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Synthesis and Absolute Configuration of Sordidin, the Male-Produced Aggregation Pheromone of the Banana Weevil, *Cosmopolites sordidus*

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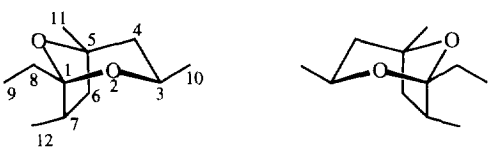
Abstract : The racemate as well as both the enantiomers of sordidin (1-ethyl-3,5,7-trimethyl-2,8-dioxabicyclo[3.2.1]octane, **1**) were synthesized, and the natural pheromone was shown to be (1*S*,3*R*,5*R*,7*S*)-(+)-**1**. Copyright © 1996 Elsevier Science Ltd

The banana weevil, *Cosmopolites sordidus* Germar, is the major pest in all banana growing countries in the world, and its larvae feed and tunnel in the rhizomes of banana plants to destroy them. The release of a volatile aggregation pheromone by male *C. sordidus* was first reported by Budenberg et al. in 1993.[1] Subsequently in 1995, Ducrot and his coworkers[2] isolated 100 μg of the major component of the pheromone, proved its bioactivity, named it sordidin, and proposed its structure including relative stereochemistry as (1*S**,3*R**,5*R**,7*S**)-**1** (Fig. 1) by the spectroscopic and synthetic studies. This Letter reports the synthesis of (±)-, (+)- and (-)-**1**, which enabled us to assign (1*S*,3*R*,5*R*,7*S*)-stereochemistry to the naturally occurring (+)-sordidin.



(1*S*,3*R*,5*R*,7*S*)-**1** (1*R*,3*S*,5*S*,7*R*)-**1**

Fig. 1. Structure of sordidin.

Fig. 2 summarizes our synthesis of **1**. Because Ducrot[2] has shown that the four diastereomers with the gross structure (±)-**1** as well as the enantiomers of **1** are separable by GLC, the absolute configuration of sordidin must be clarified, if we synthesize **1** with known absolute configuration. The alcohol (2*R*)- or (2*S*)-**5a** was therefore chosen as the key intermediate to synthesize sordidin enantiomers. (±)-Sordidin was first synthesized in order to develop a reliable synthetic route.

Alkylation of diethyl ketone with the commercially available bromide **2** in the presence of lithium diisopropylamide (LDA) yielded **3**,[3] which was converted to bromoacetal **4**. Lithiation of **4** with *s*-butyl-lithium was followed by the reaction with (±)-propylene oxide in the presence of boron trifluoride etherate[4]

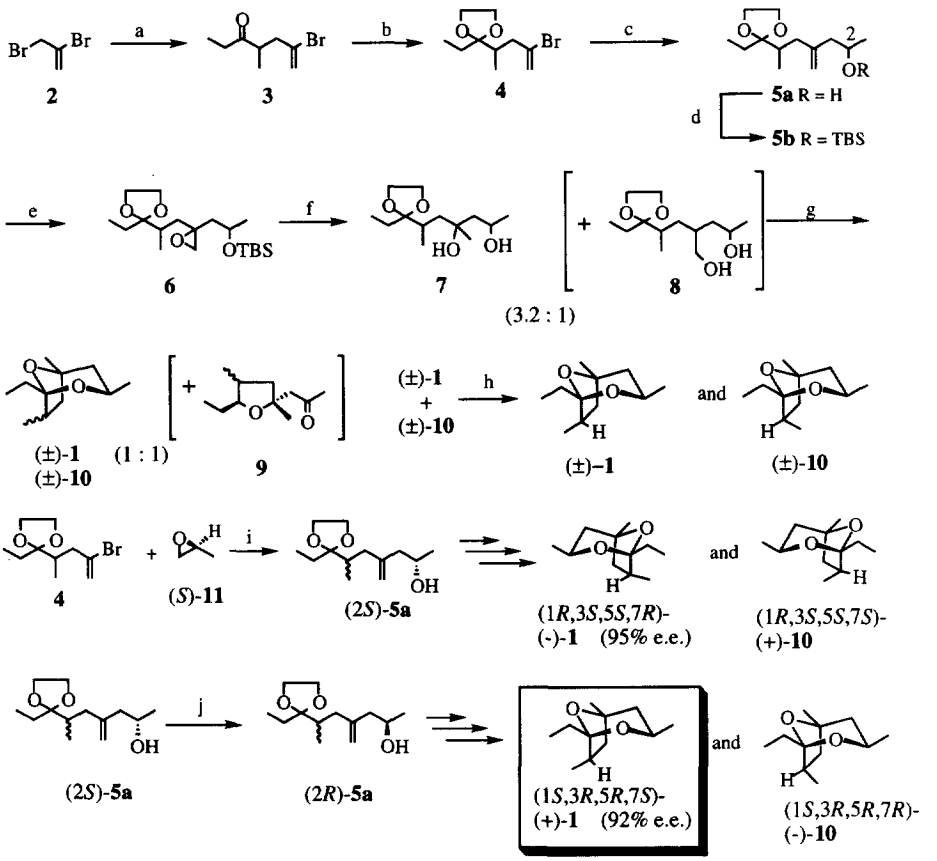


Fig. 2. Synthesis of the racemate and the enantiomers of sordidin.

Reagents:(a) 1.5 eq. Et_2CO, 1.5 eq. LDA, THF (69%).— (b) 2 eq. $HO(CH_2)_2OH$, $TsOH{\cdot}H_2O$, C_6H_6 (92%).— (c) 1) 1 eq. *s*-BuLi, THF; 2) 1.3 eq. (±)-propylene oxide (**11**); 3) 1 eq. $BF_3{\cdot}OEt_2$ (70%).— (d) 1.5 eq. TBSCl, 3 eq. imidazole, cat. DMAP, DMF (99%).— (e) 1.5 eq. MCPBA, 5 eq. $NaHCO_3$, CH_2Cl_2 (75%).— (f) 8 eq. $LiAlH_4$, THF (69%).— (g) 1.5 eq. $TsOH{\cdot}H_2O$, CH_2Cl_2; SiO_2 chromatog. [40% of a mixture of (±)-**1** and (±)-**10**].— (h) prep. GLC (PEG 20M, 6 mm i.d. x 2.5 m).— (i) 1) 1 eq. *s*-BuLi, THF; 2) 1 eq. $BF_3{\cdot}OEt_2$ (70%).— (j) 1) Ph_3P, $PhCO_2H$, $EtO_2CN{=}NCO_2Et$, THF 2) NaOMe, MeOH (82%).

to give **5a**. The hydroxy group of **5a** was protected as the corresponding *t*-butyldimethylsilyl (TBS) ether to furnish **5b**, which was epoxidized with *m*-chloroperbenzoic acid (MCPBA) to afford **6** as a stereoisomeric mixture. Reduction of **6** with lithium aluminum hydride yielded the desired 1,3-diol **7** accompanied with the 1,4-diol **8**. These were separable by silica gel chromatography, and **7** was treated with 1.5 eq. of *p*-toluenesulfonic acid monohydrate in dichloromethane for 4 h at room temperature. Although there existed in the reaction mixture the four stereoisomers of (±)-**1** at the initial stage, the material isolated after 4 h was a mixture of the two acetals [(±)-**1** and (±)-**10**] and the tetrahydrofuran compound **9**.[5] This mixture could be separated by silica gel chromatography, and the acetals were further separated by preparative GLC[6] to give (±)-**1**[7] and (±)-**10**.[8] The spectral properties of (±)-**1** were identical with those reported for it by the French

group.[2] The overall yield of the acetal mixture [(±)-**1** + (±)-**10**] was 18% based on **2** (seven steps). The field evaluation of (±)-sordidin (**1**) was carried out in Venezuela. (±)-Sordidin attracted the banana weevils when admixed with banana plant tissue, although (±)-**1** alone did not work. It thus works only when banana odours are present.[9]

(1*R*,3*S*,5*S*,7*R*)-(-)-Sordidin (**1**) and its stereoisomer (+)-**10** were then synthesized via (2*S*)-**5a** by employing (*S*)-propylene oxide (**11**) and **4** as the intermediates. Mitsunobu inversion of (2*S*)-**5a** afforded (2*R*)-**5a**, which was converted to (1*S*,3*R*,5*R*,7*S*)-(+)-sordidin (**1**), $[\alpha]_D^{21}$ = +26° (Et_2O), and its stereoisomer (-)-**10**, $[\alpha]_D^{21}$ = -7.8° (Et_2O).[10] The enantiomeric purity of (-)-**1** and that of (+)-**1** were estimated by their GLC analysis on a column coated with permethylated β-cyclodextrin (T. Hasegawa Co.), and found to be 95 and 92% e.e., respectively.[6] Our synthetic enantiomers of **1** were then compared with the natural pheromone by GLC analysis (Cyclodex B column) in France, and (+)-sordidin coincided with the natural product. The absolute configuration of natural sordidin is therefore 1*S*,3*R*,5*R*,7*S*.

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References And Notes

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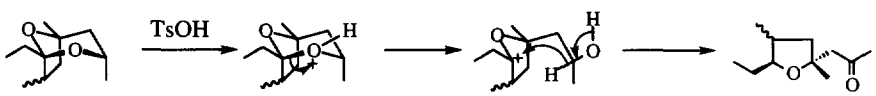
1. Budenberg, W. J.; Ndiege, I. O.; Karago, F. W. *J. Chem. Ecol.* **1993**, *19*, 1905-1916.
2. Beauhaire, J.; Ducrot, P.-H.; Malosse, C.; Rochat, D.; Ndiege, I. O.; Otieno, D. O. *Tetrahedron Lett.* **1995**, *36*, 1043-1046.
3. All the new compounds were characterized by spectroscopic (IR and NMR) and elemental (combustion or HRMS) analysis.
4. Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693-3694.
5. The stereoisomers **A** of sordidin must be unstable due to the severe 1,3-diaxial interaction of the substituents of the 1,3-dioxacyclohexane ring. After protonation to give **B**, **B** generates the carbocation **C**, which gives the rearranged compound. Its most probable structure is **9**.



A **B** **C** **9**

Properties of **9**: IR ν_{max} (film) 1715 (s, C=O), 1360 (s), 995 (m), 740 (m) cm^{-1}; ^1H NMR (270MHz, $CDCl_3$) 0.93(1.5 H, d, *J* = 6.9 Hz), 0.94 (1.5H, *J* = 6.3 Hz), 0.96 (3H, t, *J* = 7.3 Hz), 1.24 (1.5H, s), 1.34 (1.5H, s), 1.30-1.65 (3H, m), 2.00 (0.5H, dd, *J* = 7.6, 12.9 Hz), 2.16 (0.5H, dd, *J* = 7.6, 12.8 Hz), 2.20 (1.5H, s), 2.21 (1.5H, s), 2.27 (0.5H, m), 2.41(0.5H, m), 2.53(0.5H, d, *J* = 14.2 Hz), 2.63 (0.5H, d, *J* = 14.5 Hz), 2.70 (0.5 H, d, *J* = 14.2 Hz), 2.77 (0.5H, d, *J* = 14.5 Hz), 3.73-3.87 (1H, m); ^{13}C NMR (22.4 MHz, $CDCl_3$) δ

10.9, 14.6, 14.7, 23.8, 23.9, 26.7, 28.8, 31.8, 35.4, 36.0, 45.2, 45.7, 54.6, 56.4, 79.6, 79.8, 82.0, 82.6, 207.6, 208.1 (diastereomeric mixture); GC-MS (70 eV) i) The isomer with a shorter Rt :*m/z* 43 (100), 55 (10), 69 (10), 83 (8), 95 (12), 97 (9), 111 (12), 155 (9), 169 (1), 184 (M^+, < 0.05), ii) The isomer with a longer Rt :*m/z* 43 (100), 55 (9), 69 (11), 83 (6), 95 (7), 97 (9), 111 (7), 127 (8), 169 (0.2), 184 (M^+, 0.3).

6. GC conditions; preparative—PREPGC-TH (special GC) equipped with a PEG-20M, 10% on Uniport-HP (80-100 mesh), 100°C (constant). analysis—GC-14A equipped with a PEG-20M(0.25 mm i.d. x 60 m), 120°C (constant). chiral analysis—GC-14A equiped with a DMPBCD-TH {heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin}, 0.25 mm i.d. x 50 m, 70°C to 140°C (1.0°C/min).

7. Properties of (±)-**1**: $n_D^{21.4}$ 1.4468; IR ν_{max} (film) 2980 (s), 2940 (s), 2885 (s), 1455 (m), 1377 (s), 1200 (s), 1135 (s), 1005 (s), 945 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.5 Hz, 9-H), 0.98 (3H, d, *J* = 7.0 Hz, 12-H), 1.16 (3H, d, *J* = 6.1 Hz, 10-H), 1.18 (1H, ddd, *J* = 4.6, 12.7, 1.0 Hz, 6_{exo}-H), 1.30 (3H, s, 11-H), 1.34 (1H, dd, *J* = 6.1, 13.0 Hz, 4-Heq), 1.35 (1H, br dd, *J* = 8.9, 13.0 Hz, 4-Hax), 1.62 (1H, dq, *J* = 14.0, 7.5 Hz, 8-H), 1.71 (1H, dq, *J* = 14.0, 7.5 Hz, 8-H), 2.15 (1H, dd, *J* = 8.9, 12.7 Hz, 6_{endo}-H), 2.33 (1H, ddq, *J* = 8.9, 4.6, 7.0 Hz, 7-H), 3.95 (1H, ddq, *J* = 6.1, 8.9, 6.1 Hz, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.98 (C-9), 19.87 (C-12), 21.91 (C-10), 26.53 (C-11), 27.41 (C-8), 40.01 (C-7), 44.12 (C-4), 44.87 (C-6), 64.51 (C-3), 78.74 (C-5), 108.59 (C-1); GCMS (70 eV) *m/z* : 41 (24), 43 (78), 57 (100), 67 (13), 69 (9), 71 (8), 83 (17), 85 (11), 95 (78), 100 (5), 113 (16), 125 (2), 142 (9), 151 (1), 169(1), 184 (M^+, 0.5); HRMS: Calc. for $C_{11}H_{20}O_2$ = 184.1464, Found 184.1447; bp 100-105°C(bath temp.)/110 Torr for the mixture of (±)-**1** and (±)-**10**. When the pure (±)-**1** was treated with *p*-toluenesulfonic acid in dichloromethane, an equilibration mixture of (±)-**1** and (±)-**10** (48 : 52) was obtained.

   The assignment of underlined signals is different from that reported.[2] We confirmed this assignment by the NMR experiments (^1H-^1H cosy, ^1H-^1H noesy, ^1H-^{13}C cosy and HMBC).

8. Properties of (±)-**10**: $n_D^{21.4}$ 1.4446: IR ν_{max} (film) 2980 (s), 2940 (s), 2885 (s), 1455 (m), 1377 (s), 1200 (s), 1135 (s), 1005 (s), 945 (s) cm^{-1}: ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.5 Hz, 9-H), 1.08 (3H, d, *J* = 7.5 Hz, 12-H), 1.18 (3H, s, *J* = 6.1 Hz, 10-H), 1.32 (3H, s, 11-H), 1.39 (1H, dd, *J* = 4.5, 13.0 Hz, 4-H*eq*), 1.44 (3H, br dd, *J* = 10.5, 13.0 Hz, 4-H*ax*), 1.48 (1H, dd, *J* = 6.5, 12.5 Hz, 6_{endo}-H), 1.56 (1H, dq, *J* = 14.5, 7.5 Hz, 8-H), 1.72 (1H, dq, *J* = 14.5, 7.5 Hz, 8-H), 1.99 (1H, ddd, *J* = 1.5, 12.5, 12.5 Hz, 6_{exo}-H), 2.25 (1H, ddq, *J* = 6.5, 12.5, 7.5 Hz, 7-H), 4.08 (1H, ddq, *J* = 4.5, 10.5, 6.1 Hz, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.87 (C-9), 12.72 (C-12), 22.20 (C-10), 26.45 (C-11), 29.04 (C-8), 40.57 (C-7), 42.38 (C-4), 44.54 (C-6), 65.57 (C-3), 78.68 (C-5), 107.55 (C-1); GCMS (70 eV) *m/z* : 41 (24), 43 (78), 57 (100), 67 (13), 69 (9), 71 (8), 83 (17), 85 (11), 95 (78), 100 (5), 113 (16), 125 (2), 142 (9), 151 (0), 169 (1), 184 (M^+, 0.5); HRMS: Calc. for $C_{11}H_{20}O_2$ = 184.1464, Found 184.1453.

9. Ditails of the bioassay of (±)-**1** will be published separately by Prof. K. Jaffe in *J. Chem. Ecol.*

10. Properties of the optically active products: (1) (+)-**1**—$n_D^{21.6}$ 1.4471; $[\alpha]_D^{21}$ +26° (c = 0.48, Et_2O), (2) (-)-**1**—$n_D^{22.3}$ 1.4457; $[\alpha]_D^{21}$ -26° (c = 0.59, Et_2O), (3) (+)-**10**—$n_D^{22.3}$ 1.4449; $[\alpha]_D^{21}$ +7.9° (c = 0.67, Et_2O), (4) (-)-**10**—$n_D^{21.6}$ 1.4443; $[\alpha]_D^{21}$ -7.8° (c = 0.48, Et_2O).

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