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# Identification and Synthesis of Sordidin, a Male Pheromone Emitted by Cosmopolites sordidus.

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**Abstract**: The diastereoselective synthesis of  $(1S^*, 3R^*, 5R^*, 7S^*)$  2,8-dioxa 1-ethyl 3,5,7-trimethyl bicylo [3,2,1] octane 1d has been achieved using as key-step the regioselective Baeyer-Villiger reaction of 2.6-disubstituted cyclohexanone. It confirms the identification of a new male pheromone emitted by the banana weevil, Cosmopolites sordidus. The trivial name sordidin is proposed.

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.<sup>1</sup> We report here the isolation, identification and synthesis of the major pheromone.

Airbone volatile collections from males and females were done using Supelpack<sup>TM</sup>-2 as adsorbent.<sup>2</sup> After elution with pentane, the volatiles were analysed by GC and GC/MS.<sup>3</sup> Six male-specific compounds were disclosed, among which a major compound, for which we proposed the trivial name "sordidin", accounted for 80%. GC/EAD<sup>4</sup> recordings showed that these compounds, especially sordidin, had biological activity. Micropreparative GLC<sup>5</sup> performed directly from the crude extracts (1500 male/day/equivalents) led to the isolation of ca. 100  $\mu$ g of sordidin for identification.

The highest mass fragment ion observed in the low resolution GC-EIMS spectrum<sup>6</sup> of isolated sordidin was m/z 184. Spectra obtained by GC-CIMS with NH<sub>3</sub> giving ions at m/z 185 (MH<sup>+</sup>, 100%), 142 (1%) and 95 (3%), and with CH<sub>4</sub> giving ions at m/z 185 (MH<sup>+</sup>, 12%), 141 (55%), 95 (100%) and 57 (97%) confirmed the molecular weight as 184.

No hydroxyl (confirmed by the GC-(ND<sub>3</sub>) CIMS spectrum : ions at m/z 186 (MD<sup>+</sup>, 100%), 110 (5%) and 95 (12%)) nor carbonyl function was detected by GC-FTIR measurements,<sup>7</sup> and the same spectral data were obtained after catalytic micro-hydrogenation (PtO<sub>2</sub>/CH<sub>3</sub>OH).

These data led us to propose for sordidin a  $C_{11}H_{20}O_2$  formula as the most reasonable.

The <sup>1</sup>H NMR spectrum of sordidin (400 MHz,  $CDCl_3$ )<sup>8</sup> exhibited resonances for four isolated spin systems : two of six protons each corresponding to two -CH<sub>2</sub>CH(CH<sub>3</sub>)- subunits, a non coupled methyl group and an ethyl group. According to the molecular formula, we could thus assume the presence of two quaternary carbons in the molecule. According to the chemical shifts of the resonances observed for the different protons of the molecule, only one proton (H-3) might be attached to a carbon atom bearing an oxygenated function.

Since the GC-FTIR spectrum of sordidin did not reveal the presence of either hydroxy groups or carbonyl groups, we have to infer the presence of two ether linkages in the molecule : the first one between the methine carbon (C-3) and a quaternary carbon, the second one between both quaternary carbons. The only possibility is then to have an intramolecular bicyclic ketal. This would be in agreement with the high volatility and behaviour in

GC of sordidin.

At this point of the discussion we can reasonably propose four possible skeletons (1-4).

Structures 3 and 4 can be easily rejected by the observation in the GC-MS spectrum of sordidin of ion m/z 57 as a major fragment, corresponding to a [CH<sub>3</sub>CH<sub>2</sub>CO]<sup>+</sup> ion, only compatible with structures 1 or 2; it is important to note that this fragmentation is also encountered as a major one in the MS spectrum of the related multistriatin.<sup>9</sup>



We synthesized the four diastereomers of compound 1 which seemed to correspond to the most biogenetically reasonable structure for sordidin. This synthesis was first achieved without care to diastereoselectivity using as key-step the Baeyer-Villiger reaction of 4-hydroxy 2,4,6-trimethyl cyclohexanone 5 which is readily obtained in 4 steps from commercially available mono-protected 1,4-cyclohexanedione 6 as depicted on scheme 1 : action of methyl lithium on 6 afforded alcohol 7 which, after acidic workup yielded keto alcohol 8 (63 %, 2 steps). Alkylation of 8 (LDA, MeI, THF/HMPT, -78°C, 41 %) was achieved in two consecutive steps, yielding a diastereomeric mixture of ketone 5.

The Baeyer-Villiger reaction was then achieved using MCPBA in the presence of sodium bicarbonate (2 eq) to afford a mixture of caprolactones 9 which were alkylated with ethyl lithium in pentane to yield 1 in reasonable yield as a mixture of four diastereomers (73 %, 2 steps) (Scheme 1).



#### Scheme 1

The four diastereomers of 1 were separated by preparative GC and the comparison of their spectral data with those of an authentic sample of sordidin showed that sordidin was an optically pure form of diastereomer 1d (Figure 1).

The presence of sordidin in the diastereomeric mixture **1a-d** demonstrated the validity of our strategy and prompted us to undergo a diastereoselective version of this synthesis; nevertheless, we assumed that it was not worthy to try to synthesize separately all four diastereomers because of the possible isomerization at C-7 in the  $\alpha$ position to the ketal function which is observed in the natural product and also in the synthetic compound and confirmed by GC analysis (Figure 1). A similar equilibrium has also been studied in the case of related multistriatin.<sup>10</sup> However, control of the configuration at C-2 in trimethylcyclohexanone **5** prior to Baeyer-Villiger reaction should allow the sterochemical control at C-3 in the final product, leading either to compound **1a** and **1b**  or 1c and 1d.

In fact, treatment of ketone 5 in a basic medium (EtONa, EtOH) yielded the thermodynamic ketone 5a with a *cis* relationship between all the methyl substituents at C- 2, C-6 and C-4 (<sup>1</sup>H coupling constants showed that both methyl at C-2 and C-6 were in an equatorial position; NOe differences measured on 5a as well as  $^{13}$ C chemical shifts allowed to determine that the third methyl group was also equatorial, the hydroxy group at C-4 being axial). The Baeyer-Villiger reaction occurred with partial isomerization at C-2 and thus afforded a mixture of **9a** and **9b**. A subsequent alkylation yielded a mixture of **1a** (30 %) and **1b** (70 %) (Scheme 2).





Figure 1: Chromatogram of natural and synthetic (racemic) sordidin on a chiral column (WCOT CYDEX-B (SGE)) (I : natural sample of sordidin; II : mixture of synthetic 1a, 1b, 1c and 1d; III : I + II)



It is important to note that we did not observe the formation of ketone **5c** with a *cis* relationship between both methyl groups at C-2 and C-6 and the hydroxy group at C-4, which would have given acces to diasteromer **1d**; thus, the formation of **1d** in the first procedure has to be explained by isomerization at C-2 in caprolactone **9c** or at C-7 in ketal **1** under thermodynamic conditions. Therefore, we decided to synthesize compound **5b** with a *trans* relationship between both methyl substituants attached at C-2 and C-6, which might be the appropriate precursor of lactone **9c** and ketals **1c** and **1d**.

Kinetic alkylation of 6 in the  $\alpha$ ,  $\alpha'$  positions to the unprotected carbonyl group was achieved in two steps (LDA, MEI, THF/HMPT, -78°C, 48 %) and afforded as major compound diketone 10, which is immediately reduced by the action of sodium borohydride (NaBH<sub>4</sub>, MeOH, 87 %) in order to avoid isomerization at C-2 or C-6. Deprotection and,

alkylation (HCl, MeOH then MeLi, THF,  $-12^{\circ}$ C, 94 %) of the remaining carbonyl group followed by oxidation of the hydroxy group at C-1 (PCC on silicagel, CH<sub>2</sub>Cl<sub>2</sub>, 98 %) resulted in the desired trimethylketone **5b**. (Scheme 3).

As expected, the Baeyer-Villiger ring expansion<sup>11</sup> (MCPBA, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 97 %) occurred with high regioselectivity (9 : 1) with oxygen insertion between the carbonyl and the adjacent carbon atom bearing an axial methyl group so that the major caprolactone obtained **9c** has the opposite relative configuration at C-3 and C-5 than those obtained in the previous procedure (**9a** and **9b**). Alkylation with ethyl lithium thus afforded after acidic workup<sup>12</sup>(EtLi, C<sub>5</sub>H<sub>12</sub> then PTSA, CH<sub>2</sub>Cl<sub>2</sub>, 66 %) an equilibrium mixture of 1c (28 %) and 1d (72 %).

Confirmation of the configuration of 1d has been achieved by two-dimensional <sup>1</sup>H-<sup>1</sup>H NOESY experiments (400 MHz) which showed strong nOe's between protons H-3 and H-7 and also between H-3 and H-6ando.

The male pheromone emitted by Cosmopolites sordidus, sordidin, is a new natural compound related to known ketal pheromones from Scolvtids. Further experiments to define the biological role and the absolute configuration of this compound are in progress as well as the study of the thermodynamic factors inducing the diastereomeric equilibrium observed in compounds 5, 9 and 1,



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#### **References and notes**

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- Conditions-1: 25 m \* 0.32 mm id, WCOT DB-Wax, 80°C(2 min) to 240°C at 5°C/min, GC/MS Nermag R10-10C; conditions-2: 25 m \* 0.32 mm id, WCOT BPX-5, 120°C, GC/MS; condition3: 25 m \* 0.32 mm id, 35°C to 60°C at 35°C/min, and from 40 to 240°C at 5°C/min, GC HP-5890; condition-4: 50 m \* 0.32 mm id, methylsilicone (HP) 60 to 240°C at 5°C/min, GC HP-5890; condition-5: 50 m \* 0.2 mm id, Carbowax 20 M 3\_ (HP), 60 to 220°C at 10°C/min, GC HP-5790 ; MS VG-Mass Lab.
- GC/EAD : Gas chromatography-Electroantenography coupling. GC-condition : 50 m \* 0.2 mm id, Carbowax 4-20 M (HP), 60 to 220°C at 10°C/min, GC HP-5890 series II, split ratio 1:1; EAD-THC-3 temperature control unit, FID/EAD signals monitored synchronously by GC-EAD interface card installed in a PC (Harvard Professional Computer, American Megatrends Inc.
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- 6-
- <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, δ (ppm) J (Hz)) : 3.8 (m, 8 6 6, H3) ; 2.25 (m, 8 6 4, H-7) ; 2.08 (dd, 12 8, H-8-6endo); 1.65 (dq, 15 7, H-8); 1.55 (dq, 15 7, H-8); 1.1 (d, 6,H-10); 1.25 (s, H-11); 1.2-1.35 (m, H-4, H-6exo) ; 1.18 (m, H-4') ; 0.93 (t, 6 , H-9) ; 0.93 (d, 6, H12)
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