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Short Note

(3-Methylene-2,3-dihydronaphtho[2,3-*b*][1,4]dioxin-2-yl)methanol

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Abstract: (3-Methylene-2,3-dihydronaphtho[2,3-*b*][1,4]dioxin-2-yl)methanol was unexpectedly achieved as the main reaction product while applying a standard Johnson–Corey–Chaykovsky procedure to the 2,3-dihydronaphtho[2,3-*b*][1,4]dioxine-2-carbaldehyde, aiming at obtaining the corresponding epoxide. The structure of the recovered compound was confirmed through NMR and HRMS, the melting point was measured by DSC, and the organic purity was assessed using HPLC. We hypothesized the possible mechanism for the obtainment of this side product, which should involve the opening of the dioxane ring soon after the nucleophilic attack of the ylide to the carbonyl function. The consequent transfer of the negative charge allows the achievement of the phenolate function. The tautomer further rearranges, forming the unstable oxirane, which opening is favored by the acidic phenolic function, thus closing into the more stable six-membered ring compound. We confirmed the hypothesized reaction mechanism by applying the same reaction conditions while starting from the corresponding methyl ketone. This undesired compound, easily and quantitatively obtained by standard Johnson–Corey–Chaykovsky conditions, could pave the way to a new methodology for the obtainment of 2,3-disubstituted 1,4-naphthodioxanes, further derivatizable.

Keywords: 1,4-naphthodioxane; dioxane ring opening; Corey–Chaykovsky epoxidation; Corey–Chaykovsky byproducts

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1. Introduction

The Johnson–Corey–Chaykovsky reaction, which is often simplified to Corey–Chaykovsky reaction, is an important tool in organic chemistry to convert alkenes, imines, and aldehydes or ketones to cyclopropanes, aziridines, and epoxides, respectively, while adding one carbon atom to the system through the treatment with sulfur ylides [1,2]. Often, these ylides are in situ formed by treating the corresponding sulfonium (or sulfoxonium) salt with strong bases. The most exploited application of the Corey–Chaykovsky reaction is the direct obtainment of epoxides from aldehydes and ketones, with plenty of examples reported in the literature [3,4]. The reaction mechanism involves the initial nucleophilic attack of the sulfur ylide to the carbonyl of the aldehyde/ketone. Then, the so-formed intermediate undergoes ring closure via intramolecular nucleophilic substitution due to the good leaving nature of the sulfonium group [5].

Although Corey–Chaykovsky reactions usually evolve to the desired products, several other chemical transformations could occur. For instance, the excess of base and high temperatures were reported to promote Yurchenko diolefination of cyclic ketones while suppressing oxirane formation [6]. Moreover, Wang and collaborators disclosed the conversion of esters to α-chloroketones through a reaction with dimethylsulfoxonium methylide in mild conditions, followed by treatment with HCl [7]. Besides these few cases, the Corey–Chaykovsky reaction is considered a very useful and reliable tool for the insertion of an additional carbon atom with ring formation while avoiding dangerous reactants such as diazomethane.

While developing novel antimicrobials, we recently obtained promising compounds as FtsZ inhibitors [8] with a naphthodioxane benzamide structure (Figure 1). Since these derivatives are characterized by an ethylenoxy linker, which could be additionally derivatized through the insertion of specific groups, we decided to apply the Corey–Chaykovsky reaction to achieve a common epoxydic intermediate (**2**). Compound **2** could be easily further converted into the desired compounds by ring opening (Figure 1), thus obtaining a sub-family of compounds with interesting and exploitable features.

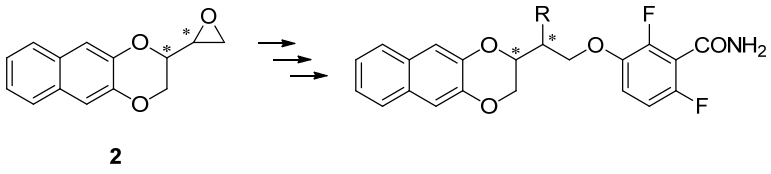

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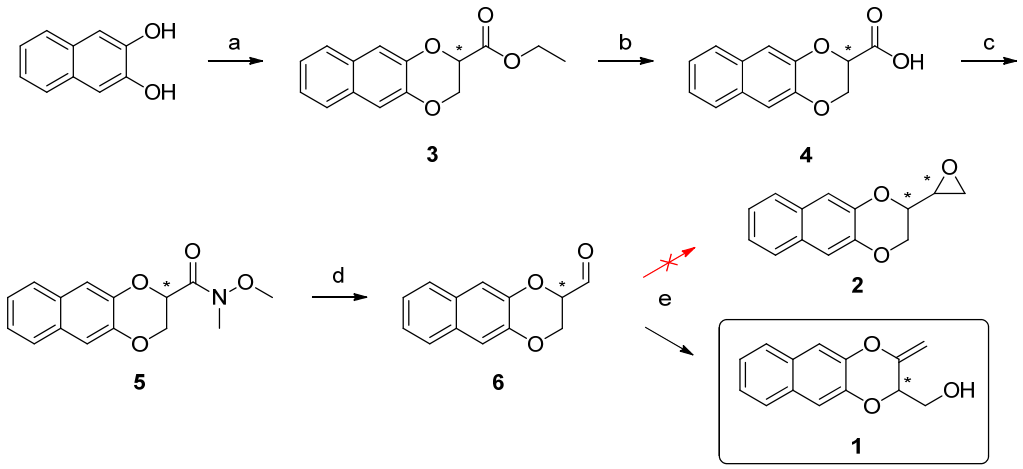
Figure 1. Structure of the epoxydic intermediate **2**, starting material for the obtainment of naphthodioxane benzamide derivatives as FtsZ inhibitors (* no defined chiral center).

For the obtainment of compound **2**, following what was previously performed on the benzodioxane derivatives [9], we designed and applied a straightforward synthetic pathway starting from naphtalen-2,3-diol, where the last step was the Corey–Chaykovsky epoxidation of the corresponding aldehyde (Scheme 1). In the present work, we report the completely unexpected evolution of the Corey–Chaykovsky reaction, leading to an unsaturated alcoholic derivative **1** with good yields and as the main outcome of the reaction. The unknown compound was exhaustively characterized, and the reaction mechanism responsible for its formation was first hypothesized and later confirmed.



Scheme 1. Synthetic pathway designed for the obtainment of compound **2**; as pointed out, also from the crossed out red arrow, the last reaction failed to give the desired epoxide **2**. Reagents and conditions: (a) Ethyl 2,3-dibromopropionate, K_2CO_3, DMF, 80 °C, 4 h; (b) 2.5 N aqueous NaOH, MeOH, RT, 18 h; (c) *N*,*O*-dimethylhydroxylamine, 1,1′-Carbonyldiimidazole, DMF, RT, 2 h; (d) $LiAlH_4$, THF, −20 °C, 30 min; (e) NaH, trimethylsulfoxonium iodide, DMSO, RT, 30 min. (* no defined chiral center).

2. Results and Discussion

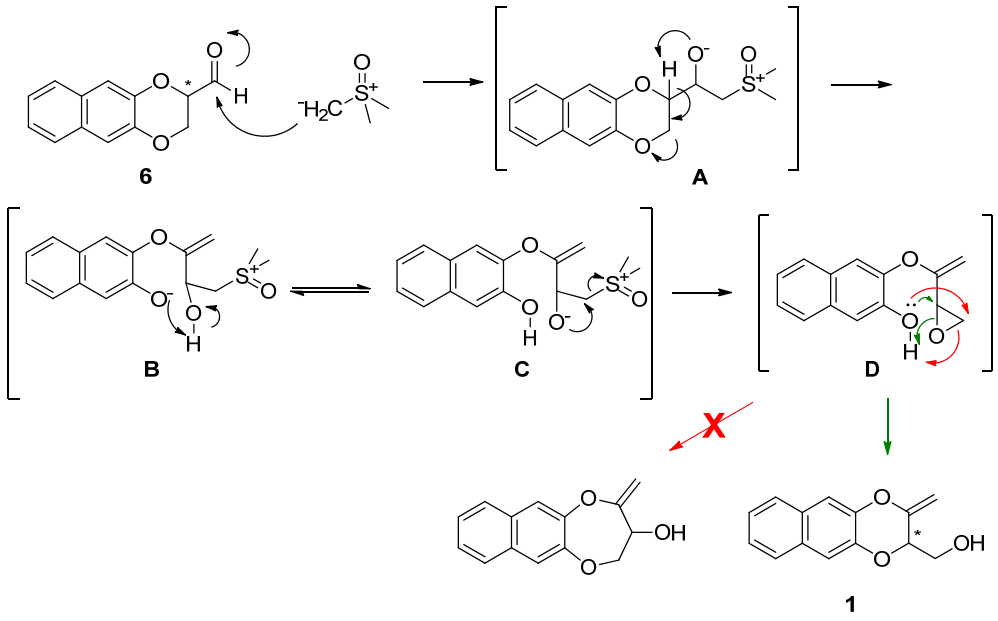
The synthetic scheme (Scheme 1) for the obtainment of compound **2** was designed considering our previous work on benzodioxane benzamides as antibacterial agents [10,11] and other described procedures on benzodioxanes [12] and naphthodioxanes [13–15]. The route started from the reaction between the commercially available naphthalen-2,3-diol with the ethyl 2,3-dibromopropionate in basic conditions, thus achieving the naphthodioxane ring (**3**). We used DMF as a solvent, differently from what was previously reported [13,14], to enhance the conversion and let the obtainment of the ester **3** without any further purification

by flash chromatography on silica gel. This ester intermediate underwent hydrolysis (**4**), using milder conditions than previously performed [15], and subsequent conversion to the corresponding Weinreb amide (**5**). Then, the aldehyde was quantitatively achieved by treatment with $LiAlH_4$ at low temperatures (**6**).

By aiming at the obtainment of **2**, **6** was added to a mixture of trimethylsulfoxonium iodide and NaH in dry DMSO. Surprisingly, immediately after the addition of **6** to the in situ formed ylide, the complete conversion of the starting material to the main reaction product was observable through TLC. After the work-up with water and brine and the purification on silica gel, the ^{1}H-NMR spectrum in $CDCl_3$ of the crude revealed the presence of a completely unexpected product, not presenting the classical and diagnostic epoxide signals in the 3 ppm range. On the contrary, four different signals were found in the 3.70–5 ppm range: two coupled doublets with a very tight coupling constant (1.5 Hz) at 4.90 and 4.48 ppm, a double of doublets at 4.69 ppm and a wide signal with an ABX pattern at 3.92–4.00 ppm.

These peculiar NMR chemical shifts and multiplicities, very similar to a 1,4-benzodioxane derivative previously described and obtained following a Pd-catalyzed reaction [16], suggested us to have achieved derivative **1**, and our hypothesis was further confirmed by ^{13}C-NMR and HRMS.

Since compound **1**, differently from **6** and **2**, is substituted not only in the 2-position but also in the 3-positions, this large structural difference moved us to hypothesize a mechanism of the reaction, in which the opening and the re-closing of the 1,4-naphthodioxane ring must occur (Scheme 2).



Scheme 2. Proposed mechanism for the obtainment of **1** (* no defined chiral center). Green arrows highlight the observed outcome of the reaction, achieving compound **1**, whereas red arrows indicate the obtainment of a second possible byproduct, which was not achieved in these conditions.

As shown in Scheme 2, our proposed mechanism involves the initial nucleophilic attack of the ylide to the carbonyl, as also expected for the correct evolution of the Corey–Chaykovsky reaction. Nonetheless, in this case, the so formed alcoholate (**A**) does not proceed through the elimination of the sulfonium cation, giving the desired product. Instead, the presence of the two oxygens of the naphthodioxane ring should be responsible for the first deprotonation of the carbon in position 2-, the consequent formation of the unsaturation, the opening of the 1,4-dioxane ring, and the final formation of the phenate function (**B**).

The prototropic equilibrium (**B**,**C**) of this compound could promote the elimination of the sulfonium group by the alcoholate, achieving the epoxide ring (**D**). Subsequently, the acidity of the phenolic function could foster the nucleophilic opening of the oxirane ring, leading to the observed product **1**. In our opinion, both the direct elimination of the sulfonium group by the phenolic function and the oxirane ring opening on the less substituted carbon might be disfavored due to the higher ring strain of the 7-membered ring in such a manner obtained.

We decided to further confirm our hypothetical reaction mechanism by conducting the reaction with a different starting material, the corresponding methyl ketone **7**. The methyl ketone **7** is characterized by the presence of an additional methyl group and could be easily achieved by treating Weinreb amide **5** with methylmagnesium bromide, as previously performed for the benzodioxane derivative [9] (Figure 2). Following our idea, the resulting derivative should be lacking the double of doublets at 4.56 ppm while showing a simplified system at the 3.60–3.96 ppm range and an additional methyl singlet around 1.6 ppm.

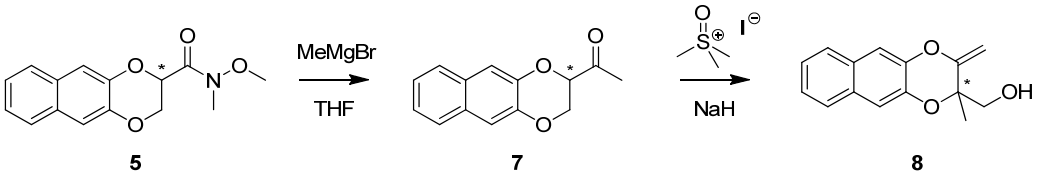


Figure 2. Structure of **8**, obtained as the main product while treating **7** with dimethylsulfoxonium methylide in DMSO at RT (* no defined chiral center).

As expected, the ^{1}H-NMR spectrum of the reaction mixture revealed the achievement of **8** as the main product (Figure 2), even if the TLC and ^{1}H-NMR of the crude showed the presence of other minor byproducts. Nevertheless, also for this derivative, very few traces of the Corey–Chaykovsky epoxide products were observed. The obtainment of **8** further strengthened the hypothesized mechanism presented in Scheme 2.

3. Materials and Methods

All the reagents and solvents were purchased from commercial suppliers (Merck, Darmstadt, DE, Fluorochem, Hadfield, UK, and TCI Europe N.V., Zwijndrecht, BE) and used without any further purifications. Silica gel matrix, with fluorescent indicator 254 nm, was used in analytical thin-layer chromatography (TLC on aluminum foils), and silica gel (particle size 40–63 µm, Merck) was used in flash chromatography on Sepachrom Puriflash XS 420. Visualizations were accomplished with UV light (λ 254 or 280 nm).

The ^{1}H-NMR spectra were measured by Varian Mercury 300 NMR spectrometer/Oxford Narrow Bore superconducting magnet operating at 300 MHz. The ^{13}C-NMR spectra were acquired operating at 75 MHz. Chemical shifts (δ) are reported in ppm relative to residual solvent as the internal standard. Signal multiplicity is used according to the following abbreviations: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet, and bs = broad singlet.

Melting points were measured with a TA Q20 DSC system. IR spectra were recorded with an FT-IR Spectrum TwoTM Perkin Elmer Spectrometer.

The final product **1** was analyzed by reverse-phase HPLC using a Waters XBridge C-18 column (5 µm, 4.6 mm × 150 mm) on an Elite LaChrom HPLC system with a diode array detector (Hitachi, San Jose, CA; USA). Mobile phase: A: H_2O; B: Acetonitrile; gradient, 90% A to 10% A in 25 min with 35 min run time and a flow rate of 1 mL/min. The purity was quantified at their λ max, and the relative retention time is reported in the experimental section. High-resolution mass spectrometry (HRMS) spectra were acquired on Q-Tof SYNAPT G2-Si HDMS 8K (Waters) coupled with an electrospray ionization (ESI) source in positive (ES+) ion mode. The complete characterization of **1** and **8**, in terms of NMR (both ^{1}H and ^{13}C), HPLC, HRMS and IR spectra, are reported in the Supplementary Material.

Ethyl 2,3-dihydronaphtho[2,3-*b*][1,4]dioxine-2-carboxylate (3): A solution of 2,3-di hydroxynaftalene (5.0 g, 31.21 mmol) in DMF (50 mL) was added of potassium carbonate (10.35 g, 74.90 mmol). The reaction mixture was kept stirring at room temperature for 30 min, then ethyl 2,3-dibromopropionate (8.92 g, 34.33 mmol) was added dropwise, and the medium was heated at 80 °C. The reaction mixture was kept stirring at that temperature for 4 h. At reaction completion, the DMF was evaporated, the crude was diluted with ethyl acetate (50 mL) and washed with 10% aqueous NaCl (5 × 20 mL), dried over Na_2SO_4, filtered, and concentrated to give 6.16 g of **3** as an orange oil. Yield: 76%. **^{1}H NMR (300 MHz, $CDCl_3$):** 7.78–7.53 (m, 2H), 7.41 (s, 1H), 7.36–7.29 (m, 2H), 7.28 (s, 1H), 4.92 (dd, *J* = 4.4, 3.1 Hz, 1H), 4.51 (dd, *J* = 11.5, 4.4 Hz, 1H), 4.45 (dd, *J* = 11.5, 4.4 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H).

2,3-Dihydronaphtho[2,3-*b*][1,4]dioxine-2-carboxylic acid (4): A solution of **3** (6.16 g, 23.85 mmol) in methanol (60 mL) was slowly added of 18 mL of 2.5 N aqueous NaOH. The reaction mixture was kept stirring at room temperature for 18 h. Once the reaction was completed, the methanol was evaporated, and the crude was diluted with ethyl acetate (50 mL) and washed firstly with 10% aqueous HCl (20 mL) and then with 10% aqueous NaCl (20 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to give 5.29 g of **4** as a brownish solid. Mp: 187 °C. Mp from the literature [15]: 186 °C. Yield: 96%. **^{1}H NMR (300 MHz, $CDCl_3$):** 7.66 (dd, *J* = 9.3, 4.9 Hz, 2H), 7.40 (s, 1H), 7.32 (dd, *J* = 6.3, 3.2 Hz, 2H), 7.29 (s, 1H), 4.98 (dd, *J* = 4.4, 3.0 Hz, 1H), 4.54 (dd, *J* = 11.6, 4.4 Hz, 1H), 4.47 (dd, *J* = 11.6, 3.0 Hz, 1H).

***N*-Methoxy-*N*-methyl-2,3-dihydronaphtho[2,3-*b*][1,4]dioxine-2-carboxamide (5):** 1,1′-Carbonyldiimidazole (5.58 g, 34.46 mmol) was added portion-wise to a solution of **4** (5.29 g, 22.97 mmol) in DMF (50 mL) at 0 °C. The reaction mixture was stirred at that temperature for 30 min, and then *N*,*O*-dimethyl hydroxylamine hydrochloride (3.36 g, 34.46 mmol) was added to one pot. The mixture was stirred at room temperature for 2 h, and then the volatile components were evaporated. The crude was resumed with ethyl acetate (50 mL), washed with 10% aqueous NaCl (3 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to yield 6.26 g of **5** as a yellowish solid. Mp: 119 °C. Yield: 98%. **^{1}H NMR (300 MHz, $CDCl_3$):** 7.65 (dd, *J* = 9.3, 4.9 Hz, 2H), 7.38 (s, 1H), 7.30 (dd, *J* = 6.4, 3.4 Hz, 2H), 7.29 (s, 1H), 5.16 (dd, *J* = 6.5, 2.8 Hz, 1H), 4.50 (dd, *J* = 11.5, 2.8 Hz, 1H), 4.39 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.81 (s, 3H), 3.27 (s, 3H).

2,3-Dihydronaphtho[2,3-*b*][1,4]dioxine-2-carbaldehyde (6): A solution of **5** (1.00 g, 3.66 mmol) in dry THF (15 mL) was added dropwise to a suspension of $LiAlH_4$ (0.18 g, 4.75 mmol) in dry THF (5 mL) at –20 °C under N_2 atmosphere. The reaction mixture was stirred at that temperature for 30 min, then diluted with DCM (15 mL), and coldly washed with 10% aqueous HCl (20 mL) and 10% aqueous NaCl (20 mL). The organic phase was then dried over Na_2SO_4, filtered, and partially concentrated to give 7.8 mL of yellowish crude. Since the aldehyde quickly degrades at room temperature when neat (aldehyde is itself a yellowish oil), a 10% solution in THF was directly used in the successive reaction. **^{1}H NMR (300 MHz, $CDCl_3$)**: 9.84 (s, 1H), 7.65 (m, 2H), 7.43 (s, 1H), 7.35 (m, 2H), 7.29 (s, 1H), 4.74 (t, *J* = 4.2 Hz, 1H), 4.44 (d, *J* = 4.2, 2H).

(3-Methylene-2,3-dihydronaphtho[2,3-*b*][1,4]dioxin-2-yl)methanol (1): A solution of trimethylsulfoxonium iodide (0.93 g, 4.21 mmol) in dry DMSO (10 mL) was added dropwise to a suspension of NaH (0.115 g, 4.40 mmol) in dry DMSO (5 mL) at RT under N_2 atmosphere. After 30 min stirring at that temperature, a solution of **6** (3.66 mmol, 0.78 g, hypothesizing quantitative yield in the previous step) in dry DMSO and THF (3 mL of DMSO and around 7.8 mL of the 10% THF solution coming from the previous step) was added dropwise. The reaction mixture was kept stirring for 1 h at RT and then diluted with Et_2O/AcOEt 9/1 (15 mL) and washed with 10% aqueous NaCl (20 mL) and water (4 × 20 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated to give a residue that was purified by flash chromatography. Elution with 85/15 cyclohexane/ethyl acetate gave 0.25 g of **1** as a white solid. Yield: 30% (two steps yield). Mp 100 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** 7.71–7.66 (m, 2H), 7.37–7.33 (m, 4H), 4.90 (d, *J* = 1.5 Hz, 1H),

4.69 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.48 (d, *J* = 1.5 Hz, 1H), 3.97 (dd, *J* = 11.7, 6.8 Hz, 1H), 3.71 (d, *J* = 11.7, 5.2 Hz, 1H), 2.08 (bs, 1H). **^{1}H NMR (300 MHz, DMSO-d_6):** 7.79–7.69 (m, 2H), 7.45 (s, 1H), 7.41 (s, 1H), 7.37–7.29 (m, 2H), 5.17 (t, *J* = 5.7 Hz, 1H), 4.83 (d, *J* = 2.0 Hz, 1H), 4.73 (t, *J* = 5.7 Hz, 1H), 4.63 (d, *J* = 2.0 Hz, 1H), 3.68 (t, *J* = 5.7 Hz, 2H). **^{13}C NMR (75 MHz, DMSO-d_6):** 150.5, 142.4, 142.3, 129.9, 129.7, 127.0, 126.8, 125.2, 125.1, 113.1, 111.6, 93.0, 74.3, 61.1. HPLC: Purity = 98.3%, T_r = 16.8 min. HRMS (TOF ES+, Na+-adduct): *m/z* 251.0695, 252.0728. Calculated mass 251.0684, evaluated mass 251.0695.

1-(2,3-Dihydronaphtho[2,3-*b*][1,4]dioxin-2-yl)ethanone (7): Methylmagnesium bromide 3.0 M in diethyl ether (5.9 mL) was added dropwise to a solution of **5** (3.23 g, 11.82 mmol) in dry THF (45 mL) at 0 °C under N_2 atmosphere. The mixture was stirred at that temperature for 15 min and then warmed to RT and kept stirring for 1 h. After that timing, it was slowly poured into 10% aqueous HCl (40 mL) and ethyl acetate (40 mL) at 0 °C. The organic layer was washed with 10% aqueous NaCl (40 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to yield 2.66 g of **7** as a colorless oil. Yield: 99%. **^{1}H NMR (300 MHz, $CDCl_3$):** 7.71–7.64 (m, 2H), 7.41 (s, 1H), 7.33 (m, 2H), 7.29 (s, 1H), 4.71 (dd, *J* = 5.0, 3.5 Hz, 1H), 4.44 (dd, *J* = 10.2, 5.0 Hz, 1H), 4.39 (dd, *J* = 10.2, 3.5 Hz, 1H), 2.34 (s, 3H).

(2-Methyl-3-methylene-2,3-dihydronaphtho[2,3-*b*][1,4]dioxin-2-yl)methanol (8): A solution of trimethylsulfoxonium iodide (1.60 g, 7.55 mmol) in dry DMSO (25 mL) was added dropwise to a suspension of NaH (0.20 g, 7.88 mmol) in dry DMSO (15 mL) at RT under N_2 atmosphere. After 30 min stirring at that temperature, a solution of **7** (1.50 g, 6.57 mmol) in dry DMSO (10 mL) was added dropwise. The reaction mixture was kept stirring for 1 h at RT and then diluted with Et_2O/AcOEt 9/1 (100 mL) and washed with 10% aqueous NaCl (50 mL) and water (4 × 50 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated to give a residue that was purified by flash chromatography. Elution with 80/20 cyclohexane/ethyl acetate gave 0.24 g of **8** as a yellowish solid. M.p. 91 °C. Yield: 15%. **^{1}H NMR (300 MHz, $CDCl_3$):** 7.71–7.64 (m, 2H), 7.37–7.31 (m, 4H), 4.90 (d, *J* = 2.4 Hz, 1H), 4.55 (d, *J* = 2.4 Hz, 1H), 3.87 (d, *J* = 11.9 Hz, 1H), 3.71 (d, *J* = 11.9 Hz, 1H), 1.93 (bs, 1H), 1.58 (s, 3H). **^{1}H NMR (300 MHz, DMSO-d_6):** 7.72 (dt, *J* = 17.9, 6.6 Hz, 2H), 7.43 (s, 1H), 7.36 (s, 1H), 7.34–7.29 (m, 2H), 5.22 (t, *J* = 5.9 Hz, 1H), 4.83 (d, *J* = 2.2 Hz, 1H), 4.66 (d, *J* = 2.2 Hz, 1H), 3.56 (dd, *J* = 9.9, 4.5 Hz, 1H), 3.51 (dd, *J* = 9.9, 4.5 Hz, 1H), 1.48 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6):** 154.2, 142.2, 142.1, 130.1, 129.6, 127.0, 126.8, 125.0, 124.8, 113.0, 111.1, 92.5, 76.6, 64.7, 21.2. HPLC: Purity= 94.5%, T_r = 10.0 min. HRMS (TOF ES+, Na+-adduct): *m/z* 265.0847, 266.0881, 267.0639, 267.0978. Calculated mass 265.0841, evaluated mass 265.0847.

4. Conclusions

The title compound, (3-methylene-2,3-dihydronaphtho[2,3-*b*][1,4]dioxin-2-yl)methanol, was obtained as the main reaction product and with good yields, treating the 2,3-dih ydronaphtho[2,3-*b*][1,4]dioxine-2-carbaldehyde with trimethylsulfoxonium iodide, following the common reaction conditions used in the Johnson–Corey–Chaykovsky reaction. Only negligible traces of the desired corresponding epoxide were found in the reaction mixture. The mechanism behind the formation of this side product was firstly hypothesized and then confirmed by applying the same synthetic protocol starting from the analogous methyl ketone. The (3-methylene-2,3-dihydronaphtho[2,3-*b*][1,4]dioxin-2-yl)methanol, as well as the (2-methyl-3-methylene-2,3-dihydronaphtho[2,3-*b*][1,4]dioxin-2-yl)methanol, were completely characterized by NMR (both ^{1}H and ^{13}C), HPLC, DSC and HRMS. This undesired product could be indeed very useful as a starting material since it bears two differently functionalizable substituents on the 1,4-naphthodioxane ring, not easily achievable via other methods.

Supplementary Materials: The following are available online: Compound **1**; Figure S1: copy of ^{1}H-NMR spectrum in $CDCl_3$; Figure S2: copy of ^{1}H-NMR spectrum in DMSO-d_6; Figure S3: copy of ^{13}C-NMR spectrum in DMSO-d_6; Figure S4: copy of HPLC chromatogram; Figure S5: copy of HRMS spectrum; Figure S6: copy of Elemental Composition Report; Figure S7: copy of IR spectrum; Compound **8**; Figure S8: copy of ^{1}H-NMR spectrum in $CDCl_3$; Figure S9: copy of ^{1}H-NMR spectrum in DMSO-d_6; Figure S10: copy of ^{13}C-NMR spectrum in DMSO-d_6; Figure S11: copy of HPLC chromatogram; Figure S12: copy of HRMS spectrum; Figure S13: copy of Elemental Composition Report; Figure S14: copy of IR spectrum.

Author Contributions: Conceptualization, L.S., V.S. and E.V.; investigation, L.S. and G.L.; data curation, L.S. and V.S.; writing—original draft preparation, V.S. and L.S.; writing—review and editing, V.S. and E.V.; supervision, V.S. and E.V. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: Authors declare no conflict of interest.

References

1. Corey, E.J.; Chaykovsky, M. Dimethyloxosulfonium Methylide ($(CH_3)_2SOCH_2$) and Dimethylsulfonium Methylide ($(CH_3)_2SCH_2$). Formation and Application to Organic Synthesis. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364. [CrossRef]
2. Corey, E.J.; Chaykovsky, M. Dimethylsulfonium Methylide, a Reagent for Selective Oxirane Synthesis from Aldehydes and Ketones. *J. Am. Chem. Soc.* **1962**, *84*, 3782–3783. [CrossRef]
3. Adamovskyi, M.I.; Artamonov, O.S.; Tymtsunik, A.V.; Grygorenko, O.O. The synthesis of a 2-azabicyclo [3.1.0]hexane by rearrangement of a spirocyclic epoxide. *Tetrahedron Lett.* **2014**, *55*, 5970–5972. [CrossRef]
4. Kavanagh, S.A.; Piccinini, A.; Fleming, E.M.; Connon, S.J. Urea derivatives are highly active catalysts for the base-mediated generation of terminal epoxides from aldehydes and trimethylsulfonium iodide. *Org. Biomol. Chem.* **2008**, *6*, 1339–1343. [CrossRef] [PubMed]
5. Li, A.-H.; Dai, L.-X.; Aggarwal, V.K. Asymmetric Ylide Reactions: Epoxidation, Cyclopropanation, Aziridination, Olefination, and Rearrangement. *Chem. Rev.* **1997**, *97*, 2341–2372. [CrossRef] [PubMed]
6. Butova, E.D.; Fokin, A.A.; Schreiner, P.R. Beyond the corey reaction: One-step diolefination of cyclic ketones. *J. Org. Chem.* **2007**, *72*, 5689–5696. [CrossRef] [PubMed]
7. Wang, D.; Schwinden, M.D.; Radesca, L.; Patel, B.; Kronenthal, D.; Huang, M.-H.; Nugent, W.A. One-carbon chain extension of esters to alpha-chloroketones: A safer route without diazomethane. *J. Org. Chem.* **2004**, *69*, 1629–1633. [CrossRef] [PubMed]
8. Straniero, V.; Sebastián-Pérez, V.; Suigo, L.; Margolin, W.; Casiraghi, A.; Hrast, M.; Zanotto, C.; Zdovc, I.; Radaelli, A.; Valoti, E. Computational Design and Development of Benzodioxane-Benzamides as Potent Inhibitors of FtsZ by Exploring the Hydrophobic Subpocket. *Antibiotics* **2021**, *10*, 442. [CrossRef] [PubMed]
9. Straniero, V.; Casiraghi, A.; Fumagalli, L.; Valoti, E. How do reaction conditions affect the enantiopure synthesis of 2-substituted-1,4-benzodioxane derivatives? *Chirality* **2018**, *30*, 943–950. [CrossRef] [PubMed]
10. Straniero, V.; Zanotto, C.; Straniero, L.; Casiraghi, A.; Duga, S.; Radaelli, A.; de Giuli Morghen, C.; Valoti, E. 2,6-Difluorobenzamide Inhibitors of Bacterial Cell Division Protein FtsZ: Design, Synthesis, and Structure-Activity Relationships. *ChemMedChem* **2017**, *12*, 1303–1318. [CrossRef] [PubMed]
11. Straniero, V.; Pallavicini, M.; Chiodini, G.; Zanotto, C.; Volontè, L.; Radaelli, A.; Bolchi, C.; Fumagalli, L.; Sanguinetti, M.; Menchinelli, G.; et al. 3-(Benzodioxan-2-ylmethoxy)-2,6-difluorobenzamides bearing hydrophobic substituents at the 7-position of the benzodioxane nucleus potently inhibit methicillin-resistant Sa and Mtb cell division. *Eur. J. Med. Chem.* **2016**, *120*, 227–243. [CrossRef] [PubMed]
12. Artasensi, A.; Angeli, A.; Lammi, C.; Bollati, C.; Gervasoni, S.; Baron, G.; Matucci, R.; Supuran, C.T.; Vistoli, G.; Fumagalli, L. Discovery of a Potent and Highly Selective Dipeptidyl Peptidase IV and Carbonic Anhydrase Inhibitor as "Antidiabesity" Agents Based on Repurposing and Morphing of WB-4101. *J. Med. Chem.* **2022**, *65*, 13946–13966. [CrossRef] [PubMed]
13. Clavier, S.; Khouili, M.; Bouyssou, P.; Coudert, G. Synthesis of naphtho [2,3-*b*][1,4]dioxin, 2-substituted naphtho [2,3-*b*][1,4]dioxins and 2,3-disubstituted naphtho [2,3-*b*][1,4]dioxins. *Tetrahedron* **2002**, *58*, 1533–1540. [CrossRef]
14. Arrault, A. A Straightforward Synthesis of 1,2-Dihydronaphtho [2,1-b]furans from 2-Naphthols. *Synthesis* **1999**, *1999*, 1241–1245. [CrossRef]

15. Howe, R.; Rao, B.S.; Chodnekar, M.S. Beta-adrenergic blocking agents. VII. 2-(1,4-benzodioxanyl) and 2-chromanyl analogs of pronethalol (2-isopropylamino-1-(2-naphthyl)ethanol). *J. Med. Chem.* **1970**, *13*, 169–176. [CrossRef] [PubMed]
16. Dominczak, N.; Lhoste, P.; Kryczka, B.; Sinou, D. Palladium-catalyzed heteroannulation of catechol with functionalized propargylic carbonates: Influence of the functional group on the regioselectivity of the cyclization. *J. Mol. Catal. A Chem.* **2007**, *264*, 110–118. [CrossRef]