H_2O$ in DMSO (50 mL).
Bicyclooctane **3a** (0.54 g, 31%) and cyclopentenol **4a** (1.14 g, 65%) were obtained from 1.60 g of diketone **5a**.
Bicyclooctane **3f** (0.51 g, 24%, colorless crystals; mp =77-78 °C, lit.[19] 77-78 °C) and cyclopentenol **4f** (0.77 g, 36%, colorless crystals; mp =218-219 °C, lit.[28] 219 °C) were obtained from 2.00 g of diketone **5b**.
Typical procedure for the reaction of 1,5-diketones 5a-c with phenylacetylene 2b.
A suspension of 1,5-diketone **5** (6 mmol) and $KOH \cdot 0.5H_2O$ (0.2 g, 3 mmol) in DMSO (40 mL) was heated (70 °C) upon stirring. Then phenylacetylene **2b** (0.8 g, 7.7 mmol) in DMSO (10 mL) was added for 20 min. The reaction mixture was heated for 3 h and, after cooling to room temperature, was diluted with H_2O (100 mL) and extracted with Et_2O (20 mL×7). The extract was washed with water (20 mL×3) and dried (K_2CO_3) for 3 h. After removal of the solvent, a crude residue was separated by column chromatography (basic Al_2O_3): first dioxabicyclooctane **3** was washed off with hexane, and then cyclopentenols **4** and **4′** were washed off with $CHCl_3$.
Bicyclooctane **3g** (0.66 g, 30%, colorless crystals; mp =97-99 °C, lit.[19] 97 °C), cyclopentenol **4g** (0.29 g, 13%, yellow crystals; mp =98-99 °C, lit.[28] 96-99 °C) and cyclopentenol **4g′** (0.63 g, 40%, yellow oil) were obtained from 1.60 g of diketone **5a**.
Bicyclooctane **3h** (0.41 g, 16%, colorless crystals, mp = 87-88 °C, lit.[19] 87-88 °C), cyclopentenol **4h** (0.52 g, 20%, colorless crystals; mp =202-204 °C, lit.[28] 204-207 °C) and cyclopentadiene **4h″** (0.93 g, 50%, yellow crystals; mp =75-76 °C, lit.[28] 75-76 °C) were obtained from 2.00 g of diketone **5b**.
Cyclopentenol **4i** (1.40 g, 66%, colorless crystals; mp =102-103 °C, lit.[28] 102-105 °C) and cyclopentenol **4i′** (0.38 g, 25%, yellow oil) were obtained from 1.51 g of diketone **5c**.

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