Short Report

Oxone®-Mediated Direct α-Hydroxylation of β-Dicarbonyl Compounds: Racemic Synthesis of Harzialactone A

Marcus M. Sá,[*,a] *Marcos M. Peterle* [a] *and Marcelo V. Marques*[b]

aDepartamento de Química, Universidade Federal de Santa Catarina, 88040-900 Florianópolis-SC, Brazil

bInstituto Federal Catarinense (IFC), Campus Fraiburgo, 89580-000 Fraiburgo-SC, Brazil

An environmentally benign method is described for the α-hydroxylation of malonates and cyclic analogues in aqueous medium at room temperature under mild conditions, based on the *in situ* generation of dimethyldioxirane through the combination of acetone and Oxone®. This procedure was found to be substrate-dependent and was successfully performed to provide α-hydroxylated γ-lactones. To demonstrate the synthetic potential of this mild α-hydroxylation, two different concise routes were developed to synthesize harzialactone A in the racemic form with a moderate (3:1) diastereomeric ratio.

Keywords: harzialactone, α-hydroxylation, α-hydroxy malonates, α-hydroxy-γ-lactone, Oxone®

Introduction

Many natural products and pharmaceuticals contain the α-hydroxy-β-dicarbonyl framework as a common structural feature. α-Hydroxy-β-dicarbonyl compounds are also useful synthetic building blocks for the synthesis of a variety of biologically active substances, including naturally occurring carbocycles and heterocycles.[1,2] The most common strategy to prepare α-hydroxy-β-dicarbonyl compounds involves the direct α-hydroxylation of the parent β-dicarbonyls (or their corresponding enolates and analogues) using different oxidizing agents such as peroxides,[3] peroxyacids,[4,5] oxaziridines[6] and O$_2$,[7] usually in the presence of appropriate catalysts and additives.[8-12] Despite their recognized applicability, these methods are associated with a number of disadvantages, such as the use of expensive reagents and catalysts, the need to handle and dispose of toxic chemicals and byproducts, the generation of large amounts of residues, and/or the limited substrate scope.

Oxone® (potassium peroxymonosulfate) is a safe and inexpensive oxidizing reagent of widespread application, including the oxidation of acetone to give dimethyldioxirane (DMD), an unstable oxidant employed in the α-hydroxylation of β-dicarbonyl compounds.[13,14] However, DMD itself is reluctant to oxidize α-substituted malonates, with high conversions to the corresponding α-hydroxy-β-dicarbonyls being achieved only in the presence of a nickel catalyst.[15] To circumvent the tedious preparation of DMD solutions and the risks associated with their handling, Zhang and co-workers[16] reported the direct use of Oxone® for the α-hydroxylation of a great variety of cyclic β-keto esters, β-keto amides, and β-diketones in aqueous medium at 60 °C. However, simple diesters such as malonates proved ineffective as substrates. On the other hand, treating β-dicarbonyl compounds with a combination of Oxone® and AlCl$_3$ led to 1,2-diketones through unexpected oxidative cleavage.[17] As far as we are aware, there is no precedent for the preparation of α-hydroxy malonates using Oxone® as the oxidizing agent.

During studies involving the base-mediated epoxidation of the γ,δ-unsaturated malonate **1a** with Oxone®, *en route* to functionalized cyclopropanecarboxamides[18] and γ-lactones of the catechin family,[19] we found that epoxide **2a** could be efficiently prepared in an aqueous biphasic system, while the α-hydroxylated epoxide **3a** was the major product under homogeneous conditions (Scheme 1). Due to the synthetic potential of this transformation, we conducted further studies to establish the scope and limitation of the Oxone®-mediated α-hydroxylation of malonates.

In this paper, we report an environmentally benign route to α-hydroxy malonates through a mild Oxone®-mediated α-hydroxylation of malonates and analogues in aqueous medium under slightly alkaline conditions (phosphate buffer, pH 8) at room temperature. These simple conditions were successfully employed in a flexible

*e-mail: marcus.sa@ufsc.br

strategy for the racemic synthesis of both diastereoisomers of harzialactone A (**4a**, Scheme 1), an α-hydroxy-γ-lactone of marine origin which exhibits cytotoxic activity.[20-24]
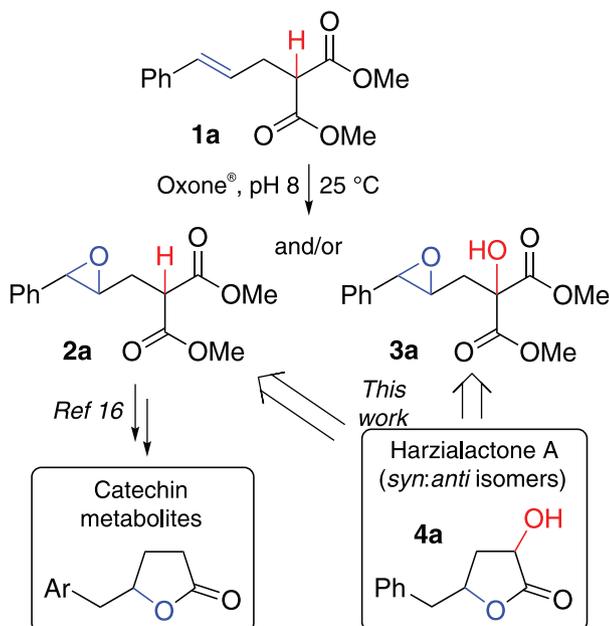
Scheme 1. Previous work on the synthesis of γ-lactones and current research on the Oxone® mediated α-hydroxylation.

Results and Discussion

Firstly, the preparation of the α-hydroxylated epoxide **3a** from the domino epoxidation/α-hydroxylation of γ,δ-unsaturated malonate **1** with Oxone® in aqueous acetone was optimized. While the use of a EtOAc:H$_2$O biphasic system was efficient to selectively produce epoxide **2a**,[18,19] the homogeneous condition obtained in the absence of ethyl acetate (EtOAc) led to the almost exclusive formation of α-hydroxylated epoxide **3a** from **1a** (Scheme 2).

In both cases, the mild alkaline medium employed (phosphate buffer, pH ca. 8) was crucial to the success of the oxidation. In fact, running the reaction in the presence

of carbonated bases such as NaHCO$_3$ or K$_2$CO$_3$ (pH > 8) led to mixtures of **2a** and **3a**, along with side products, due to a partial loss of chemoselectivity under more basic conditions. As expected, treating epoxide **2a** with Oxone® under homogeneous conditions gave cleanly the α-hydroxylated epoxide **3a** in good isolated yield, thus supporting the intermediacy of **2a** in the domino epoxidation/α-hydroxylation from γ,δ-unsaturated malonate **1a**. Similar results were observed for the related unsaturated malonate **1b**, which was selectively transformed into the desired epoxide **2b** and then to the α-hydroxylated epoxide **3b** (Scheme 2).

The remarkable dependence of the reactivity profile on the solvent used is related to whether the unsaturated malonate **1**, as well as the preformed epoxide **2**, are intimately exposed to the alkaline medium. In the particular case of the homogeneous conditions (i.e., in the absence of EtOAc), the basic medium favors the initial deprotonation of malonates to generate stabilized enolates, which are the proposed intermediates for the subsequent α-hydroxylation.[15] Conversely, the use of a biphasic system due to the presence of EtOAc as a cosolvent segregates the substrate **1** and the product **2** in the organic phase, while the basic species (phosphate and related ions) are maintained solvated in the aqueous phase, thus avoiding the extensive enolization of malonates and the concurrent overoxidation to **3**.[25]

Based on the above results, the scope and limitations of the α-hydroxylation of malonates were studied from a synthetic perspective using a combination of Oxone® and acetone in a slightly alkaline phosphate buffer. Under these homogeneous conditions, the unsubstituted malonates **5a,b** were rapidly consumed in a few minutes to generate the corresponding α-hydroxylated malonates **6a,b** (Scheme 3).

A dihydroxylated malonate **7** was also observed after prolonged reaction times, possibly due to overoxidation of the preformed product **6**. The relatively high solubility of hydroxylated malonates **6** in water caused extensive loss of mass during the work-up and purification steps, leading
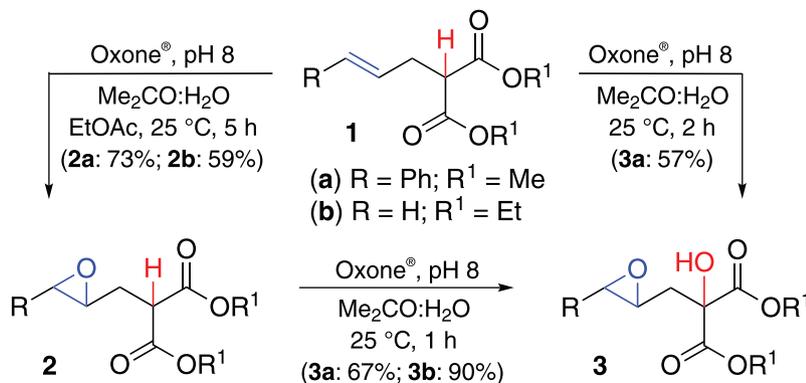
Scheme 2. Domino epoxidation/α-hydroxylation of γ,δ-unsaturated malonates **1** with Oxone® in aqueous acetone.
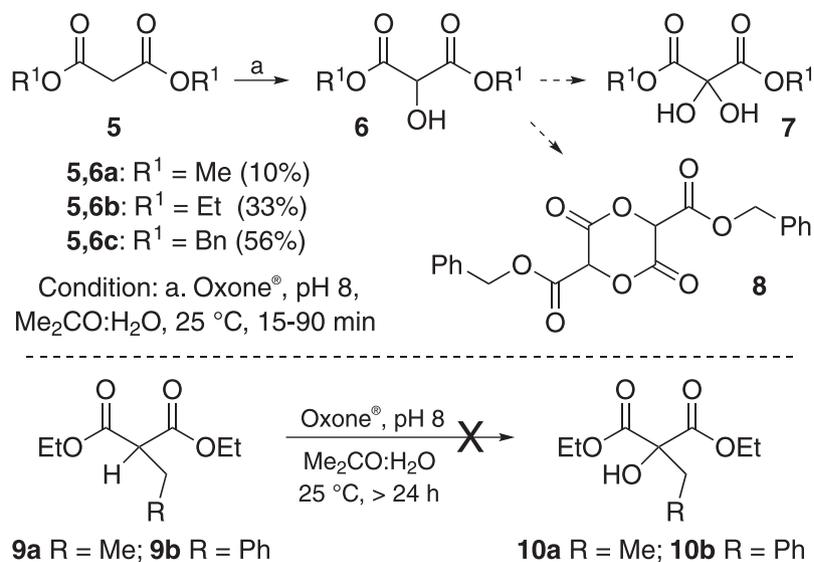
Scheme 3. Scope and limitations of the α-hydroxylation.

to low isolated yields (10-33%) for the expected products. This was not the case for the more hydrophobic dibenzyl α-hydroxymalonate (**6c**, Scheme 3), which was readily prepared from the related dibenzyl ester **5c** in good yield after a conventional aqueous work-up. However, a side product, which was tentatively assigned by ¹H nuclear magnetic resonance (NMR) as the dimeric adduct **8** (10-20%, see Experimental section) was also formed as a non-separable contaminant.

In contrast to the high propensity of γ,δ-epoxide malonates **2** and unsubstituted malonates **5** to undergo α-hydroxylation with Oxone under homogeneous conditions, the α-substituted malonates **9a** and **9b** (Scheme 3) were very reluctant to be oxidized, with negligible conversions (10-15%) being observed even after running the reaction for prolonged periods (> 24 h) or using a higher excess of the oxidant (> 2 equiv). This limited

reactivity of malonates **9a,b** is possibly related to the lower α-H acidity due to the electron-donating effect displayed by the α-alkyl groups, which is not favorable to the generation of the reactive enolate involved in the α-hydroxylation.[15] These combined results strongly indicate that the α-hydroxylation of γ,δ-epoxide malonates **2** is favored due to the higher α-H acidity, which is related to the electron-withdrawing effect exerted by the remote oxirane group.

As a proof of concept, we investigated the α-hydroxylation of α-carboxy-γ-lactone **11**, which is a cyclic malonate containing electronegative groups (ring oxygen and exo-hydroxyl) in remote positions that should enhance the α-H acidity and, consequently, favor the oxidation (Scheme 4). The synthesis of the starting γ-lactone **11** (as a 2:1 mixture of diastereoisomers) was readily achieved through a Lewis acid-mediated rearrangement[26] of epoxide **2a** under microwave irradiation.
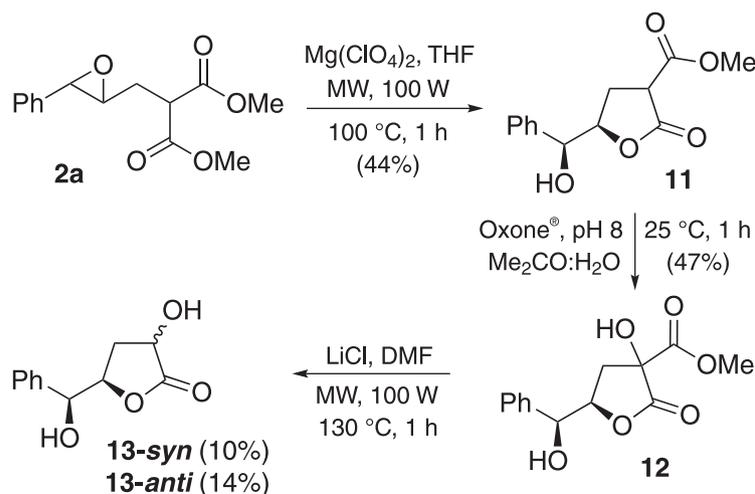
**Scheme 4.** Synthesis of α,δ-dihydroxy-γ-lactones **12** and **13** from **2a**.

As expected, the base-mediated α-hydroxylation of **11** with Oxone® under homogeneous conditions occurred rapidly and cleanly to give a diastereoisomeric mixture of α,δ-dihydroxy-γ-lactones **12** in a 2:1 ratio. Subsequent microwave-assisted Krapcho decarboxylation of γ-lactone **12** was readily achieved to furnish the corresponding dihydroxylated lactone **13** as a diastereomeric pair. The epimers **13**-*syn* and **13**-*anti* could be carefully separated by chromatography, although in low isolated yields, and were fully characterized (see Experimental section).

To demonstrate further the synthetic and strategic potential of applying this mild α-hydroxylation of activated malonates to prepare valuable compounds, we designed a concise racemic synthesis of harzialactone A (**4a**) by two interrelated strategies starting with epoxide **2a** as the common precursor (Scheme 5).

In the first route, the α-hydroxylated epoxide **3a** was employed as an advanced intermediate, which was obtained by the α-hydroxylation of **2a** or, alternatively, from the γ,δ-unsaturated malonate **1a** through the domino epoxidation/α-hydroxylation process, as described above. Thus, the palladium-catalyzed hydrogenolysis of the benzylic C–O bond in **3a** led directly to the α-hydroxylated lactone **16**, possibly through the intermediacy of the

expected γ-hydroxy malonate **17**, in 47% yield. However, the observed diastereoselectivity for the cyclization was low, giving lactone **16** as a 1.7:1 mixture of epimers. Subsequent decarboxylation of **16** under Krapcho conditions, as described above for the dihydroxylated lactone **12**, led to the desired γ-lactone **4** as the sole product in 45% yield (2:1 *syn*:*anti* mixture of diastereoisomers). The relative *syn*:*anti* stereochemistry of each diastereomer of **4** was assigned based on the NMR data described in the literature,[23] wherein the carbinolic H-α hydrogen for the **4**-*anti* isomer is shifted upfield (4.02 ppm) relative to the **4**-*syn* epimer (4.5-4.6 ppm); conversely, H-γ for the **4**-*anti* isomer is shifted downfield (ca. 4.9 ppm) relative to **4**-*syn* (4.5-4.6 ppm).

In the second designed strategy for the synthesis of harzialactone A (**4**, Scheme 5), the known γ-hydroxy malonate **14** (which was readily obtained from the hydrogenolysis of epoxide **3a** in excellent yield)[19] underwent a Lewis acid-mediated cyclization to the corresponding α-carboxy-γ-lactone **15** in high yield but with poor diastereoselectivity (ca. 1.1:1). Nevertheless, the subsequent Oxone®-mediated α-hydroxylation of **15** proved to be straightforward, due to not only the high yields and simplicity of the method but also the amplification of
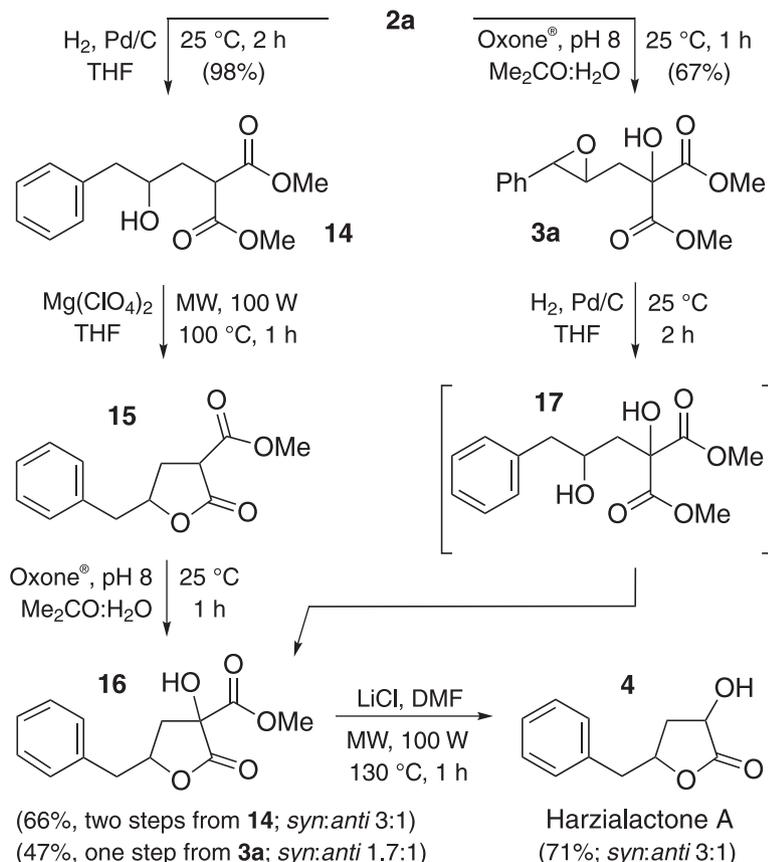
Scheme 5. Two strategies for the racemic synthesis of harzialactone A (**4a**) starting with epoxide **2a**.

diastereoselectivity (3:1 *syn*:*anti*). This improvement in the stereoselectivity from the starting lactone **15** to the α-hydroxylated derivative **16** is possibly related to the reaction mechanism involving the formation of a planar enolate with distinct pro-chiral faces for the approaching of the oxidizing agent DMD,[15] but at this point no definitive conclusions could be drawn. Finally, the microwave-assisted Krapcho decarboxylation of **16** led to the target γ-lactone **4** as a 3:1 *syn*:*anti* mixture of diastereomers (Scheme 5), indicating that the diastereoselectivity gained during the α-hydroxylation was maintained after the removal of the methoxycarbonyl group.

Conclusions

In summary, we have reported herein a simple methodology for the α-hydroxylation of malonates, which showed dependence on the electronic character of the α-substituent present in the starting malonates. Furthermore, we demonstrated that α-carboxy-γ-lactones are useful substrates for the α-hydroxylation and this strategy was successfully employed in the racemic synthesis of both diastereoisomers of harzialactone A, which could be isolated and fully characterized. Although the diastereomeric ratio is dependent upon the synthetic route chosen to obtain harzialactone A, further investigation should be undertaken to unfold the mechanistic aspects of the α-hydroxylation and work along these lines is underway.

Experimental

General methods

Melting points were determined using a hot plate apparatus and are uncorrected. Infrared spectra were acquired with a Fourier transform infrared (FTIR) spectrometer (range 4000-400 cm^{-1}) using KBr for solids and film for liquid samples. ^{1}H NMR spectra were recorded at 400 or at 200 MHz and ^{13}C NMR spectra (fully decoupled) were recorded at 100 or at 50 MHz. Splitting patterns are designated as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), t (triplet), dt (doublet of triplet), appdt (apparent doublet of triplet), m (multiplet). Coupling constants (*J*) are measured in hertz (Hz). Chemical shifts were presented in parts *per* million (ppm, *δ*) relative to tetramethylsilane (TMS) (at 0.00 ppm) or CDCl$_3$ (at 7.26 ppm for ^{1}H NMR and at 77.16 ppm for ^{13}C NMR) as the internal standard. Column chromatography was performed using silica gel (70-230 mesh) and hexane/ethyl acetate as the eluent. Thin layer chromatography (TLC) analysis was performed in silica gel plates. The electrospray-ionization quadrupole time-of-flight (ESI-QTOF) mass spectrometer was operated in the positive ion mode at 4.5 kV and at a desolvation temperature of 180 °C. The standard electrospray ion (ESI) source was used to generate the ions. The instrument was calibrated in the range *m/z* 50-3000 using a calibration standard (low concentration tuning mix solution) and data were processed with the aid of computer software. Microwave-assisted reactions were performed in 10 mL sealed tubes in a monomode microwave CEM Explorer reactor instrument with infrared temperature monitoring and a noninvasive pressure transducer. All chemicals were of reagent grade and were used as received.

Procedures

Typical procedure for the synthesis of epoxides

To a round-bottomed flask containing alkene **1**[18] (1.0 mmol), ethyl acetate (10 mL), acetone (5.0 mL) and phosphate buffer (1.0 mol L^{-1} K$_2$HPO$_4$/KH$_2$PO$_4$, pH 8, 10 mL), under magnetic stirring, was added a solution of Oxone® (1.3 mmol for **1a** or 1.5 mmol for **1b**) in water (5.0 mL) over a period of 1 h. The reaction mixture was stirred until TLC (hexane/EtOAc, 80:20, v/v) showed completion of the reaction (see below). The insoluble solid was separated by filtration under reduced pressure and washed with EtOAc. The filtrate was washed with 1.0 mol L^{-1} Na$_2$S$_2$O$_3$ and brine, dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure to give the epoxides as pale yellow oil. The crude mixture was purified by silica gel chromatography (hexane:EtOAc, 80:20, v/v) to provide epoxides **2a** and **2b**.

Methyl 4,5-epoxy-2-(methoxycarbonyl)-5-phenylpentanoate (2a)[18]

Pale yellow oil; 1 h; yield 193 mg (73%); IR (KBr) ν / cm^{-1} 3002, 2955, 1736, 1436, 1238, 1158, 881, 755, 700, 553; ^{1}H NMR (200 MHz, CDCl$_3$) *δ* 7.35-7.29 (m, 3H), 7.26-7.21 (m, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 3.67 (d, *J* 2.0 Hz, 1H), 3.65 (dd, *J* 8.8, 5.8 Hz, 1H), 3.06 (ddd, *J* 6.4, 4.8, 2.0 Hz, 1H), 2.41 (ddd, *J* 14.2, 8.8, 4.8 Hz, 1H), 2.19 (appdt, *J* 14.2, 6.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) *δ* 169.3 (C), 169.2 (C), 136.9 (C), 128.5 (2 × CH), 128.3 (CH), 125.6 (2 × CH), 60.1 (CH), 58.9 (CH), 52.9 (CH$_3$), 52.8 (CH$_3$), 48.5 (CH), 31.6 (CH$_2$).

Ethyl 4,5-epoxy-2-(ethoxycarbonyl)pentanoate (2b)[18]

Colorless oil; 14 h; yield 127 mg (59%); IR (KBr) ν / cm^{-1} 2986, 2939, 1748, 1732, 1446, 1371, 1260, 1238, 1179, 1156, 1030, 861; ^{1}H NMR (400 MHz, CDCl$_3$)

δ 4.25-4.20 (m, 4H), 3.54 (dd, *J* 8.4, 6.2 Hz, 1H), 3.03-3.01 (m, 1H), 2.77 (t, *J* 4.5 Hz, 1H), 2.52 (dd, *J* 4.5, 2.5 Hz, 1H), 2.25 (ddd, *J* 14.0, 8.4, 4.4 Hz, 1H), 2.00 (dt, *J* 14.0, 6.2 Hz, 1H), 1.30-1.26 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.7 (C), 168.6 (C), 61.44 (CH$_2$), 61.41 (CH$_2$), 49.6 (CH), 48.8 (CH), 47.0 (CH$_2$), 31.5 (CH$_2$), 13.9 (CH$_3$), 13.8 (CH$_3$).

General procedure for the α-hydroxylation of malonates and γ-lactones

To a round-bottomed flask containing the corresponding 1,3-dicarbonyl compound (1.0 mmol), acetone (5.0 mL) and phosphate buffer (1.0 mol L^{-1} K$_2$HPO$_4$/KH$_2$PO$_4$, pH 8, 10 mL), under magnetic stirring, was added a solution of Oxone® (921 mg, 1.5 mmol) in water (5.0 mL) over a period of 1 h. The reaction was monitored through TLC (hexane:EtOAc, 70:30, v/v) until completion (0.5-3 h, see below). The insoluble solid was separated by filtration under reduced pressure and washed with EtOAc. The filtrate was washed with 1.0 mol L^{-1} Na$_2$S$_2$O$_3$ and brine, dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (hexane:EtOAc, 70:30, v/v) to give the corresponding hydroxylated product.

Methyl 4,5-epoxy-2-hydroxy-2-(methoxycarbonyl)-5-phenyl-pentanoate (3a)

From epoxide 2a

Pale yellow oil; 1 h; yield 188 mg (67%); IR (KBr) ν / cm^{-1} 3482, 3008, 2957, 1744, 1438, 1287, 1228, 1150, 883, 748, 700; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34-7.22 (m, 5H), 4.07 (s, 1H, exchange with D$_2$O), 3.84 (s, 3H), 3.81 (s, 3H), 3.68 (d, *J* 2.0 Hz, 1H), 3.16 (ddd, *J* 6.6, 4.6, 2.0 Hz, 1H), 2.49 (dd, *J* 14.4, 4.6, 1H), 2.39 (dd, *J* 14.4, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.8 (C), 170.2 (C), 136.9 (C), 128.5 (2 × CH), 128.3 (CH), 125.7 (2 × CH), 77.4 (C), 58.5 (CH), 57.9 (CH), 53.8 (CH$_3$), 53.6 (CH$_3$), 37.8 (CH$_2$); high-resolution mass spectrometry (HRMS) (ESI) *m/z*, calcd. for C$_{14}$H$_{16}$O$_6$Na$^+$ [M + Na]$^+$: 303.0839; found: 303.0845.

From alkene 1a through a one-pot epoxidation/α-hydroxylation process

To a round-bottomed flask containing alkene **1a** (248 mg, 1.0 mmol), acetone (5.0 mL) and phosphate buffer (1.0 mol L^{-1} K$_2$HPO$_4$/KH$_2$PO$_4$, pH 8, 10 mL), under magnetic stirring, was added a solution of Oxone® (921 mg, 1.5 mmol) in water (5.0 mL) over a period of 1 h. After stirring for an additional 1 h, a second solution of Oxone®

(1.5 mmol in 5.0 mL of H$_2$O) was slowly added during 1 h and the resulting mixture was stirred for an additional 1.5 h. Next, the insoluble solid was separated by filtration under reduced pressure and washed with EtOAc. The filtrate was washed with 1.0 mol L^{-1} Na$_2$S$_2$O$_3$ and brine, dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography (hexane:EtOAc, 70:30, v/v) to provide the title compound **3a** as a pale yellow oil, yield 160 mg (57%).

Ethyl 4,5-epoxy-2-hydroxy-2-(ethoxycarbonyl)pentanoate (3b)

Colorless oil; 3 h; yield 209 mg (90%); IR (KBr) ν / cm^{-1} 3480, 2984, 1740, 1369, 1240, 1218, 1146, 1034, 861, 608; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.34-4.24 (m, 4H), 3.14-3.09 (m, 1H), 2.76 (t, *J* 5.0 Hz, 1H), 2.53 (dd, *J* 5.0, 2.8 Hz, 1H), 2.29 (dd, *J* 14.4, 5.0 Hz, 1H), 2.29 (dd, *J* 14.4, 6.6 Hz, 1H), 1.31-1.27 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.1 (C), 169.6 (C), 77.3 (C), 62.5 (CH$_2$), 62.3 (CH$_2$), 47.5 (CH$_2$ or CH), 46.7 (CH or CH$_2$), 37.6 (CH$_2$), 13.8 (CH$_3$), 13.7 (CH$_3$); HRMS (ESI) *m/z*, calcd. for C$_{10}$H$_{16}$O$_6$Na$^+$ [M + Na]$^+$: 255.0839; found: 255.0839.

Diethyl 2-hydroxymalonate (6b)[27]

Colorless oil; 0.5 h; yield 58 mg (33%); IR (KBr) ν / cm^{-1} 3467, 2986, 1754, 1468, 1238, 1120, 1024, 861; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.71 (d, *J* 8.2 Hz, 1H), 4.33-4.26 (m, 4H), 3.72 (d, *J* 8.2 Hz, 1H, exchange with D$_2$O), 1.31 (t, *J* 7.2 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.5 (C), 71.6 (CH), 62.6 (CH$_2$), 14.0 (CH$_3$); HRMS (ESI) *m/z*, calcd. for C$_7$H$_{12}$O$_5$Na$^+$ [M + Na]$^+$: 199.0577; found: 199.0583.

Dibenzyl 2-hydroxymalonate (6c)[28]

White solid; 2.5 h; yield 159 mg (53%), mp 60-62 °C; IR (KBr) ν / cm^{-1} 3431, 3037, 2959, 1744, 1456, 1342, 1277, 1169, 732; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35-7.25 (m, 10H), 5.23 (d, *J* 12.2 Hz, 2H), 5.18 (d, 12.2 Hz, 2H), 4.80 (d, *J* 8.4 Hz, 1H), 3.49 (d, *J* 8.4 Hz, 1H). Data for the cyclic bis-adduct **8** (10-20%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.4-7.2 (m, 10H), 5.07-4.98 (m, 2H), 4.81 (d, *J* 8.4 Hz, 2H), 3.49 (d, *J* 8.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.4 (C), 134.7 (C), 128.79 (CH), 128.78 (CH), 128.5 (CH), 71.7 (CH), 68.3 (CH$_2$); HRMS (ESI) *m/z*, calcd. for C$_{17}$H$_{16}$O$_5$Na$^+$ [M + Na]$^+$: 323.0890; found: 323.0886.

Methyl 5-[hydroxy(phenyl)methyl]-2-oxotetrahydrofuran-3-carboxylate (11)

To a 10 mL glass tube containing a solution of epoxide **2a** (264 mg, 1.0 mmol) in tetrahydrofuran (THF) (2.5 mL) was added Mg(ClO$_4$)$_2$ (223 mg, 1.0 mmol). The vessel was sealed

with a septum, placed into the microwave cavity, and the mixture was heated to 100 °C (maximum power = 100 W) under stirring for 1 h. After cooling to 25 °C, the mixture was diluted with EtOAc and washed with water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with 0.1 mol L^{-1} HCl and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to furnish a yellow oil. The crude product was purified by silica gel chromatography (hexane:EtOAc, 70:30, v/v) to provide the title compound **11** (yellow oil, 110 mg, 44%) as a 2:1 mixture of diastereoisomers (**11a**:**11b**).

Isomer **11a** (major)

IR (2:1 mixture) (KBr) ν / cm^{-1} 3496, 3031, 2955, 1779, 1738, 1452, 1163, 1026, 757, 706; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37-7.29 (m, 5H), 5.10 (d, *J* 2.6 Hz, 1H), 4.77 (ddd, *J* 8.0, 4.6, 2.6 Hz, 1H), 3.82-3.73 (m, 1H), 3.72 (s, 3H), 2.48 (ddd, *J* 13.5, 10.0, 4.6 Hz, 1H), 2.31 (dt, *J* 13.5, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 173.0 (C), 168.7 (C), 138.5 (C), 128.6 (2 × CH), 128.0 (CH), 126.0 (2 × CH), 82.6 (CH), 73.1 (CH), 53.0 (CH$_3$), 46.7 (CH), 24.9 (CH$_2$).

Isomer **11b** (minor)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37-7.29 (m, 5H), 5.07 (d, *J* 3.8 Hz, 1H), 4.59 (ddd, *J* 8.8, 6.6, 3.8 Hz, 1H), 3.76 (s, 3H), 3.57 (t, *J* 9.8 Hz, 1H), 2.79-2.70 (m, 1H), 2.17 (ddd, *J* 13.2, 9.8, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.2 (C), 168.3 (C), 138.5 (C), 128.5 (2 × CH), 128.1 (CH), 126.1 (2 CH), 82.1 (CH), 72.4 (CH), 53.1 (CH$_3$), 46.6 (CH), 25.3 (CH$_2$); HRMS (2:1 mixture) (ESI) *m/z*, calcd. for C$_{13}$H$_{14}$O$_5$Na$^+$ [M + Na]$^+$: 273.0733; found: 273.0731.

Methyl 3-hydroxy-5-[hydroxy(phenyl)methyl]-2-oxotetrahydrofuran-3-carboxylate (**12**)

Obtained from lactone **11** (250 mg, 1.0 mmol) through the general procedure for α-hydroxylation (1.5 h) as a pale yellow oil, yield 125 mg (47%) as a 2:1 mixture of diastereoisomers (**12a**:**12b**).

Isomer **12a** (major)

IR (2:1 mixture) (KBr) ν / cm^{-1} 3459, 2957, 1783, 1750, 1452, 1265, 1207, 1024, 704; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39-7.33 (m, 5H), 5.19 (d, *J* 3.6 Hz, 1H), 4.80 (ddd, *J* 8.4, 6.8, 3.6 Hz, 1H), 4.27 (br s, 1H), 3.83 (s, 3H), 2.63 (dd, *J* 13.8, 8.4 Hz, 1H), 2.41 (dd, *J* 13.8, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 173.1 (C), 170.2 (C), 137.9 (C), 128.9 (2 × CH), 128.5 (CH), 126.1 (2 × CH), 80.9 (CH), 77.2 (C), 72.4 (CH), 54.1 (CH$_3$), 33.4 (CH$_2$).

Isomer **12b** (minor)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39-7.33 (m, 5H), 5.21 (d, *J* 3.6 Hz, 1H), 4.89 (ddd, *J* 9.4, 5.8, 3.6 Hz, 1H), 4.08 (br s, 1H), 3.89 (s, 3H), 2.95 (dd, *J* 13.6, 9.4 Hz, 1H), 2.02 (dd, *J* 13.6, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.6 (C), 170.6 (C), 137.8 (C), 128.8 (2 × CH), 128.5 (CH), 126.1 (2 × CH), 82.2 (CH), 77.4 (C), 72.0 (CH), 54.2 (CH$_3$), 33.5 (CH$_2$); HRMS (2:1 mixture) (ESI) *m/z*, calcd. for C$_{13}$H$_{14}$O$_6$Na$^+$ [M + Na]$^+$: 289.0683; found: 289.0682.

Methyl 5-benzyl-3-hydroxy-2-oxotetrahydrofuran-3-carboxylate (**16**)[29]

From γ-hydroxy malonate **14**

To a 10 mL glass tube containing a solution of alcohol **14**[19] (266 mg, 1.0 mmol) in THF (3.5 mL) was added Mg(ClO$_4$)$_2$ (223 mg, 1.0 mmol). The vessel was sealed with a septum, placed into the microwave cavity, and the mixture was heated to 100 °C (maximum power = 100 W) under stirring for 1 h. After cooling to 25 °C, the mixture was diluted with EtOAc and washed with water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with 0.1 mol L^{-1} HCl and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to provide methyl 5-benzyl-2-oxotetrahydrofuran-3-carboxylate (**15**, pale yellow oil, 203 mg, 87%) as a ca. 1.1:1 mixture of diastereoisomers, which was used in the next step without further purification.

Methyl 5-benzyl-2-oxotetrahydrofuran-3-carboxylate (**15**)

IR (KBr) ν / cm^{-1} 3029, 2953, 1781, 1738, 1438, 1356, 1163, 1016, 704; ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.36-7.20 (m, 10H), 4.98-4.85 (m, 1H), 4.72-4.58 (m, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.62 (dd, *J* 10.8, 9.4 Hz, 1H), 3.34 (dd, *J* 9.4, 5.4 Hz, 1H), 3.17 (dd, *J* 13.6, 6.6 Hz, 1H), 3.01-2.91 (m, 3H), 2.63 (ddd, *J* 13.4, 7.0, 5.6 Hz, 1H), 2.48-2.37 (m, 2H), 2.20 (ddd, *J* 13.4, 9.6, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.7 (C), 171.5 (C), 168.28 (C), 168.26 (C), 135.7 (C), 135.3 (C), 129.7 (2 × CH), 129.4 (2 × CH), 128.9 (2 × CH), 128.8 (2 × CH), 127.3 (CH), 127.2 (CH), 80.0 (CH), 79.9 (CH), 53.2 (2 × CH$_3$), 47.2 (CH), 46.7 (CH), 41.4 (CH$_2$), 41.2 (CH$_2$), 31.8 (CH$_2$), 31.1 (CH$_2$).

α-Hydroxylation of lactone **15** prepared above (203 mg, 0.87 mmol) was achieved through the general procedure (1.5 h) to give a pale yellow oil, yield 127 mg (76%) as a 3:1 mixture of diastereoisomers (**16**-*syn*:**16**-*anti*).

Isomer **16**-*syn* (major)

IR (3:1 mixture) (KBr) ν / cm^{-1} 3467, 3029, 2955, 1781, 1748, 1438, 1283, 1195, 1010, 704; ^{1}H NMR (400 MHz,

CDCl$_3$) δ 7.35-7.22 (m, 5H), 4.98-4.90 (m, 1H), 4.08 (br s, 1H), 3.85 (s, 3H), 3.19 (dd, *J* 14.4, 6.6 Hz, 1H), 2.97 (dd, *J* 14.4, 6.6 Hz, 1H), 2.51 (dd, *J* 13.6, 8.8 Hz, 1H), 2.38 (dd, *J* 13.6, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.5 (C), 170.6 (C), 135.5 (C), 129.4 (2×CH), 128.8 (2×CH), 127.2 (CH), 79.7 (CH), 77.4 (C), 54.0 (CH$_3$), 41.0 (CH$_2$), 39.6 (CH$_2$).

Isomer **16**-*anti* (minor)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35-7.22 (m, 5H), 4.90-4.81 (m, 1H), 4.05 (br s, 1H), 3.83 (s, 3H), 3.18 (dd, *J* 14.0, 6.6 Hz, 1H), 2.96 (dd, *J* 14.0, 6.6 Hz, 1H), 2.73 (dd, *J* 13.6, 6.0 Hz, 1H), 2.22 (dd, *J* 13.6, 9.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 172.9 (C), 170.3 (C), 135.5 (C), 129.5 (2×CH), 128.9 (2×CH), 127.3 (CH), 78.6 (CH), 77.3 (C), 54.1 (CH$_3$), 41.6 (CH$_2$), 39.6 (CH$_2$); HRMS (3:1 mixture) (ESI) *m/z*, calcd. for C$_{13}$H$_{14}$O$_5$Na$^+$ [M + Na]$^+$: 273.0733; found: 273.0732.

From the α-hydroxylated epoxide **3a**

To a round-bottomed flask containing the α-hydroxylated epoxide **3a** (280 mg, 1.0 mmol) and THF (10 mL), under magnetic stirring, was added Pd/C 10% (28 mg, 10% m/m), then the system was charged with H$_2$ (balloon) and the mixture was stirred at 25 °C for 4 h. Next, the reaction mixture was filtered through a Celite pad and the filter cake was exhaustively washed with MeOH. The filtrate was concentrated under reduced pressure to provide the title compound **16** (pale yellow oil, 118 mg, 47%), as a 1.7:1 mixture of diastereoisomers (**16**-*syn*:**16**-*anti*). Spectroscopic data are in fully agreement with the same product **16** prepared from α-hydroxylation of lactone **15** as described above.

General procedure for the decarboxylation of lactones **12** and **16**

To a 10 mL glass tube containing a solution of lactone **12** or **16** (1.0 mmol) in dimethylformamide (DMF) (3.5 mL) was added LiCl (42 mg, 1.0 mmol). The vessel was sealed with a septum, placed into the microwave cavity, and the mixture was heated to 130 °C (maximum power = 100 W) under stirring for 30 min. After cooling to 25 °C, the mixture was diluted with EtOAc and washed with water. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with 0.1 mol L^{-1} HCl and brine, dried over anhydrous Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (hexane:EtOAc, 70:30, v/v).

3-Hydroxy-5-[hydroxy(phenyl)methyl]dihydrofuran-2(3*H*)-one (**13**)[26]

Orange oil, obtained as a mixture of two diastereoisomers. After careful separation by column chromatography, each epimer was isolated and properly characterized.

Isomer **13**-*syn*

Orange oil; yield 21 mg (10%); RF = 0.30 (hexane:EtOAc, 50:50, v/v); IR (KBr) ν / cm^{-1} 3512, 3398, 2956, 1764, 1734, 1450, 1209, 1114, 1003, 720, 702; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36-7.26 (m, 5H), 5.08 (d, *J* 2.0 Hz, 1H), 4.73 (dt, *J* 8.8, 2.0 Hz, 1H), 4.67 (t, *J* 8.8 Hz, 1H), 2.57-2.51 (m, 1H), 1.95 (dt, *J* 13.5, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 179.2 (C), 138.5 (C), 128.8 (2×CH), 128.2 (CH), 126.0 (2 × CH), 81.7 (CH), 73.6 (CH), 67.5 (CH), 29.5 (CH$_2$); HRMS (ESI) *m/z*, calcd. for C$_{11}$H$_{12}$O$_4$Na$^+$ [M + Na]$^+$: 231.0628; found: 231.0626.

Isomer **13**-*anti*

Orange oil; yield 29 mg (14%); RF = 0.15 (hexane:EtOAc, 50:50, v/v); IR (KBr) ν / cm^{-1} 3406, 3064, 1777, 1452, 1326, 1203, 1126, 1008, 704; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34-7.26 (m, 5H), 5.13 (d, *J* 3.0 Hz, 1H) 4.56 (ddd, *J* 9.6, 8.0, 3.0 Hz, 1H), 4.40 (t, *J* 8.8 Hz, 1H), 4.28 (br s, 1H), 2.29-2.17 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 177.9 (C), 138.1 (C), 128.7 (2×CH), 128.2 (CH), 126.1 (2 × CH), 80.8 (CH), 72.2 (CH), 68.2 (CH), 29.6 (CH$_2$); HRMS (ESI) *m/z*, calcd. for C$_{11}$H$_{12}$O$_4$Na$^+$ [M + Na]$^+$: 231.0628; found: 231.0629.

3-Hydroxy-5-benzyldihydrofuran-2-one (**4**)[30]

Orange oil; yield 136 mg (71%), obtained as a 3:1 mixture of the **4**-*syn* and **4**-*anti* isomers. After chromatography, each diastereoisomer was isolated and properly characterized.

Isomer **4**-*syn*

White solid; yield 69 mg (36%); mp 70-72 °C; RF = 0.36 (hexane:EtOAc, 50:50, v/v); IR (3:1 mixture) (KBr) ν / cm^{-1} 3406, 2925, 1774, 1454, 1195, 1126, 991, 702; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33-7.20 (m, 5H), 4.60-4.49 (m, 2H), 3.88 (br s, 1H), 3.11 (dd, *J* 14.0, 6.4 Hz, 1H), 2.93 (dd, *J* 14.0, 6.4 Hz, 1H), 2.59 (ddd, *J* 13.2, 8.4, 5.2 Hz, 1H), 2.00-1.91 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 177.8 (C), 135.6 (C), 129.4 (2×CH), 128.8 (2×CH), 127.2 (CH), 77.5 (CH), 68.6 (CH), 41.3 (CH$_2$), 36.7 (CH$_2$); HRMS (ESI) *m/z*, calcd. for C$_{11}$H$_{12}$O$_3$Na$^+$ [M + Na]$^+$: 215.0679; found: 215.0677.

Isomer **4**-*anti*

Orange oil; yield 25 mg (13%); RF = 0.42

(hexane:EtOAc, 50:50, v/v); ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.35-7.17 (m, 5H), 4.96-4.85 (m, 1H), 4.03 (t, *J* 7.8 Hz, 1H), 3.18 (br s, 1H), 2.97 (d, *J* 5.8 Hz, 2H), 2.36-2.19 (m, 2H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 177.6 (C), 135.4 (C), 129.7 (2 × CH), 128.9 (2 × CH), 127.4 (CH), 78.5 (CH), 67.2 (CH), 41.3 (CH$_2$), 34.6 (CH$_2$); HRMS (ESI) *m/z*, calcd. for C$_{11}$H$_{12}$O$_3$Na$^+$ [M + Na]$^+$: 215.0679; found: 215.0678.

Supplementary Information

Supplementary information (^{1}H and ^{13}C NMR spectra) is available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

References

1. Christoffers, J.; Baro, A.; Werner, T.; *Adv. Synth. Catal.* **2004**, *346*, 143.

2. Reddy, D. S.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; *Angew. Chem., Int. Ed.* **2009**, *48*, 803.

3. Terent'ev, A. O.; Vil, V. A.; Gorlov, E. S.; Nikishin, G. I.; Pivnitsky, K. K.; Adam, W.; *J. Org. Chem.* **2016**, *81*, 810.

4. Feng, Y.; Huang, R.; Hua, L.; Xiong, Y.; Coeffard, V.; *Synthesis* **2016**, *48*, 2637.

5. Asahara, H.; Nishiwaki, N.; *J. Org. Chem.* **2014**, *79*, 11735.

6. Davis, F. A.; Liu, H.; Chen, B.-C.; Zhou, P.; *Tetrahedron* **1998**, *54,* 10481.

7. Li, Z.; Li, T.; Li, J.; He, L.; Jia, X.; Yang, J.; *Synlett* **2015**, *26*, 2863.

8. Miao, C.-B.; Wang, Y.-H.; Xing, M.-L.; Lu, X.-W.; Sun, X.-Q.; Yang, H.-T.; *J. Org. Chem.* **2013**, *78*, 11584.

9. Chuang, G. J.; Wang, W.; Lee, E.; Ritter, T.; *J. Am. Chem. Soc.* **2011**, *133*, 1760.

10. Monguchi, Y.; Takahashi, T.; Iida, Y.; Fujiwara, Y.; Inagaki, Y.; Maegawa, T.; Sajiki, H.; *Synlett* **2008**, 2291.

11. Christoffers, J.; Werner, T.; Unger, S.; Frey, W.; *Eur. J. Org. Chem.* **2003**, 425.

12. Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E.; *Org. React.* **2003**, *62*, DOI: 10.1002/0471264180.or062.01.

13. Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M.; *J. Am. Chem. Soc.* **2006**, *128*, 14010.

14. Adam, W.; Mijller, M.; Prechtl, F.; *J. Org. Chem.* **1994**, *59*, 2358.

15. Adam, W.; Smerz, A. K.; *Tetrahedron* **1996**, *52*, 5799.

16. Yu, J.; Cui, J.; Zhang, C.; *Eur. J. Org. Chem.* **2010**, 7020.

17. Stergiou, A.; Bariotaki, A.; Kalaitzakis, D.; Smonou, I.; *J. Org. Chem.* **2013**, *78*, 7268.

18. Marques, M. V.; Sá, M. M.; *J. Org. Chem.* **2014**, *79*, 4650.

19. Oliveira, C. C.; Marques, M. V.; Godoi, M. N.; Regiani, T.; Santos, V. G.; Santos, E. A. F.; Eberlin, M. N.; Sá, M. M.; Correia, C. R. D.; *Org. Lett.* **2014**, *16*, 5180.

20. Amagata, T.; Usami, Y.; Minoura, K.; Ito, T.; Numata, A.; *J. Antibiot.* **1998**, *51*, 33.

21. Pawar, V. U.; Ghosh, S.; Chopade, B. A.; Shinde, V. S.; *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7243.

22. Kumar, D. N.; Reddy, C. R.; Das, B.; *Synthesis* **2011**, *19*, 3190.

23. Sabitha, G.; Srinivas, R.; Das, S. K.; Yadav, J. S.; *Beilstein J. Org. Chem.* **2010**, *6*, DOI: 10.3762/bjoc.6.8.

24. Shu, C.; Liu, M.; Sun, Y.; Ye, L.; *Org. Lett.* **2012**, *4*, 4958.

25. Hashimoto, N.; Kanda, A.; *Org. Process Res. Dev.* **2002**, *6*, 405.

26. Antoniotti, S.; Duñach, E.; *Tetrahedron Lett.* **2009**, *50*, 2536.

27. Companyó, X.; Mazzanti, A.; Moyano A.; Janecka, A.; Rios, R.; *Chem. Commun.* **2013**, *49*, 1184.

28. Kurz, T.; Geffken, D.; *Z. Naturforsch. B* **1999**, *54b*, 667.

29. Achmatowicz, O.; Bialecka-Florjańczyk, E.; *Tetrahedron* **1996**, *52*, 8827.

30. Kumar, A. N.; Bhatt, S.; Chattopadhyay, S.; *Tetrahedron: Asymmetry* **2009**, *20*, 205.