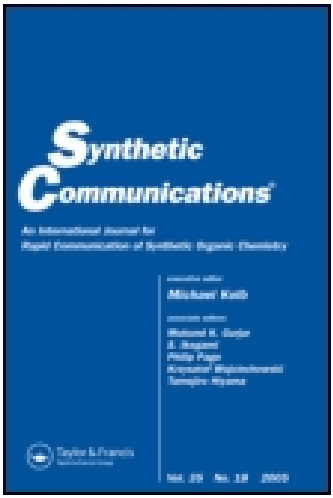

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Efficient Synthesis of Sordidin, A Male Pheromone Compound Emitted by Cosmopolites Sordidus

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EFFICIENT SYNTHESIS OF SORDIDIN, A MALE PHEROMONE COMPOUND EMITTED BY *COSMOPOLITES SORDIDUS.*

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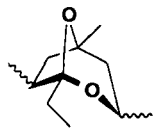
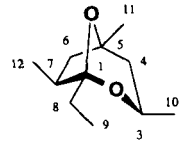
Abstract *: A multigram-scale synthesis of sordidin ((1S*,3R*,5R*,7S*) 2,8-dioxa 1-ethyl 3,5,7-trimethyl bicylo [3,2,1] octane) is described. Sordidin is obtained as a racemic mixture of its four isomers* ***1a-d*** *(10 steps, 27% overall yield)*

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 have already reported the isolation, identification and synthesis of the major pheromone.[2,3]



1a-c

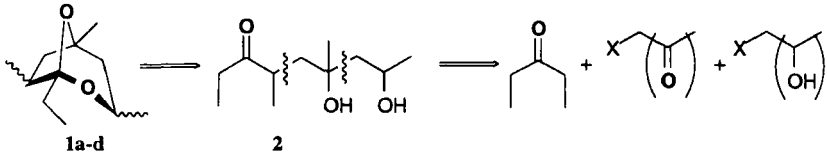


1d

However, this first diastereoselective synthesis did not allowed the preparation of large quantities of sordidin due to the low yield of the last step of the synthesis when done on a large scale.[3] In order to check the activity of the pheromone in laboratory and

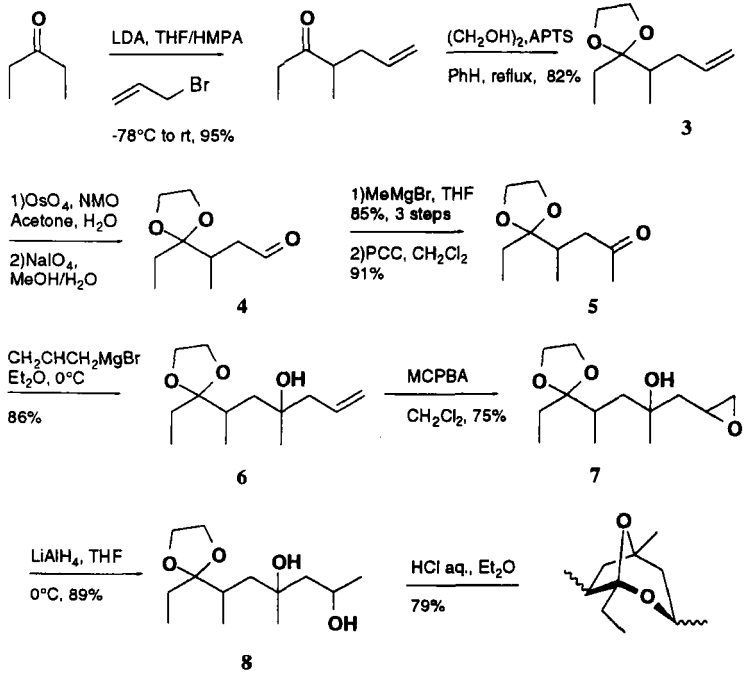
field behavioural bioassay, we decided to manage a straightforward synthesis of sordidin without taking care of the diastereoselectivity of the reactions sequence.

In this paper, we want to report the synthesis of a mixture of the four isomers of sordidine (**1a-d**) in a 10 steps procedure (27 % overall yield) which can easily be performed without purification of most of the synthetic intermediates. For this purpose, we designed the following retrosynthetic scheme, assuming that sordidin should be easily obtained by intramolecular ketalization of the corresponding 1,3-diol **2** which should be obtained by alkylation of 3-pentanone (Scheme 1).



1a-d **2**

Scheme 1



3-Pentanone was first alkylated by allyl bromide using standart conditions (LDA, THF/HMPA, -40°C ; then CH_2CHCH_2Br, -78°C to room temperature, 4 h, 95%), leading after protection of the carbonyl group ($(CH_2OH)_2$, APTS, C_6H_6 reflux, 82%) to ketal **3**.

Oxidative cleavage of the terminal olefin was achieved in two steps : oxidation to the corresponding diol (OsO_4 cat., NMO, acetone/water) and periodate cleavage ($NaIO_4$, H_2O/MeOH) of the resulting glycol afforded aldehyde **4**. Then, alkylation of the carbonyl was performed using methyl magnesium bromide (MeMgBr, THF, 0°C, 85%, 3 steps) to afford the secondary alcohol which was oxidized to the corresponding ketone **5** (PCC/SiO_2, CH_2Cl_2, 12 h., 91%). Further alkylation of the carbonyl group by allyl magnesium bromide afforded the desired tertiary alcohol **6** (CH_2CHCH_2MgBr, Et_2O, 0°C, 86%) which, upon epoxidation of the olefin (MCPBA, CH_2Cl_2, 2 days, 75%) led to compound **7**. Reduction of **7** by lithium aluminium hydride ($LiAlH_4$, THF, 0°C to room temperature, 2 h, 89%) allowed quantitative formation of the corresponding secondary alcohol **8** regioselectively. Deprotection of the carbonyl group was then performed using biphasic conditions (aqueous HCl (1N)/Et_2O, 79%) to afford the desired diol **2** which underwent spontaneous intramolecular ketalization to yield sordidin **1**. The conditions of the last step of this synthesis have been optimized to avoid problems in the purification of the sordidin, which could be due otherwise to the high volatility of this compound.

The first results of the laboratory bioassay performed with this mixture of the four isomers of sordidin have already shown a significant activity of this compound. Field bioassay is now on progress and biological results will be reported elsewhere.

Experimental

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). Occasionnaly, Me_4Si (0.0 ppm for ^1H) was used as internal reference. Coupling constants (*J*) are given in Herz (Hz). Multiplicities are recorded as s (singlet), d (doublet), t (triplet), q (quadruplet) and m (multiplet) and br. (broad).

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

(3) : 4-methyl heptene 5-one ethylene ketal:

To a solution of LDA (prepared in 150 ml of THF from 13.1 ml of diisopropylamine and 62.5 ml of butyllithium (1.6 N in hexanes) at -40°C) is added at -78°C 3-pentanone (10.09 ml, 100 mmol) in 65 ml HMPA. After stirring at -78°C for 2 hours, allyl bromide (13 ml) is added over a 5 min period. Temperature is then allowed to warm to room temperature and stirring is continued for 1 hour. The reaction mixture is hydrolysed with aqueous ammonium chloride, extracted with ether and the organic layer is dried over magnesium sulfate. Evaporation of the solvent afforded 11.95 g of an oily product (95%) which is used without purification.

m/z = 126 ($M^{+\cdot}$, 75), 84 (100).

^{1}H NMR (δ, ppm) : 1.05 (m, 6H, $2CH_3$) ; 2.1 (m, 1H) ; 2.3-2.5 (m, 3H) ; 2.6 (m, 1H) ; 5.0 (m, 2H) ; 5.68 (m, 1H).

^{13}C NMR (δ, ppm) : 214.5 ; 135.6 ; 116.3 ; 45.8 ; 37.3 ; 34.4 ; 16.3 ; 8.0.

To this oily product dissolved in 200 ml of benzene is added 30 ml of ethylene glycol and 200 mg of APTS. The reaction mixture is heated at reflux in a Dean-Stark apparatus and the reaction is monitored by TLC analysis. When all the starting material has reacted, the reaction mixture is cooled at room temperature and extracted with ether. The organic layer is dried over magnesium sulfate and concentrated under reduced pressure to afford 13.2 g (82%) of **3** as a colourless oil.

m/z = 170 ($M^{+\cdot}$, 1), 141 (10), 101 (100), 57 (48), 41 (22).

^{1}H NMR (δ, ppm) : 0.92 (m, 6H, $2CH_3$) ; 1.65 (m, 2H) ; 1.65 (m, 2H) ; 2.38 (m, 1H) ; 3.95 (m, 4H) ; 5.05 (m, 2H) ; 5.75 (m, 1H).

^{13}C NMR (δ, ppm) : 138.3 ; 115.4 ; 113.8 ; 65.5 ; 63.8 ; 39.8 ; 36.0 ; 27.3 ; 14.2 ; 8.0

(4) : 3-methyl 4-oxo hexanal 4-ethylene ketal.

To a solution of **3** (3.9 g, 23 mmol) in acetone (10 ml) and water (5 ml) is added NMO (3 g, 1.1 eq.) and osmium tertoxide (2.5% solution in t-butanol, 10 ml). After stirring at room temperature during 2 hours, saturated aqueous solution of sodium bisulfite (7 ml) is added. The reaction mixture is diluted with ethyl acetate (50 ml), filtred, dried over magnesium sulfate and concentrated to afford an oily product (4.5 g).

To this crude product dissolved in 40 ml methanol and 40 ml water is added $NaIO_4$ (10 g, 47 mmol). After stirring at room temperature for 2 hours, methanol is removed under reduced pressure and the residue extracted with CH_2Cl_2. The organic layer is dried over magnesium sulfate and concentrated under vacuuo to afford the desired aldehyde (3.6 g, 21 mmol, 91%) which is used in the naxt step without purification.

m/z = 143 (10), 101 (100), 71 (8), 57 (36), 43 (16).

^{1}H NMR (δ, ppm) : 0.86 (t, 3H, CH_3) ; 1.02 (d, 3H, CH_3) ; 1.6 (m, 2H) ; 2.15 (m, 1H) ; 2.48 (m, 2H) ; 3.95 (m, 4H) ; 9.53 (d, 1H).

^{13}C NMR (δ, ppm) : 202.0 (C-1) ; 113.3 (C-4) ; 65.1, 65.8 (2C) ; 46.2 (C-3) ; 34.8 ; 27.1 ; 15.8 ; 7.8.

(5) : 4-methyl 2,5-heptanedione 5-ethylene ketal.

To the crude aldehyde previously obtained (3.6 g, 21 mmol) dissolved in anhydrous THF (50 ml) is added at 0°C methyl magnesium bromide (3N solution in THF, 11 ml); after stirring 15 min at 0°C, the reaction is quenched by carefull addition of a saturated aqueous soluion of ammonium chloride. The reaction mixture is allowed to warm at room temperature and then extracted with ether. The organic layer is washed with brine, dried over magnesium sulfate and concentrated under vaccuum to afford a colorless oily product (This compound can be purified by flash chromatography on silica gel eluted with ethyl acetate/cyclohexane (30/70); 3.4 g of analytically pure compound are obtained, 85% from **3**) This product (3.4 g, 18 mmol) is directly poured in dichloromethane. PCC on silicagel (5 g PCC) is then added in one portion and the resulting mixture stirred overnight at room temperature. The reaction is quenched by addition of pentane, stirred 1 hour at room temperature and filtred to afford after removal of the sovents **5** (3 g, 91%). Analytical sample can be obtained by flash chromatography on silica gel eluted with cyclohexane/Ethyl acetate (30/70).

m/z =157 (20), 101 (100) 57 (82), 43 (88).

^{1}H NMR (δ, ppm) : 0.85 (t, 3H, CH_3) ; 0.92 (d, 3H, CH_3) ; 1.6 (m, 2H) ; 2.1 (s, 3H, CH_3) ; 2.15 (dd, 1H) ; 2.45 (m, 1H) ; 2.6 (dd, 1H) ; 3.95 (m, 4H).

^{13}C NMR (δ, ppm) : 208.3 (C-2) ; 113.5 (C-5) ; 65.2 (2C) ; 46.1 (C-3) ; 35.6 ; 30.1 ; 26.3 ; 15.8 ; 7.8.

(6) : 4,6-dimethyl 4-hydroxy 1-nonen 7-one ethylene ketal.

To a solution of **5** (3 g, 16 mmol) in ether (10ml) is added through a canula 3 eq. of a solution of allyl magnesium bromide prepared from magnesium (1g) and allyl bromide (3.6 ml) in ether (30 ml) at 0°C. The reaction mixture is stirred at 0°C during 1 hour and quenched by addition of ammonium chloride. After warming at room temperature, the reaction is extracted with ether, washed with brine and the combined organic layers are dried over magnesium sulfate. After concentration under vaccuum, alcohol **6** is obtained as a pale yellow oil (3.15 g, 86%) and used in the following step without purification.

^{1}H NMR (δ, ppm) : 0.89 (m, 3H, CH_3) ; 1.02 (m, 3H, CH_3) ; 1.15 (m, 3H, $1CH_3$) ; 1.2-1.4 (m, 2H) ; 1.6-1.8 (m, 3H) ; 2.22 (m, 2H) ; 3.95 (m, 4H) ; 5.1 (m, 2H) ; 5.85 (m, 1H).

^{13}C NMR (δ, ppm) :134.4; 118.2; 114 (C-7) ; 71.3,71.9 (C-4) ; 65 (2C).

(7) : 1,2-epoxy 4,6-dimethyl 4-hydroxy nonan 7-one ethylene ketal.

To compound **6** (3.15 g) dissolved in dichloromethane (10 ml) is added MCPBA (70% in water, 4 g) at 0°C. The reaction mixture is allowed to warm at room temperature and stirred 48 hours. Potassium fluoride (3.8 g) is then added and the reaction is stirred for 1 hour; dichloromethane is then evaporated under vaccum and the resulting semi solid residue is suspended in pentane. After stirring 2 hours, the precipitate is filtred and the resulting solution is concentrated under vaccuum to afford epoxide **7** in 75% yield (2.6 g) after chromatography on silica gel eluted with cyclohexane/ethyl acetate (50/50).

m/z = 226 (M^+-18·, 1), 187, 101 (100) 57 (46).

^{1}H NMR (δ, ppm) : 0.8 (m, 3H, CH_3) ; 0.98 (m, 3H, CH_3) ; 1.2 (m, 3H, $1CH_3$) ; 1.2-2.0 (m, 7H) ; 2.45 (m, 1H) ; 2.77 (m, 1H) ; 3.10 (m, 1H) ; 3.95 (m, 4H).

^{13}C NMR (δ, ppm) :114 (C-7) ; 71.5,71.9 (C-4) ; 65 (2C).

(8) : 4,6-dimethyl 2,4-dihydroxy nonan 7-one ethylene ketal.

To a solution of **7** (2.5 g, 10.3 mmol) in THF (50 ml) is added at 0°C a solution of lithium aluminium hydride (1.0 M solution in THF, 14 ml). The reaction mixture is allowed to warm at room temperature over a 2 hours period and quenched by the consecutive addition of water (0.6 ml), NaOH (15% solution in water, 0.6 ml) and water (1.8 ml). After stirring 1 hour at room temperature, the reaction mixture is filtred, dried over magnesium sulfate and concentrated under vaccuum to afford compound **8** (2.2 g, 89 %).

m/z = 246 (M^+·, 1), 159 (15), 141 (10), 101 (100) 57 (48).

^{1}H NMR (δ, ppm) : 0.8 (m, 3H, CH_3) ; 0.95 (m, 3H, CH_3) ; 1.1 (m, 6H, $2CH_3$) ; 1.15 (m, 2H) ; 1.2-2 (m, 5H) ; 3.85 (m, 4H) ; 4.11 (m, 1H).

^{13}C NMR (δ, ppm) :117 (C-7) ; 72-73.5 (C-2) ; 65 (2C) ;

(1a-d) sordidine

To a solution of **8** (2.2 g, 9.1 mmol) in ether (20 ml) is added a few drops of hydochloric acid (1N), the reaction mixture is monitored by TLC and stirred at room temperature until complete disappearance of the starting material (3-5 hours). The reaction mixture is then hydrolysed by addition of solid sodium bicarbonate, the organic layer is dried over sodium sulfate and concentrated under vaccuum without heating to afford **1** as a colorless oil (1.33 g, 79 %).

^{13}C NMR (75 MHz, $CDCl_3$, δ (ppm))(chemical shifts of the natural pheromone **1d** are typed in bold face) :

C-1 : 109.2, **108.7**, 107.8, 107.7; C-5 : **78.9**, 78.8, 78.3, 78.2; C-3 : 65.5, **64.5**, 63.6, 63.0; C-6 : 59.7*, 58.8*, **44.9**, 44.7*; C-4: 47.6*, 47.0*, **44.2**, 42.2*; C-7: 42.1, 40.6, **40.2**; C-8: 28.9, **27.5**, 27.1; C-11: 28.2, 27.5, **26.6**; C-10: 22.1, **22.0**, 21.3, 21.1; C-9,C-12: **20.0**, 18.3, 14.7, 12.6, 8.0, **7.9**. (chemical shifts noted with a "*" have not been unambiguously assigned)

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