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Synthesis of endoperoxides by domino reactions of ketones and molecular oxygen†‡

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Domino reactions of ketones with molecular oxygen in the presence of potassium hydroxide and potassium *t*-butoxide afford cyclic hydroperoxy acetals (3,5-dihydroxy-1,2-dioxanes). Mixed endoperoxides can also be obtained in a three-component reaction of two ketones and oxygen.

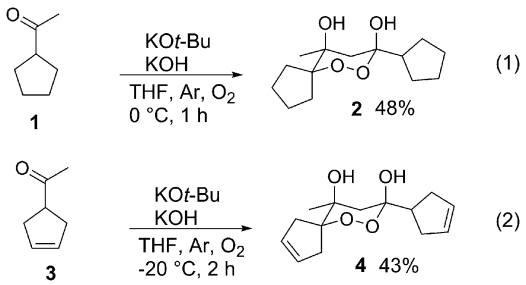
Introduction

Endoperoxides are important pharmacophores in a number of natural and synthetic, biologically active compounds. Although best known as potent antimalarials,[1] cyclic peroxides also exhibit a range of activities which encompasses anti-tripanosomal,[2] antifungal, antiviral and anticancer activity.[3,4] Whereas tetraoxanes and trioxanes are important units of synthetic bioactive peroxides, 1,2-dioxanes and dioxenes are the most frequent constituents of naturally occuring endoperoxides. Therefore, synthetic chemists have invested considerable efforts in developing synthetic approaches to this class of compounds.[5]

Results and discussion

During the course of a synthetic study of platensimycin, we exposed methyl cyclopentyl ketone **1** to the enolization conditions under a presumed argon atmosphere, aiming to perform a Michael addition with the thermodynamic enolate. Surprisingly, spectral data of the isolated compound did not match the expected product, but indicated a dimeric structure with a higher oxidation level. Detailed analysis of spectra indicated the product structure **2** (Scheme 1). Stereochemical assignment of the compound **2**, as deduced from NOESY spectrum, was confirmed by the results of X-ray diffraction structural analysis, as represented in Fig. 1. As it was clear that the product arose from the reaction of ketone enolate with molecular oxygen, the reaction was performed under an oxygen atmosphere, in order to improve the yield; this time, surprisingly, endoperoxide **2** was not observed. The optimization of the reaction conditions involved variations of the base, solvent, atmosphere and the reaction temperature. We found that the highest yield of endoperoxide **2** could be obtained when the reaction was performed in THF, using a mixture of KO*t*-Bu and KOH as a base, under an argon atmosphere where oxygen was present only in low concentration; under these conditions, peroxide **2** could be isolated in 48% yield as a crystalline, analytically pure compound (Scheme 1, example 1). Cyclopent-3-enyl methyl ketone **3** behaved similarly, affording endoperoxide **4** in 43% yield (Scheme 1, example 2).

In subsequent experiments, attempts were made to accomplish cross-cyclotrimerization of two different ketones with oxygen. Indeed, the reaction of methyl cyclopentyl ketone and acetone afforded peroxide **6a** in 64% yield (Table 1, entry 1). Several other ketones (**5**) were also submitted to the cross-cyclotrimerization sequence with methyl cyclopentyl ketone **1** and oxygen, to give the desired peroxide products (mostly as crystalline compounds) in modest to fair yields. In some cases the products (**6**) contained variable amounts of the side product of homo-trimerization (**2**) (entries 2, 3, 4 and 5).



Scheme 1 Formation of 1,2-dioxanes **3** and **4** in the base-catalyzed reactions of ketones **1** and **2** with oxygen.

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† Dedicated to the memory of our colleague and friend Dr Suren Husinec (1953–2015).

‡ Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra for all compounds, CIF files for compounds **2**, **6c**, **6e** and **6f** are deposited. CCDC 1411164–1411167. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ra13476e

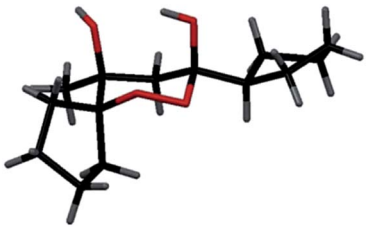


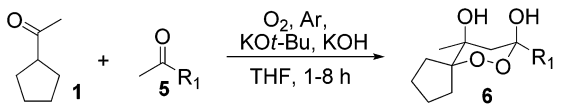
Fig. 1 X-ray diffraction analysis of compound **2**.

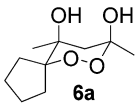
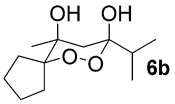
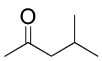
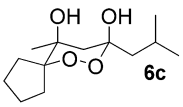
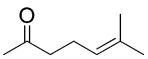
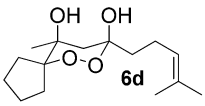
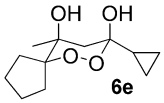
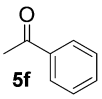
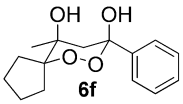
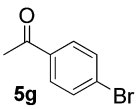
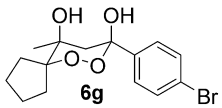
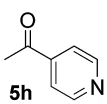
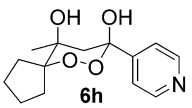
However, the preponderance of the cross-products (**6**) is of note, given the fact that ketones were used in equimolar amounts. The results of these experiments are represented in Table 1. All products were obtained as single stereoisomers, with both hydroxy groups assuming axial positions (Fig. 2).

A literature search revealed that Barton and collaborators encountered this reaction while inspecting more closely autooxidation of isobutyrophenone.[6] However, no subsequent report on this reaction ensued, although "the phenomenon certainly deserves further study".[7]

The proposed reaction mechanism is represented in Scheme 2. It involves the oxidation of methyl cyclopentyl ketone enolate **7** with molecular oxygen to give hydroperoxide **8**, which then acts as the electrophile in subsequent aldol addition of enolate **9**. Selectivity in cross-cyclotrimerization can be explained by the well known propensity of methyl cyclopentyl ketone for the formation of a thermodynamic enolate **7**,[8] which undergoes the reaction with molecular oxygen.[9] This reaction could proceed either as a direct reaction of the enolate with triplet oxygen, or *via* a cage radical pair mechanism; the intermediacy of free

Table 1 Cross-cyclotrimerizations of methyl cyclopentyl ketone with other ketones and molecular oxygen



Entry	Reactant ($MeC(O)R_1$)	Product	T (°C)	Time (h)	Yield[a] (%)
1	 **5a**	 **6a**	−20	5	64
2	 **5b**	 **6b**	−20	2	38[b,c]
3	 **5c**	 **6c**	−40	3.5	43 56[b,d]
4	 **5d**	 **6d**	−40	2	42[b,e]
5	 **5e**	 **6e**	−40	5	39 59[b,f]
6	 **5f**	 **6f**	−40	6	31 54[b,g]
7	 **5g**	 **6g**	−40	6	67
8	 **5h**	 **6h**	−40	4	28

[a] Unless otherwise stated, the yields refer to the highest isolated yields of recrystallized, analytically pure compounds. [b] Yield determined from ^{1}H NMR spectrum. [c] **6b : 2** = 2.9 : 1. [d] **6c : 2** = 17 : 1. [e] **6d : 2** = 5 : 1. [f] **6e : 2** = 6 : 1. [g] **6f : 2** = 9 : 1.

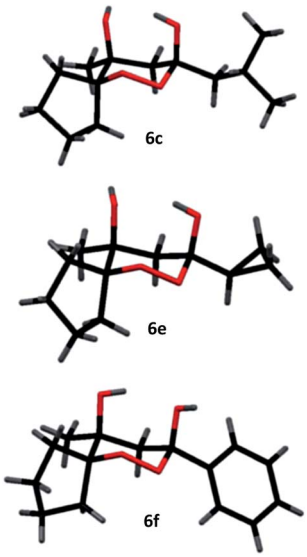
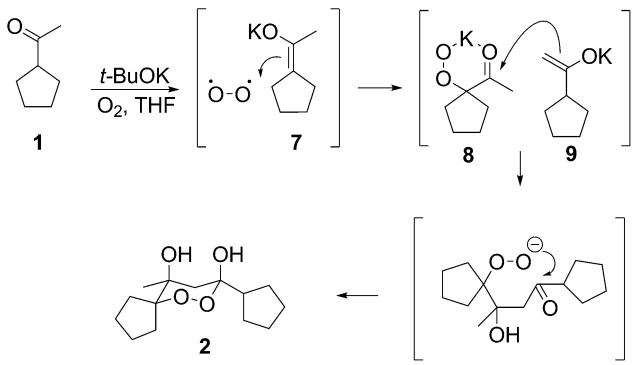


Fig. 2 Crystal structures of compounds **6c**, **6e** and **6f**.



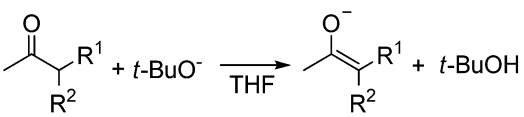
Scheme 2 Proposed reaction mechanism.

radical species can be ruled out, as the addition of BHT did not inhibit the reaction. The hydroperoxide thus formed would then act as the acceptor (probably activated by intramolecular hydrogen bond) in the cross aldol addition. Surprisingly, this mechanistic pathway was not corroborated with experimental evidence. Hydroperoxide **8** (represented in Scheme 2 in the form of the corresponding potassium salt) could be separately prepared in 71% yield, when the reaction of methyl cyclopentyl ketone with KO*t*-Bu was performed under an oxygen atmosphere (this reaction is also unaffected by the presence of BHT).[10] However, a mixture of hydroperoxide **8** and methyl cyclopentyl ketone **1** did not produce observable amounts of endoperoxide **2** when exposed to the action of KO*t*-Bu.

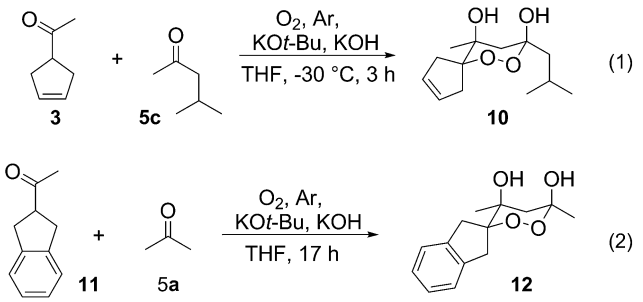
To clarify the relationship between enolate stability and the course of cross cyclotrimerization, and to explain the specific reactivity of methyl cyclopent(en)yl ketone(s) **1** and **3**, dispersion corrected density functional theory calculations (DFT) were performed. Free energy changes for the *t*-BuO$^-$ mediated formation of more substituted enolates in THF solution have been calculated at BP86-D3/TZP level of theory (COSMO) with two methods. (The first one is based on direct calculation of thermodynamic properties in THF within the COSMO model,[11] while in the second, indirect method, the gas-phase free energies of reactants and products are corrected by solvation energies and energies due to the geometry relaxation of a molecule in the solvent,[12] see Computational details Section for details). The results of both, direct and indirect method, are consistent, and Gibbs free energies for the formation of more substituted enolates, corresponding to all aliphatic ketones used in cross trimerization reactions (**1**, **3**, **5a–e**) are listed in Table 2.[14] It can be seen that methyl cyclopentyl ketone **1** and methyl cyclopentenyl ketone **3** have the most stable thermodynamic enolates. This indicates that methyl cyclopentenyl ketone **3** should also act as the acceptor in the cross cyclotrimerization reaction. Indeed, when **3** was submitted to the cyclotrimerization conditions in the presence of methyl isobutyl ketone **5c**, endoperoxide **10** was obtained in 37% yield (Scheme 3, example 1). With these results in hand, we searched for some other ketone structures that would give rise to stable thermodynamic enolates and hence be good partners for the cross cyclotrimerization. Calculations showed that indanyl methyl ketone **11** should be such a compound (Table 2), and indeed, its' cyclotrimerization with acetone provided endoperoxide **12** in 77% yield (Scheme 3, example 2).

Some ketones did not participate in the cross-cyclotrimerization; these include progesterone, α-ionone, and 2-acetylnorbornene, *inter alia*. Therefore, we searched for a method to introduce the endoperoxide structural unit into various structures, not directly obtainable by the reaction. To this aim, cross-cyclotrimerisation was performed with acetylstyrene **13**. Ozonolysis of the product **14** provided aldehyde **15**, which could be submitted to further synthetic transformations, as examplified by the organometallic addition represented in Scheme 4, which gave peroxy-triol **16**. In this way, various structural entities could be linked to the peroxide moiety, *via* nucleophilic addition.

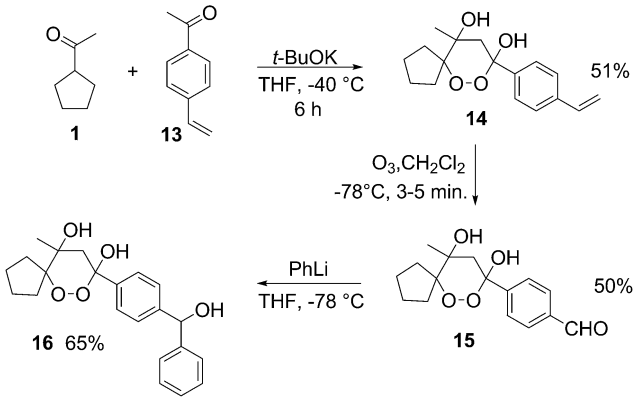
Table 2 Gibbs free energy changes for the formation of more substituted enolates, calculated with two methods at BP86-D3/TZP level of theory[13]



	ΔG (kcal mol^{-1})	
Ketone	Method I	Method II
1	−3.92	−3.99
3	−4.08	−4.48
5a	−3.34	−3.05
5b	−3.72	−3.14
5c	−3.13	−2.46
5d	−3.81	−3.54
5e	7.04	7.32
11	−5.45	−5.40



Scheme 3 Reactions of ketones **3** and **11**, as predicted by calculations.



Scheme 4 Linking the endoperoxide structural unit to other structures *via* organometallic addition.

Conclusions

The new method for the synthesis of endoperoxides (1,2-dioxanes) is described, which relies on the base-catalyzed cyclotrimerization of two ketones with molecular oxygen. The domino reaction involves the oxidation of 1-cyclopentylethanone with molecular oxygen, cross-aldol addition and cyclization. The product of the reaction with acetylstyrene is amenable to further synthetic transformations, which allows for the linkage of the endoperoxide structural unit with other molecules.

Experimental

General experimental

All chromatographic separations were performed on silica, 10–18, 60A, ICN Biomedicals. Standard techniques were used for the purification of reagents and solvents. NMR spectra were recorded on a Bruker Avance III 500. Chemical shifts are expressed in ppm (δ) using tetramethylsilane as internal standard. IR spectra were recorded on a Nicolet 6700 FT instrument, and are expressed in cm^{-1}. Mass spectra were obtained on Agilent technologies 6210 TOF LC/MS instrument (LC: series 1200). Melting points were determined on an electrothermal apparatus and are corrected. Microanalyses were performed using the Vario EL III instrument CHNOS Elementar Analyzer, Elementar Analysensysteme GmbH, Hanau, Germany. Diffraction data were collected on an Oxford Diffraction KM4 four-circle goniometer equipped with Sapphire CCD detector.

General procedure for the synthesis of endoperoxides: 8-cyclopentyl-10-methyl-6,7-dioxaspiro[4.5]decane-8,10-diol (2). KO*t*-Bu (55.2 mg; 0.493 mmol; 1.97 equiv.) and KOH (4.8 mg, 0.085 mmol, 0.34 equiv.) were added to a cold (0 °C) solution of 1-cyclopentylethanone (28 mg; 0.25 mmol) in THF (0.5 mL), with stirring, under an argon atmosphere. During the addition of the base, the cork was opened for 10 s, so that the air could enter into the reaction flask. The reacting solution should occupy $\frac{1}{4}$ of the flask volume (in this experiment a 2 mL flask was used). The reaction mixture was stirred for 1 h, when TLC indicated the consumption of the starting material. The reaction was quenched by the addition of water and 10% citric acid to attain pH 4, followed by ethyl acetate extraction. The organic extract was dried over $MgSO_4$ anh., filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 8/2) afforded 15.5 mg (48%) of the title compound (**2**), as white solid. Crystallization from petroleum-ether/ethyl acetate gave white crystals, mp 111–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05 (d, J = 1.0 Hz, 1H, OH), 3.61 (s, 1H, OH), 2.26–2.18 (m, 1H), 2.06–1.92 (m, 2H), 1.91–1.43 (m, 14H), 1.83 (d, J = 14.1 Hz, 1H), 1.75 (dd, J = 14.0 and 0.8 Hz, 1H), 1.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 103.2 (C), 96.3 (C), 71.0 (C), 47.5 (CH), 39.6 (CH_2), 32.1 (CH_2), 31.4 (CH_2), 26.6 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 24.8 (CH_2), 24.3 (CH_3). IR (film) ν_{max}: 3456, 3367, 2953, 2868, 1730, 1665, 1451 1379, 1305. HRMS (ESI-TOF high acc.) calcd for $C_{14}H_{24}O_4$ (M + NH_4^+): 274.2013, found: 274.2010. Microanalysis: calcd for $C_{14}H_{20}O_4$: C 65.60; H 9.44%; found: C 65.37; H 9.51.

8-(Cyclopent-3-enyl)-10-methyl-6,7-dioxaspiro[4.5]dec-2-ene-8,10-diol (4). According to the procedure for the preparation of compound **2**, using 1-(cyclopent-3-enyl)ethanone (48.6 mg, 0.44 mmol), KO*t*-Bu (134 mg; 1.2 mmol; 2.7 equiv.) and KOH (12 mg, 0.2 mmol, 0.45 equiv.) in THF (1.2 mL) at −20 °C for 2 h. Purification of the crude material by column chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 8/2) afforded 24 mg (43%) of the title compound (**4**), as white solid. Crystallization from petroleum-ether/ethyl acetate gave white crystals, mp 68–70 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69–5.62 (m, 4H), 3.94 (d, J = 1.3 Hz, 1H, OH), 3.72 (s, 1H, OH), 3.05–2.97 (m, 1H), 2.85–2.78 (m, 1H), 2.50–2.31 (m, 6H), 2.21–2.12 (m, 1H), 1.85 (d, J = 14.1 Hz, 1H), 1.75 (dd, J = 14.1 and 1.2 Hz, 1H), 1.16 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.5 (CH), 129.3 (CH), 128.1 (2 × CH), 103.3 (C), 94.9 (C), 70.8 (C), 45.1 (CH), 39.1 (CH_2), 38.6 (CH_2), 37.9 (CH_2), 33.6 (CH_2), 32.7 (CH_2), 24.3 (CH_3). IR (film) ν_{max}: 3422, 3056, 2929, 2856, 1707, 1622, 1547, 1430, 1379, 1345. HRMS (ESI-TOF high acc.) calcd for $C_{14}H_{20}O_4$ (M + K^+): 291.0993, found: 291.0988. Microanalysis: calcd for $C_{14}H_{20}O_4$: C 66.65; H 7.99%; found: C 66.28; H 8.04.

8,10-Dimethyl-6,7-dioxaspiro[4.5]decane-8,10-diol (6a). According to the procedure for the preparation of compound **2**, using 1-cyclopentylethanone (20 mg; 0.179 mmol), propan-2-one (10.35 mg; 0.179 mmol), KO*t*-Bu (80 mg; 0.714 mmol; 4 equiv.) and KOH (4.3 mg; 0.107 mmol; 0.6 equiv.) in THF 1 mL

at −20 °C for 5 h. Purification of the residue by column chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 8/2) afforded 23 mg (64%) of title compound (**6a**), as white solid, mp 98 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (s, 1H, OH), 3.50 (s, 1H, OH), 2.27–2.19 (m, 1H), 1.98–1.83 (m, 3H), 1.82–1.72 (m, 2H), 1.68–1.45 (m, 4H), 1.34 (s, 3H), 1.18 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 100.3 (C), 96.1 (C), 71.3 (C), 42.1 (CH_2), 32.0 (CH_2), 31.3 (CH_2), 26.0 (CH_3), 25.7 (CH_2), 24.7 (CH_2), 24.1 (CH_3). IR (film) ν_{max}: 3421, 2960, 2872, 1446, 1378, 1323, 1214, 1170, 1080. HRMS (ESI-TOF high acc.) calcd for $C_{10}H_{18}O_4$ (M + Na)$^+$: 225.1097, found: 225.1094.

8-Isopropyl-10-methyl-6,7-dioxaspiro[4.5]decane-8,10-diol (6b). According to the procedure for the preparation of compound **2**, using 1-cyclopentylethanone (28 mg; 0.25 mmol), 4-methylpentan-2-one (21 mg; 0.25 mmol), KO*t*-Bu (110.5 mg; 0.986 mmol; 3.94 equiv.) and KOH (9.5 mg; 0.17 mmol; 0.68 equiv.) in THF (1 mL) at −20 °C for 2 h. Purification of the crude material by column chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 8/2) afforded 36 mg of white solid, the mixture of the title compound **6b** and 8-cyclopentyl-10-methyl-6,7-dioxaspiro[4.5]decane-8,10-diol (**2**) in 2.9 : 1 ratio, as determined from the integrals of OH signals in the ^{1}H NMR spectrum. This sample contained a small amount of an unidentified impurity which could not be separated by column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (d, J = 1.3 Hz, 1H, OH), 3.56 (s, 1H, OH), 2.26–2.16 (m, 1H), 2.03–1.92 (m, 1H), 1.91–1.43 (m, 7H), 1.79 (d, J = 14.0 Hz, 1H), 1.72 (dd, J = 14.0 and 1.2 Hz, 1H), 1.19 (s, 3H), 0.97 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 103.3 (C), 96.3 (C), 71.0 (C), 37.7 (CH_2), 36.3 (CH), 32.1 (CH_2), 31.4 (CH_2), 25.8 (CH_2), 24.8 (CH_2), 24.3 (CH_3), 16.5 (CH_3), 15.8 (CH_3). IR (film) ν_{max}: 3365, 3443, 3404, 2960, 2872, 1730, 1659, 1453, 1382, 1327. HRMS (ESI-TOF high acc.) calcd for $C_{12}H_{22}O_4$ (M + NH_4^+): 248.1856, found: 248.1848.

8-Isobutyl-10-methyl-6,7-dioxaspiro[4.5]decane-8,10-diol (6c). According to the procedure for the preparation of compound **2**, using 1-cyclopentylethanone (28 mg; 0.25 mmol), 4-methylpentan-2-one (21 mg; 0.25 mmol; 1 equiv.), KO*t*-Bu (110.5 mg; 0.99 mmol; 3.94 equiv.) and KOH (9.5 mg; 0.17 mmol; 0.68 equiv.) in THF (1 mL) at −40 °C for 3.5 h. Purification of the crude material by column chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 8/2) afforded 39 mg of white solid, which is the mixture of the title compound (**6c**) and 8-cyclopentyl-10-methyl-6,7-dioxaspiro[4.5]decane-8,10-diol (**2**), in a 17 : 1 ratio, as determined from the integrals of OH signals in the ^{1}H NMR spectrum. Crystallization from petroleum-ether/ethyl acetate gave white crystals (43%), mp 64–65 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (d, J = 1.0 Hz, OH), 3.42 (s, 1H, OH), 2.26–2.18 (m, 1H), 1.99–1.72 (m, 4H), 1.84 (d, J = 14.0 Hz, 1H), 1.75 (dd, J = 13.9 and 1 Hz, 1H), 1.70–1.39 (m, 6H), 1.18 (s, 3H), 0.98 (d, J = 9.1 Hz, 3H), 0.96 (d, J = 9.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 102.3 (C), 96.2 (C), 71.2 (C), 47.8 (CH_2), 41.1 (CH_2), 32.3 (CH_2), 31.4 (CH_2), 25.9 (CH_2), 24.8 (CH_2), 24.3 (CH_3), 24.2 (CH_3), 23.9 (CH_3), 23.2 (CH). IR (film) ν_{max}: 3412, 2957, 2871, 1711, 1454, 1380, 1297. HRMS (ESI-TOF high acc.) calcd for $C_{15}H_{26}O_4$ (M + NH_4^+): 288.2169, found: 288.2161.

10-Methyl-8-(4-methylpent-3-enyl)-6,7-dioxaspiro[4.5]decane-8,10-diol (6d). According to the procedure for the preparation of compound **2**, using 1-cyclopentylethanone (28 mg; 0.25 mmol; 1 equiv.), 6-methylhept-5-en-2-one (31.5 mg; 0.25 mmol; 1 equiv.), KO*t*-Bu (110.5 mg; 0.986 mmol; 3.94 equiv.) and KOH (9.5 mg; 0.17 mmol; 0.68 equiv.) in THF (1 mL) at −40 °C for 2 h. Purification of the crude material by column chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 8/2) afforded 33 mg of the pale yellow oil, which is the mixture of the title compound (**6d**) and 8-cyclopentyl-10-methyl-6,7-dioxaspiro[4.5]decane-8,10-diol (**2**) in a 5 : 1 ratio, as determined from the integrals of OH signals in the ^{1}H NMR spectrum. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09 (t, J = 7.0 Hz, 1H), 4.43 (s, 1H, OH), 3.69 (s, 1H, OH), 2.28–2.03 (m, 3H), 2.03–1.91 (m, 1H), 1.91–1.42 (m, 10H), 1.68 (s, 3H), 1.62 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.6 (C), 123.3 (CH), 101.7 (C), 96.4 (C), 71.0 (C), 40.6 (CH_2), 38.9 (CH_2), 32.1 (CH_2), 31.4 (CH_2), 25.8 (CH_2), 25.6 (CH_3), 24.8 (CH_2), 24.1 (CH_3), 21.2 (CH_2), 17.6 (CH_3). IR (film) ν_{max}: 3432, 3374, 2958, 2931, 2869, 1666, 1450, 1449, 1379. HRMS (ESI-TOF high acc.) calcd for $C_{15}H_{26}O_4$ (M + NH_4^+): 288.2169, found: 288.2161.

8-Cyclopropyl-10-methyl-6,7-dioxaspiro[4.5]decane-8,10-diol (6e). According to the procedure for the preparation of compound **2**, using 1-cyclopentylethanone (46.7 mg; 0.417 mmol; 1 equiv.), 1-cyclopropylethanone (35 mg; 0.417 mmol; 1 equiv.), KO*t*-Bu (186.9 mg; 1.668 mmol; 4 equiv.) and KOH (16.1 mg; 0.287 mmol; 0.69 equiv.) in THF (1.6 mL) at −40 °C for 5 h. Purification of the crude material by column chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 8/2) afforded 63.2 mg of the white solid, the mixture of the title compound (**6e**) and 8-cyclopentyl-10-methyl-6,7-dioxaspiro[4.5]decane-8,10-diol (**2**) in a 6 : 1 ratio, as determined from the integrals of OH signals in the ^{1}H NMR spectrum. Crystallization from petroleum-ether/ethyl acetate gave white crystals (39%), mp 106–107 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04 (s, 1H, OH), 3.42 (s, 1H, OH), 2.30–2.19 (m, 1H), 2.00–1.90 (m, 1H), 1.90–1.82 (m, 1H), 1.86 (s, 2H), 1.82–1.71 (m, 1H), 1.72–1.52 (m, 3H), 1.43–1.43 (m, 1H), 1.19 (s, 3H), 0.97 (tt, J = 8.4 and 5.3 Hz, 1H), 0.66–0.58 (m, 1H), 0.55–0.38 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.5 (C), 96.3 (C), 71.3 (C), 41.5 (CH_2), 32.1 (CH_2), 31.3 (CH_2), 25.7 (CH_2), 24.7 (CH_2), 24.2 (CH_3), 18.1 (CH), 0.7 (CH_2), 0.1 (CH_2). IR (film) ν_{max}: 3424, 3362, 2960, 2872, 1659, 1636, 1471, 1381, 1322. HRMS (ESI-TOF high acc.) calcd for $C_{12}H_{20}O_4$ (M + H^+): 229.1434, found: 229.1431. Microanalysis: calcd for $C_{12}H_{20}O_4$: C 63.14; H 8.83%; found: C 62.93; H 8.82.

10-Methyl-8-phenyl-6,7-dioxaspiro[4.5]decane-8,10-diol (6f). According to the procedure for the preparation of compound **2**, using 1-cyclopentylethanone (46.7 mg; 0.417 mmol; 1 equiv.), 1-phenylethanone (50 mg; 0.417 mmol; 1 equiv.), KO*t*-Bu (186.9 mg; 1.668 mmol; 4 equiv.) and KOH (16.1 mg; 0.287 mmol; 0.69 equiv.) in THF (1.6 mL) at −40 °C for 6 h. Purification of the crude material by column chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 8/2) afforded 66.5 mg of white solid, the mixture of the title compound (**6f**) and 8-cyclopentyl-10-methyl-6,7-dioxaspiro[4.5]decane-8,10-diol (**2**) in a 9 : 1 ratio, as determined from the integrals of OH signals in the ^{1}H NMR spectrum. Crystallization from petroleum-ether/ethyl acetate gave white crystals (31%), mp (dec.) 125 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.50 (m, 2H), 7.42–7.32 (m, 3H), 4.54 (s, 1H, OH), 3.60 (s, 1H, OH), 2.48–2.40 (m, 1H), 2.06 (s, 2H), 2.02 (dd, J =

14.8 and 7.6 Hz, 1H), 1.99–1.91 (m, 1H), 1.89–1.78 (m, 1H), 1.77–1.52 (m, 4H), 1.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0 (C), 128.9 (CH), 128.4 (CH), 125.4 (CH), 101.1 (C), 96.5 (C), 71.3 (C), 43.7 (CH_2), 32.4 (CH_2), 31.5 (CH_2), 25.9 (CH_2), 24.9 (CH_2), 24.1 (CH_3). IR (film) ν_{max}: 3357, 3139, 2976, 2933, 2867, 1707, 1657, 1632, 1492, 1449, 1431, 1381. HRMS (ESI-TOF high acc.) calcd for $C_{15}H_{20}O_4$ (M + NH_4^+): 282.1700, found: 282.1697. Microanalysis: calcd for $C_{12}H_{20}O_4$: C 68.16; H 7.63%; found: C 68.55; H 7.54.

8-(4-Bromophenyl)-10-methyl-6,7-dioxaspiro[4.5]decane-8,10-diol (6g). According to the procedure for the preparation of compound **2**, using 1-cyclopentylethanone (37 mg; 0.33 mmol), 1-(4-bromophenyl)ethanone (102 mg; 0.512 mmol), KO*t*-Bu (154 mg; 1.38 mmol) and KOH (8.3 mg; 0.207 mmol; 0.6 equiv.) in THF (2 mL) at −40 °C for 5 h. Purification of the residue by column chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 8/2) afforded 76 mg (67%) of title compound (**6g**), as a white solid, mp 143 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.47 (m, 2H), 7.40–7.36 (m, 2H), 5.02 (s, 1H, OH), 3.44 (s, 1H, OH), 2.43–2.35 (m, 1H), 2.00 (s, 2H), 1.98–1.91 (m, 1H), 1.86–1.77 (m, 1H),1.75–1.59 (m, 4H), 1.58–1.51 (m, H), 1.20 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0 (C), 131.8 (CH), 127.3 (CH), 123.3 (C), 101.3 (C), 96.5 (C), 71.9 (C), 43.7 (CH_2), 32.7 (CH_2), 31.8 (CH_2), 26.1 (CH_2), 25.0 (CH_2), 24.4 (CH_3). IR (film) ν_{max}: 3453, 3408, 3375, 2928, 2856, 1593, 1446, 1388, 1226, 1137, 1057. HRMS (ESI-TOF high acc.) calcd for $C_{15}H_{19}BrO_4$ (M + K)$^+$: 381.0098, found: 381.0091.

10-Methyl-8-(pyridin-4-yl)-6,7-dioxaspiro[4.5]decane-8,10-diol (6h). According to the procedure for the preparation of compound **2**, using 1-cyclopentylethanone (28 mg; 0.25 mmol; 1 equiv.), 1-(pyridin-4-yl)ethanone (30 mg; 0.25 mmol; 1 equiv.), KO*t*-Bu (110.5 mg; 0.99 mmol; 3.94 equiv.) and KOH (9.5 mg; 0.17 mmol; 0.68 equiv.) in THF (1 mL) at −40 °C for 4 h. Purification of the crude material by column chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 1/4) afforded 18.4 mg (28%) of the title compound (**6h**) as a pale yellow solid, mp (dec.) 128–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (dd, J = 11.5 and 6.2 Hz), 7.40 (dd, J = 4.7 and 1.4 Hz, 2H), 4.54–4.09 (s, 1H, OH), 2.46–2.34 (m, 1H), 2.11–1.87 (m, 2H), 1.99 (d, J = 14.1, 1H), 1.91 (d, J = 14.0 Hz, 1H), 1.87–1.77 (m, 1H), 1.77–1.51 (m, 4H), 1.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2 (C), 149.2 (2CH), 120.2 (2CH), 100.3 (C), 96.8 (C), 71.0 (C), 43.5 (CH_2), 32.5 (CH_2), 31.5 (CH_2), 25.9 (CH_2), 24.9 (CH_2), 24.0 (CH_3). IR (film) ν_{max}: 3331, 2962, 2870, 1702, 1671, 1606, 1454, 1412, 1379, 1326. HRMS (ESI-TOF high acc.) calcd for $C_{14}H_{19}O_4$ (M + H^+): 266.1387, found: 266.1386.

1-(1-Hydroperoxycyclopentyl)ethanone (8).[10] KO*t*-Bu (531 mg; 4.74 mmol; 1.77 equiv.) was dissolved in a solvent mixture: *t*-BuOH (4.3 mL) and DME (4.3 mL) under an argon atmosphere, and the resulting yellow-orange solution was cooled to −30 °C. After that, oxygen was bubbled through the solution until the reaction was complete. 1-Cyclopentylethanone (300 mg; 2.68 mmol; 1 equiv.) was added and the reaction mixture was stirred for the next 75 minutes, when TLC (petroleum-ether/ethyl acetate = 4 : 1, PAA) indicated that nearly all of the substrate was converted and the product was starting to decay. Ice-cold sat. $NaHCO_3$ (3 mL) was added, layers were separated, pH of the aqueous layer was adjusted to 3–4 using conc. H_3PO_4 (~0.5 mL), diluted with water and extracted with diethyl ether (2 × 10 mL). The combined etheral extract was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 6 : 1). Pure hydroperoxyde **8** (275.8 mg, 71%) was isolated as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H, OO*H*), 2.33 (s, 3H), 2.03–1.85 (m, 4H), 1.83–1.64 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7 (C), 99.0 (C), 33.3 (CH_2), 25.2 (CH_3), 25.0 (CH_2). IR (film) ν_{max}: 3385, 2961, 2874, 1707, 1435, 1358. HRMS (ESI-TOF high acc.) calcd for $C_7H_{12}O_3$ (M + NH_4^+): 162.1125, found: 162.1120.

8-Isobutyl-10-methyl-6,7-dioxaspiro[4.5]dec-2-ene-8,10-diol (10). According to the procedure for the preparation of compound **2**, using 1-(cyclopent-3-enyl)ethanone **3** (10 mg; 0.091 mmol), 4-methylpentan-2-one **5c** (9.1 mg; 0.091 mmol; 1 equiv.), KO*t*-Bu (30.6 mg; 0.272 mmol; 3 equiv.) and KOH (2.6 mg; 0.047 mmol; 0.5 equiv.) in THF (0.5 mL) at −30 °C for 3 h. The yield of the crude product **10**, as determined from ^{1}H NMR spectrum, was 37%. Purification of the residue by column chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 3/1) afforded 5.3 mg (19%) of title compound **10**, as a white solid, mp 54–56 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67–5.64 (m, 2H), 3.93 (d, J = 1.4 Hz, 1H, OH), 3.70 (s, 1H, OH), 3.03–2.99 (m, 1H), 2.83–2.79 (m, 1H), 2.42–2.37 (m, 1H), 2.18–2.14 (m, 1H), 1.93–1.93 (m, 1H), 1.87 (d, J = 14.0 Hz, 1H), 1.77 (dd, J = 14.0 and 1.4 Hz, 1H), 1.52 (dd, J = 14.5 and 5.7 Hz, 1H), 1.45 (dd, J = 14, 5 and 7.2 Hz), 1.14 (s, 3H), 0.98 (d, J = 8.7 Hz, 3H), 0.97 (d, J = 8.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.2 (CH), 128.1 (CH), 102.4 (C), 94.8 (C), 70.8 (C), 48.0 (CH_2), 40.2 (CH_2), 39.2 (CH_2), 38.6 (CH_2), 24.3 (CH_3), 23.9 (CH_3), 23.2 (CH). IR (film) ν_{max}: 3402, 3059, 2955, 2871, 1460, 1429, 1190, 1034, 870. HRMS (ESI-TOF high acc.) calcd for $C_{13}H_{22}O_4$ (M + K^+): 281.1150, found: 281.1154.

4,6-Dimethyl-1′,3′-dihydrospiro[[1,2]dioxane-3,2′-indene]-4,6-diol (12). According to the procedure for the preparation of compound **2**, using 1-(2,3-dihydro-1*H*-inden-2-yl)ethanone **11** (40 mg; 0.25 mmol; 1 equiv.), propan-2-one (14.5 mg; 0.25 mmol; 1 equiv.), KO*t*-Bu (112 mg; 1 mmol; 4 equiv.) and KOH (9.8 mg; 0.175 mmol; 0.7 equiv.) in THF (1 mL) at −20 °C for 17 h. Purification of the crude material by column chromatography (SiO_2; eluent: petroleum ether/ethyl acetate = 7/3) afforded 45.2 mg of the title compound **12** as a white solid. Crystallization from petroleum-ether/ethyl acetate gave white crystals (64%), mp 136–137 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19–7.12 (m, 4H), 4.79 (s, 1H, OH), 4.14 (s, 1H, OH), 3.60 (d, J = 17.2, 1H), 3.44 (d, J = 18.2, 1H), 3.02 (d, J = 17.2, 1H), 2.79 (d, J = 18.2, 1H), 1.94 (d, J = 14.2, 1H), 1.85 (d, J = 14.1, 1H), 1.37 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5 (C), 140.2 (C), 126.7 (CH), 126.6 (CH), 124.7 (CH), 124.5 (CH), 100.7 (C), 95.1 (C), 70.9 (C), 41.4 (CH_2), 38.6 (CH_2), 38.2 (CH_2), 26.1 (CH_3), 24.3 (CH_3). IR (ATR) ν_{max}: 3412, 3024, 2934, 2851, 2867, 1710, 1484, 1459, 1424, 1378, 1322. HRMS (ESI-TOF high acc.) calcd for $C_{14}H_{18}O_4$ (M + K^+): 289.0837, found: 289.0834. Microanalysis: calcd for $C_{14}H_{18}O_4$: C 67.18; H 7.25%; found: C 66.83; H 7.54.

10-Methyl-8-(4-vinylphenyl)-6,7-dioxaspiro[4.5]decane-8,10-diol (14). According to the procedure for the preparation of

compound **2**, using 1-cyclopentylethanone (70 mg, 0.62 mmol), 1-(4-vinylphenyl)ethanone (137 mg, 0.94 mmol), potassium *tert*-butoxide (280 mg, 2.5 mmol) and potassium hydroxide (21 mg; 0.37 mmol; 0.59 equiv.) in THF (4 mL) at −40 °C, 6 h. Purification of the residue by column chromatography (SiO_2; eluent: petroleum-ether/ethyl acetate = 8/2) afforded 93 mg (51%) of title compound, as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.45 (m, 2H), 7.41–7.38 (m, 2H), 6.70 (dd, J = 17.6, J = 10.9, 1H), 5.76 (dd, J = 17.6, J = 0.8, 1H), 5.27 (dd, J = 10.9, J = 0.8, 1H), 4.78 (s, 1H, OH), 3.70 (s, 1H, OH), 2.45–2.39 (m, 1H), 2.20–1.98 (m, 1H), 2.03 (s, 2H), 1.96–1.90 (m, 1H),1.84–1.78 (m, 1H), 1.72–1.62 (m, 3H), 1.58–1.52 (m, 1H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2 (C), 138.6 (C), 136.1 (CH), 126.1 (CH), 125.3 (CH), 114.6 (CH_2), 101.3 (C), 96.6 (C), 71.3 (C), 43.5 (CH_2), 32.3 (CH_2), 31.3 (CH_2), 25.8 (CH_2), 24.6 (CH_2), 23.9 (CH_3). IR (film) ν_{max}: 3406, 2964, 2871, 1608, 1432, 1379, 1307, 1229, 1138, 1055, 840, 737. HRMS (ESI-TOF high acc.) calcd for $C_{17}H_{22}O_4$ (M + K^+): 329.1150, found: 329.1145.

4-(8,10-Dihydroxy-10-methyl-6,7-dioxaspiro[4.5]decan-8-yl)-benzaldehyde (15). Ozone was bubbled through a cold (−78 °C) solution of 10-methyl-8-(4-vinylphenyl)-6,7-dioxaspiro[4.5] decane-8,10-diol (**9**; 40 mg, 0.138 mmol) in dichloromethane (10 mL). As soon as the blue color of dissolved ozone was detected, argon was bubbled through the reaction mixture for 3–5 min and dimethylsulfide (0.5 mL) was added. The reaction mixture was stirred at room temperature for 6 h, volatiles were removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/ethyl acetate = 8/2), to yield 20.2 mg (50%) of aldehyde **15**, as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.88–7.86 (m, 2H), 7.71–7.68 (m, 2H), 5.48 (s, 1H, OH), 3.54 (s, 1H, OH), 2.46–2.40 (m, 1H), 2.03 (s, 2H), 2.02–1.92 (m, 2H),1.85–1.80 (m, 1H), 1.75–1.62 (m, 3H), 1.60–1.53 (m, 1H), 1.23 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1 (CH), 146.9 (C), 136.3 (C), 129.7 (CH), 125.6 (CH), 101.0 (C), 96.6 (C), 71.6 (C), 43.5 (CH_2), 32.3 (CH_2), 31.3 (CH_2), 25.9 (CH_2), 24.8 (CH_2), 24.8 (CH_3). IR (film) ν_{max}: 3388, 2964, 2870, 1702, 1453, 1383, 1214, 1169, 1056, 830. HRMS (ESI-TOF high acc.) calcd for $C_{16}H_{20}O_5$ (M + K^+): 331.0942, found: 331.0940.

8-(4-(Hydroxyl(phenyl)methyl)phenyl)-10-methyl-6,7-dioxaspiro[4.5]decane-8,10-diol (16). A solution of phenyllithium (1.5 M in dibutyl ether; 0.233 mL; 0.35 mmol; 1.5 equiv.) was added to a cold (−78 °C) solution of aldehyde **11** (25.5 mg, 0.087 mmol) in dry THF (1 mL), under an argon atmosphere. After 1 h of stirring, the reaction was quenched with saturated $NaHCO_3$ and the product was extracted with ethyl acetate. The organic extract was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The residue was purified by dry-flash chromatography (petroleum-ether/ethyl acetate = 9/1), to yield 21.1 mg (65%) of 8-(4-(hydroxyl(phenyl)methyl)phenyl)-10-methyl-6,7-dioxaspiro [4.5]decane-8,10-diol (**16**), as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.44 (m, 2H), 7.42–7.30 (m, 6H), 5.83 (s, 1H), 4.60 (s, 1H, OH), 3.56 (s, 1H, OH), 2.45–2.37 (m, 1H), 2.33 (broad s, 1H, OH), 2.02 (s, 2H), 2.01–1.87 (m, 2H), 1.86–1.77 (m, 1H), 1.72–1.61 (m, 3H), 1.57–1.51 (m, 1H), 1.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4 (C), 143.5 (C), 140.1 (C), 128.5 (CH), 127.9 (CH), 126.5 (CH), 125.3 (CH), 101.2(C), 96.4 (C), 75.9 (CH), 71.2 (C), 43.5 (CH_2), 32.3 (CH_2), 31.4 (CH_2), 25.8 (CH_2), 24.7 (CH_2), 24.1 (CH_3). IR (film) ν_{max}: 3364, 2926, 2857, 1599, 1452, 1380, 1230, 1168, 1021, 737. HRMS (ESI-TOF high acc.) calcd for $C_{22}H_{26}O_5$ (M + Na^+): 393.1673, found: 393.1677.

Computational details

All the calculations have been carried out with the Amsterdam Density Functional program package, ADF2013.01.[15] An all electron Triple-zeta Slater-type orbitals (STO) plus one polarization function (TZP) basis set has been used for all atoms. Solvent effects in THF solution are described with the COSMO model[16] as implemented in ADF.[17] Geometry optimizations of all investigated molecules, both in the gas phase and in solution, were performed using general gradient functional consisting of Becke's exchange[18] and Perdew's correlation[19] with Grimme's third-generation dispersion energy correction[20] and Becke–Johnson dumping,[21] *i.e.* BP86-D3 functional, with Becke's integration grid of good quality.[22] Analytical harmonic frequencies[23] were calculated at the same level of theory, in order to ascertain that all the optimized structures correspond to the minima on the potential energy surface. In addition, vibrational analysis have been used to evaluate zero point effects, entropic and thermal corrections to the Gibbs free energy. Gibbs free energy changes for a reaction of a ketone with *tert*-butoxide, forming corresponding enolate and *tert*-butanol in THF solution, have been calculated with two methods. The two methods are employed because accurate description of reactions in solutions are still not at the same high levels as those in the gas phase, and there are debates in the literature concerning the free energy calculations with implicit solvation methods.[24] The first method is direct calculation of thermodynamic properties within the COSMO model. COSMO model takes effectively into account cavitation, internal energy and entropy effects of the solvent, and therefore can yield an estimate of the Gibbs free energies.[25] The second method is indirect, and is based on the thermodynamic cycle for proton exchange reactions, commonly employed for the calculations of pK_a values.[12] With the indirect method, the gas-phase free energies of reactants and products are corrected by solvation energies and energies due to the geometry relaxation in the solvent. These corrections are straightforwardly acquired from energy differences between the gaseous and solvated states, since COSMO implementation in ADF reports the energies relative to the gas phase fragments.[17]

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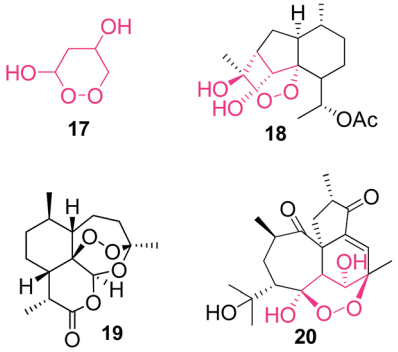

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