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Synthesis of (±)-7-episordidin

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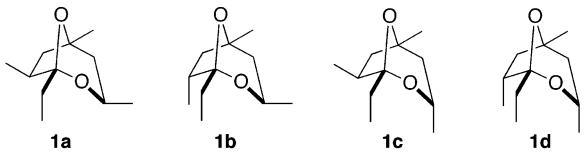
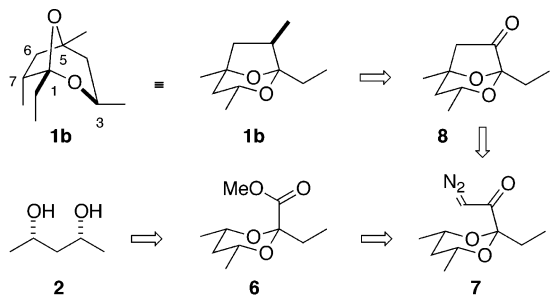
Abstract—The stereoselective synthesis of (±)-7-episordidin, an aggregation pheromone from the male banana weevil, *Cosmopolites sordidus* Germar, is reported. The key step of this work is a regioselective rhodium(II)-catalyzed diazocarbonyl C–H insertion reaction that simultaneously generates three of the natural product's four stereocenters. The work reported herein also represents a formal synthesis of sordidin.

The exploitation of symmetry as a means to simplify the synthesis of natural products has found considerable success.[1] In this regard, we recently reported an approach to the bicyclic acetal core of the zaragozic acids which hinged upon the desymmetrization of a 2-diazoacetyl-1,3-dioxane precursor through dirhodium(II)–carbenoid mediated C–H insertion.[2] Herein we report the extension of this strategy to the synthesis of the insect pheromones (±)-sordidin (**1a**) and (±)-7-episordidin (**1b**).



The banana weevil, *Cosmopolites sordidus* Germar, is a widespread and highly destructive pest of banana trees.[3] The impact on crop production is particularly acute since current methods for controlling this insect are hampered by its longevity, propensity to reproduce, and resistance to most classes of insecticides. In 1993, Budenberg first reported evidence that the male of this species releases a volatile aggregation pheromone.[4] The major component of this mixture, 1-ethyl-3,5,7-trimethyl-2,8-dioxabicyclo[3.2.1]octane (**1a**), was subsequently isolated, identified, and synthesized by Ducrot and co-workers who gave it the trivial name sordidin.[5a] More recently, Kitching has shown that, in addition to **1a**, 7-episordidin (**1b**) is also released by *C. sordidus* from Australia,[5d] while Oehlschlager reported that all four isomers of sordidin (**1a–d**) are produced by weevils collected in Kenya.[5d] Field trials in Costa Rica[3] have shown that traps baited with mixtures of **1** have a high capture rate and offer a viable method for controlling the population of this pest. Since the natural abundance of these pheromones is very low (1500 weevils yield ca. 100 μg),[5a] synthesis provides the only practical method for securing quantities of **1**. All reported syntheses of the sordidin family involve formation of the acetal moiety through acid-catalyzed cyclization of the corresponding acyclic keto-1,3-diols.[5] Under these conditions, however, the C-7 stereocenter readily epimerizes and mixtures of diastereomers are obtained. To date, no stereoselective syntheses of **1** have been reported.

As outlined in Scheme 1, we envisioned **1b** arising from ketone **8** which could, in turn, be accessed through the metal-catalyzed intramolecular C–H insertion of symmetric diazoketone **7**. This strategy would enable us to generate three of the four stereocenters centers present in the target molecule in a single transformation. With regards to the regioselectivity of this process, we expected insertion into the axial C–4/6 C–H bonds of **7**



Scheme 1.

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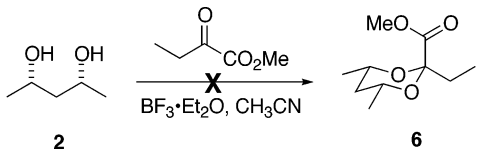
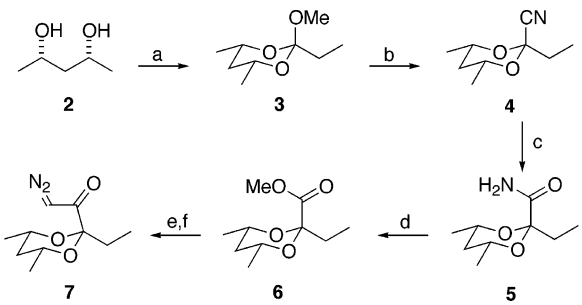
to be highly favored since these bonds are activated by the adjoining ether oxygens.[6] While our initial synthetic efforts focused on the preparation of **6** through acetalization of methyl 2-oxopropylbutyrate and *cis*-2,4-pentanediol (**2**),[7] all attempts to achieve this goal using a variety of conditions led to the decomposition of **2**.[8]



2 **6**

Accordingly, we opted to follow a stepwise approach to **6** (Scheme 2).[2] Thus, **2** was treated with trimethyl orthopropionate in the presence of a catalytic amount of *p*-TsOH to generate the *ortho* ester **3**, which was immediately treated in situ with trimethylsilyl cyanide and $BF_3{\cdot}Et_2O$. Upon stirring at room temperature for 16 h, cyanation proceeded with retention of configuration to furnish 2-cyano-1,3-dioxane **4** as a single diastereomer.[9] Hydrolysis of this nitrile with alkaline hydrogen peroxide then gave **5** in excellent overall yield from **2**. The relative configuration of **5** was confirmed by a NOESY experiment, which revealed correlations between the axial protons at C–4 and C–6 and the amide protons.

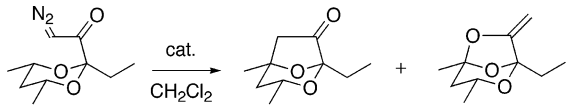
Although the prospect of now converting **5** to the corresponding methyl ester **6** was somewhat daunting, Brocchetta and co-workers recently described the use of dimethylformamide dimethyl acetal (DMF–DMA) as a mild reagent for this traditionally difficult transformation.[10] Gratifyingly, upon heating **5** and DMF–DMA in anhydrous methanol at 110°C in a sealed tube for 48 h, ester **6** was formed in 97% yield. Diazoketone **7** was prepared in 94% overall yield by a sequence of saponification, mixed-anhydride formation and in-situ treatment with diazomethane. We now proceeded to evaluate a range of catalysts for the cyclization of **7**; the results of this study are summarized in Table 1. In all cases diazo decomposition of **7** led to the formation of **8**, the product of transannular C–H insertion, as well as bicyclic enol ether **9**. The formation of this type of



2 **3** **4** **5** **6** **7**

Scheme 2. *Reagents and conditions*: (a) $CH_3CH_2C(OCH_3)_3$, *p*-TsOH (2 mol%), CH_2Cl_2, rt, 16 h; (b) Me_3SiCN, $BF_3{\cdot}Et_2O$ (10 mol%), CH_2Cl, rt, 16 h, 99%; (c) NaOH, H_2O_2, EtOH, reflux, 3 h, 91%; (d) DMF–DMA (3 equiv.), MeOH, 110°C (sealed tube), 48 h, 97%; (e) NaOH, H_2O, THF, reflux, 16 h, 98%; (f) (i) Et_3N, *i*-BuOCOCl, CH_2Cl_2, –20°C, 5 min. (ii) CH_2N_2, Et_2O, –20°C to rt, 16 h, 96%.

Table 1. Intramolecular C–H Insertion of diazoketone **7**[a]



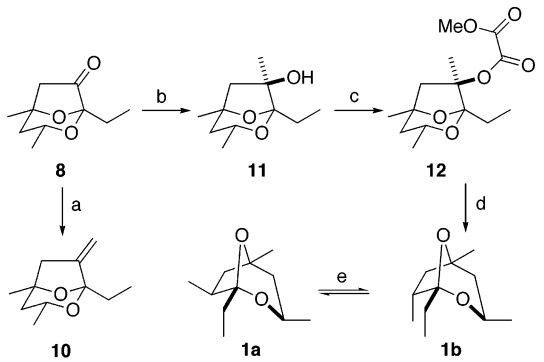
7 **8** **9**

Entry	Catalyst[b]	Isolated yield (%)[c,d]		ee (%)[e,f]	
		8	**9**	**8**	**9**
1	$Rh_2(OAc)_4$[g]	58	28	–	–
2	$Rh_2(PTPA)_4$[11a,b]	36	10	20	10
3	$Rh_2(DOSP)_4$[11c]	31	0	7	–
4	$Rh_2(TBSP)_4$[11c]	17	5	<5	<5
5	$Rh_2(MEPY)_4$[11d]	11	8	<5	7
6	$Cu(acac)_2$[h]	15	30	–	–
7	$Cu(tfacac)_2$[h]	19	20	–	–
8	$Cu(hfacac)_2$[h]	7	17	–	–

[a] Unless otherwise noted, reactions were carried as follows: a solution of **7** (50 mg, 0.24 mmol) in CH_2Cl_2 was added via syringe pump to a solution of catalyst (2 mol%) in CH_2Cl_2 (0.015 M) at reflux, over 20 h.
[b] $Rh_2(PTPA)_4$ was prepared according to the method of Taber (see Ref. 11b). The other catalysts are available commercially.
[c] Yields after purification by flash chromatography.
[d] The mass balance was due to polar, intractable material.
[e] Enantiomeric excesses were determined by capillary GC analysis prior to purification using a J&W cyclodex-B column.
[f] Absolute configuration was not determined.
[g] Reaction carried out on 8.5 mmol scale.
[h] 4 mol% catalyst used.

anomalous product has recently been reported by a number of groups[2,12] and is believed to arise from intramolecular hydride transfer to the initially formed metallocarbenoid followed by cyclization of the resulting zwitterionic species. As expected, products arising from insertion into the C–H bonds of the ethyl chain were not observed under any conditions. It is clear from Table 1 that $Rh_2(OAc)_4$ (entry 1) was the most efficient catalyst for effecting cyclization while chiral dirhodium(II) tetracarboxylates (entries 2–4) and tetracarboxyamides (entry 5) failed to provide improvement in efficiency or useful levels of asymmetric induction. Copper salts[6e] (entries 6–8) were also investigated but gave only modest yields of C–H insertion. The more electrophilic copper carbenoids appear to favor the formation of **9** through the hydride abstraction pathway.

Continuing with our synthesis of (±)-**1b**, we now attempted to install the remaining stereocenter at C–7 through a sequence of olefination and reduction. However, **10**, the α,β-unsaturated acetal generated upon methylenation of **8**, proved to be highly unstable and we were unable to isolate this material.[13] Fortunately, addition of methylmagnesium iodide to **8** proceeded very efficiently to provide **11** as a single diastereomer (Scheme 3). After considerable investigation, we found that this tertiary alcohol could be most effectively deoxygenated to generate **1b** using the method of Dolan and Macmillan.[14] Thus, sequential treatment of **11** with



Scheme 3. *Reagents and conditions*: (a) $Ph_3P{=}CH_2$, THF, rt, 16 h; (b) MeMgI, Et_2O, 0°C, 3 h, 98%; (c) *n*-BuLi, THF, −78°C, 5 min; (ii) $ClCOCO_2Me$, −78 to 0°C, 2 h, 78%; (d) Bu_3SnH (1.5 equiv.), AIBN (1.5 equiv.), PhH, reflux, 16 h, 50%; (e) *p*-TsOH, CH_2Cl_2 (Ref. 5e).

n-BuLi and methyl oxalyl chloride gave **12** which, after purification, was heated with Bu_3SnH and AIBN in benzene for 16 h. The reaction mixture was then concentrated by distillation (1 atm) and the residue purified by radial chromatography (pentane/Et_2O, SiO_2) to provide (±)-7-episordidin (**1b**) as the sole reduction product.[15] The moderate yield of this final transformation is primarily a reflection of the volatility of **1b** which leads to significant losses during isolation. A comparison of the spectral and physical properties of our material (MS, IR and ^1H and ^{13}C NMR) with those reported by Mori[5e] indicated a close match.

In summary, we report the first stereoselective synthesis of 7-episordidin (**1b**), which is accomplished in nine steps starting from *cis*-2,4-pentanediol (**2**), with an overall yield of 18%. Since the conversion of (±)-7-episordidin (**1b**) to sordidin (**1a**) has previously been described by Mori,[5e] the work reported here also represents a formal synthesis of sordidin (**1a**).

Acknowledgements

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15. 7-Episordidin (**1b**): IR ν_{max} (film) 2961, 2931, 2887, 1475, 1375, 1195, 1163, 1094, 992 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.10–4.05 (m, 1 H), 2.25–2.22 (m, 1 H), 1.99 (t, $J=12.5$ Hz, 1 H), 1.75–1.62 (m, 1 H), 1.57–1.49 (m, 1 H), 1.49–1.41 (m, 2 H), 1.40–1.37 (m, 1 H), 1.32 (s, 3 H), 1.79 (d, $J=7.2$ Hz, 3 H), 1.18 (d, $J=6.1$ Hz, 3 H), 0.93 (t, $J=7.5$ Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.6, 78.7, 65.6, 44.6, 42.4, 40.6, 29.1, 26.5, 22.2, 12.7, 7.9; GCMS (EI, 70 eV) *m*/*z* 51, 57, 67, 83, 95, 100, 113, 142, 169 184. High resolution mass spectrum (CI) *m*/*z* 185.1545 [$(M+H)^+$; calcd for $C_{11}H_{21}O_2$ 185.1542].