

On the Regioselectivity of the Baeyer–Villiger Reaction of 2,6-Dialkyl Cyclohexanones: Application to the Synthesis of Sordidin, a Male Pheromone Emitted by *Cosmopolites sordidus*

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Abstract—The diastereoselective synthesis of (1*S**,3*R**,5*R**,7*S**)-2,8-dioxa-1-ethyl-3,5,7-trimethylbicyclo[3.2.1]octane (**1d**) has been achieved using as the key step the regioselective Baeyer–Villiger reaction of 2,6-disubstituted cyclohexanone. Copyright © 1996 Elsevier Science Ltd

Introduction

Evidence for the male-produced aggregation pheromone in the banana weevil (BW), *Cosmopolites sordidus*, a major pest of banana crops in the world, was published recently.¹ We already have reported² the isolation and identification of the major pheromone compound **1d**, for which we proposed the trivial name sordidin (Fig. 1). Since the relative configurations of all stereogenic centers of the natural pheromone were not easily deduced from the spectroscopic data, we first synthesized compound **1** as a racemic mixture of its four stereoisomers **1a–d**.²

The key step of this first synthesis was the Baeyer–Villiger (BV) ring expansion reaction of a stereomeric mixture of 2,4,6-trimethyl-4-hydroxycyclohexanone (**2**). It is well known that the stereochemistry of polysubstituted cyclohexanones can be controlled under thermodynamic or kinetic conditions; then, opening of the six-membered ring by the BV reaction might afford stereocontrolled polysubstituted acyclic compounds. Such a methodology has previously been reported in the literature in the context of pheromone synthesis for the stereocontrolled preparation of 1,4-dialkyl-1,6-diols.³ However, although the regioselectivity of this reaction is easily controlled in the case of unsymmetrical ketones, our methodology would be limited since the regiochemistry of the BV reaction of 2,6-dialkyl cyclohexanones should be controlled by stereoelectronic factors and is hardly predictable. We want to report in this paper how the regiochemistry and therefore from the stereochemistry of this reaction depends in our case on the configuration of the starting tetrasubstituted cyclohexanone which controls the regiochemistry of the oxygen insertion and thus allows the control of the configuration at C-3 of the final product (Fig. 2).

Key words: *Cosmopolites sordidus*, regioselective Baeyer–Villiger reaction, tetrasubstituted cyclohexanone, caprolactone.

Results and Discussion

For this purpose, the first step of the study was to prepare separately the three possible diastereomers of **2**. The *trans* isomer **2a** was easily obtained by oxidation (PCC, CH₂Cl₂, sonication) of compound **5a**, which is available in two steps from **3a**. Compound **3a** is the result of the kinetic dialkylation of commercial mono-protected cyclohexanedione (Scheme 1). This dialkylation was achieved in two steps, the second one being

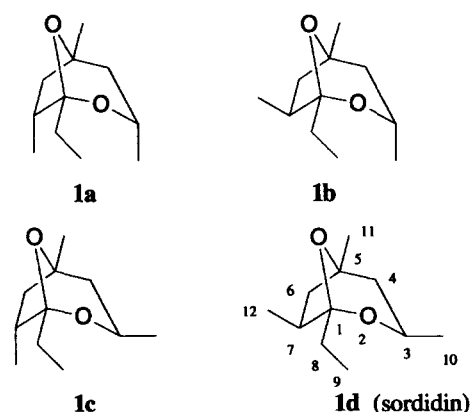


Figure 1. The four stereoisomers of sordidin.

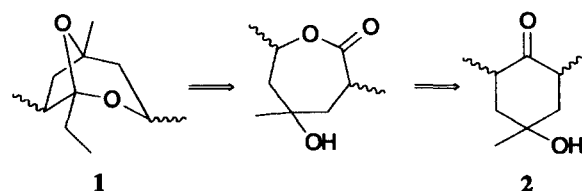
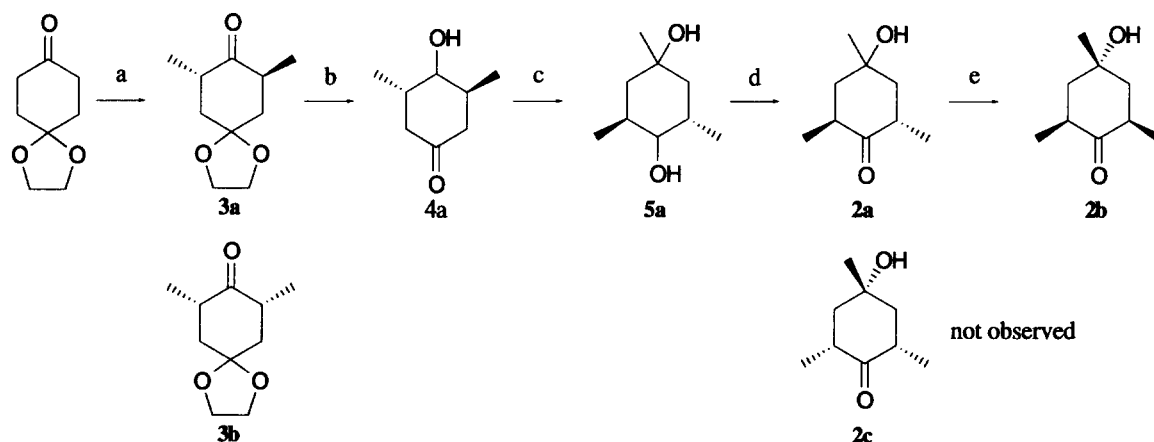


Figure 2. Retrosynthetic planning.



Scheme 1. Reagents and conditions: (a) 1. LDA, MeI, THF:HMPA (3:1) -40°C ; 2. LDA, MeI THF:HMPA (3:1) -78°C , 48%; (b) 1. NaBH_4 , MeOH; 2. HCl, MeOH; (c) MeLi, THF, -12°C ; (d) PCC, CH_2Cl_2 , 80% (four steps); (e) MeONa, MeOH, 100%.

the most critical as the temperature has a significant influence on the result of the reaction. Indeed, if the temperature is allowed to be warmer than -60°C , the thermodynamic 2,2-disubstituted compound is obtained as the major product of the reaction. On the other hand, if the temperature is maintained between -70 and -60°C , the reaction furnishes a mixture of **3a** and **3b**; however, careful quenching of the reaction at -78°C allowed obtention of **3a** as a single isomer in reasonable overall yield. Reduction of the carbonyl group at C-1 (NaBH_4 , MeOH) was then necessary to limit the rate of epimerization at C-2 (or C-6) leading to the *cis* isomer **3b** and afforded ketoalcohol **4a** after acidification of the reaction mixture (HCl, 1 N), which induced the deprotection of the carbonyl group at C-4. C-alkylation of this remaining carbonyl group was then achieved in the usual manner (MeLi, THF, -12°C) and provided the desired compound **5a**.[†]

The corresponding *cis* product **2b** can be obtained at this stage of the synthesis by thermodynamic epimerization at C-2 (MeONa, MeOH, 100%) of **2a**, the other possible *cis* isomer **2c** not being observed.

At this stage of the synthesis, it was necessary to determine the correct position (axial or equatorial) of all substituents on the chair six-membered ring of compounds **2a** and **2b**. In fact, the desired configuration for the caprolactone leading to the right configuration of sordidin is that depicted in Figure 3(a) and would be derived from cyclohexanone **2c**. However, as this product is not obtained in the course of our synthesis, we noticed that the BV reaction performed on the *trans* compound **2a** should occur via two possible routes, leading to the formation of two different caprolactones having the opposite configuration at C-6, one of them being the desired one for the

sordidin synthesis [Fig. 3(b)]. Furthermore, we assumed that the configuration at C-7 of the bicyclic ketal could be controlled in a later step of the synthesis by thermodynamic epimerization at C-7 of the ketal or at C-2 of the caprolactone. Thus, since the position of both substituents at C-4 of compound **2a** would be fixed in a chair conformation of the six-membered ring, the rate of control of the configuration at C-3 of the ketal would be given by the regioselectivity of the

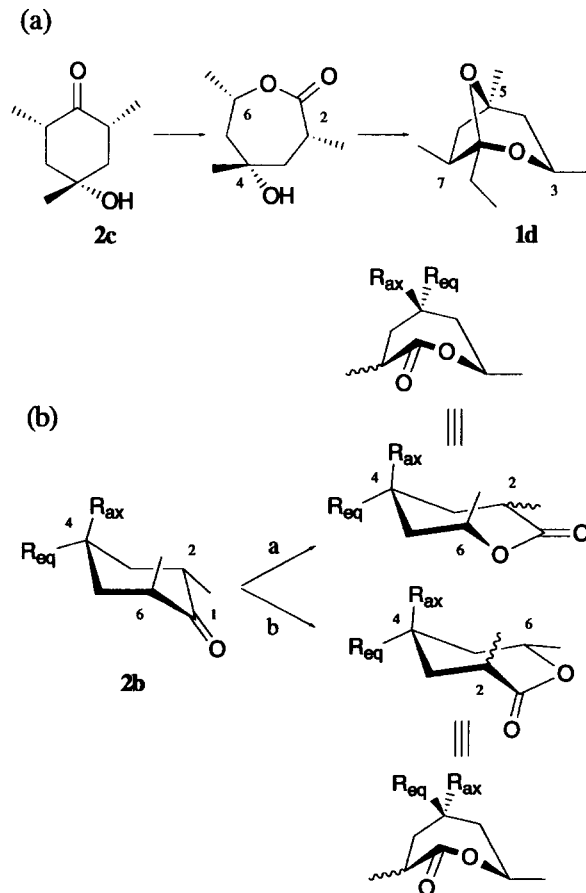


Figure 3.

[†]This alkylation occurred without diastereofacial selectivity and **5a** is therefore obtained as a mixture of two isomers. However, the hydroxy group at C-4 is in both cases in an axial position, the hydroxy group at C-1, which was in a pseudoaxial position in compound **4a**, becoming equatorial in one of these two isomer (see Experimental) resulting from a change of the chair conformation of the six-membered ring.

oxygen insertion in either the C-1/C-2 or the C-1/C-6 bond, the only difference between these two bonds being the position (axial or equatorial) of the methyl group.

Two spectroscopic criteria were derived from the NMR data to determine the configuration at C-4 in **2a** and **2b**. First, the chemical shift of C-4 (69.9 and 69.5 ppm) as well as the ^1H chemical shift of the methyl group in both compounds (1.3 and 1.25 ppm, respectively) were in agreement with an axial hydroxy group. Secondly, extensive ^1H – ^1H decoupling and 1-D NOE difference measurements indicated a strong NOE between the methyl group at C-4 and the axial protons at C-3 and C-6, as well as the equatorial position of both methyl groups at C-2 and C-6 in compound **2b** ($J_{\text{H-2, H-3ax}} = 13$ Hz; Figure 4).

It is important to note that another possible route used for the preparation of **2** (depicted in Scheme 2), based on the dialkylation of 4-hydroxy-4-methylcyclohexanone gave the same stereoselectivity. The monoprotected cyclohexanedione was treated with methyl lithium in order to introduce at first the quaternary hydroxy group at C-4; the remaining carbonyl group was then deprotected and monoalkylated in the α position to afford **6** as a mixture of two stereoisomers, **6a**

and **b** (**6a**:**6b** 9:1). Observation of the spectroscopic data for these products indicated that in both cases the hydroxy group at C-4 was in the axial position, as observed for **2a** and **2b** (Fig. 4). The second kinetic alkylation in the α' position of the carbonyl group was then possible, but afforded a mixture of **2a** and **2b** without any control of the stereochemistry of the reaction. Compound **2c**, which would have resulted from the axial alkylation of the minor compound **6b**, was once more not observed.

The BV reaction⁴ was first achieved on **2b** using MCPBA in the presence of sodium bicarbonate (2 equiv) to afford a mixture of caprolactones **7a** and **7b** (**7a**:**7b** >95:5) (Scheme 3). Obtention of **7b** is explainable by the possible isomerization at C-2; indeed, treatment of the thus obtained mixture in basic conditions afforded an equilibrium mixture (1:1) of **7a** and **7b**. Treatment of **2a** in the same conditions furnished a mixture of the four caprolactones **7a**–**d** (**7a**:**b**:**c**:**d** = 1:9). Caprolactones **7b** and **7c** were obtained via route b and route a, respectively [Fig. 3(b)], **7a** and **7d** being the result of the epimerization at C-2 of **7b** and **7c**, respectively (**7a**:**7b** 1:1.5; **7c**:**7d** 4:1). This result demonstrated the high regioselectivity of this BV reaction in this case with a good preference (90%) for oxygen insertion between the carbon atom

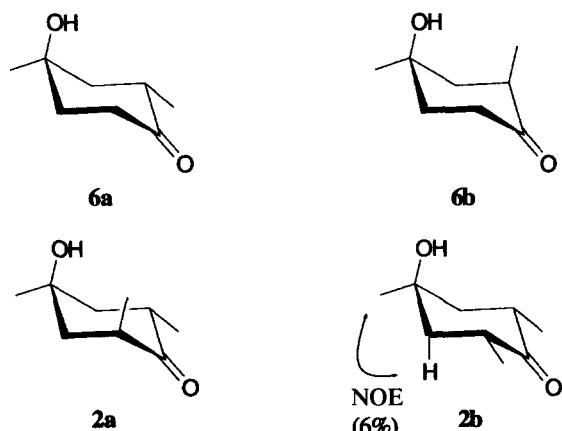
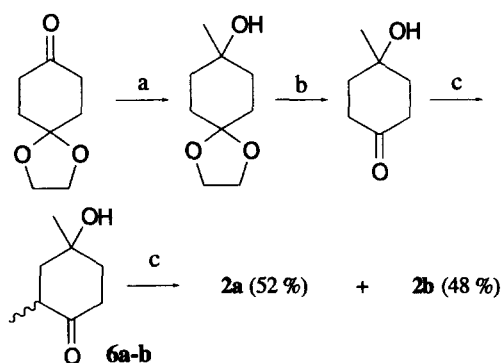
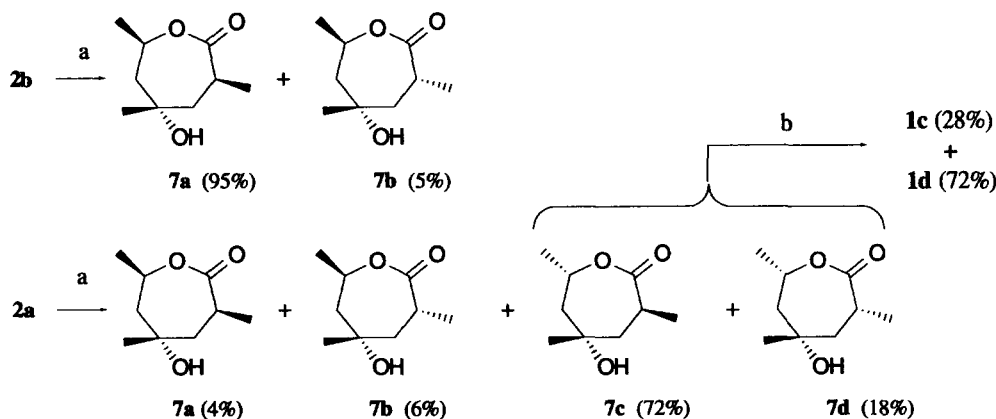


Figure 4. Conformations of **2a** and **b**, and **6a** and **b**.



Scheme 2. Reagents and conditions: (a) MeLi, THF -12°C ; (b) HCl, 1 N, MeOH 40°C , 63% (two steps); (c) LDA, THF:HMPA (3:1), -78°C , MeI, 41% (two steps).



Scheme 3. Reagents and conditions: (a) MCPBA, NaHCO_3 , CH_2Cl_2 (96%); (b) EtLi, pentane (66%).

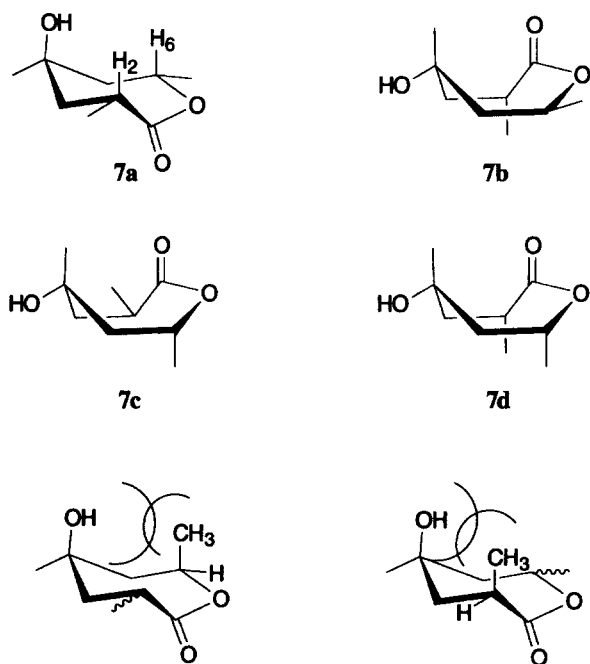


Figure 5. Conformations of lactones 7a–d.

of the carbonyl group and the adjacent one bearing a methyl substituent in the axial position [Fig. 3(b), route a, $R_{ax} = OH$, $R_{eq} = CH_3$].

Conformations of caprolactones⁵ 7a–d were easily inferred from their spectroscopic data (Fig. 5). Lactone 7a has the same chair-like conformation as its precursor 2b, all three methyl groups being in an equatorial position while the hydroxy group at C-4 remains axial. This assumption is supported by the fact that both protons H-6 and H-2 are shifted at low field in the 1H NMR spectrum of 7a (7a: 5.35 and 3.18 ppm, 7b: 4.1 and 2.87 ppm, respectively) due to the anisotropic effect of the hydroxy group at C-4. However, if the configuration at either C-2 or C-6 is inverted (compounds 7b–d), steric interactions between the hydroxy group at C-4 and the methyl group at C-2 (7b and 7d) and/or C-6 (7c and 7d) force the seven-membered ring to adopt a boat-like conformation with the hydroxy group at C-4 becoming equatorial. This change of conformation of the seven-membered ring is supported by the difference in ^{13}C chemical shifts of the C-4 carbon atom in 7a (69.6 ppm) and in the other lactones (7b: 83.9, 7c: 84.1, 7d: 80.5 ppm); furthermore, the equatorial methyl group at C-4 in 7a is shifted at higher field in the 1H NMR spectrum than the corresponding methyl in the other lactones (see Experimental).

As last step of the synthesis, the action of ethyl lithium on a mixture of 7c and 7d afforded, in moderate yield, a complex mixture of products, which was immediately treated in acidic medium (PTSA) to afford an equilibrium mixture of sordidin (1d) and 7-epi sordidin (1c) (66%), which were purified on milligram scale by preparative GC.

Conclusion

The main feature of this paper resides in the regioselectivity encountered in the BV reaction of 2,6-disubstituted cyclohexanones; indeed, this is to our knowledge the first reported example of such a selectivity due only to stereoelectronic effects. This strategy therefore seems very attractive for the preparation of 2,4,6-trialkyl-1,4,6-triols, allowing the stereocontrolled formation of an oxygenated quaternary center. However, the use of the methodology developed in this paper to the synthesis of sordidin is limited to the preparation of small quantity of pheromone as the yield of the last step of this synthesis became low when the reaction was achieved on a gram-scale quantity of caprolactone. We thus are now developing a more straightforward synthesis of 1 as an isomeric mixture of 1a–d, to confirm the field activity of the pheromone.

Experimental

Melting points are recorded on a Buchi 510 and are uncorrected. NMR data (1H : 300 MHz; ^{13}C : 75.5 MHz) are recorded on a Varian Gemini 300 instrument. All NMR spectra are recorded in 99.8% deuteriochloroform ($CDCl_3$) unless otherwise stated. Chemical shifts are reported in δ ppm relative, in most cases, to $CHCl_3$ ($CDCl_3$) as internal reference: 7.27 ppm for 1H (77.14 ppm for ^{13}C). Occasionally, Me_4Si (0.0 ppm for 1H) was used as internal reference. Coupling constants (J) are given in Hz. Multiplicities are recorded as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and br (broad). MS spectral data are obtained in electron impact at 70 eV on a Nermag R10–10C quadrupole analyzer piloted by a SIDAR acquisition system.

Visualization of TLC plates is accomplished by treatment with an ethanolic solution of phosphomolybdic acid (5%)

(3*S,5*S**)-3,5-Dimethyl-7,10-dioxabicyclo[5,4,0]decane (3a).** To a solution of LDA [prepared from diisopropylamine (13.1 mL, 100 mmol) and butyllithium (1.6 N in hexanes, 62.5 mL, 100 mmol)] in THF (150 mL) was added, at $-30^\circ C$, commercial cyclohexanedione monoethylene ketal (15.6 g, 100 mmol) in HMPA (50 mL); the solution was stirred for 30 min and MeI (6.2 mL, 100 mmol) was then added at $-40^\circ C$. The reaction mixture was then allowed to warm to room temperature, hydrolyzed with aqueous ammonium chloride and extracted twice with diethyl ether (2×200 mL). The organic layers were carefully washed with water and dried over magnesium sulfate. After filtration, the solvent was removed under vacuum to afford 16.8 g of a brown oily product, which was used in the next step without purification.

To a solution of LDA [prepared from diisopropylamine (13.1 mL, 100 mmol) and butyl lithium (1.6 N in hexanes, 62.5 mL, 100 mmol)] in THF (150 mL) was added at $-78^\circ C$, the previously obtained product in

HMPA (50 mL). MeI (6.2 mL, 100 mmol) was then added and the solution was stirred for 2 h at -78°C . Aqueous ammonium chloride was then added, while the temperature was maintained at -78°C . The temperature was then allowed to warm to room temperature and the reaction extracted with diethyl ether. The combined organic layers were washed with water and dried over magnesium sulfate. After evaporation of the solvent, **3a** (8.8 g, 48%), after purification by flash chromatography (ethyl acetate:cyclohexane 40:60), was obtained as an oily product and used in the next step without purification.

(3S*,5S*) 3,5-Dimethyl-4-hydroxycyclohexanone (4a).

To a solution of **3a** (8.8 g, 48 mmol) in MeOH (120 mL) was added NaBH_4 (1.8 g, 48 mmol) at 0°C . The solution was stirred overnight at room temperature; HCl, 1 N (100 mL) was then added and the solution stirred for 2 h at room temperature. After neutralization (NaOH , 1 N) and concentration under vacuum, the reaction mixture was extracted with diethyl ether and washed with brine. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford **4a** (6.6 g, 96%) after purification by flash chromatography on silica gel (ethyl acetate:cyclohexane 30:70). Compound **4a** m/z 142 (M^+), 124 ($\text{M}^+ - \text{H}_2\text{O}$), 109, 99, 82 (100%). ^1H NMR: δ (ppm) 3.6 (dd, $J = 3, 4.5$ Hz, H-1), 1.85–2.7 (m, 6H), 0.95 (d, 3H, $J = 7.5$ Hz), 0.85 (d, 3H, $J = 7.5$ Hz). ^{13}C NMR: δ (ppm) 217.5, 78.9, 49.6, 48.5, 41.6, 38.6, 23.1, 21.2.

(2S*,6S*)-2,4,6-Trimethyl-4-hydroxycyclohexanol (5a).

To a solution of **4a** (6.6 g, 46.5 mmol) in THF (80 mL) was added, at -12°C , MeLi (1.6 N in diethyl ether, 58 mL, 93 mmol). After stirring at -12°C for 1 h, the reaction was quenched by the addition of aqueous ammonium chloride, extracted with diethyl ether, washed with brine; the combined organic layers were then dried over magnesium sulfate. Evaporation of the solvent under reduced pressure afforded **5a** (7 g) as an oily product which was not further purified. Compound **5a** m/z (158 (M^+) not observed), 140 ($\text{M}^+ - \text{H}_2\text{O}$), 125, 107, 97, 85 (100%). ^1H NMR: δ (ppm) 3.6 (dd, $J = 3, 4.5$ Hz, 0.5 H, H-1 first isomer), 3.3 (dd, $J = 5, 9$ Hz, 0.5 H, H-1 second isomer), 1.6–2.7 (m, 6H, both isomers), 1.2 (s, 3H both isomers), 1.15 (m, 3H both isomers), 0.95 (m, 3H both isomers). ^{13}C NMR: δ (ppm) 74.3 (C-1 first isomer), 70.7, 69.8 (C-4, both isomers), 68.0 (C-1, second isomer).

(2S*,6S*) 2,4,6-Trimethyl 4-hydroxy cyclohexanone (2a).

First method. To a solution of **5a** (7 g) in dichloromethane was added PCC (9.9 g, 46 mmol), which was preliminary mixed in a mortar with dry silica gel (9.9 g). The resulting suspension was sonicated for 20–30 min. The reaction was quenched by addition of diethyl ether, the black precipitate washed with diethyl ether and the combined organic extracts concentrated. Filtration on Florisil using diethyl ether furnished **2a** [6.1 g, 84% (2 steps) after purification] as a colorless oil, which was immediately used in the next step without purification. An analytical sample can be obtained by

rapid flash chromatography (ethyl acetate:cyclohexane 30:70). Compound **2a**: m/z 156 (M^+), 141 ($\text{M}^+ - \text{CH}_3$), 138 ($\text{M}^+ - \text{H}_2\text{O}$), 123 ($\text{M}^+ - \text{H}_2\text{O} - \text{CH}_3$), 83 (100%). ^1H NMR: δ (ppm) 2.85 (m, H-6), 2.35 (m, 2H, H-2, OH), 1.95 (m, 2H, H-3ax, H-5eq), 1.75 (m, H-3eq), 1.55 (t, $J = 14$ Hz H-5ax), 1.25 (s, 3H), 1.17 (d, 3H, $J = 7$ Hz), 0.9 (d, 3H, $J = 6$ Hz). ^{13}C NMR: δ (ppm) 218 (C-1), 69.9 (C-4), 46.4, 44.9 (C-3, C-5), 41.7, 37.2 (C-2, C-6), 31.3, 17.9, 14.8.

Second method. (1) 2,4-dimethyl 4-hydroxy cyclohexanone (6a-b).

To a solution of cyclohexanedione monoethylene ketal (15.6 g, 100 mmol) in THF (200 mL) was added, at -12°C , MeLi (1.6 N in diethyl ether, 62.5 mL, 100 mmol). After stirring at -12°C for 1 h, the reaction was quenched by the addition of aqueous ammonium chloride and extracted with diethyl ether. The combined organic layers were washed with brine and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure afforded an oily product (12.5 g), which was directly poured into a solution of aqueous HCl, 1 N (40 mL), in methanol (300 mL) and stirred at 40°C overnight. After cooling at room temperature, the reaction mixture was neutralized with aqueous NaOH (1 N), concentrated under vacuum to remove the methanol and extracted with diethyl ether. The combined organic extracts were dried over magnesium sulfate and concentrated to afford an oily product (8.1 g), which was used in the next step without purification. To a solution of LDA [prepared from diisopropylamine (16.5 mL, 126 mmol) and butyl lithium (126 mmol)] in THF (300 mL) was added, at -70°C , the previously obtained oil in HMPA (100 mL); the solution was stirred for 30 min and MeI (8 mL) was then added at -70°C . The reaction mixture was then allowed to warm to room temperature, hydrolyzed with aqueous ammonium chloride and extracted twice with diethyl ether. The organic layers were carefully washed with water and dried over magnesium sulfate. After filtration, the solvent was removed under vacuum to afford **6a** and **b**, which can be used without purification. Analytical samples can be obtained by chromatography on silica gel (ethyl acetate:cyclohexane 20:80). Compound **6a**: m/z 142 (M^+), 124 ($\text{M}^+ - \text{H}_2\text{O}$), 109, 96, 82, 69 (100%). ^1H NMR: δ (ppm), 2.85 (m, H-2), 2.75 (td, $J = 13, 6$ Hz, H-6ax), 2.2 (ddd, $J = 13, 5, 2$ Hz, H-6eq), 1.72–2.05 (m, 3H), 1.62 (t, $J = 14$ Hz, H-3ax), 1.3 (s, 3H), 0.90 (d, 3H, $J = 7$ Hz). ^{13}C NMR: δ (ppm) 214.5 (C-1) 68.8 (C-4), 39.7 (C-2), 48.0, 39.6, 37.2 (C-3, C-5, C-6), 30.1, 13.9. Compound **6b**: m/z 142 (M^+), 124 ($\text{M}^+ - \text{H}_2\text{O}$), 109, 96, 82, 69. ^1H NMR: δ (ppm), 2.2–2.5 (m, 3H), 1.5–2.0 (m, 4H), 1.4 (s, 3H), 0.95 (d, 3H, $J = 7$ Hz). ^{13}C NMR: δ (ppm) 212.9 (C-1), 69.6 (C-4), 41.5 (C-2), 47.9, 39.5, 37.9 (C-3, C-5, C-6), 26.3, 15.0.

(2) To a solution of LDA [prepared from diisopropylamine (16.5 mL, 126 mmol) and butyl lithium (126 mmol)] in THF (300 mL) was added, at -78°C **6a** and **6b** in HMPA (100 mL); the solution was stirred for 30 min, MeI (8 mL) was added and the solution was stirred for 2 h at -78°C ; aqueous ammonium chloride was then added. Temperature was allowed to warm to

room temperature and the reaction was extracted with diethyl ether; combined organic layers were washed with water and dried over magnesium sulfate. After evaporation of the solvent and flash chromatography on silica gel (ethyl acetate:cyclohexane = 50:50), a mixture of **2a** and **b** (4.1 g, 26% overall yield from monoprotected cyclohexanedione; (**2a**:**2b** = 52:48) was obtained.

(2*S,6*R**)-2,4,6-Trimethyl-4-hydroxycyclohexanone (2b).**

To a solution of MeONa (prepared from 40 mg of Na) in MeOH (20 mL) was added **2a** (250 mg, 1.6 mmol) in MeOH (5 mL); the solution was stirred for 5 min at room temperature. The solvent was removed under vacuum, diethyl ether was added and the reaction mixture was filtered to afford, after evaporation of the solvent, **2b** (250 mg, 1.6 mmol) as a colorless oil in quantitative yield. Compound **2b**: *m/z* 156 (M^+), 141 ($M^+ - CH_3$), 123 ($M^+ - H_2O - CH_3$), 83 (100%). 1H NMR: δ (ppm), 2.85 (m, H-2), 1.95 (m, H-3eq), 1.5 (t, $J = 13$ Hz, H-3ax), 1.25 (s, 3H), 0.95 (d, $J = 7$ Hz, CH_3 eq). ^{13}C NMR: δ (ppm) 218 (C-1), 69.5 (C-4), 49.3 (C-3), 40.2 (C-2), 30.5; 14.2.

(2*R,4*S**,6*S**)-2,4,6-Trimethyl-4-hydroxycaprolactone (7a), (2*S**,4*S**,6*S**)-2,4,6-trimethyl-4-hydroxycaprolactone (7b), (2*R**,4*S**,6*R**)-2,4,6-trimethyl-4-hydroxycaprolactone (7c) and (2*S**,4*S**,6*R**)-2,4,6-trimethyl-4-hydroxycaprolactone (7d).** To **2a** (or **2b**) (312 mg, 2 mmol) in solution in dry dichloromethane (6 mL) was added sodium bicarbonate (340 mg, 4 mmol) and MCPBA (70% in water, 990 mg, 4 mmol) at 0 °C. The temperature was allowed to warm to room temperature and the solution was stirred for 2 h. Potassium fluoride (470 mg, 8 mmol) was then added and the reaction mixture stirred for 30 min before evaporation of the solvent. Diethyl ether (20 mL) was added and the resulting white precipitate was filtered. After concentration under vacuum, a mixture of caprolactones **7a–d** (335 mg, 97%) was obtained from **2a**. From **2b**, the reaction afforded a mixture of **7a** and **b** (330 mg, 96%). Purification by chromatography on silica gel (ethyl acetate:cyclohexane 30:70) allowed the separation of **7a–d**. Compound **7a**: 1H NMR: δ (ppm) 5.35 (m, H-2), 3.18 (m, H-6), 1.4–1.9 (m, 4H), 1.25 (d, 3H, $J = 7$ Hz); 1.2 (s, 3H), 1.1 (d, 3H, $J = 7$ Hz). ^{13}C NMR: δ (ppm) 178.5 (C-1), 70.5 (C-6), 69.6 (C-4), 48.5, 44.9, 31.9 (C-2, C-3, C-5), 31.5, 22.3, 18.31. Compound **7b**: 1H NMR: δ (ppm), 4.10 (m, H-2), 2.87 (m, H-6), 2.3 (m, 1H), 1.7–1.9 (m, 3H), 1.4 (s, 3H), 1.25 (d, 3H, $J = 7$ Hz); 1.18 (d, 3H, $J = 7$ Hz). ^{13}C NMR: δ (ppm) 179.5 (C-1), 83.9 (C-4), 64.3 (C-6), 50.1, 42.9, 34.3 (C-2, C-3,

C-5), 25.0, 24.5, 15.5. Compound **7c**: 1H NMR: δ (ppm) 3.97 (m, H-2), 2.8 (m, H-6), 2.45 (m, 1H), 1.5–1.8 (m, 3H), 1.4 (s, 3H), 1.15 (d, 3H, $J = 7$ Hz), 1.10 (d, 3H, $J = 7$ Hz). ^{13}C NMR: δ (ppm) 178.3 (C-1), 84.1 (C-4), 64.3 (C-6), 48.3, 43.0, 35.2 (C-2, C-3, C-5), 27.5, 24.9; 16.0. Compound **7d**: 1H NMR: δ (ppm) 3.95 (m, H-2), 2.75 (m, H-6), 2.60 (m, 1H), 1.5–1.8 (m, 3H), 1.35 (s, 3H), 1.15 (d, 3H, $J = 7$ Hz), 1.05 (d, 3H, $J = 7$ Hz). ^{13}C NMR: δ (ppm) 178.5 (C-1), 80.5 (C-4), 70.3 (C-6), 48.6, 45.0, 35.0 (C-2, C-3, C-5), 27.5, 25.4; 15.4.

Sordidin (1d) and 7-epi sordidin (1c). To a suspension of ethyl lithium (1.5 mmol) in dry pentane (25 mL) at -30 °C, was added caprolactones **7c** and **7d** (0.93 mg, 0.54 mmol) in dry THF. The solution was stirred for 2 h and then allowed to warm to room temperature overnight. The reaction mixture was hydrolyzed at 0 °C with aqueous ammonium chloride, extracted with ether and washed with brine. The organic layers were dried over magnesium sulfate and concentrated under reduced pressure. To the resulting mixture in solution in dichloromethane was added PTSA (0.2 mg), the reaction was stirred for 2 h at room temperature and the solvent evaporated to afford a mixture of sordidin and 7-epi sordidin (1.5 mg, 66%), which were purified by preparative GC. Spectral data are in agreement with those reported for the natural compound.

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