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Short Note

Methyl 6-Benzyl-3-Hydroxy-3,6-Dimethyl-1,2-Dioxane-4-Carboxylate

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Abstract: *Plasmodium falciparum* is a fast-evolving parasite responsible for the fatal disease malaria, making it crucial to renew our therapeutic arsenal. Modulating the artemisinin's endoperoxide pharmacophore is a promising route to synthesizing new antimalarial derivatives. For the first step of our 20 mmol scale synthesis, catalyzed by manganese (III) acetylacetonate, we applied the conditions previously described in the literature to one of our low-yielding asymmetrically disubstituted alkenes, (2-methylallyl)benzene. Under conditions designed for alkyl derivatives, manganese (II) and (III) acetate catalyzed its peroxycyclization with methyl 3-oxobutanoate to a 1,2-dioxane ring in the presence of oxygen from air at room temperature with a 36% yield, while an oxygen atmosphere, as described in the literature, decreased the yield to 7%. Finally, under conditions designed for aryl derivatives, the yield was reduced to 30%, showing that methylallyl derivatives have an intermediate reactivity that needs further optimization to produce 1,2-dioxane ring by manganese catalyzation in good yields. This work characterizes the product obtained and discusses the most suitable reaction conditions.

Keywords: malaria; 1,2-dioxane; endoperoxide; manganese (III) acetate; radical chemistry; methylallyl derivative

Citation: Benech, A.; Khoumeri, O.; Curti, C.; Vanelle, P. Methyl 6-Benzyl-3-Hydroxy-3,6-Dimethyl-1,2-Dioxane-4-Carboxylate. *Molbank* **2024**, *2024*, M1825. https://doi.org/10.3390/M1825

Academic Editor: Nicola Della Ca'

Received: 25 March 2024
Revised: 15 May 2024
Accepted: 18 May 2024
Published: 23 May 2024

1. Introduction

Malaria is a life-threatening disease vectorized to humans by some types of mosquitoes, and it was responsible for 608,000 deaths worldwide in 2022 [1]. It is predominantly found in tropical countries, but its vectors are also present in temperate regions such as Europe [2].

Derivatives of artemisinin are the primary active drugs against *Plasmodium falciparum* (Figure 1). Its pharmacophore, the endoperoxide ring (1,2-dioxane), was synthesized using a manganese (III) acetylacetonate ($Mn(acac)_3$) strategy in the early 1990s [3,4]. Twenty years later, the synthetic route was adapted to a 20 mmol scale with manganese (II) ($Mn(OAc)_2$) and (III) ($Mn(OAc)_3$) acetate in catalytic concentrations, and several series of derivatives were evaluated in vitro with good results (Figure 2) [5–8]. However, using manganese acetate requires the concomitant use of an activated methylene compound. The synthetic route was investigated for both aryl and alkyl alkene derivatives, with large variations in yield due to the slightest change in substituent or conditions. Some works are oriented towards the synthesis of 1,2-dioxanes with aryl substituents catalyzed by manganese (III) acetylacetonate at room temperature under dried air [3,4], whereas others are focused on 1,2-dioxanes with alkyl substituents catalyzed by manganese (III) acetate with manganese (II) acetate at room temperature in an oxygen atmosphere (i.e., an O_2-filled balloon) [5,7].

Using a methylallyl derivative, we conducted a comparative analysis between these alkyl-oriented conditions, both with and without an oxygen atmosphere, and the aryl-oriented conditions, utilizing manganese (II) and (III) acetate [9].

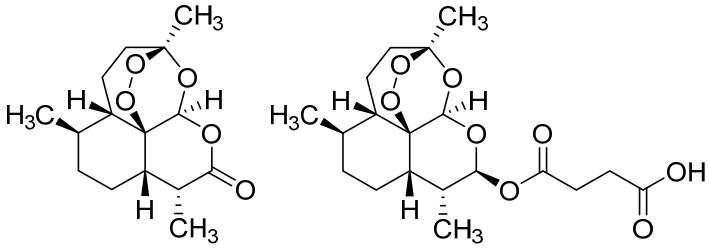


Figure 1. Structures of artemisinin (**left**) and one of its therapeutic derivatives, artesunate (**right**).

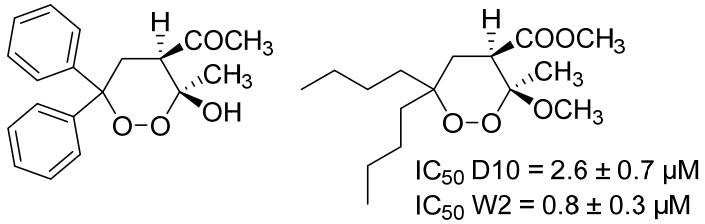


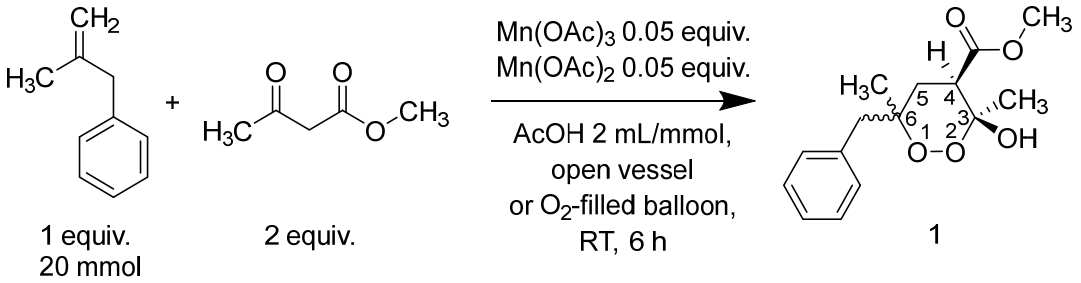
Figure 2. Structures of one of the first 1,2-dioxane synthesized with $Mn(acac)_3$ (**left**) [3] and hit derivative (**right**) [5].

This study aims to investigate the reactivity and improve the yield of a methylallyl derivative, specifically (2-methylallyl)benzene, with methyl 3-oxobutanoate β-ketoester. This short note reports the synthesis of a novel derivative identified as methyl 6-benzyl-3-hydroxy-3,6-dimethyl-1,2-dioxane-4-carboxylate (compound **1**).

2. Results

Synthesis

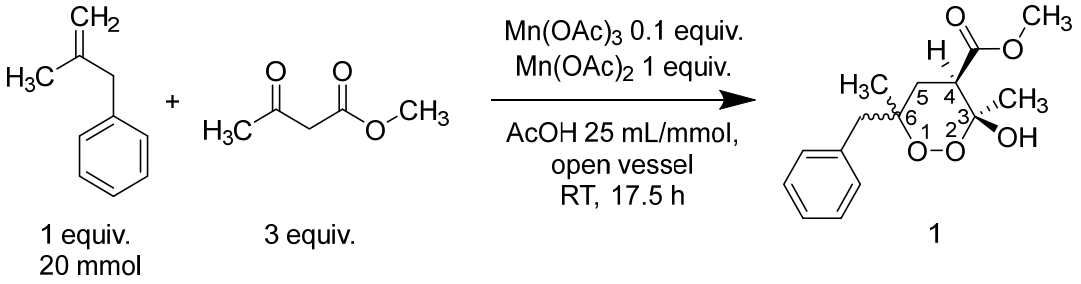
The best yielding synthesis of methyl 6-benzyl-3-hydroxy-3,6-dimethyl-1,2-dioxane-4-carboxylate (compound **1**) was achieved using commercially available (2-methylallyl)benzene and methyl 3-oxobutanoate in glacial acetic acid (AcOH) at room temperature, using catalytic amounts of manganese (III) acetate and manganese (II) acetate (Scheme 1) [7].



Scheme 1. Synthesis of compound **1** using alkyl-oriented conditions.

Two distinct conditions were evaluated for this reaction: in an open vessel, resulting in a 36% yield, and under an oxygen atmosphere (O_2-filled balloon) following a protocol from the literature, which yielded 7%.

Furthermore, an alternative protocol utilizing a stoichiometric quantity of Mn(II) acetate, designed for aryl-oriented derivatives [9], provided a 30% yield (Scheme 2). This protocol was initially designed for 1 mmol scale reactions; however, we scaled up the alkene quantity by 10-fold at first. Compared to the 1 mmol reaction described in the literature, we extended the reaction time from 12 to 15 h and obtained a first yield of 23%.



Scheme 2. Synthesis of compound **1** using aryl-oriented conditions.

The 500 mL volume of solvent required for the 20 mmol scale seemed substantial. We finally tried this scale to assess whether this volume allowed enough gaseous exchanges for the molecular oxygen from the air to be incorporated. The reaction time was also extended to 17.5 h. Surprisingly, this 20-fold scale-up still gave us a decent 30% yield. This further extension of the reaction's duration may have contributed to an improvement in yield.

A reduction in the amount of solvent was considered, but we stuck to conditions already selected in the existing literature: reactions of 1,1-diphenylethene with *N*-(4-methylphenyl)acetoacetamide in the presence of manganese (III) acetate and molecular oxygen in AcOH gave 1,2-dioxanes with a 92% yield in 25 mL/mmol, an 89% yield in 60 mL/mmol, and only a 59% yield in 10 mL/mmol [10]. This volume was further used in later aryl-oriented studies.

Due to the asymmetrically *gem*-disubstituted alkene, all conditions led to compound **1** as a racemic mixture of two diastereoisomers differing in their C-6 configuration.

3. Discussion

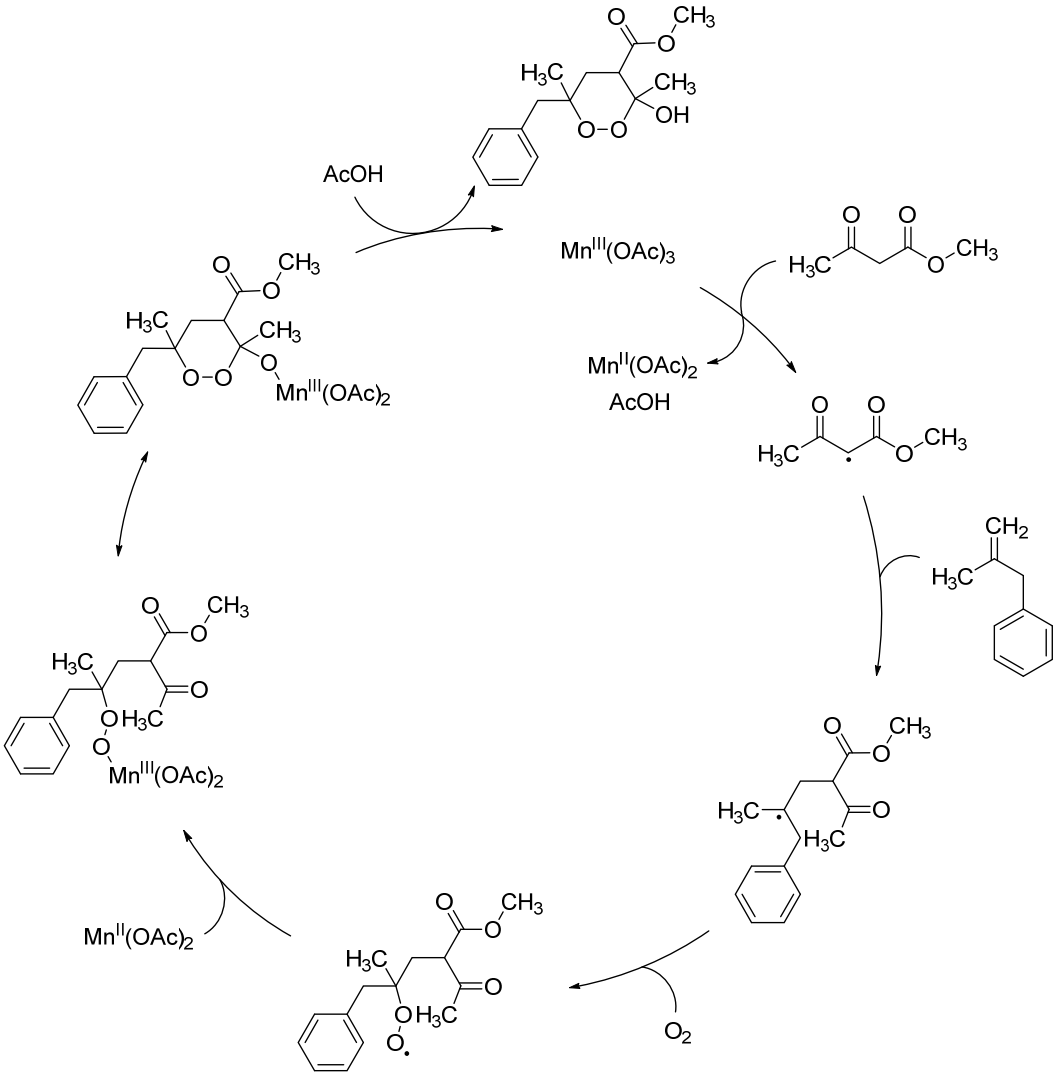
As previously reported in the literature, the ligand exchange reaction occurs between the acetate of manganese (III) acetate and the *β*-ketoester methyl 3-oxobutanoate, generating an enolate in situ. This enolate undergoes collapse into an electrophilic carbon radical via a single electron transfer from the electron-rich carbon–carbon double bond to manganese (III). This carbon radical then attacks the alkene double bond. The resulting nucleophilic tertiary radical takes molecular oxygen from the air to form a peroxyl radical. This peroxyl radical then restores manganese (III) by a further one-electron transfer from manganese (II) and undergoes cyclization to an alkoxide, ultimately resulting in the formation of a 1,2-dioxane ring in acetic acid (Scheme 3) [3,5].

Among other methods to synthesize similar endoperoxides, we can mention cycloaddition of molecular oxygen, cyclic 1,3-diketone, and alkene by electrochemical oxidation. This reaction, initiated by electrolysis, was found to have a radical chain mechanism, prompting the authors to investigate using a radical initiator, the azobis(isobutyronitrile) (AIBN), in the same 1989 study [11]. Although both methods gave cyclic peroxides from styrene and *α*-methylstyrene in 11–90% yields, acyclic 1,3-diketones did not give similar products.

Another study used manganese (III) acetate to produce endoperoxide from 1,1-diphenylethene, *N*-(4-methylphenyl)acetoacetamide and molecular oxygen with a 92% yield. Manganese (II) acetate was as effective as Mn(III), but other metal acetates gave lower yields: Co(II), 60% and Co(III), 66% [10].

The conditions tailored to aryl-oriented derivatives and that we chose were taken from a 1993 study. Both acyclic and cyclic *β*-ketoesters gave 1,2-dioxanes; most of the screening was based on ethyl 3-oxobutanoate, but the methyl derivative we used was included. Alkenes having no phenyl substituent did not give 1,2-dioxanes; 1,1-diphenylethene was the main candidate for catalyst and oxidant screening. As catalysts, copper (II), nickel (II), and thallium (III) acetates were not reactive. Chromium (VI) trioxide, cobalt (III) acetate, and iron (III) perchlorate did not yield 1,2-dioxane. Unsatisfactory yields were obtained from potassium permanganate (42%) and ammonium cerium nitrate in acetic acid (51%) and in acetonitrile (13%). From the metal salts tested, manganese (II) acetate (1 equivalent) gave good results, with 72% (23 °C, 96 h) and 68% (60 °C, 24 h) yields. Manganese (III)

acetate gave comparable yields of 74% (1 equivalent, 23 °C, 12 h) and 65% (0.1 equivalent, 23 °C, 24 h).



Scheme 3. The formal catalytic cycle for the Mn(III) acetate promoted the synthesis of 1,2-dioxane [5].

Then, reactions using a combination of manganese (II) acetate and various oxidizing reagents were investigated. In all cases, the reactions were carried out under a dry air steam, as molecular oxygen is required to form the endoperoxide. A 1:0.1 molar mixture of manganese (II) and manganese (III) acetates gave the maximum 95% yield for ethyl 3-oxobutanoate and a 90% yield for methyl 3-oxobutanoate after 12 h. Other suitable oxidants were cobalt (III) acetate (93%), chromium (VI) trioxide (80%), potassium permanganate (79%), thallium (III) acetate (73%), and ammonium cerium nitrate (62%) [9]. Although less effective on 1,1-diaryl derivatives, these oxidants might be good candidates for a future screening on (methylallyl)benzene derivatives.

The stereoselectivity of this reaction has been previously investigated: the hydroxyl group at C3 and the carbomethoxy at C4 consistently adopt a fixed 3,4-*cis* stereo relationship regardless of the alkene derivative employed (aliphatic or aromatic, symmetric or asymmetric) [5,11,12]. As anticipated, our reaction with an asymmetrically disubstituted alkene yielded only two of the four possible diastereoisomers.

Purification by gravity column chromatography did not allow total separation of the diastereoisomers. The initial NMR spectrum integrated with a 50/50 ratio. However, the isolation of the first and last pure fractions modulated their ratio. Then, NMR analysis

of separated fractions with a 1:0.7 ratio enabled the discrimination of diastereoisomers, making one major and one minor, as identifiable by their relative ratio.

Finally, COSY 2D NMR analysis enabled precise attribution within the multiplets. For example, in the doublet of triplets at 2.22 ppm integrating for two protons, the right side of this "multiplet" correlates with the doublet of doublets at 1.84 ppm, which integrates for one proton of the major diastereoisomer. This right side also correlates with the doublet of doublets at 3.10 ppm, also integrating for one proton of the major diastereoisomer. This describes the expected situation of the three protons located directly in the endoperoxide of the major diastereoisomer.

On the other hand, the left side of the 2.22 ppm multiplet correlates with the doublet of doublets at 1.63 ppm and the doublet of doublets at 2.92 ppm, each integrating for one proton of the minor diastereoisomer. This describes the expected situation of the three protons located directly in the endoperoxide of the minor diastereoisomer.

Finally, the slight superposition of the correlation signal indicated the overcrossing between the extreme pics of these two triplets, rather than a simple juxtaposition, which made them look like a multiplet before this 2D analysis.

The yield obtained in the open vessel was 36%; however, when we tried the O_2 atmosphere protocol (typically used for alkyl-oriented derivatives), the yield dropped to 7%. This result is in line with observations from previous studies on aryl derivatives, where reactions under a pure oxygen atmosphere resulted in lower yields of 1,2-dioxane [3,12].

Previous studies using manganese (III) acetylacetonate have identified the formation of hexanedione (3-acetyl-4-hydroxy-3-hexene-2,5-dione) regardless of the substrate used when oxygen was bubbled into the reaction mixture. This process involves the dimerization of diacetylmethyl radicals followed by oxidation with oxygen to form a hydroperoxide, which then undergoes rearrangement [3,13].

Based on these findings, we hypothesized that a similar reaction occurred during the initial steps of our catalytic route, involving dimerization of the electrophilic carbon radical resulting from the enolate rather than attack on the double bond of the alkene.

In addition, LC-MS analyses strongly suggested the formation of a dihydrofuran byproduct, indicating the presence of a mass corresponding to the β-ketoester fused with the alkene, without the addition of molecular oxygen, namely methyl 5-benzyl-2,5-dimethyl-4,5-dihydrofuran-3-carboxylate (Figure 3).

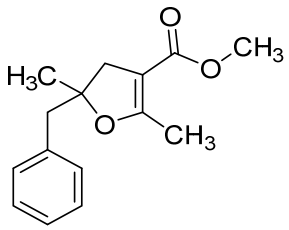


Figure 3. Structure of the methyl 5-benzyl-2,5-dimethyl-4,5-dihydrofuran-3-carboxylate presumed by-product.

This by-product has a predicted exact mass of 246.126 and appears on (ESI+) LC-MS as a 247.15 peak in all our crude batches, but we could not isolate it for NMR confirmation.

Although highly visible on the TLC, the masses of the isolated impurities were negligible, apart from the excess methyl 3-oxobutanoate, which remained unchanged.

The reactivity of alkyl and aryl alkenes varies significantly in Mn(III)-mediated oxidative cyclization. Phenyl derivatives, such as 1,1-diphenylethylene, exhibit higher reactivity due to the better stability of the tertiary carbon radical conjugated with two phenyl groups [3,5,12]. A comparison of the yields obtained with those reported in the literature revealed an intermediate reactivity of the alkene (2-methylallyl)benzene. Our 36% and 7% yields can be compared with a yield of 82% obtained for a 20 mmol-scale alkyl derivative, 2-butyl-2-hexene, with methyl 3-oxobutanoate under an oxygen atmosphere [7]. Similarly,

our 30% yield compares to a range of 27–91% for 1 mmol-scale aryl derivatives (with 90% yield reported for 1,1-diphenylethene with methyl 3-oxobutanoate) [9].

Our results highlight the need for further optimization specific to (methylallyl)benzene derivatives. We propose that the alkyl-oriented protocol without an oxygen atmosphere represents the most viable option at present, and the most practical and economical in reagents. Other oxidants like cobalt (III) acetate, chromium (VI) trioxide, potassium permanganate, and thallium (III) acetate might be considered in association with manganese (II) acetate, with a wide range of reaction durations to assess, i.e., 1.5 to 96 h according to previous studies.

To our knowledge, this study is the first report of a 1,2-dioxane synthesized using a methylallyl benzene derivative. However, our previous investigations into Mn(III)-mediated oxidative cyclization under heating (80 °C) revealed two distinct mechanisms depending on the alkene substrate. Vinylbenzene and 1,1-diphenylethylene yielded dihydrofuran derivatives, while allylbenzene yielded tetrahydronaphthalene. The degree of substitution on the allylic bond itself influences reactivity, with (2-methylallyl)benzene yielding a 2,3-dihydrofuran derivative [14].

4. Materials and Methods

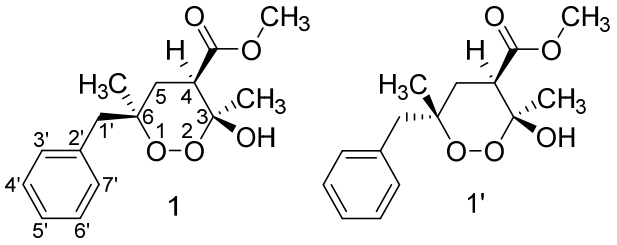
4.1. General

The melting point was determined through capillary tubes, with a B-540 Büchi melting point apparatus. TLC was performed on 5 cm × 10 cm aluminum plates coated with silica gel (layer 0.2 mm) 60F-254 (Merck) in an appropriate eluent. The following adsorbent was used for column chromatography: silica gel 60 (Merck KGaA, Darmstadt, Germany, particle size 0.063–0.200 mm, 70–230 mesh ASTM). Visualization was performed with ultraviolet light (234 nm). The HRMS spectrum (ESI) was recorded on a SYNAPT G2 HDMS (Waters) at the Faculté des Sciences de Saint-Jérôme (Marseille). NMR spectra were recorded on a Bruker Avance NEO 400 MHz NanoBay spectrometer at the Faculté de Pharmacie of Marseille. (^{1}H NMR: reference $CDCl_3$ δ = 7.26 ppm and ^{13}C NMR: reference $CDCl_3$ δ = 77.160 ppm). The purity of synthesized compounds was checked by LC/MS analyses, which were carried out at the Faculté de Pharmacie of Marseille with a Thermo Scientific Vanquish® (Dionex Softron GmbH, Part of Thermo Fisher Scientific, Germering, Germany) coupled using a single quadrupole mass spectrometer Thermo MSQ Plus®. The LC-MS data were processed with Chromeleon 7 and MZmine 3 [15] software. The RP-HPLC column was a Thermo Hypersil Gold® 50 × 2.1 mm (C18 bounded) with particles of a diameter of 1.9 mm. The volume of the sample injected into the column was 5 µL. Chromatographic analysis, total duration of 10 min, was on the gradient of the following solvents: t = 0 min, methanol/water 5:95; 0 < t < 5 min, with a linear increase in the proportion of methanol to a methanol/water ratio of 100:0; 5 < t < 7 min, methanol/water 100:0; t = 7 min, return to a methanol/water ratio of 5:95; 7 < t < 10 min, methanol/water 5:95. The water and methanol used were buffered with 0.1% formic acid. The flow rate of the mobile phase was 0.4 mL/min. The retention times (tR) of the molecules analyzed were indicated in min. Reagents were purchased from Thermo Fisher Scientific and used without further purification. Copies of ^{1}H NMR and COSY NMR, ^{13}C NMR, and DEPT NMR are available in the Supplementary Materials.

4.2. Methyl 6-Benzyl-3-Hydroxy-3,6-Dimethyl-1,2-Dioxane-4-Carboxylate (Compound **1***)*

The alkene (2-methylallyl)benzene (20 mmol, 2.64 g, 3 mL) was added at room temperature to a mixture of the *β*-ketoester methyl 3-oxobutanoate (40 mmol, 4.64 g, 4.3 mL), $Mn^{III}(OAc)_3{\cdot}2H_2O$ (1 mmol, 268 mg), and $Mn^{II}(OAc)_2{\cdot}4H_2O$ (1 mmol, 245 mg) in glacial acetic acid (40 mL). The reaction mixture was stirred at room temperature for 6 h in an open vessel. The reaction mixture was neutralized with stoichiometric NaOH (3 M aqueous solution) and then made slightly basic with a saturated $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure. Compound **1** was obtained as a white solid after purification

by chromatography on silica gel (eluent: cyclohexane/ethyl acetate mixtures starting from 9/1). The first and last fractions of the mixture of two diastereoisomers obtained from the first column were further purified with dichloromethane/cyclohexane 9/1 as starting eluent to dichloromethane/methanol 9.6/0.4 in an attempt to separate the diastereoisomers, resulting in a slight modification of the ratio. Another attempt at diastereoisomer separation with cyclohexane/ethyl acetate/dichloromethane/acetone 6.5/2/1/0.5 gave better results. With a ≈1/0.7 diastereoisomeric ratio, the ^{1}H COSY NMR enabled spectral characterization of each diastereoisomer, followed by ^{13}C DEPT NMR. Yield 36% (2 g). mp 101 °C. HRMS (ESI): *m*/*z* [M + Na]+ calcd for $C_{15}H_{20}O_5$: 280.1311; found: 280.1311. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33–7.18 (m, 10H), 3.93 (s, 1H), 3.83 (s, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.30 (d, *J* = 13.7 Hz, 1H), 3.10 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.92 (dd, *J* = 13.2, 4.9 Hz, 1H), 2.88–2.70 (m, 3H), 2.22 (dt, *J* = 21.0, 13.8 Hz, 2H), 1.84 (dd, *J* = 14.2, 5.0 Hz, 1H), 1.63 (dd, *J* = 13.9, 4.9 Hz, 1H), 1.59 (s, 3H), 1.50 (s, 3H), 1.31 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 172.1, 136.9, 135.5, 130.7, 130.5, 128.3, 128.3, 126.9, 126.7, 98.1, 79.9, 79.7, 52.4, 52.3, 46.6, 45.1, 45.0, 40.2, 32.3, 31.9, 24.6, 24.4, 24.2, 20.2.



Diastereoisomer 1 = methyl (3*S*,4*R*,6*R*)-6-benzyl-3-hydroxy-3,6-dimethyl-1,2-dioxane-4-carboxylate. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34–7.18 (m, 5Ar), 3.93 (s, OH), 3.76 (s, COOMe), 3.30 (d, *J* = 13.7 Hz, H-1′a), 3.10 (dd, *J* = 13.1, 5.0 Hz, H-5a), 2.75 (d, *J* = 13.7 Hz, H-1′b), 2.25–2.13 (m, H-4), 1.84 (dd, *J* = 14.2, 5.0 Hz, H-5b), 1.59 (s, Me-3), 1.07 (s, Me-6). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 (C, C<u>O</u>OMe), 136.9 (C, C-2′), 130.5 (2CH, *meta* CH-4′ and CH-6′), 128.3 (2CH, *ortho* CH-3′ and CH-7′), 126.7 (CH, *para* CH-5′), 98.1 (C, C-3), 79.7 (C, C-6), 52.4 (CH_3, COO<u>Me</u>), 45.0 (CH, CH-4), 40.2 (CH_2, CH_2-1′), 32.3 (CH_2, CH_2-5), 24.6 (CH_3, Me-6), 24.2 (CH_3, Me-3).

Diastereoisomer 1′ = methyl (3*S*,4*R*,6*S*)-6-benzyl-3-hydroxy-3,6-dimethyl-1,2-dioxane-4-carboxylate. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34–7.18 (m, 5Ar), 3.83 (s, OH), 3.72 (s, COOMe), 2.92 (dd, *J* = 13.2, 4.9 Hz, H-5a), 2.85 (d, *J* = 13.8 Hz, H-1′a), 2.77 (d, *J* = 13.8 Hz, H-1′b), 2.24 (t, *J* = 13.5 Hz, H-4), 1.63 (dd, *J* = 13.9, 4.9 Hz, H-5b), 1.50 (s, Me-3), 1.31 (s, Me-6). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (C, C<u>O</u>OMe), 135.5 (C, C-2′), 130.7 (2CH, *meta* CH-4′), 128.3 (2CH, *ortho* CH-3′), 126.9 (CH, *para* CH-5′), 98.1 (C, C-3), 79.9 (C, C-6), 52.3 (CH_3, COO<u>Me</u>), 46.6 (CH_2, CH_2-1′), 45.1 (CH, CH-4), 31.9 (CH_2, CH_2-5), 24.4 (CH_3, Me-6), 20.2 (CH_3, Me-3).

Supplementary Materials: Figure S1: ^{1}H NMR (400 MHz, $CDCl_3$) complete spectrum of the new compound **1**. Figure S2: ^{1}H COSY NMR (400 MHz, $CDCl_3$) spectrum of the new compound **1**. Figure S3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the diastereoisomer 1. Figure S4: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the diastereoisomer 1′. Figure S5: ^{13}C NMR (101 MHz, $CDCl_3$) complete spectrum of the new compound **1**. Figure S6: ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of the diastereoisomer 1. Figure S7: ^{13}C NMR (101 MHz, $CDCl_3$) spectrum of the diastereoisomer 1′. Figure S8: ^{13}C DEPT NMR (101 MHz, $CDCl_3$) spectrum of the new compound **1**.

Author Contributions: Conceptualization, C.C. and A.B.; methodology, C.C.; software, A.B.; validation, O.K. and C.C.; formal analysis, A.B.; investigation, A.B.; resources, P.V.; writing—original draft preparation, A.B.; writing—review and editing, A.B., O.K., C.C. and P.V.; supervision, O.K., C.C. and P.V.; project administration, C.C. and P.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Not applicable.

Acknowledgments: We want to thank Vincent Remusat (Institut de Chimie Radicalaire, Marseille) for his help with NMR analysis, Valérie Monnier and Gaëlle Hisler (Spectropole, Marseille) for performing HRMS analysis.

Conflicts of Interest: The authors declare no conflicts of interest.

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