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Selective transformation of tricyclic peroxides with pronounced antischistosomal activity into 2-hydroxy-1,5-diketones using iron (II) salts

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ABSTRACT

The present work deals with selective transformations of peroxides into organic compounds via the cleavage of the O–O bond using variable valence metals. A selective transformation of tricyclic peroxides promoted by Fe^{2+} salts was discovered. This selective transformation is unexpected for compounds with structural features which allow diverse decomposition pathways. 2-Hydroxy-1,5-diketones are prepared in yields up to 92% in the reactions of tricyclic peroxides with $FeSO_4$, $Fe(ClO_4)_2$, or $FeCl_2$. This is a new preparative method for the synthesis of 1,5-diketones. 2-Hydroxy-1,5-diketones in $CDCl_3$ at 25 °C exist mainly in the open-chain form of the hydroxyketone over the cyclic hemiacetal. The results of this work can be of interest to understand the mechanism of the antiparasitic action of peroxides.

1. Introduction

The chemistry of peroxides is of interest in organic synthesis largely due to the potential of oxidative transformations associated with a weak O–O bond, which can be cleaved via both homo- and heterolytic mechanisms. The most well-known and commonly used processes are reactions without the involvement of variable valence metals: the synthesis of lactones by the Baeyer–Villiger oxidation,[1] the Story synthesis of lactones,[2] the Hock synthesis of phenol and acetone,[3] the Criegee cleavage of peresters,[4] the Kornblum–DeLaMare rearrangement and related processes giving carbonyl compounds and alcohols,[5] the Schenck and Smith rearrangements of steroid hydroperoxides.[6] Other oxidative transformations of peroxides giving acids,[7] esters,[8] ketones,[9] and epoxides[10] are also known. The present work deals with selective transformations of peroxides into organic compounds via the cleavage of O–O bond using variable valence metals. There are a limited number of examples of the preparative application of peroxide cleavage by such salts.

For instance, the β-scission of cyclic ketone peroxides to form omega-functionalized,[11] unsaturated,[12] and dicarboxylic acids,[13] the formation of C-centered radicals from ketone peroxides and their addition to alkenes[14] and diazonium salts[15] were documented. The cleavage of hydroperoxides promoted by metal salts can be used to synthesize macrocycles,[16,17] ketones,[18] haloketones,[19] and diketones.[20]

The main problem with the metal salt-promoted cleavage of peroxides is low selectivity of the reactions. In the present work, we succeeded in finding a non-trivial example of reaction, in which tricyclic monoperoxides[21] are transformed into hydroxydiketones in high yield under the action of iron ions. To the best of our knowledge the discovered process is the first example of the oxidative deacylation of β-diketones to afford α-hydroxylated ketones. This transformation provides a facile approach to the preparation of 1,5-diketones. Selected methods of the synthesis of 1,5-diketones are based mainly on the reaction of ketones with paraformaldehyde,[22] the Wacker-type oxidation of 1,6-dienes,[23] the oxidation of 1,6-alkynes,[24] the reaction of glutaric acid chloride

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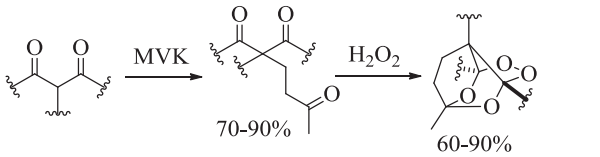
0040-4020/

with Grignard-[25] and organolithium reagents,[26] and the oxidation of various compounds containing a cyclopentane ring.[27]

It was found that the tricyclic monoperoxides studied in this paper show pronounced antischistosomal activity.[28] Schistosomiasis is a neglected tropical disease, caused basically by three Schistosoma species, *S. mansoni*, *S. haematobium*, and *S. japonicum*. Chemotherapy using praziquantel is the mainstay of control. Praziquantel is a broad-spectrum antischistosomal drug and the treatment of choice since its discovery in the 1970s. Every year millions of people are treated with praziquantel in the frame of mass drug administration programs. For instance, in 2012, 27.5 million people in 21 countries were treated with praziquantel. In 2018, the World Health Organization aims to treat as many as 235 million people. The risk for praziquantel resistance or tolerance is rising with increasing drug applications.[29] These facts stimulate for new antischistosomal drugs development.[30]

In recent years, various semisynthetic and synthetic peroxide classes have been tested for antischistosomal properties.[31] It is proposed that a reaction of the peroxide moiety with ferrous iron in heme is responsible for both the antischistosomal and antimalarial activity.[32] As a consequence of this iron-dependent antiparasitic activity, the results of this work may be helpful for understanding some steps of the biological mode of action of peroxides.

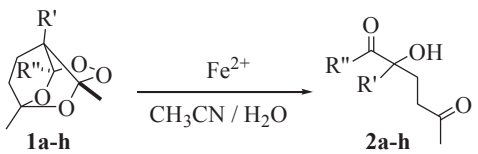
It is important to note that tricyclic monoperoxides could be easily prepared from hydrogen peroxide and β,δ-triketones, which are the products of Michael addition of β-diketones to vinyl ketones (Scheme 1).[21]



Scheme 1. General approach to the synthesis of tricyclic peroxides.

2. Results and discussion

The treatment of tricyclic monoperoxides **1a**–**h** with Fe^{2+} salts resulted in the selective formation of 2-hydroxy-1,5-diketones **2a**–**h** (Scheme 2).

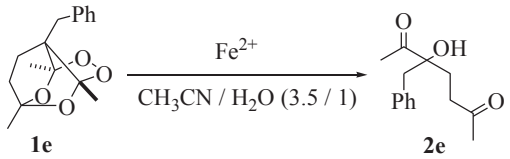


a: R' = H, R" = CH_3; **b**: R' = CH_3, R" = CH_3;
c: R' = *n*-Bu, R" = CH_3; **d**: R' = CH_2CH_2CN, R" = CH_3;
e: R' = CH_2Ph, R" = CH_3; **f**: R' = 4-$MeC_6H_4CH_2$, R" = CH_3;
g: R' = 4-$NO_2C_6H_4CH_2$, R" = CH_3; **h**: R' = H, R" = Ph

Scheme 2. Synthesis of 2-hydroxy-1,5-diketones **2a**–**h** from tricyclic peroxides **1a**–**h** using iron salts.

The transformation of peroxides was performed by treatment with a series of iron salts, such as $FeSO_4 \cdot 7H_2O$, $Fe(ClO_4)_2 \cdot 6H_2O$, $FeCl_2$, $Fe(acac)_2$, and $FeBr_2$, in aqueous acetonitrile, which ensures the solubility of both tricyclic monoperoxide and inorganic salts. The conditions for the synthesis of hydroxydiketones were optimized by studying the preparation of 3-benzyl-3-hydroxyheptane-2,6-dione **2e** from 3a-benzyl-3,6,7a-trimethyltetrahydro-3*H*,4*H*-3,6-epoxy[1,2]-dioxolo[3,4-*b*]pyran **1e**. For the reaction, we examined the effect of the nature of the catalyst, the reaction time, and the addition of sulfuric acid on the yield of hydroxydiketone **2e** (Table 1).

Table 1
Results of the optimization of the synthesis of **2e** from tricyclic peroxide **1e**[a]



Entry	Metal salt	Time, h	Yield of **2e**, %
1	$FeSO_4 \cdot 7H_2O$	1	84
2[b]	$FeSO_4 \cdot 7H_2O$	1	92
3	$FeSO_4 \cdot 7H_2O$	3	85
4	$FeSO_4 \cdot 7H_2O$	24	85
5	$Fe(ClO_4)_2 \cdot 6H_2O$	1	90
6	$FeCl_2$	1	88
7	$Fe(acac)_2$	36	55
8	$FeBr_2$	2	40

[a] **General reaction conditions**: Peroxide **1e** (300 mg, 1.09 mmol) was dissolved in MeCN (7 mL), and the solution was added at 20–25 °C to a solution of $FeSO_4 \cdot 7H_2O$, $Fe(ClO_4)_2 \cdot 6H_2O$, $FeCl_2$, $Fe(acac)_2$, or $FeBr_2$ (1.5 mol Fe^{2+}/1 mol **1e**) in H_2O (2 mL).

[b] H_2SO_4 (0.2 g, 1.99 mmol) was additionally added to a solution of $FeSO_4 \cdot 7H_2O$ in H_2O.

The best results were obtained in runs 1–6 (Table 1) using a 1.5-fold molar excess of $FeSO_4 \cdot 7H_2O$, $Fe(ClO_4)_2 \cdot 6H_2O$, or $FeCl_2$. Diketone **2e** was obtained in the highest yield in run 2 in the presence of H_2SO_4. The salts $Fe(acac)_2$ and $FeBr_2$ are less efficient in the synthesis of diketone **2e** (runs 7 and 8, respectively). The cleavage of tricyclic peroxide **1e** by other variable valence metal salts, such as CuBr, $CuBr_2$, $CoBr_2$, $Mn(OAc)_3 \cdot 2H_2O$, and $Mn(OAc)_2 \cdot 4H_2O$, which are often used in reactions with peroxides,[33] did not produce target diketone **2e**. The results of runs 1–6 show that diketone **2e** can be obtained in good yield using a 1.5-fold molar excess of $FeSO_4$ and in the presence of sulfuric acid (run 2). Under the conditions of run 2 (Table 1), we synthesized a series of hydroxydiketones **2a**–**h** containing various functional groups: cyano group (**2d**), nitro group (**2g**), or aromatic rings **2e**–**h** (Table 2).

The cleavage of monoperoxides **1a**–**h** produced hydroxydiketones **2a**–**h** in yields from 28% to 92%. The best results were obtained for hydroxydiketones **2b**–**h** containing a bulky substituent between the keto-groups. Hydroxydiketone **2a**, without a substituent in α-position was obtained in lower yield.

2.1. Proposed mechanism of the transformation of tricyclic monoperoxides

The proposed mechanism of the formation of the target products (as exemplified by **2e**) involves the oxidation of Fe^{2+} ions to Fe^{3+} by peroxide **1e** with two equivalent oxygen atoms in the peroxide bridge to form the radical anion (**A**) as the first step, followed by the rearrangement of **A** into the stabilized tertiary C-centered radical (**B**) through characteristic for peroxides β-scission.[11–13] The radical (**B**) is oxidized by Fe^{3+} to form the cation (**C**), which is transformed into the intermediate (**D**) upon exposure to water. Finally, hydrolysis of the two acetal moieties gives target hydroxydiketone **2e** (Scheme 3).

Similar mechanisms were reported in the literature for the cleavage of ketone peroxides to form omega-functionalized[11] and unsaturated[12] acids.

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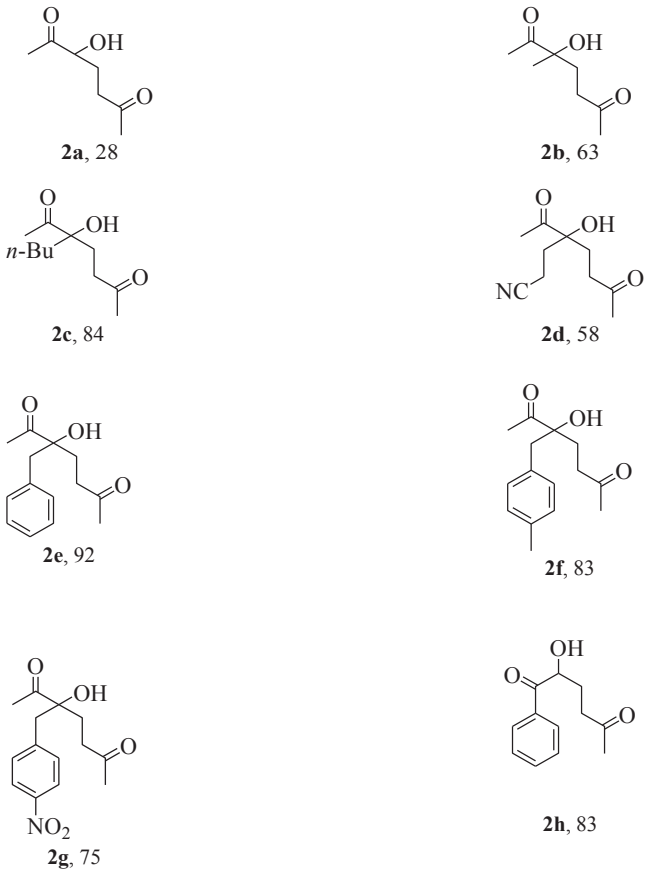
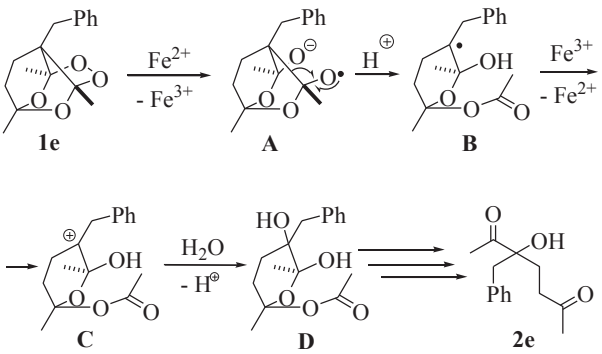
Table 2
Structures and yields (%) of hydroxydiketones **2a**–**h**[a]



[a] Peroxide **1a**–**h** (300 mg, 0.94–1.61 mmol) was dissolved in MeCN (7 mL), and the solution was added at 20–25 °C to a solution of $FeSO_4 \cdot 7H_2O$ (392–673 mg, 1.41–2.42 mmol, 1.5 mol $FeSO_4 \cdot 7H_2O$/1 mol **1a**–**h**) in H_2O (2 mL) containing H_2SO_4 (0.2 g, 1.99 mmol). The reaction mixture was stirred at 20–25 °C for 1 h.

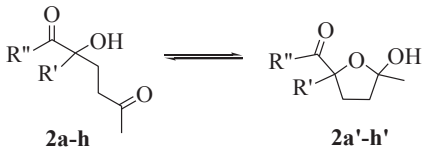


Scheme 3. Proposed mechanism of the formation of 2-hydroxy-1,5-diketones from tricyclic monoperoxides by an example of the transformation of **1e** into **2e** promoted by iron salts.

2.2. Establishment of the structures of compounds 2a–h

The structures of products **2a**–**h** were established based on the ^1H and ^{13}C NMR spectroscopic data. The ^1H NMR spectra show signals characteristic of the open form **2a**–**h** and the cyclic form **2a′**–**h′** (Scheme 4).

The percentage of the cyclic form varies from 3% in the case of 2-hydroxy-1,5-diketone **2a** to 30% in the case of 2-hydroxy-1,5-diketone **2g**. This is attributed to the fact that the bulky substituent favors the cyclization. The assignment of the signals corresponding to the structures that form an equilibrium mixture was made based on the results of 2D NMR experiments (^1H, ^1H-COSY, NOESY (EXSY) and ^1H, ^{13}C-HSQC, HMBC). The ^1H NMR spectra of the open forms of **2a**–**h** show characteristic signals of acetyl groups at δ 2.1–2.3 ppm and specific splitting of the signals of CH_2–CH_2 groups. The ^{13}C NMR spectra exhibit a signal for the carbon atom of the carbinol (COH) at δ 75.6–81.5 ppm. The NMR spectra of the cyclic forms show characteristic signals of the methyl protons at δ 1.4–1.6 ppm (^1H), as well as signals for the carbon atoms of $CH_3C(O)$**C**O at δ 91.4–91.9 ppm and signals for the hemiketal carbon atom at δ 106.6–106.9 ppm (^{13}C).



Scheme 4. Equilibrium between the linear form **2a**–**h** and the cyclic form **2a′**–**h′**.

3. Conclusions

The selective transformation of tricyclic peroxides promoted by Fe^{2+} salts was discovered. This selective transformation is unexpected for compounds with structural features which allow diverse decomposition pathways. Tricyclic peroxides are transformed into 2-hydroxy-1,5-diketones in yields up to 92% by the treatment with $FeSO_4$, $Fe(ClO_4)_2$, or $FeCl_2$. Vinyl ketones and β-diketones were the starting compounds for β,δ-triketone syntheses, from which tricyclic peroxides are prepared using hydrogen peroxide. To the best of our knowledge we have found the first example of the oxidative deacylation of β-diketones for the preparation of α-hydroxylated ketones. This work can be of interest to understand the iron-dependent antiparasitic action of peroxides.

4. Experimental section

Caution: Although we have encountered no difficulties in working with peroxides, precautions, such as the use of shields, fume hoods, and the avoidance of heating and shaking, should be taken whenever possible.

NMR spectra were recorded on Bruker Avance II 300 and Bruker Avance 400 instruments (300.13 and 400.13 MHz for ^1H, 75.48 and 100.61 MHz for ^{13}C in $CDCl_3$ referenced to residual solvent signal 7.25 ppm for ^1H and 77.0 ppm for ^{13}C spectra). High-resolution mass spectra were recorded on a Bruker micrOTOF instrument equipped with an electrospray ionization (ESI) ion source.[34] All measurements were carried out in positive (+MS) ion mode (interface capillary voltage e 4500 V) with the *m*/*z* scan range of 50–3000; the external/internal calibration was carried out with Electrospray Calibrant Solution. A syringe injection was used for solutions in MeCN (flow rate 3 μL/min). Nitrogen was used as both the nebulizer gas (0.4 bar) and the dry gas (4.0 L/min); the interface temperature was set at 180 °C.

Refraction indices were determined using IRF-22 refractometer. Analytical TLC: Macherey-Nagel Alugram UV254; Sorbent: Silica 60, specific surface (BET) ~500 m^2/g, mean pore size 60 Å, specific pore volume 0.75 mL/g, particle size 5–17 μm; Binder: highly polymeric product, which is stable in almost all organic solvents and resistant towards aggressive visualization reagents. Melting points were determined on a Kofler hot-stage apparatus. Chromatography was performed on silica gel (0.060–0.200 mm, 60 A, CAS 7631-86-9).

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Petroleum ether (PE) (40/70), EtOAc, CH_3CN, CH_2Cl_2, $FeSO_4{\cdot}7H_2O$, $Fe(acac)_2$, $FeBr_2$, $Fe(ClO_4)_2{\cdot}6H_2O$, $FeCl_2$, CuBr, $CuBr_2$, $CoBr_2$, $Mn(OAc)_3{\cdot}2H_2O$, $Mn(OAc)_2{\cdot}4H_2O$, $NaHCO_3$, H_2SO_4 (98%), and Na_2SO_4 were commercial reagents and were used as received. Tricyclic monoperoxides **1a**–**h** were synthesized according to a procedure described previously.[21]

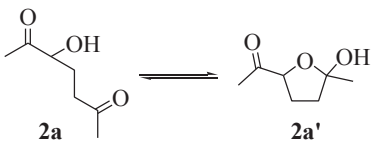
4.1. General procedure for the transformation of 3a-benzyl-3,6,7a-trimethyltetrahydro-3*H*,4*H*-3,6-epoxy[1,2]-dioxolo[3,4-*b*]pyran 1e (Table 1, runs 1–8). Synthesis of 3-benzyl-3-hydroxyheptane-2,6-dione 2e

Peroxide **1e** (300 mg, 1.09 mmol) was dissolved in MeCN (7 mL), and the solution was added with stirring at 20–25 °C to a solution of $FeSO_4{\cdot}7H_2O$, $Fe(ClO_4)_2{\cdot}6H_2O$, $FeCl_2$, $Fe(acac)_2$, or $FeBr_2$ (1.63 mmol) in H_2O (2 mL). In run 2 (Table 1), H_2SO_4 (200 mg, 1.99 mmol) was additionally added to a solution of $FeSO_4{\cdot}7H_2O$ in H_2O. The reaction mixture was stirred at 20–25 °C for 1–36 h. Then CH_2Cl_2 (20 mL) was added. In run 2 solid $NaHCO_3$ (340 mg, 4.00 mmol) was added to neutralize the acid. The brown precipitate that formed was filtered off. Water (10 mL) was added to the filtrate, and the filtrate was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed with water (2×10 mL), dried over Na_2SO_4, and filtered. The solvent was removed using a water-jet vacuum pump. Hydroxydiketone **2e** was isolated by chromatography on silica gel eluted with PE-EA using an elution gradient of EA from 10 to 50% (v/v). In similar experiments with CuBr, $CuBr_2$, $CoBr_2$, $Mn(OAc)_3{\cdot}2H_2O$, and $Mn(OAc)_2{\cdot}4H_2O$, hydroxydiketone **2e** was not detected.

4.2. General procedure for the synthesis of 2-hydroxy-1,5-diketones 2a–h from tricyclic monoperoxides 1a–h (Table 2)

Peroxide **1a**–**h** (300 mg, 0.93–1.61 mmol) was dissolved in MeCN (7 mL), and the solution was added with stirring at 20–25 °C to a solution of $FeSO_4{\cdot}7H_2O$ (389–673 mg, 1.40–2.42 mmol, 1.5 mol $FeSO_4{\cdot}7H_2O$/1 mol **1a**–**h**) in H_2O (2 mL) containing H_2SO_4 (0.2 g, 1.99 mmol). The reaction mixture was stirred at 20–25 °C for 1 h. Then CH_2Cl_2 (20 mL) and solid $NaHCO_3$ (340 mg, 4.00 mmol) were added to neutralize the acid. The brown precipitate that formed was filtered off. Water (10 mL) was added to the filtrate, and the filtrate was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed with water (2×10 mL), dried over Na_2SO_4, and filtered. The solvent was removed using a water-jet vacuum pump. Hydroxydiketones **2a**–**h** were isolated by chromatography on silica gel eluted with PE-EA using an elution gradient of EA from 10 to 50% (v/v).

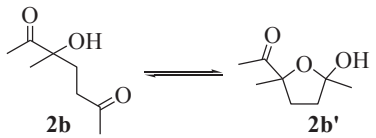
*4.2.1. 3-Hydroxyheptane-2,6-dione, **2a** (1-(5-hydroxy-5-methyltetrahydro-2-furanyl)ethanone, **2a**′).*



Acyclic : cyclic > 0.97 : 0.03

Yellow oil. Yield 28%, 65 mg. n_D^{25}=1.5245. R_f=0.41 (TLC, PE:EA, 2:1). ^{1}H NMR (major isomer) (300.13 MHz, $CDCl_3$), δ: 1.70 (dddd, *J*=14.0, 8.3, 7.4, 5.8 Hz, 1 H), 2.16 (s, 3 H), 2.19 (dddd, *J*=14.0, 7.3, 7.2, 3.7 Hz, 1 H), 2.24 (s, 3 H), 2.56 (ddd, *J*=18.3, 7.3, 5.8 Hz, 1 H), 2.68 (ddd, *J*=18.3, 7.4, 7.2 Hz, 1 H), 3.50 (br s, 1 H, OH), 4.17 (dd, *J*=8.3, 3.7 Hz, 1 H). ^{13}C NMR (75.48 MHz, $CDCl_3$), δ: 25.1, 27.0, 29.9, 38.3, 75.6, 208.1, 209.6. Anal. Found (%): C, 58.00; H, 8.42. $C_7H_{12}O_3$ Calcd (%): C, 58.32; H, 8.39. HRMS (ESI): *m*/*z* $[M+Na]^+$: Found: 167.0679. Calcd for $[C_7H_{12}NaO_3]^+$: 167.0676.

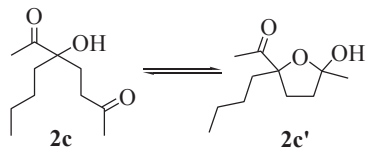
*4.2.2. 3-Hydroxy-3-methylheptane-2,6-dione, **2b** (1-(5-hydroxy-2,5-dimethyltetrahydro-2-furanyl)ethanone, **2b**′).*



Acyclic : cyclic > 0.9 : 0.1

Yellow oil. Yield 63%, 149 mg. n_D^{25}=1.5240. R_f=0.51 (TLC, PE:EA, 2:1). ^{1}H NMR (300.13 MHz, $CDCl_3$), δ: 1.34 (s, 3 H×0.9), 1.41 (s, 3 H×0.1), 1.54 (s, 3 H×0.1), 1.58–1.86 (m, 2 H×0.1), 1.86–2.04 (m, 2 H×0.9+1 H×0.1), 2.11 (s, 3 H×0.9), 2.21 (s, 3 H×0.9), 2.32 (ddd, *J*=17.9, 8.4, 6.2 Hz, 1 H×0.9), 2.39–2.47 (m, 1 H×0.1), 2.55 (ddd, *J*=17.9, 8.7, 6.1 Hz, 1 H×0.9), 3.88 (br s, 1 H). ^{13}C NMR (75.48 MHz, $CDCl_3$), δ: 23.7, 25.2, 29.9, 32.4, 37.5, 77.8, 208.1, 212.1. Anal. Found (%): C, 60.52; H, 8.76. $C_8H_{14}O_3$ Calcd (%): C, 60.74; H, 8.92. HRMS (ESI): *m*/*z* $[M+Na]^+$: Found: 181.0838. Calcd for $[C_8H_{14}NaO_3]^+$: 181.0835.

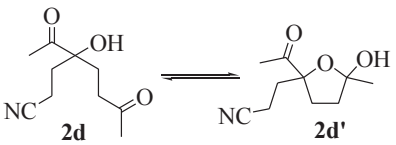
*4.2.3. 3-Butyl-3-hydroxyheptane-2,6-dione, **2c** (1-(2-butyl-5-hydroxy-5-methyltetrahydro-2-furanyl)ethanone, **2c**′).*



Acyclic : cyclic > 0.9 : 0.1

Yellow oil. Yield 84%, 208 mg. n_D^{25}=1.5360. R_f=0.81 (TLC, PE:EA, 2:1). ^{1}H NMR (major isomer) (300.13 MHz, $CDCl_3$), δ: 0.87 (t, *J*=7.2 Hz, 3 H), 0.85–0.99 (m, 1 H), 1.21–1.35 (m, 2 H), 1.30–1.45 (m, 1 H), 1.62–1.75 (m, 2 H), 1.93–2.04 (m, 2 H), 2.11 (s, 3 H), 2.19 (s, 3 H), 2.20–2.33 (m, 1 H), 2.54 (ddd, *J*=17.9, 8.1, 6.7 Hz, 1 H) 3.88 (br s, 1 H). ^{13}C NMR (75.48 MHz, $CDCl_3$), δ: 13.8, 22.9, 24.0, 25.3, 29.9, 31.9, 37.5, 38.4, 80.7, 208.0, 212.1. Anal. Found (%): C, 65.97; H, 10.20. $C_{11}H_{20}O_3$ Calcd (%): C, 65.97; H, 10.07. HRMS (ESI): *m*/*z* $[M+Na]^+$: Found: 223.1306. Calcd for $[C_{11}H_{20}NaO_3]^+$: 223.1305.

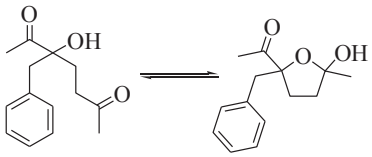
*4.2.4. 4-Acetyl-4-hydroxy-7-oxooctanenitrile, **2d** (3-(2-acetyl-5-hydroxy-5-methyltetrahydrofuran-2-yl)propanenitrile, **2d**′).*



Acyclic : cyclic = 0.8 : 0.2

Yellow oil. Yield 58%, 143 mg. n_D^{25}=1.5340. R_f=0.35 (TLC, PE:EA, 2:1). ^{1}H NMR (400.13 MHz, $CDCl_3$), δ: 1.55 (s, 3 H×0.1) 1.57 (s, 3 H×0.1), 1.72–2.21 (m, 4 H×0.8+6 H×0.1+6 H×0.1), 2.08 (s, 3 H×0.8), 2.14 (s, 3 H×0.1), 2.23 (s, 3 H×0.8), 2.24–2.53 (m, 4 H×0.8+2 H×0.1+2 H×0.1), 2.25 (s, 3 H×0.1). ^{13}C NMR (major isomer) (100.61 MHz, $CDCl_3$), δ: 11.4, 24.2, 29.8, 31.2, 33.6, 37.0, 79.3, 119.0, 207.7, 210.7. Anal. Found (%): C, 60.76; H, 7.58; N, 7.06. $C_{10}H_{15}NO_3$. Calcd (%): C, 60.90; H, 7.67 N, 7.10. HRMS (ESI): *m*/*z* $[M+Na]^+$: Found: 220.0952. Calcd for $[C_{10}H_{15}NNaO_3]^+$: 220.0944.

4.2.5. 3-Benzyl-3-hydroxyheptane-2,6-dione, ***2e*** *(1-(5-hydroxy-5-methyl-2-(phenylmethyl)tetrahydro-2-furanyl)ethanone,* ***2e'****).*



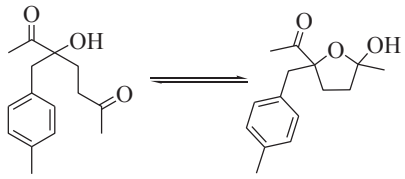
2e **2e'** (mixture of isomers: A and B)

Acyclic : cyclic (A + B) = 0.7 : 0.3

A : B = 0.2 : 0.1

Yellow oil. Yield 92%, 234 mg. n_D^{25}=1.5355. R_f=0.60 (TLC, PE:EA, 2:1). ^{1}H NMR (300.13 MHz, $CDCl_3$), δ ppm: 1.22 (ddd, J=12.5, 11.0, 8.8 Hz, 1 H×0.2), 1.48 (s, 3 H×0.2), 1.54 (s, 3 H×0.1), 1.59–1.68 (m, 1 H×0.1), 1.78 (ddd, J=12.5, 8.1, 2.2 Hz, 1 H×0.2), 1.83–1.90 (m, 1 H×0.1), 1.90–1.98 (m, 1 H×0.2), 1.96–2.07 (m, 1 H×0.7), 1.99–2.09 (m, 1 H×0.1), 2.09–2.17 (m, 1 H×0.7), 2.12 (s, 3 H×0.7), 2.20 (s, 3 H), 2.29 (ddd, J=18.0, 9.2, 5.5 Hz, 1 H×0.7), 2.29–2.44 (m, 1 H×0.1+1 H×0.2), 2.56 (ddd, J=17.6, 8.8, 6.0 Hz, 1 H×0.7), 2.80 (d, J=13.5 Hz, 1 H×0.2), 2.95 (d, J=13.9 Hz, 1 H×0.1), 2.99 (s, 2 H×0.7), 3.02 (d, J=13.5 Hz, 1 H×0.2), 3.10 (d, J=13.9 Hz, 1 H×0.1), 3.80 (br s, 1 H), 7.16–7.30 (m, 5 H). ^{13}C NMR (75.48 MHz, $CDCl_3$), δ: 24.9, 26.4, 26.91, 29.93, 31.5, 31.9, 32.8, 37.4, 37.5, 37.8, 43.1, 44.2, 44.6, 81.3, 91.9, 106.6, 127.0, 127.9, 128.2, 129.9, 130.6, 135.2, 208.0, 211.4. Anal. Found (%): C, 71.69; H, 7.71. $C_{14}H_{18}O_3$ Calcd (%): C, 71.77; H, 7.74. HRMS (ESI): m/z $[M+Na]^+$: Found: 257.1149. Calcd for $[C_{14}H_{18}NaO_3]^+$: 257.1148.

4.2.6. 3-Hydroxy-3-(4-methylbenzyl)heptane-2,6-dione, ***2f*** *(1-(5-hydroxy-5-methyl-2-((4-methylphenyl)methyl)tetrahydro-2-furanyl) ethanone,* ***2f****).*



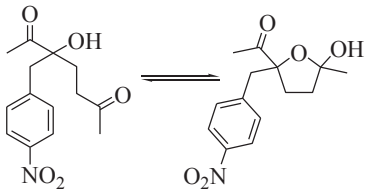
2f **2f '** (mixture of isomers: A and B)

Acyclic : cyclic (A + B) = 0.82 : 0.18

A : B = 0.12 : 0.06

Yellow oil. Yield 83%, 213 mg. n_D^{25}=1.5280. R_f=0.69 (TLC, PE:EA, 2:1). ^{1}H NMR (300.13 MHz, $CDCl_3$), δ ppm: 1.27 (m, 1 H×0.12), 1.49 (s, 3 H×0.12), 1.54 (s, 3 H×0.06), 1.65 (m, 1 H×0.06), 1.79 (ddd, J=12.5, 8.1, 2.9 Hz, 1 H×0.12), 1.84–1.94 (m, 1 H×0.06), 1.96–2.04 (m, 1 H×0.12), 2.04–2.07 (m, 1 H×0.82), 2.04–2.14 (m, 1 H×0.06), 2.13 (s, 3 H×0.82), 2.14–2.34 (m, 2 H×0.82), 2.20 (s, 3 H), 2.30 (s, 3 H×0.82), 2.29–2.39 (m, 1 H×0.06), 2.36–2.43 (m, 1 H×0.12), 2.56 (ddd, J=17.6, 8.8, 5.9 Hz, 1 H×0.82), 2.76 (d, J=13.2 Hz, 1H×0.12), 2.90 (d, J=13.2 Hz, 1 H×0.06), 2.96 (s, 2 H×0.82), 2.99 (d, J=13.2 Hz, 1 H×0.12), 3.06 (d, J=13.2 Hz, 1 H×0.06), 3.76 (br s, 1 H), 7.07 (m, 4 H). ^{13}C NMR (major isomer) (75.48 MHz, $CDCl_3$), δ: 21.1, 25.0, 30.1, 31.6, 37.7, 44.4, 81.5, 129.1, 129.8, 132.2, 136.6, 208.1, 211.6. Anal. Found (%): C, 72.40; H, 8.15. $C_{15}H_{20}O_3$ Calcd (%): C, 72.55; H, 8.12. HRMS (ESI): m/z $[M+Na]^+$: Found: 271.1305. Calcd for $[C_{15}H_{20}NaO_3]^+$: 271.1305.

4.2.7. 3-Hydroxy-3-(4-nitrobenzyl)heptane-2,6-dione, ***2g*** *(1-(5-hydroxy-5-methyl-2-((4-nitrophenyl)methyl)tetrahydro-2-furanyl) ethanone,* ***2g'****).*



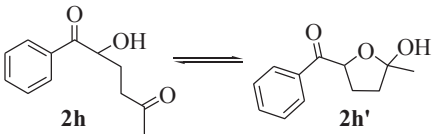
2g **2g '** (mixture of isomers: A and B)

Acyclic : cyclic (A + B) = 0.7 : 0.3

A : B = 0.16 : 0.14

Yellow plates (EA/PE=1/1 (v/v)). Yield 75%, 196 mg. Mp=84–85 °C. R_f=0.20 (TLC, PE:EA, 2:1). ^{1}H NMR (300.13 MHz, $CDCl_3$), δ ppm: 1.31–1.44 (m, 1 H×0.16), 1.52 (s, 3 H×0.16), 1.60 (s, 3 H×0.14), 1.66–1.82 (m, 1 H×0.14), 1.88 (ddd, J=12.5, 8.1, 2.2 Hz, 1 H×0.16), 1.89–2.00 (m, 1 H×0.16), 1.80–2.15 (m, 2 H×0.7+2 H×0.14), 2.12 (s, 3 H×0.7), 2.16 (s, 3 H×0.14), 2.17 (s, 3 H×0.16), 2.22 (s, 3 H×0.7), 2.18–2.28 (m, 1 H×0.14), 2.32 (ddd, J=18.3, 8.1, 5.9 Hz, 1 H×0.7) 2.41 (ddd, J=13.2, 8.1, 2.9 Hz, 1 H×0.16), 2.56 (ddd, J=18.3, 8.1, 6.6 Hz, 1 H×0.7), 2.87 (d, J=13.2 Hz, 1 H×0.16), 3.05 (d, J=13.2 Hz, 1 H×0.14), 3.07 (s, 2 H×0.7), 3.16 (d, J=13.2 Hz, 1 H×0.16), 3.30 (d, J=13.2 Hz, 1 H×0.14), 4.03 (br s, 1 H), 7.38 (d, J=8.8 Hz, 2 H), 8.10 (d, J=8.8 Hz, 2 H). ^{13}C NMR (major isomer) (75.48 MHz, $CDCl_3$), δ: 24.7, 29.9, 31.5, 37.4, 44.2, 81.0, 123.1, 130.9, 143.1, 147.1, 208.0, 210.8. Anal. Found (%): C, 60.17; H, 6.18, N, 5.06. $C_{14}H_{17}NO_5$ Calcd (%): C, 60.21; H, 6.14, N, 5.02. HRMS (ESI): m/z $[M+NH_4]^+$: Found: 297.1444. Calcd for $[C_{14}H_{21}N_2O_5]^+$: 297.1445.

4.2.8. 2-Hydroxy-1-phenylhexane-1,5-dione, ***2h*** *((5-hydroxy-5-methyltetrahydro-2-furanyl)(phenyl)methanone,* ***2h'****).*



2h **2h'**

Acyclic : cyclic > 0.95 : 0.05

Yellow oil. Yield 83%, 207 mg. n_D^{25}=1.5250. R_f=0.37 (TLC, PE:EA, 2:1). ^{1}H NMR (major isomer) (300.13 MHz, $CDCl_3$), δ: 1.55 (dddd, J=14.2, 9.3, 6.3, 5.3 Hz, 1 H), 2.16 (s, 3 H), 2.28 (dddd, J=14.2, 8.5, 6.4, 2.9 Hz, 1 H), 2.55 (ddd, J=18.5, 6.4, 5.3 Hz, 1 H), 2.86 (ddd, J=18.5, 8.5, 6.3 Hz, 1 H), 3.68 (br.s 1 H), 5.09 (dd, J=9.3, 2.9 Hz, 1 H), 7.47–7.54 (m, 2 H), 7.58–7.65 (m, 1 H), 8.03–8.09 (m, 2 H). ^{13}C NMR (75.48 MHz, $CDCl_3$), δ: 29.7, 29.9, 38.4, 71.7, 128.7, 128.8, 133.1, 134.0, 201.6, 208.3. Anal. Found (%): C, 69.72; H, 6.85. $C_{12}H_{14}O_3$ Calcd (%): C, 69.89; H, 6.84. HRMS (ESI): m/z $[M+Na]^+$: Found: 229.0826. Calcd for $[C_{12}H_{14}NaO_3]^+$: 229.0835.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.04.054. These data include MOL files and InChiKeys of the most important compounds described in this article.

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