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Oxidation of cyclopentane-1,2-dione: a study with ^{18}O labeled reagents

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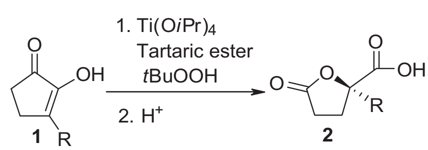
ABSTRACT

The asymmetric oxidation of 3-alkyl-cyclopentane-1,2-diones with the $Ti(O^iPr)_4$/tartaric ester/*t*-BuOOH complex, which gives, in a cascade process, highly enantiomerically enriched γ-lactone acids, was studied by ^{18}O isotopic labeling in the substrate and in the oxidant. The path of the labeled atoms was followed by ^{13}C NMR spectroscopy. It was found that the oxidative ring cleavage of 1,2-dione proceeds via a Baeyer–Villiger-type oxidation mechanism.

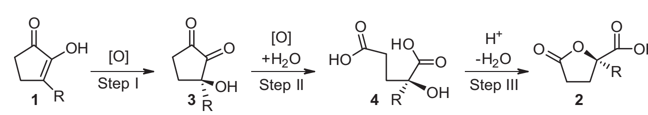
1. Introduction

Asymmetric oxidation of 3-alkyl- and 3-aryl-cyclopentane-1,2-diones **1** with the $Ti(O^iPr)_4$/tartaric ester/*t*-BuOOH complex[1] is an efficient tool in organic synthesis that provides γ-lactone acids **2**[2,3] in high optical purity and good yield (Scheme 1). These γ-lactone acids have been used in the synthesis of natural products as homocitric acid,[4] alkyl-,[5] and aryl-[6] substituted nucleoside analogues, and have high potential for many other applications.



Scheme 1. Asymmetric oxidation of 3-alkyl-cyclopentane-1,2-diones to 2-alkyl-γ-lactone acids.

The transformation of 3-alkyl-cyclopentane-1,2-diones to 2-alkyl-γ-lactone acids includes several chemical reactions and can be outlined on the basis of identified intermediates as presented in Scheme 2. The first oxidation step determines the stereochemical outcome of the whole reaction and is formally an asymmetric 3-hydroxylation of substrate **1** (intermediate **3** has been isolated and identified by us as described,[7,8] Scheme 2, Step I). In the second step, the cyclopentane ring is oxidatively cleaved, yielding intermediate diacid **4** (Scheme 2; Step II). Subsequent esterification of the diacid affords γ-lactone acid **2** and other esters of the diacid[2] (Scheme 2; Step III). The formal reaction scheme does not reveal neither all the chemical reactions nor the mechanisms of the transformations. Thus, more detail information is needed about the whole multi-step process.



Scheme 2. Formal reaction steps according to isolated and identified intermediates.

The mechanism of the oxidation of 1,2-diketones has been studied on the model of non-enolizable 1,2-diphenyl-1,2- ethanedione[9,10] (benzil). Contradictions in the obtained experimental results do not make it possible to establish whether the oxidative C–C bond cleavage proceeds via a Baeyer–Villiger-type reaction, which is a well-studied and established reaction for oxidizing ketones[11] (Scheme 5), or via the formation of an intermediate epoxide[12] (Scheme 6). There is no data on the mechanism of oxidation of enolizable 1,2-diketones in the literature. The mechanistic uncertainty is an obstacle in generating efficient oxidation processes for these compounds.

Herein, we present the results of a detailed study of the $Ti(O^iPr)_4$/tartaric ester catalyzed transformations of 3-alkyl-cyclopentane-1,2-diones (enols **1**) with labeled *t*-$Bu^{18}O^{18}OH$ **5**, and labeled enols **1a** and **1b** with *t*-BuOOH (Fig. 1), in order to elucidate how the oxidation proceeds and to understand whether the

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oxidative cleavage of 1,2-diones is a Baeyer–Villiger-type transformation. ^{18}O Labeled t-Bu$^{18}O^{18}$OH **5** and labeled enols **1a** and **1b** were prepared and subjected to the reaction. Heavy oxygen isotope-induced changes in chemical shifts in natural abundance ^{13}C NMR[13] were used to track the position of ^{18}O in the reaction intermediates and products originating from differently labeled cyclopentane diones **1**, **1a** or **1b** or from ^{18}O labeled *tert*-butyl hydroperoxide **5**. NMR data were further confirmed by LC/MS/MS.

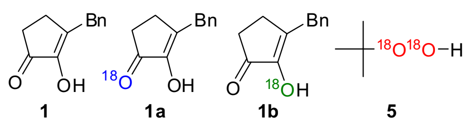


Fig. 1. Labeled substrates **1a** and **1b** and labeled reagent **5**.

2. Results and discussion

2.1. Preparation of the labeled reagent and substrates

The labeled oxidation reagent di-^{18}O-*tert*-butyl hydroperoxide **5** was prepared from a commercial *tert*-butyl Grignard reagent and $^{18}O_2$ gas, according to a known procedure.[14] The differently labeled 3-benzyl-cyclopentane diones with ^{18}O labels at C1 (compound **1a**) and at C2 (compound **1b**) were prepared separately by means of different synthetic routes.

Labeled ketoenol **1a** was obtained by subjecting unlabeled ketoenol **1** to an acid-catalyzed (HCl in $H_2{}^{18}O$) isotope exchange reaction[15] in dioxane-d_8 at room temperature. The reaction was run and the transformation monitored by ^{13}C NMR spectroscopy in an NMR tube (Fig. 2).[16] According to NMR, the formation of **1a** (95% of ^{18}O) was almost complete in 4 h. Surprisingly, none of the differently labeled compound **1b** (isotope exchange of the enolic oxygen) or the di-labeled compound **1c** with both oxygen atoms exchanged for ^{18}O were observed.[17]

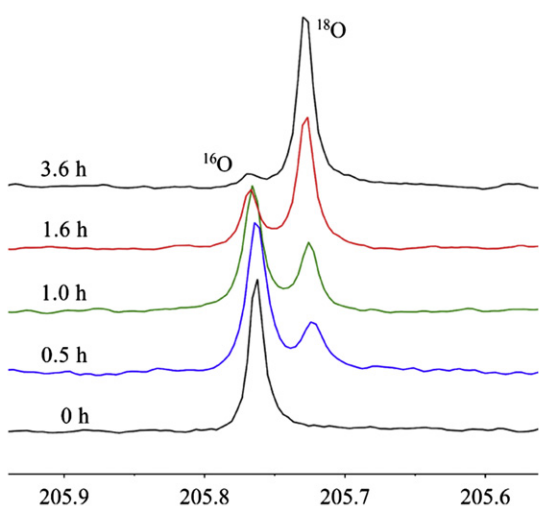
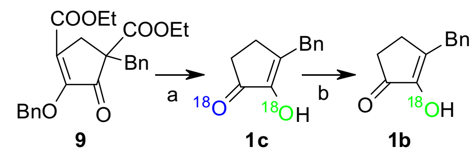


Fig. 2. Time dependence of oxygen isotope exchange at C1 of 3-benzyl-2-hydroxycyclopent-2-ene-1-one **1**, monitored by NMR.

To prepare ketoenol **1b**, we took advantage of the different mobility of the oxygen atoms attached to C1 and C2 in ketoenol **1a**. Thus, intermediate **9** from the synthesis scheme of ketoenol **1**[5] was decarboxylated in a mixture of dry dioxane and $H_2{}^{18}O$ in the presence of HCl, resulting in di-labeled ketoenol **1c** (Scheme 3). Then the ^{18}O atom at C1 was replaced with ^{16}O, using an acid-catalyzed isotope exchange with $H_2{}^{16}O$, under the same conditions that were used for the preparation of compound **1a**. As a result, mainly compound **1b** with ^{18}O saturation at C2 was obtained. According to NMR and GC/MS, the obtained product contained 1% of **1a**, 81% of **1b**, 5% of di-labeled **1c**, and 13% of **1** without any labels.[18]



Scheme 3. Preparation of 2-labeled 3-benzyl-2-hydroxycyclopent-2-en-1-one. (a) Dioxane, $H_2{}^{18}O$, cat. HCl, reflux; (b) Dioxane, H_2O, cat. HCl.

2.2. Oxidation of ketoenol 1 with labeled oxidation reagent 5

In order to follow the path of the oxygen atoms from the oxidation reagent, unlabeled diketone **1** was oxidized with labeled t-Bu$^{18}O^{18}$OH reagent **5**. The oxidation products diacid **4** and lactone acid **2** were analyzed by ^{13}C NMR and LC/MS/MS. According to ^{13}C NMR, there was no isotope shift observed at C2, which was due to the high ^{18}O saturation (close to 100%) at this position.

The intermediate diacid **4** had an almost equal distribution of ^{18}O at C1 and C5 (which corresponds to **4a** and **4b** in Scheme 5; Fig. 3; Table 1) according to ^{13}C NMR. In LC/MS/MS spectra, diacid **4** revealed 95% with two ^{18}O isotopes. This result is in good agreement with NMR data.

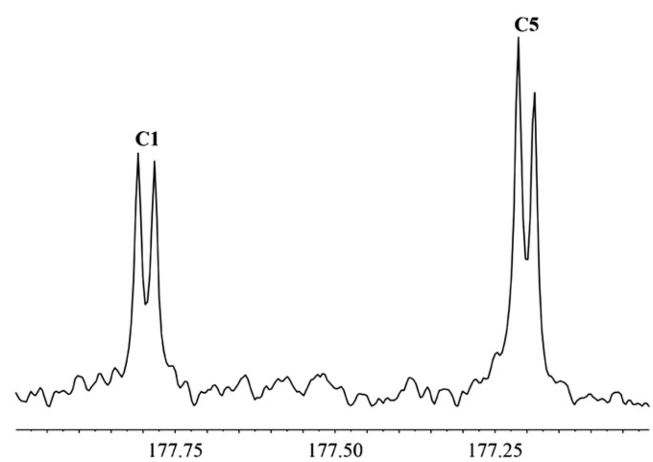


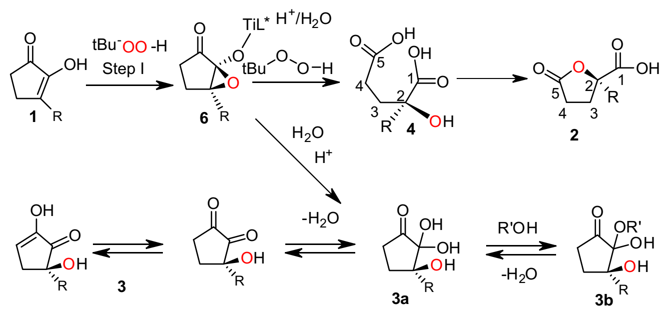
Fig. 3. ^{13}C NMR shifts for C1 and C5 of the labeled diacids **4a** and **4b**.

Table 1
Distribution of ^{18}O labels at C1 and C5 in intermediate **4** and product **2**, according to ^{13}C NMR from the oxidation of ketoenol **1** with labeled t-Bu$^{18}O^{18}$OH

Product	Calcd[a]	Calcd[b]	Exptl[c]
4a	50	100	43
4b	50	0	48
2a	25	50	24
2b	25	50	24
2c	50	0	49

[a] Calculated distribution based on expected isotope paths in the 'Baeyer–Villiger-type' mechanism.
[b] Calculated distribution based on expected isotope paths in the 'epoxide-type' mechanism.
[c] Experimental value determined by NMR.

It is very likely that the first oxidation is a typical Sharpless process,[19,20] similar to the epoxidation of allylic alcohols, yielding intermediate **6**. The intermediate affords, in hydrolytic conditions, 3-hydroxylated product 3[7] (Scheme 4). Our attempts to detect epoxide **6** by NMR were not successful. This was probably due to epoxidation being the rate-limiting step and epoxide **6** transforming fast in the following reaction cascade sequence. Still, the hydrolysis products **3**, that we have isolated, identified, and reported previously,[2,7] could have been formed from epoxide **6** and indirectly hint at its existence. In addition to enol **3** we have also isolated hydrate **3a** and hemiacetal **3b** from the reaction mixture in certain conditions.[7]



Scheme 4. Step I—epoxidation of the double bond according to a Sharpless mechanism.

Our main interest was directed to the next oxidation step: further transformations leading to **4** and **2**. The substrate for these transformations may either be epoxide **6** or diketone derivatives **3a** and **3b**. All these intermediates lead to the same oxidation products **4** and **2**. Diketone **3**, which according to NMR is exclusively in its enol form in solution, does not oxidize further under present reaction conditions and remains unaffected.[8] It means that the second oxygen atom adds to the C1 carbonyl carbon. The intermediate compounds **3a** and **3b** can not be formed under the oxidation conditions. Thus we may suggest that the second oxidation proceeds directly from epoxide **6**.

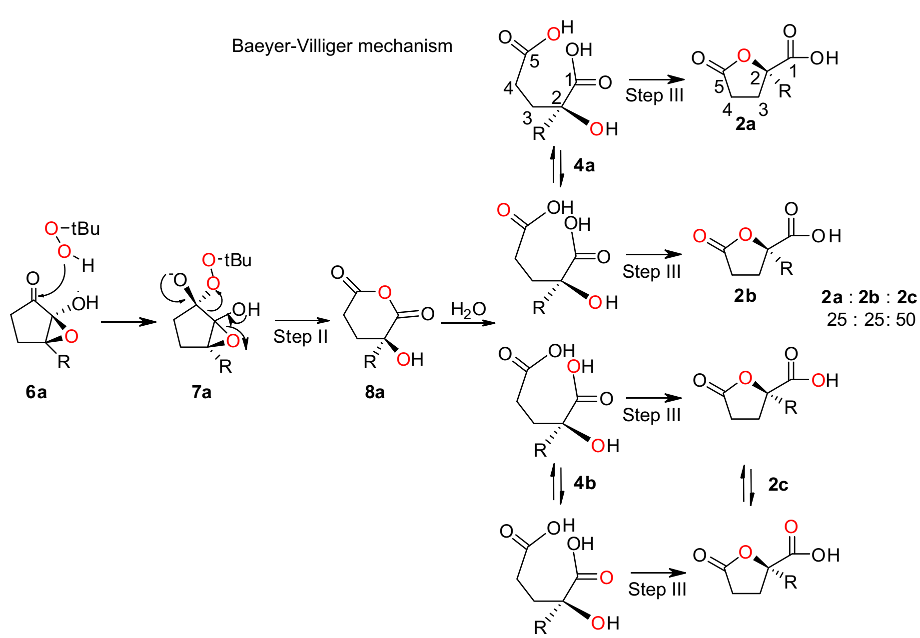
The process may proceed either via a Baeyer–Villiger-type rearrangement[9] or via a pathway involving the formation of a second epoxide,[12] as in the case of the oxidation of benzil. If the second oxidation proceeds via the classic Baeyer–Villiger approach (Scheme 5) in accordance with the Doering and Dorfman labeling experiments,[21] that confirmed the mechanism suggested by Criegee,[22] the second oxygen atom from **5**, which is involved in the ring cleavage reaction, should appear in one of the carboxylic groups of diacid **4** and either in the carboxylic group of **2c** or **2b**. Also, at a 25% extent, one of the labeled carboxylic oxygen atoms from **4** is eliminated during the lactonization, which yields product **2a**. As a result, the ratio of mono-labeled compound **2a** to di-labeled compounds **2b** and **2c** should be 1:3. If the reaction proceeds according to an epoxide formation pathway, the labels should appear only in the furanone ring (Scheme 6).

When compound **4a** is cyclized to the lactone acid, we should obtain a mixture of compound **2a** (one label) and compound **2b** (two labels); when **4b** cyclizes, compound **2c** (two labels) should form, with the ratio of **2a**, **2b**, and **2c** being 25:25:50. Indeed, such a distribution was observed by NMR[23] (and was supported by LC/MS/MS), with the ratio of **2a**/**2b**/**2c** being 22:22:43. The result corresponded to that expected from the 'Baeyer–Villiger-type' mechanism (Table 1).

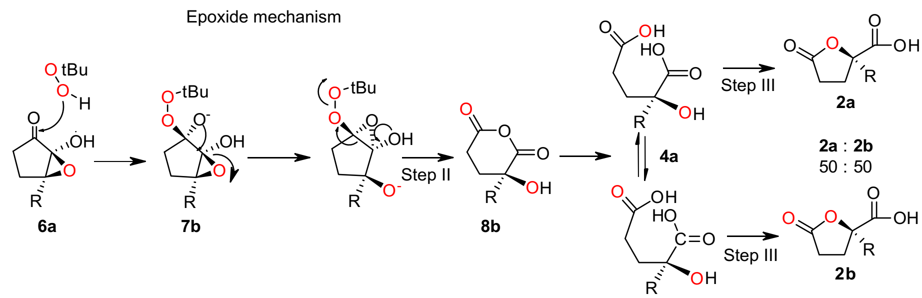
2.3. Oxidation of labeled substrates

In order to elucidate the path of the two oxygen atoms from substrate **1** to the product, and confirm the conclusions drawn from the labeled reagent experiments, we performed oxidation experiments with the labeled substrates **1a** and **1b**. Thus, labeled diketone **1a** was subjected to the oxidation reaction with unlabeled *t*-BuOOH, and the isolated diacids **4** were analyzed. The NMR spectra showed clear ^{18}O saturation at C5 of the molecule, which corresponded to compound **4c** (Table 2). No ^{18}O shift was observed at other carbon atoms in the compound. The lactonization of **4c** resulted in a mixture of compounds **2** and **2d** (Table 2), which facilitated a two-fold loss in the ^{18}O saturation on C5 in the ^{13}C spectra of the mixture of products.[24] The obtained results were confirmed by LC/MS/MS and were in good accordance with the 'Baeyer–Villiger-type' mechanism (Scheme 5, Fig. 2), which suggests that **1a** will produce a diacid **4c** with the isotope label solely at the C5 carboxyl group and should lose 50% of the label during the lactonization step, giving rise to equal amounts of lactone acids **2** with no label and **2d** with the label on C5 (Fig. 4).

Using the labeled diketone **1b** as the asymmetric oxidation substrate provided diacid **4d** with good ^{18}O saturation at C1. When compound **4d** was cyclized, there was no isotope effect observable



Scheme 5. The path of oxygen labels from the labeled oxidant **5** in the reaction cascade, according to the 'Baeyer–Villiger-type' mechanism.



Scheme 6. The path of different oxygen labels in the reaction cascade, according to the 'epoxide-type' mechanism.

Table 2
Distribution of ^{18}O labels in intermediate **4** and product **2**, according to ^{13}C NMR, from the oxidation of labeled ketoenols **1a** and **1b** with *t*-BuOOH

Product	Substrate					
	1a			**1b**		
	Calcd[a]	Calcd[b]	Exptl[c]	Calcd[a]	Calcd[b]	Exptl[c]
4c	100	50	84	0	0	0
4d	0	50	0	100	100	76
2	50	25	54	0	0	0
2d	50	25	46	0	0	0
2e	0	50	0	100	100	76

[a] Calculated distribution based on expected isotope paths in the 'Baeyer–Villiger-type' mechanism.
[b] Calculated distribution based on expected isotope paths in the 'epoxide-type' mechanism.
[c] Experimental value determined by NMR.

Table 3
Upfield ^{18}O isotope shifts on ^{13}C chemical shifts of labeled compounds in ppb

Compound	C1	C2/C4	C5
1a[a]	41		
1b[b]	38	C2 10	
1c[b]	42		
2a–c[b,d]	23		38
2d[b]		C4 07	38
2e[b,d]	23		
4a–b[c]	26		25
4c[c]			25
4d[c]	26		

[a] Dioxane-d_8.
[b] $CDCl_3$.
[c] CD_3OD.
[d] Spectra obtained at sub ambient temperatures.

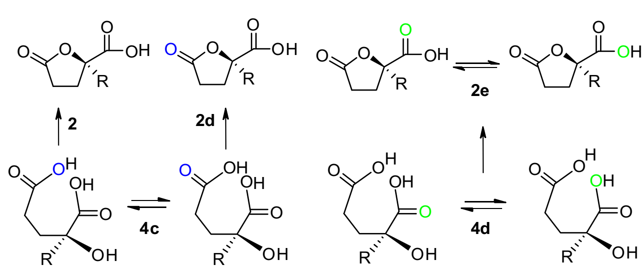


Fig. 4. Expected isotope ^{18}O location from labeled substrates **1a** and **1b**, according to the Baeyer–Villiger mechanism.

in the C1 of the lactone acid **2e** at room temperature. When the sample was cooled to 248 K, labeling in the carboxylic moiety, with no loss in isotope saturation when compared to **4d**, was observed (Table 2).

As expected from a Baeyer–Villiger-type mechanism, the enolic oxygen from **1b** appeared in the carboxylic acid group in the end product **2e** and the carbonylic oxygen from **1a** either appeared in the furanone carbonyl group or was eliminated in half of the cases (Scheme 5, Fig. 4).

3. Conclusion

The first step of the oxidative reaction cascade for 3-benzyl-1,2-cyclopentanedione **1**—asymmetric epoxidation—is a key step in the whole process, which selectively generated a stereogenic center at C2 of diacid **4** and lactone acid **2**. This step is similar to the asymmetric oxidation of allylic alcohols developed by Sharpless et al.[1] The formed stereogenic center retains its configuration throughout the following reaction cascade: the labeled oxygen from the reagent appeared in the hydroxyl group of the intermediate diacid **4** and in the furan oxygen atom in lactone acid **2**. The cascade continues with the second oxidation reaction with *tert*-butyl hydroperoxide. In all cases with labeled substrates **1a** and **1b** and reagent **5**, the isotope distribution in the intermediate diacid **4** and lactone acid **2** unambiguously confirmed that the oxidative cleavage of the cyclopentane ring proceeds by a Baeyer–Villiger-type mechanism.

4. Experimental section

4.1. General experimental details

All reagents were purchased from common suppliers and used without further purification. ^{18}O Labeled organic compounds were stored at −80 °C. CH_2Cl_2 was distilled from CaH_2, toluene and dioxane were distilled from Na. Silica gel 40–100 μm was used for column chromatography for compounds **1a–c** and **2**, **2a–e**; silica gel 100–160 μm was used for chromatography for compounds **4a–d**. All NMR spectra were obtained at room temperature unless noted otherwise. NMR spectra were normalized according to solvent peaks, except for ^{1}H NMR spectra measured in $CDCl_3$ that was normalized by internal standard (TMS δ=0.00). ^{13}C chemical shifts are given in three decimal numbers where isotopes are observed, otherwise in two decimal numbers. Mass spectra and HRMS of substrates were recorded using EI. LC/MS/MS spectra and HRMS of products were recorded using ESI.

4.2. General procedure for the oxidation of 3-benzyl-2-hydroxy-cyclopent-2-en-1-one 1 with *tert*-butyl hydroperoxide

An Ar-filled Schlenck tube was charged with CH_2Cl_2 (0.167 M compared to the substrate). MS 4 Å powder (100 mg/mmol) and 1 equiv of $Ti(O^iPr)_4$ were added, followed by dropwise addition of 1.6 equiv of (+)-diethyl tartrate at −20 °C. The mixture was stirred for 20 min, then 1 equiv of 3-benzyl-2-hydroxy-cyclopent-2-en-1-one was added dropwise as a 0.5 M solution in CH_2Cl_2 and stirred for a further 30 min, followed by the slow addition of 2.5 equiv of *tert*-butyl hydroperoxide. The reaction was stirred for 20 min and then left to stand at −20 °C for 68h. The reaction was quenched with 6 ml/mmol of H_2O and stirred for 2 h; then, 1.2 ml/mmol of 30% NaOH solution in brine was added and stirred for a further 1.5 h. The mixture was filtered through Celite and rinsed with CH_2Cl_2; the phases were separated and the aqueous phase was acidified and extracted with EtOAc. All of the organics were combined, dried over $MgSO_4$ and the product was purified by column chromatography over silica gel (3:10 to 4:10 acetone/petroleum ether) to give 2-benzyl-2-hydroxy-pentanedioic acids **4**, which at ambient temperature spontaneously cyclize to lactone acids **2**. Samples of **4** always contained increasing amount of **2** and, therefore, were fully characterized after cyclization as lactone acids **2**.

4.3. General procedure for the cyclization of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids

An Ar-filled round bottom flask was charged with ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acid and toluene; the material did not dissolve completely. The reaction was stirred at 100 °C for 2 h, the now homogeneous mixture was allowed to cool to room temperature and the solvent was removed on a rotary evaporator to give ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acid.

4.4. Preparation of C1 ^{18}O labeled 3-benzyl-2-hydroxycyclopent-2-enone 1a

An oven dried NMR tube was filled with Ar and charged with 101 mg (0.538 mmol) 3-benzyl-2-hydroxycyclopent-2-enone, 480 μl of $H_2{}^{18}O$, 0.5 ml of dioxane-d_8, and 0.1 ml of dioxane. After the substrate was dissolved 20 μl of 22.8% HCl in $H_2{}^{18}O$ (prepared by bubbling dry HCl into $H_2{}^{18}O$) was added. The reaction was run at room temperature and monitored by ^{13}C NMR. After 60 h the NMR revealed 95% of ^{18}O saturation at C1. Reaction mixture ^1H NMR (400 MHz, dioxane-d_8/dioxane/$H_2{}^{18}O$) δ=7.14–7.04 (m, 5H, Ph), 3.52 (br s, 2H, Ph–CH_2–), 2.11 (br s, 4H, H-4, H-5); ^{13}C NMR (400 MHz, dioxane-d_8/dioxane/$H_2{}^{18}O$) δ=205.766 ($C^{18}O$), 205.725 (CO), 149.98 (C–OH), 148.81 (C-3), 139.13 (s), 129.80 (*o*), 129.55 (*m*), 127.41 (*p*), 35.27 (Ph–CH_2–), 32.85 (C-5), 25.41 (C-4). The reaction mixture was extracted with CH_2Cl_2 (5×1 ml), dried over a small amount of $MgSO_4$, and concentrated to give (99 mg, 96%) 95% saturated C1 ^{18}O labeled 3-benzyl-2-hydroxycyclopent-2-enone **1a** as yellowish solid. An analytical sample was crystallized from CH_2Cl_2/petroleum ether to give **1a** as white crystals, mp 95–97 °C: ^1H NMR (400 MHz, $CDCl_3$) δ=7.32–7.21 (m, 5H, Ph), 6.59 (br s, 1H, O*H*), 3.74 (s, 2H, Ph–CH_2–), 2.39–2.34 (m, 4H, H-4, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ=203.71 ($C^{18}O$), 148.78 (C–OH), 146.33 (C-3), 137.73 (s), 128.95 (*o*), 128.67 (*m*), 126.61 (*p*), 34.88 (Ph–CH_2–) 31.96 (C-5), 24.75 (C-4); IR: 3320, 2924, 1682, 1641, 1385, 1218, 1107, 762, 699 cm^{-1}; MS (EI, 70 eV): m/z (%)=190 (100, M^+), 188 (5.1), 172 (3.4), 159 (16.4), 142 (25.3), 129 (32.2), 117 (44.8), 104 (21.6), 91 (46.6). C1 ^{18}O saturation 95% based on MS. HRMS (EI): M^+ m/z calcd for $C_{12}H_{12}O^{18}O$ 190.0880; found 190.0874.

4.5. Preparation of C2 ^{18}O labeled 3-benzyl-2-hydroxycyclopent-2-enone 1b

1-Benzyl-4-benzyloxy-5-oxo-cyclopent-3-ene-1,3-dicarboxylic acid diethyl ester (422 mg, 1 mmol) was dissolved in 2 ml of dioxane and 1 ml of 22.8% HCl in $H_2{}^{18}O$ was added. The reaction was stirred at 105 °C under Ar overnight. The reaction mixture was extracted with CH_2Cl_2 (6×1 ml), all extracts combined, concentrated, and purified by column chromatography over silica gel (2:10 EtOAc/petroleum ether) to give 132 mg of di-labeled 3-benzyl-2-hydroxycyclopent-2-enone **1c** as white crystals, mp 94–97 °C: ^1H NMR (400 MHz, $CDCl_3$) δ=7.33–7.22 (m, 5H, Ph), 5.82 (br s, 1H, O*H*), 3.74 (s, 2H, Ph–CH_2–), 2.40–2.34 (m, 4H, H-4, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ=203.421 (CO), 203.379 ($C^{18}O$), 148.617 (C–^{18}OH), 145.66 (C-3), 137.80 (s), 129.08 (*o*), 128.85 (*m*), 126.81 (*p*), 35.01 (Ph–CH_2–) 31.97 (C-5), 24.89 (C-4); IR: 3308, 2923, 1679, 1638, 1378, 1194, 1098, 762, 699 cm^{-1}; MS (EI, 70 eV): m/z (%)=192 (100, M^+), 190 (35.1), 188 (2.8), 172 (5.1), 170 (1.2), 161 (24.9), 159 (3.9), 142 (31.5), 129 (38.9), 117 (59.9), 104 (26.0), 91 (55.3). HRMS (EI): M^+ m/z calcd for $C_{12}H_{12}{}^{18}O_2$ 192.0922; found 192.0926.

Di-labeled 3-benzyl-2-hydroxycyclopent-2-enone **1c** (104 mg, 0.538 mmol) was dissolved in 650 μl of dioxane, 500 μl of H_2O and 20 μl of 22% HCl was added. The reaction was left overnight at room temperature, then extracted with CH_2Cl_2 (8×1 ml), all extracts combined, dried over $MgSO_4$, and purified by chromatography over silica gel (2:10 EtOAc/petroleum ether) to give crude C2 ^{18}O labeled 3-benzyl-2-hydroxycyclopent-2-enone **1b** (83 mg, 81%) as yellowish crystals. ^1H NMR (400 MHz, $CDCl_3$) δ=7.25–7.15 (m, 5H, Ph), 6,19 (br s, 1H, –O*H*), 3.67 (br s, 2H, Ph–CH_2–), 2.32–2.26 (m, 4H, H-4, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ=203.619 (*C*O), 203.581 (*C*^{18}O), 148.793 (*C*–OH), 148.783 (*C*–^{18}OH), 146.02 (C-3), 137.84 (s), 129.08 (*o*), 128.82 (*m*), 126.77 (*p*), 35.01 (Ph–CH_2–), 32.03 (C-5), 24.89 (C-4). An analytical sample was crystallized from CH_2Cl_2/petroleum ether to give **1b** as white crystals, mp 92–95 °C: ^1H NMR (400 MHz, $CDCl_3$) δ=7.33–7.22 (m, 5H, Ph), 6.08 (br s, 1H, O*H*), 3.74 (s, 2H, Ph–CH_2–), 2.39–2.34 (m, 4H, H-4, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ=203.540 (CO), 148.705 (C–^{18}OH), 145.86 (C-3), 137.82 (s), 129.08 (*o*), 128.83 (*m*), 126.79 (*p*), 35.00 (Ph–CH_2–), 32.01 (C-5), 24.88 (C-4); IR: 3308, 2922, 1695, 1655, 1379, 1194, 1099, 762, 699 cm^{-1}; MS (EI, 70 eV): m/z (%)=192 (6.4), 190 (100, M^+), 188 (14.3), 170 (3.4), 161 (23.5), 142 (51.2), 129 (52.1), 117 (81.8), 104 (46.3), 91 (99.9). HRMS (EI): M^+ m/z calcd for $C_{12}H_{12}O^{18}O$ 190.0880; found 190.0884.

4.6. Preparation of di-^{18}O-*tert*-butyl hydroperoxide 5

A reaction setup consisting of a 250 ml round bottom flask connected to a 98% ^{18}O gas cylinder through a needle and capillary tubing was charged with 60 ml of Et_2O in argon atmosphere. The flask was cooled to −78 °C and ^{18}O gas was slowly bubbled through (∼1 bubble/s) the solvent for 10 min to saturate the solvent with labeled oxygen. Then 60 ml of 0.52 M *t*-BuMgCl solution in Et_2O was added dropwise, a noticeable amount of white precipitate formed. The reaction was stirred for 10 min at −78 °C, then allowed to warm to room temperature and poured into a flask containing ice. The mixture was acidified with 6 M HCl, the phases separated and the aqueous phase extracted twice with 30 ml of Et_2O. All organics were combined, dried over $MgSO_4$, and concentrated to 50 ml on a rotary evaporator (30 °C, 0.5 atm). Further Et_2O was removed by distillation through a 20 cm Vigreux column to give 2 g of clear solution. The solution was dissolved with 10 ml of hexane and 10 ml of azeotrope was removed by Dean–Stark apparatus to give 2.1 ml of clear colorless solution that contained 1.56 M of *t*-Bu^{18}O^{18}OH **5** by titration.

4.7. Oxidation of 3-benzyl-2-hydroxy-cyclopent-2-en-1-one 1 with di-^{18}O-*tert*-butyl hydroperoxide 5

Using the general procedure for the oxidation of 3-benzyl-2-hydroxy-cyclopent-2-en-1-one **1** with *tert*-butyl hydroperoxide with 6 ml of CH_2Cl_2, 100 mg of MS 4 Å powder, Ti(O^{i}Pr)$_4$ (300 μl, 1 mmol), (+)-diethyl tartrate (270 μl, 1.6 mmol), 3-benzyl-2-hydroxy-cyclopent-2-en-1-one (188 mg, 1 mmol) solution in 1.8 ml of DCM and di-^{18}O-*tert*-butyl hydroperoxide **5** (1.6 ml, 1.56 M, 1.5 mmol) and quenching the reaction with 6 ml of H_2O followed by 1.2 ml of 30% NaOH solution in brine gave, after extraction and purification, a mixture of di-^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids **4a** and **4b** (149 mg, 61%) as a yellow oil: ^{1}H NMR (400 MHz, CD_3OD) δ=7.29–7.19 (m, 5H, Ph), 3.08 and 2.92 (2d, *J*=13.5 Hz, 2H, Ph–C*H*$_2$–), 2.56–2.46 and 2.26–2.12 (m, 2H, H3), 2.56–2.46 and 2.00–1.91 (m, 2H, H4); ^{13}C NMR (100 MHz, CD_3OD) δ=177.684 (C1–OOH), 177.658 (C1–^{18}OOH), 177.090 (C5–OOH), 177.065 (C5–^{18}OOH), 137.49 (s), 131.48 (*o*), 128.94 (*m*), 127.66 (*p*), 78.30 (C2), 46.49 (Ph–*C*H$_2$–), 35.33 (C3), 29.77 (C4); LC/MS/MS (ESI): *m*/*z* (%)=243 (2.6, [M–H]$^-$), 241 (100, [M–H]$^-$), 239 (4.5, [M–H]$^-$), 237 (0.8, [M–H]$^-$); Fragments of 241 (ESI): *m*/*z* (%)= 223 (100), 221 (36.3), 219 (0.9), 179 (0.9), 177 (10.6), 175 (9.1), 131 (6.3).

4.8. Cyclization of the mixture of di-^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids 4a and 4b into ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acids 2a, 2b, and 2c

Using the general procedure for the cyclization of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids with the mixture of di-^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids **4a** and **4b** (39 mg, 0.162 mmol) and 2 ml of toluene gave a mixture of ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acids **2a**, **2b**, and **2c** (34 mg, 100%) as yellow oil that solidified at cooling into the yellowish-white crystals, mp 106–108 °C: ^{1}H NMR (400 MHz, $CDCl_3$, 244 K) δ=9.48 (s, 1H, COO*H*), 7.35–7.29 (m, 5H, Ph), 3.42 and 3.16 (2d, *J*=14.4 Hz, 2H, Ph–C*H*$_2$–), 2.58–2.48 and 2.40–2.28 (m, 2H, H3), 2.58–2.48 and 2.23–2.11 (m, 2H, H4); ^{13}C NMR (100 MHz, $CDCl_3$, 244 K) δ=176.901 (C1–OOH), 176.878 (C1–^{18}OOH), 176.524 (C5–O), 176.486 (C5–^{18}O), 133.33 (s), 130.67 (*o*), 128.72 (*m*), 127.67 (*p*), 85.90 (C2), 41.73 (Ph–*C*H$_2$–), 30.00 (C3), 28.05 (C4); IR: 3059, 1769, 1734, 1707, 1496, 1462, 1408, 1178, 1033, 919, 709 cm^{-1}; LC/MS/MS (ESI): *m*/*z* (%)=223 (100, [M–H]$^-$), 221 (35.7, [M–H]$^-$), 219 (2.3, [M–H]$^-$); Fragments of 223 (ESI): *m*/*z* (%)=179 (7.6), 177 (98.1), 175 (79.5), 131 (100). HRMS (ESI): calcd for $C_{12}H_{12}O_4$ [M+H]$^+$ 221.0808; found 221.0798. HRMS (ESI): calcd for $C_{12}H_{12}O_3{}^{18}O$ [M+H]$^+$ 223.0851; found 223.0840. HRMS (ESI): calcd for $C_{12}H_{12}O_2{}^{18}O_2$ [M+H]$^+$ 225.0893; found 225.0881.

4.9. Oxidation of C1 ^{18}O labeled 3-benzyl-2-hydroxycyclopent-2-enone 1a with *tert*-butyl hydroperoxide

Using the general procedure for the oxidation of 3-benzyl-2-hydroxy-cyclopent-2-en-1-one **1** with *tert*-butyl hydroperoxide with 1.5 ml of DCM, 15 mg of MS 4 Å powder, Ti(O^{i}Pr)$_4$ (75 μl, 0.25 mmol), (+)-diethyl tartrate (67.5 μl, 0.4 mmol), C1 ^{18}O labeled 3-benzyl-2-hydroxy-cyclopent-2-en-1-one **1a** (47 mg, 0.25 mmol) solution in 0.5 ml of DCM and *tert*-butyl hydroperoxide (90 μl, 6.8M in decane, 0.6 mmol) and quenching the reaction with 1.25 ml of H_2O followed by 0.3 ml of 30% NaOH solution in brine gave, after extraction and purification, a mixture of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids **4c** (10 mg, 17%) as a light brown oil: ^{1}H NMR (400 MHz, CD_3OD) δ=7.30–7.17 (m, 5H, Ph), 3.08 and 2.92 (2d, *J*=13.5 Hz, 2H, Ph–C*H*$_2$–), 2.51–2.46 and 2.26–2.12 (m, 2H, H3), 2.51–2.46 and 2.01–1.91 (m, 2H, H4); ^{13}C NMR (100 MHz, CD_3OD) δ=177.72 (C1–OOH), 177.096 (C5–OOH), 177.071 (C5–^{18}OOH), 137.50 (s), 131.48 (*o*), 128.94 (*m*), 127.65 (*p*), 78.34 (C2), 46.49 (Ph–*C*H$_2$–), 35.34 (C3), 29.78 (C4); LC/MS/MS (ESI): *m*/*z* (%)=239 (100, [M–H]$^-$), 237 (9.8, [M–H]$^-$); Fragments of 239 (ESI): *m*/*z* (%)=221 (100), 219 (93.8), 177 (2.9), 175 (31.9), 131 (12.8).

4.10. Cyclization of the mixture of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids 4c into ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acid 2d and unlabeled acid 2

Using the general procedure for the cyclization of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids with ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids **4c** (4 mg, 0.018 mmol) and 0.5 ml of toluene gave a mixture of ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acid **2d** and unlabeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acid **2** (8 mg) as a light brown solid, mp 103–105 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.99 (s, 1H; COO*H*), 7.24–7.11 (m, 5H, Ph), 3.32 and 3.08 (2d, *J*=14.4 Hz, 2H, Ph–C*H*$_2$–), 2.46–2.37 and 2.25–2.16 (m, 2H; H3), 2.46–2.37 and 2.11–2.00 (m, 2H, H4); ^{13}C NMR (100 MHz, $CDCl_3$) δ=176.06 (C1–OOH), 175.927 (C5–O), 175.889 (C5–^{18}O), 133.68 (s), 130.74 (*o*), 128.79 (*m*), 127.75 (*p*), 86.14 (C2), 42.26 (Ph–*C*H$_2$–), 30.07 (C3), 28.11 (C4); IR: 3032, 2925, 1784, 1750, 1714, 1496, 1456, 1419, 1192, 1042, 931, 699 cm^{-1}; LC/MS/MS (ESI): *m*/*z* (%)=221 (95.5, [M–H]$^-$), 219 (100, [M–H]$^-$); Fragments of 221 (ESI): *m*/*z* (%)=177 (5.1), 175 (100), 131 (37.7). HRMS (ESI): calcd for $C_{12}H_{12}O_4$ [M+H]$^+$ 221.0808; found 221.0813. HRMS (ESI): calcd for $C_{12}H_{12}O_3{}^{18}O$ [M+H]$^+$ 223.0851; found 223.0855.

4.11. Oxidation of C2 ^{18}O labeled 3-benzyl-2-hydroxycyclopent-2-enone 1b with *tert*-butyl hydroperoxide

Using the general procedure for the oxidation of 3-benzyl-2-hydroxy-cyclopent-2-en-1-ones **1** with *tert*-butyl hydroperoxide with 2.5 ml of DCM, 39 mg of MS 4 Å powder, Ti(O^{i}Pr)$_4$ (116 μl, 0.391 mmol), (+)-diethyl tartrate (109 μl, 0.625 mmol), C2 ^{18}O labeled 3-benzyl-2-hydroxy-cyclopent-2-en-1-one **1b** (86 mg, 0.391 mmol) solution in 0.8 ml of DCM and *tert*-butyl hydroperoxide (160 μl, 6.15M in decane, 0.977 mmol) and quenching the reaction with 2.34 ml of H_2O followed by 0.5 ml of 30% NaOH solution in brine gave, after extraction an purification, ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acid **4d** (27 mg, 29%) as a yellowish oil: ^{1}H NMR (400 MHz, CD_3OD) δ=7.29–6.19 (m, 5H, Ph), 3.08 and 2.92 (2d, *J*=13.5 Hz, 2H, Ph–C*H*$_2$–), 2.54–2.46 and 2.27–2.13 (m, 2H, H3), 2.54–2.46 and 2.01–1.90 (m, 1H, H4); ^{13}C NMR (100 MHz, CD_3OD) δ=177.688 (C1–OOH), 177.662 (C1–^{18}OOH), 177.08 (C5–OOH), 137.49 (s), 131.48 (*o*), 128.94 (*m*), 127.66 (*p*), 78.32(C2), 46.49 (Ph–*C*H$_2$–), 35.33 (C3), 29.78 (C4); LC/MS/MS (ESI): *m*/*z* (%)= 239 (100, [M–H]$^-$), 237 (20.8, [M–H]$^-$); Fragments of 239 (ESI): *m*/*z* (%)=221 (100), 219 (13.5), 177 (11.5), 175 (4.2), 131 (5.1).

4.12. Cyclization of the mixture of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acid 4d into ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acid 2e

Using the general procedure for the cyclization of ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acids with ^{18}O labeled 2-benzyl-2-hydroxy-pentanedioic acid **4d** (11 mg, 0.046 mmol) and 1.0 ml of toluene gave ^{18}O labeled 2-benzyl-5-oxo-tetrahydrofuran-2-carboxylic acid **2e** (19 mg) as white crystals, mp 107–110 °C: ^{1}H NMR (800 MHz, $CDCl_3$, 248 K) δ=10.39 (s, 1H, COO*H*), 7.26–7.19 (m, 5H, Ph), 3.33 and 3.08 (2d, *J*=14.5 Hz, 1H, Ph–C*H*$_2$–), 2.46–2.40 and 2.26–2.22 (m, 2H, H3), 2.46–2.40 and 2.11–2.05 (m, 2H, H4); ^{13}C NMR (200 MHz, $CDCl_3$, 248 K) δ=176.780 (C1–OOH), 176.757 (C1–^{18}OOH), 176.28 (C5–O), 133.46 (s), 130.70 (*o*), 128.75 (*m*), 127.71 (*p*), 85.98 (C2), 41.97 (Ph–*C*H$_2$–), 30.04 (C3), 28.06 (C4); IR: 3060, 1769, 1497, 1461, 1421, 1180, 1042, 946, 706 cm^{-1}; LC/MS/MS (ESI): *m*/*z* (%)=221 (100, [M–H]$^-$), 219 (26.0, [M–H]$^-$); Fragments of 221 (ESI): *m*/*z* (%)=177 (100), 175 (51.3), 131 (69.7). HRMS (ESI):

calcd for $C_{12}H_{12}O_4$ $[M+H]^+$ 221.0808; found 221.0818. HRMS (ESI): calcd for $C_{12}H_{12}O_3{}^{18}O$ $[M+H]^+$ 223.0851; found 223.0844.

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Supplementary data

NMR spectra and graphic representation of isotope exchange in **1**–**1a**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.06.036.

References and notes

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16. ^{13}C NMR is used to track ^{18}O atoms in organic molecules because of exchanging an ^{16}O atom for ^{18}O causes a small upfield chemical shift of the carbon attached to the oxygen.[13,15] The magnitude of the shift is specific to functional group,[25] which allows good interpretation of experimental data: in our case the shift is 41 ppb,[17] which is typical for a conjugated carbonyl unit.
17. ^{18}O saturation was measured by the relative peak heights of different oxygen isotope bound ^{13}C peaks. As the change of the isotope does not noticeably alter the relaxation time (and hence the peak shape) of the carbon nucleus, the peak heights are as good quantitative measurements as peak areas.[26]
18. The isotope shift at C2 is noticeably smaller than at C1 and also smaller than typical values for allylic alcohols, which is probably due to the electronic effects from the adjacent carbonyl group (Table 3).
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23. Sample was cooled down to render the isotope shifts observable; shifts were smaller than in **2d** and **2e** (Table 3).
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