EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701671

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701671

Supported by
ACES Asian Chemical Editorial Society

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10.1002/ejoc.201701671

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Direct oxidation of cyclopropanated cyclooctanes as a synthetic approach to polycyclic cyclopropylketones

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Abstract: A series of polycyclic hydrocarbons containing cyclopropane moieties 1,2-annelated or spiro-condensed with cyclooctane ring were investigated under oxidative conditions. Four oxidizing systems (O_3 on SiO_2, dioxirane derived from trifluoroacetone, CrO_3 and RuO_4, generated in situ), were employed to evaluate and compare their reactivity and usefulness. RuO_4 was found to be the best one, considering its oxidative power together with a simple preparative procedure. The conditions for specific oxidation of polycyclic hydrocarbons were found. Novel cyclooctane derivatives containing cyclopropyl carbonyl moieties were obtained.

Introduction

Cyclopropane ring is an outstanding moiety which combines a unique structure and bonding characteristics. Due to its high strain cyclopropane may be involved in a variety of chemical transformations that makes functionalized cyclopropanes extremely valuable starting compounds with a diverse reactivity, widely employed in organic and especially heterocyclic synthesis.[1] Polycyclic cyclopropylketones can be used as starting material for the preparation of unique strained molecules, such as rotanes and triangulanes.[2]

The application of cyclopropane derivatives in a rational drug-design can hardly be overestimated. A large number of examples exist showing the improvement of pharmaceutical properties of the molecules after incorporation of a three-membered ring (Figure 1).[3] The most usual grounds for introducing cyclopropane moiety is reducing the conformational flexibility in order to improve binding properties and ligands selectivity,[4] to increase chemical and metabolic stability,[5] for fine tuning of hydro/lipophilicity.[6]

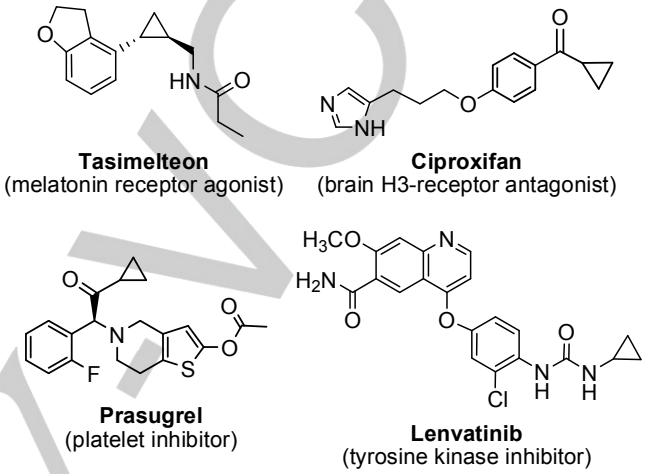

Figure 1. Examples of cyclopropane-containing clinical drugs.

Taking these facts into account, the need for the efficient practical methods of cyclopropanes functionalization is evident. Selective oxidation of $C(sp^3)H_2$ groups activated by adjacent cyclopropane moiety represents a direct approach to cyclopropylketones, in accordance with a principle of atom-economy allowing to reduce synthetic steps.[7] Most of preparative methods of cyclopropane-containing compounds oxidation into cyclopropylketones employ such powerful oxidants as ozone[2a,8], dioxiranes,[9] chromium (VI)[10] and ruthenium (VIII) oxides[11] as the sources of oxygen; catalytic methods of oxidation[12] also are used. Nevertheless, though the oxidation of cyclopropane-containing compounds was described in a number of works, a systematic study of these processes has been never made previously. In this connection, the aim of the present work was to investigate a series of cyclopropane-containing cyclooctanes under the treatment of various oxidizing systems in order to compare their reactivity and practical use.

Results and Discussion

Four available and widely used oxidative systems were chosen for this work: O_3 adsorbed on SiO_2 (method of "dry" ozonation),[2a,8,13] TFDO (methyl(trifluoromethyl)dioxirane),[9,14] CrO_3[10] and RuO_4, generated in situ from $RuCl_3$ and $NaIO_4$.[11] Under selected oxidative conditions hydrocarbons containing three-membered rings annelated with cyclooctane were studied in order to compare the oxidative power and selectivity of the systems under investigation and the reactivity of CH_2-groups adjacent to 1,2-annelated or spiro-annelated cyclopropanes. The

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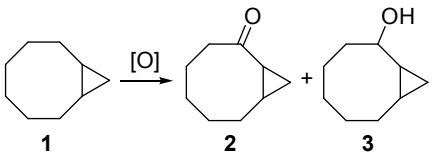
possibility to obtain the products of multiple oxidation was also studied.

Bicyclononane **1**[15] was the first hydrocarbon to be systematically studied under various oxidative conditions (Table 1). Though discrete literature data[8a,9c,11a] exist for the oxidation of hydrocarbon **1**, it seemed reasonable to check up their reproducibility. The best results were obtained with ozone or RuO_4, generated in situ from $RuCl_3$: the reactions selectively afforded the product of activated α-CH_2 group oxidation – cyclopropylketone **2**.[8a] Oxidation of hydrocarbon **1** by CrO_3 also led to ketone **2**, but the yield was lower due to decomposition of the organic material in the reaction media. At last, the treatment of compound **1** with TFDO provided the mixture of oxidation products **2** and **3** with alcohol **3**[9c] being the major component.

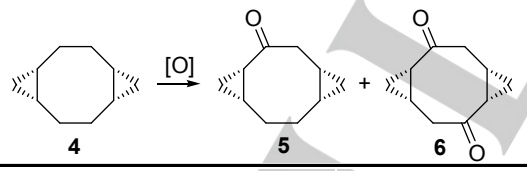
Table 1. Oxidation of bicyclo[6.1.0]nonane (**1**)



Conditions	Conversion, %	Yield **2**,[a] %	Yield **3**, [a] %
O_3/SiO_2, -50 °C, 2 h	29	58	-
TFDO, -20 °C, 2 h	84	19	30
CrO_3, CH_2Cl_2/CH_3CN, 0 °C, 2 h	100	10	-
$RuCl_3$, $NaIO_4$, r.t., 24 h[b]	91	46	-

[a] Isolated yield calculated from consumed **1**. [b] RuO_4 is generated in situ.

Table 2. Oxidation of tricyclodecane **4**.



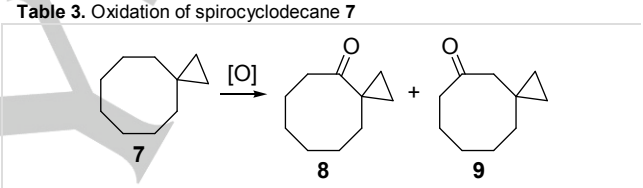
Conditions	Conversion, %	Yield **7**, %[a]	Yield **8**, %[a]
O_3/SiO_2, -50 °C, 1 h	51	60	0
TFDO, -20 °C, 2 h	90	62	0
CrO_3, CH_2Cl_2/CH_3CN, 0 °C, 6 h	100	53	12
$RuCl_3$, $NaIO_4$, r.t., 24 h	100	20	21
$RuCl_3$, $NaIO_4$, 60 °C, 7 h	100	0	35

[a] Isolated yield calculated from consumed **4**.

Oxidation of tricyclododecane **4**[16] under the conditions of "dry" ozonation afforded selectively ketone **5**, which could not be oxidized further on exposure to ozone (Table 2). The same result was obtained after the treatment with TFDO. The *cis*-orientation of cyclopropane rings was proven by DFT calculations of energy and ^1H NMR parameters for ketone **5** (see SI). In the case of CrO_3 and RuO_4 the formation of diketone **6** was observed. The optimal conditions affording the double oxidation product demand the treatment of **4** with RuO_4 at 60 °C for 7 h.

The oxidation of spirocyclodecane **7**[17] was also studied (Table 3). It was shown that in all cases the main product was ketone **8**[18], which resulted from the oxidation of α-CH_2 group adjacent to spiro-linked cyclopropane. The product of the oxidation of β-site, compound **9**[19], was also detected in small amounts. Yet, no traces of the product of the double oxidation were to be found in the reaction mixtures. The most efficient and selective methods include the oxidation by ozone and RuO_4, while TFDO showed rather poor selectivity (**8**:**9** 3:0.8), and the application of CrO_3 led to low yield of the product due to decomposition of organic material.

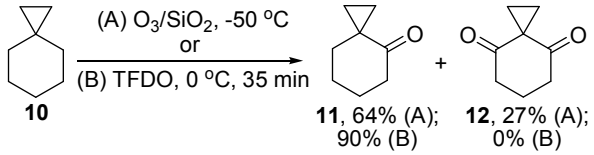
Table 3. Oxidation of spirocyclodecane **7**



Conditions	Conversion, %	Yield **8**, %[a]	Yield **9**, %[a]
O_3/SiO_2, -50 °C, 1 h	51	67	4
TFDO, -20 °C, 2 h	80	54	14
CrO_3, CH_2Cl_2/CH_3CN, 0 °C, 6 h	89	30	4
$RuCl_3$, $NaIO_4$, r.t., 24 h	93	60	3

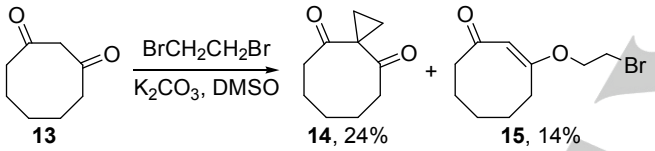
[a] Isolated yield calculated from consumed **7**.

It is interesting to compare the oxygenation processes in the case of compounds **7** and **10**, the analogue with a cyclohexane core. According to the literature data, oxidation of **10** under treatment with TFDO affords monoketone **11**[9c] together with small amounts of the isomeric spiro[2.5]octan-5-one and -6-one (3% and 4%, respectively) (Scheme 1). "Dry" ozonation of this hydrocarbon gives also the product of the double oxidation **12** in notable amount,[8a] while no traces of diketone were found in the case of spiro compound **7**. Thus, the activation of α-position is more efficient when a six-membered ring is spiro-annelated with cyclopropane.



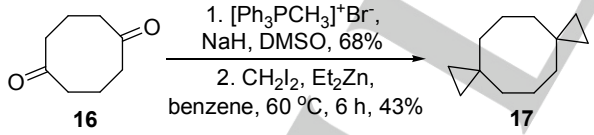
Scheme 1. Oxidation of spirocyclooctane **10** (for the method A – the composition of the reaction mixture is given;[8a] for the method B the yield calculated from reacted **10** is given (conversion 42%)[9c]).

An alternative route to diketone **14** was elaborated using the cyclic dialkylation of cyclooctane-1,3-dione (**13**) under the treatment with dibromoethane in the presence of K_2CO_3 in DMSO (Scheme 2). The side O-alkylation of ketone gave the vinyl ether **15** as a by-product in **14**:**15** ratio 1:0.6. It should be noted that this reaction, though widely used for open-chain compounds, is not trivial for cyclic diketones. To the best of our knowledge, the only dicarbonyl compound that could be involved into this process was 1H-indene-1,3(2H)-dione,[20] while alicyclic compounds such as cyclohexane-1,3-dione[21] and dimedone[20] could not be dialkylated under the treatment with dibromoethane and formed exclusively O-alkylation products.



Scheme 2. Alkylation of cyclooctane-1,3-dione (**13**).

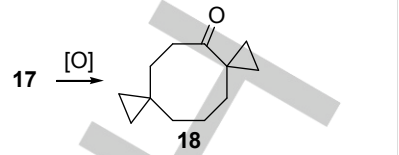
Previously unknown tricyclic hydrocarbon **17** was obtained from the diketone **16** via the sequence of Wittig methylenation and Simmons-Smith cyclopropanation employing diethylzinc (Scheme 3).



Scheme 3. Synthesis of dispirocyclododecane **17**.

The oxidation of compound **17** demonstrated the tendencies similar to those characteristic for the compound **4**, but dispirocyclic hydrocarbon appeared to be less reactive in the oxidation processes (Table 4). Product of monooxidation **18** was obtained by most of the methods and oxidation with RuO_4 provided the best result, but in the case of CrO_3 complete destruction of starting cyclopropane took place. Under all the conditions no products of polyoxidation were formed.

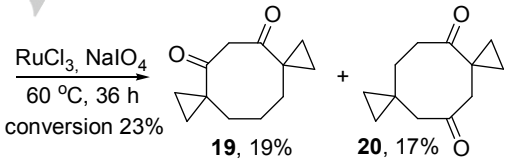
Table 4. Oxidation of dispirocyclododecane **17**



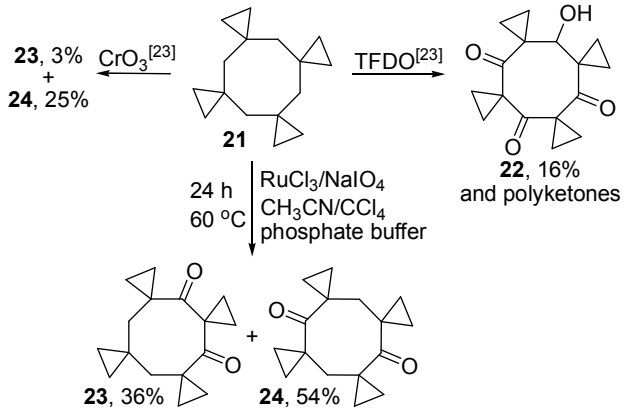
Conditions	Conversion, %	Yield **18**, %[a]
O_3/SiO_2, -50 °C, 1 h	93	26
TFDO, -20 °C, 2 h	71	53
CrO_3, CH_2Cl_2/CH_3CN, 0 °C, 6 h	-	-
$RuCl_3$, $NaIO_4$, r.t., 24 h	100	74

[a] Isolated yield calculated from consumed **17**.

The subsequent oxidation of ketone **18** with RuO_4 (but not with O_3 or TFDO) led slowly to the mixture of diketones **19** and **20** (Scheme 4). This again makes the difference from a more reactive analogous tricycle based on cyclohexane, ozonation of which afforded the mixture of monoketone and isomeric diketones in a similar ratio.[8a]



Scheme 4. Oxidation of ketone **18**.



Scheme 5. Oxidation of tetraspirocyclic hydrocarbon **21**.

The synthesis and oxygenation of tetraspirocyclic hydrocarbon **21** via various methods was previously reported by our

group.[22,23] The most complete oxidation was achieved when using TFDO and triketoalcohol **22** was obtained among other products (Scheme 5).

Encouraged by the abovementioned results of oxidation of **4** and **18**, we investigated the compound **23** in the reaction with RuO_4 generated in situ (Scheme 5). The oxidation under the standard conditions (r.t., 24 h) afforded the mixture of monoketone, 1,3-diketone **23** and 1,5-diketone **24** in 1:3:4 ratio. The increase of the reaction time up to 72 h or the reaction temperature up to 60 ^oC gave the mixture of diketones **23**, **24** in 1:1.5 ratio, and though monoketone was not present, further oxidation did not proceed. This oxidant did not surpass the oxidizing ability of CrO_3, though it should be noted that the preparative yields increased significantly. The fact that the reaction terminated after the insertion of two carbonyl groups may be explained by steric hindrances of the oxidized CH bonds, which prevent deeper oxidation in the case of CrO_3 and RuO_4.

Conclusions

Direct oxidation of the series of cyclopropane-containing cyclooctanes was studied. Three-membered rings spiro- and 1,2-annelated with cyclooctane core were shown to efficiently activate adjacent site toward oxidation. 1,2-Annelated cyclopropane demonstrated stronger activating effect that was shown comparing the oxidation of hydrocarbons **17** and **4**. It should be mentioned that cyclooctane-based hydrocarbons **7** and **17** were found to be less reactive than analogues containing six-membered ring.

The comparison of four oxidative methods revealed the following general tendencies. The most practical approach to cyclopropylketones is the use of RuO_4 generated in situ. This method is easy to be employed and, when necessary, allows the variation of the reaction time and temperature in broad limits that is impossible for O_3 and TFDO. It should be noted that RuO_4 promotes double oxidation, when more than one cyclopropane moiety is present in the structure, that makes it the reagent of choice for the synthesis of diketones. "Dry" ozonation is a reasonable alternative for monooxidation of cyclopropanes, as a selective and metal-free method. CrO_3 is hardly to be chosen in any case, due to difficult work-up and low yields. At last, TFDO, though lacking selectivity and employing the most complicated synthetic procedure, may be recommended in selected cases, such as polyoxidation of **21**. The moderate yields of oxidation products are offset by one-step procedure to introduce the carbonyl group into cyclopropane-containing molecule that is useful for the synthesis of structurally complex compounds.

Experimental Section

General experimental details. ^1H and ^{13}C NMR spectra were recorded on a spectrometer Agilent 400MR (400.0 MHz for ^1H and 100.6 MHz and for ^{13}C) at room temperature; chemical shifts δ were measured with reference to the solvent for ^1H ($CDCl_3$, δ = 7.24 ppm) and ^{13}C ($CDCl_3$, δ = 77.0ppm). When necessary, assignments of signals in NMR spectra were made using 2D techniques. Accurate mass measurements (HRMS) were measured on Jeol GCMate II mass spectrometer (70 eV). Infrared spectra were recorded with a Thermo Nicolet FTIR-200 spectrometer. Analytical thin layer chromatography was carried out with silica gel plates (supported on aluminum); the detection was done by UV lamp (254 nm). Column chromatography was performed on silica gel (0.015-0.04 mm). Hydrocarbons **1**[15], **6**[16], cyclooctane-1,3-dione (**15**)[24] and cyclooctane-1,5-dione (**18**)[25] were obtained via literature procedures. Spiro[2.7]decane (**7**) was obtained from methylidenecyclooctane via Simmons-Smith cyclopropanation.[26] All the other starting materials were commercially available. All reagents except commercial products of satisfactory quality were purified by literature procedures prior to use.

Oxidation of hydrocarbons. General methods. Molar ratios are given for one α-CH_2-group. If several sites were supposed to be oxidized, the corresponding excess of the reagents was used.

Oxidation via "dry" ozonation. Hydrocarbon (1 mmol), silica gel (1:100 mass ratio) and pentane or CH_2Cl_2 (70 mL) were stirred for 1 h. The solvent was evaporated in vacuo. Silica gel containing adsorbed hydrocarbon was placed into "U"-tube, cooled down to -50-(-60) ^oC and ozonated at this temperature for 1-2 h. Then the system was allowed to warm up to r.t., silica gel washed with CH_2Cl_2 (200 mL), the solvent was evaporated in vacuo. The product was isolated via preparative column chromatography (SiO_2).

Oxidation with TFDO. To the solution of $NaHCO_3$ (1 mol, 75.4 g) and 1,1,1-trifluoroacetone (1.32 mol, 100 mL) in water (140 mL) Oxone (0.26 mol, 159 g) was added carefully in portions at 0-3 ^oC, 200 torr, under vigorous stirring. The reaction mixture was stirred until the end of foam generation. The solution of TFDO in trifluoroacetone (0.33 M, 32 mmol, 98 mL) was collected at -70 ^oC into the flack containing hydrocarbon (1 mmol), allowed to warm up to -20 ^oC and stirred at this temperature for 2 h. The solvent was condensed at 25 ^oC into the flack cooled down to -78 ^oC. The product was isolated via preparative column chromatography (SiO_2).

Oxidation with chromium trioxide. To the suspension of CrO_3 (2g, 20 mmol) in CH_2Cl_2 (4 mL) and acetonitrile (4 mL) the hydrocarbon (1 mmol) was added. The reaction mixture was stirred at 0 ^oC for 2-6 h and filtered through silica gel. The solvent was evaporated in vacuo, the product was isolated via preparative column chromatography (SiO_2).

Oxidation with ruthenium tetroxide. To the solution of hydrocarbon (1 mmol) in CCl_4 (1 mL), CH_3CN (1 mL) and phosphate buffer (1.5 mL, pH = 7) $NaIO_4$ (3 mmol, 0.64 g) and $RuCl_3 \cdot xH_2O$ (ca. 0.2 mmol, 58 mg, ω(Ru) 35-40%) were added in the atmosphere of argon. The reaction mixture was stirred, diluted with H_2O (3 mL), and extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were washed with a mixture (6 mL) of saturated $Na_2S_2O_3$, $NaHCO_3$, and NaCl (1:1:1) and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo, the product was isolated via preparative column chromatography (SiO_2).

*Tricyclo[7.1.0.0^{4,6}]decan-2-one (**5**).* Yield 46 mg (60% with O_3), 84 mg (62% with TFDO), 80 mg (53% with CrO_3), 30 mg (20% with RuO_4); white crystals, m.p. 49 ^oC (from CH_2Cl_2), R_f 0.12 (CH_2Cl_2:petroleum ether 1:1). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = -0.15 (m, ^3J = 5.3, ^3J = 5.2, ^2J = -4.9, 1 H, CH_2, *cy*-Pr), 0.77 (m, ^3J = 8.5, ^3J = 8.4, ^2J = -4.9, 1 H, CH_2, *cy*-Pr), 0.79 (m, ^3J = 8.9, ^3J = 7.6, ^3J = 11.7, ^2J = -15.5, 1 H, CH_2), 0.88 (m, ^3J = -8.1, ^3J = 7.5, ^2J = -5.2, 1 H, CH_2, *cy*-Pr), 0.94 (m, ^3J = 11.7, ^3J = 3.7, ^3J = 5.3, ^3J = 8.8, ^3J = 8.5, 1 H, CH), 1.05 (m, ^3J = 6.3, ^3J = -6.4, ^3J = -5.2, 1 H, CH_2, *cy*-Pr), 1.25 (m, ^3J = 8.4, ^3J = 8.8, ^3J = 5.2, ^3J = 9.8, ^3J = 7.4, 1 H, CH), 1.28 (m, ^3J = 9.2, ^3J = 4.2, ^3J = 7.6, ^2J = -15.1, 1 H, CH_2), 1.47 (m, ^3J = 6.0, ^3J = 9.2, ^3J = -6.4, ^3J = -8.1, ^3J = 10.3, 1 H, CH), 1.94 (m, ^3J =

7.5, ^3J = 4.2, ^3J = 3.7, ^2J = -15.5, 1 H, CH_2), 1.98 (dd, ^3J = 9.8, ^2J = -16.4, 1 H, CH_2), 2.01 (m, ^3J = 6.3, ^3J = 7.5, ^3J = 10.3, 1 H, CH), 2.08 (m, ^3J = 6.0, ^3J = 7.5, ^3J = 8.9, ^2J = -15.1, 1 H, CH_2), 2.85 (dd, ^3J = 7.4, ^2J = -16.4, 1 H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 11.6 (CH_2, *cy*-Pr), 12.1 (CH), 12.5 (CH_2, *cy*-Pr), 14.4 (CH), 19.0 (CH), 24.2 (CH_2), 25.4 (CH_2), 27.7 (CH), 43.1 (CH_2), 212.8 (C=O) ppm; IR (film): ν = 3072, 2956, 2918, 2879, 2850, 1695, 1468, 1277, 1178, 1161, 1060 cm^{-1}; HRMS (ESI$^+$, 70 eV, *m*/*z*): calcd. for $C_{10}H_{14}O$ [M+Na]: 173.0937, found: 173.0935.

Tricyclo[7.1.0.0^{4,6}]decane-2,7-dione (***6***). Yield 20 mg (12% with CrO_3), 34 mg (21%, with RuO_4, r.t.), 57 mg (35%, with RuO_4, 60°C); white crystals, m.p. 88 °C (from CH_2Cl_2), R_f 0.18 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.04-1.15 (m, 4 H, 2 CH_2, *cy*-Pr), 1.66-1.79 (m, 2 H, 2 CH), 1.97-2.04 (m, 2 H, 2 CH), 2.08 (dd, ^2J = 15.5, ^3J = 10.2, 2 H, 2 CH_2), 2.82 (dd, ^2J = 15.5, ^3J 6.6, 2 H, 2 CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.2 (J_{CH} = 162, 2 CH_2, *cy*-Pr), 17.6 (J_{CH} = 164, 2 CH), 28.0 (J_{CH} = 167, 2 CH), 40.1 (J_{CH} = 129, 2 CH_2), 208.5 (2 C=O) ppm; IR (film): ν = 3020, 2999, 2925, 2854, 1739, 1693, 1464, 1452, 1383, 1363, 1167, 1097, 1045 cm^{-1}; HRMS (ESI$^+$, 70 eV, *m*/*z*): calcd. for $C_{10}H_{12}O_2$ [M+H]: 165.0910, found: 165.0912.

Dispiro[2.3.2.3]dodecan-4-one (***18***). Yield 43 mg (26% with O_3), 67 mg (67% with TFDO), 131 mg (74%, with RuO_4); yellowish liquid, R_f 0.33 (CH_2Cl_2:petroleum ether 1:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.27-0.34 (m, 2 H, 2 CH_2, *cy*-Pr), 0.35-0.42 (m, 2 H, 2 CH_2, *cy*-Pr), 0.60-0.70 (m, 2 H, 2 CH_2, *cy*-Pr), 1.17-1.27 (m, 2 H, 2 CH_2, *cy*-Pr), 1.40-1.47 (m, 2 H, CH_2), 1.48-1.53 (m, 2 H, CH_2), 1.53-1.68 (m, 2 H, CH_2), 1.87-1.92 (m, 2 H, CH_2), 2.65-2.70 (m, 2 H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.9 (J_{CH} = 160, 2 CH_2, *cy*-Pr), 17.9 (C_{spiro}), 18.5 (J_{CH} = 164, 2 CH_2, *cy*-Pr), 25.8 (J_{CH} = 126, CH_2), 31.4 (C_{spiro}), 32.8 (J_{CH} = 125, CH_2), 33.0 (J_{CH} = 126, CH_2), 38.6 (J_{CH} = 128, CH_2), 40.2 (J_{CH} = 127, CH_2), 216.3 (C=O) ppm; IR (film): ν = 3070, 2999, 2922, 2852, 1684, 1462, 1444, 1365, 1329, 1176, 1095, 1016, 901, 889, 837 cm^{-1}; HRMS (ESI$^+$, 70 eV, *m*/*z*): calcd. for $C_{12}H_{18}O$ [M+H]: 179.1430, found: 179.1434.

Dispiro[2.3.2.3]dodecane-4,6-dione (***19***) and *dispiro[2.3.2.3]dodecane-4,11-dione* (***20***). Yield 4.2 mg (36%, **19**:**20** 1.1:1); white crystals, R_f 0.29 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): for **19** δ = 0.67-0.77 (m, 4 H, 2 CH_2, *cy*-Pr), 1.24-1.34 (m, 4 H, 2 CH_2, *cy*-Pr), 1.64-1.70 (m, 2 H, CH_2), 1.78-1.83 (m, 4 H, 2 CH_2), 3.72 (s, 2 H, CH_2); for **20** δ = 0.46-0.53 (m, 4 H, 2 CH_2, *cy*-Pr), 0.78-0.88 (m, 2 H, 2 CH_2, *cy*-Pr), 1.35-1.45 (m, 2 H, 2 CH_2, *cy*-Pr), 1.70-1.75 (m, 2 H, CH_2), 2.48 (s, 2H, CH_2), 2.81-2.87 (m, 2 H, CH_2), 2.87 (s, 2 H, CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): for **19** δ = 18.7 (4 CH_2, *cy*-Pr), 26.4 (CH_2), 31.6 (2 CH_2), 31.9 (2 C_{spiro}), 56.7 (CH_2), 205.3 (C=O) ppm; for **20** δ = 14.5 (2 CH_2, *cy*-Pr), 17.0 (C_{spiro}), 19.7 (2 CH_2, *cy*-Pr), 28.9 (C_{spiro}), 39.3 (CH_2), 39.5 (CH_2), 48.2 (CH_2), 49.7 (CH_2), 209.9 (C=O), 213.3 (C=O) ppm. IR (film): ν = 3078, 3003, 2929, 2856, 1691, 1674, 1460, 1446, 1419, 1360, 1350, 1325, 1153, 1107, 1095, 1024, 935 cm^{-1}; HRMS (ESI$^+$, 70 eV, *m*/*z*): calcd. for $C_{12}H_{16}O_2$ [M+H]: 193.1223, found: 193.1224.

Alkylation[20] **of cyclooctane-1,3-dione (13).** To the suspension of K_2CO_3 (4 mmol, 552 mg) in DMSO (1 mL) cyclooctane-1,3-dione (1 mmol, 140 mg) and dibromoethane (2 mmol, 376 mg) were added under stirring. In 10 min the temperature of the reaction mixture reached 30 °C. It was cooled down to r. t. and stirred for 11 h. Then the reaction mixture was diluted with H_2O (3 mL), and extracted with ether (3x5 mL). The combined organic layers were washed with water (3x5 mL) and dried over anhydrous $MgSO_4$. The solvent and unreacted dibromoethane were evaporated in vacuo, the products **14** and **15** were isolated via preparative column chromatography (SiO_2).

Spiro[2.7]decane-4,10-dione (***14***). Yield 40 mg (24%); yellow liquid, R_f 0.61 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.34 (s, 4 H, 2 CH_2, *cy*-Pr), 1.66-1.75 (m, 2 H, CH_2), 1.83-1.92 (m, 4 H, 2 CH_2), 2.54-2.60 (m, 4 H, 2 CH_2CO) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 17.7 (J_{CH} = 168, 2 CH_2, *cy*-Pr), 21.9 (J_{CH} = 126, 2 CH_2), 28.3 (J_{CH} = 126, CH_2), 41.4 (C_{spiro}), 43.2 (J_{CH} = 127, 2 CH_2), 207.2 (2 C=O) ppm; IR (film): ν = 3091, 3008, 2945, 2879, 2864, 1680, 1464, 1446, 1414, 1333, 1300, 1171, 1110, 1055, 997 cm^{-1}; HRMS (ESI$^+$, 70 eV, *m*/*z*): calcd. for $C_{10}H_{14}O_2$ [M+H]: 167.1067, found: 167.1089.

3-(2-Bromoethoxy)cyclooct-2-en-1-one (***15***). Yield 35 mg (14%); yellow liquid, R_f 0.23 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ: 1.51-1.61 (m, 2 H, CH_2), 1.63-1.76 (m, 4 H, 2 CH_2), 2.75 (t, ^3J 7.1, 2 H, CH_2), 2.80 (t, ^3J 7.1, 2 H, CH_2), 3.55 (t, ^3J 5.9, 2 H, CH_2Br), 4.05 (t, ^3J 5.9, 2 H, CH_2O) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ: 23.1 (CH_2), 23.2 (CH_2), 23.6 (CH_2), 28.2 (CH_2Br), 32.7 (CH_2), 41.5 ($\underline{CH_2}CO$), 67.7 (CH_2O), 108.9 (CH=), 171.2 (C=), 201.1 (C=O) ppm; IR (film) ν: 2935, 2860, 1712, 1689, 1635, 1603, 1458, 1446, 1410, 1329, 1257, 1226, 1176, 1128, 1076 cm^{-1}; HRMS (ESI$^+$, 70 eV, *m*/*z*): calcd. for $C_{10}H_{15}BrO_2$ [M+H]: 247.0328, 249.0308, found: 247.0330, 249.0312.

Dispiro[2.3.2.3]dodecane (***17***) was obtained from cyclooctane-1,5-dione (**16**) via the sequence of Wittig reaction[27] and Simmons-Smith cyclopropanation.[26] Yield 0.47 g (29% from **16**); colorless liquid, R_f 0.64 (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$, 25° C): δ = 0.25 (s, 8 H, 4 CH_2, *cy*-Pr), 1.44-1.50 (m, 8 H, 4 CH_2), 1.53-1.61 (m, 4 H, 2 CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.3 (J_{CH} = 160, 4 CH_2, *cy*-Pr), 19.3 (2 C_{spiro}), 24.7 (J_{CH} = 126, 2 CH_2), 37.0 (J_{CH} = 125, 4 CH_2) ppm; IR (film): ν = 3066, 2995, 2920, 2854, 1460, 1446, 1427, 1375, 1011, 843 cm^{-1}; GC-MS (EI) *m*/*z* (*I*, %): 149 (3) [M-15]$^+$, 136 (9) [M-28]$^+$, 121 (16) [M-43]$^+$, 108 (89) [M-56]$^+$.

Acknowledgements

We thank the Russian Foundation for Basic Research (Project 16-03-00467-a) and the Grant of the President of the Russian Federation (NSh-10268.2016.3) for financial support. The research work was carried out using NMR spectrometer Agilent 400-MR purchased under the program of MSU development.

Keywords: oxidation • small ring systems • ketones • polycycles • ruthenium

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