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Bidirectional, Organocatalytic Synthesis of Lepidopteran Sex Pheromones

Renata Marcia de Figueiredo, Raphael Berner, Jennifer Julis, Ting Liu, David Türp, and Mathias Christmann*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, D-52074 Aachen, Germany

christmann@oc.rwth-aachen.de

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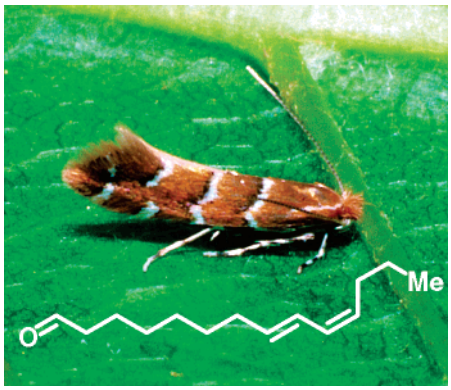

Shuffling of two simple building blocks and a regioselective transfer hydrogenation allow for the rapid synthesis of a small collection of lepidopteran sex pheromones, e.g., 8*E*,10*Z*-tetradeca-8,10-dienal **5c**, from the horse chestnut leafminer (*Cameraria ohridella*).

The information transfer among individuals of the same species can be mediated by small organic molecules commonly referred to as pheromones.[1] Lepidopteran sex pheromones are rather simple straight-chain hydrocarbons terminated by hydroxyl, aldehyde, or acetate groups. The hydrocarbon chain is often garnished with varying degrees of unsaturation with the *E*,*Z*-diene moiety being a frequent motif. Its most prominent member "bombykol" was isolated in 1959 after a 20-year effort by Butenandt et al. from the abdominal glands of over 500 000 female silkworm moths (*Bombyx mori*).[2] In the past decade, the horse chestnut leafminer *Cameraria ohridella*[3] has spread from Macedonia over Europe and infested the majority of the local horse chestnut trees (*Aesculus hippocastanum*). The identification of its sex pheromone 8*E*,10*Z*-tetradeca-8,10-dienal (**5c**) was hampered by the extremely low amounts (<10 pg) of the active principle, insufficient for mass spectroscopic identification. Using gas chromatography coupled with electroantennographic detection (GC-EAG), Svatoš et al. identified **5c** on the basis of a combination of polarity indices and synthesis.[4]

In this communication, we report a divergent approach to **5c** and other members of this class of lepidopteran pheromones, which takes advantage of the recently discovered organocatalytic transfer hydrogenation of enals.[5] Although the development of new chemoselective catalytic reactions usually evolves novel synthetic strategies for the synthesis of natural products, pheromones[6] are often neglected and their syntheses still involve many steps.

We chose α,β-unsaturated dialdehydes as readily available starting materials. Nicolaou et al. synthesized **3b** from 1,10-decanediol which was successively oxidized and dehydrogenated with IBX,[7] and Blechert used cycloalkenes, which were subjected to a ring-opening/cross-metathesis sequence.[8] For our purposes, a double Wittig reaction of the dialdehydes **1a**−**e**[9] with commercially available phosphonium salt **2** gave the α,β-unsaturated dienedials **3a**−**e**[10] in good to excellent yields. It should be noted that the isomerization to thermodynamically more stable *E*-enals occurs upon acidic hydrolysis of the α,β-unsaturated acetals. The results are summarized in Table 1.

A second Wittig reaction with 0.8 equiv of the required alkylphosphonium salt afforded the desired trienals in good selectivity (*Z*/*E* > 9:1) albeit in low yield. It has been described that Wittig reactions with α,β-unsaturated aldehydes are somewhat problematic[11] which is attributed to the basicity of the ylide. The trienals **4a**−**f** obtained by this procedure were subjected to a conjugate reduction protocol developed by List

(1) (a) Francke, W.; Schulz, S. *Comprehensive Natural Products Chemistry*; Mori, K., Ed.; Elsevier: Amsterdam, Netherlands, 1999; Vol. 8, pp 197−261. (b) Mori, K. *Top. Curr. Chem.* **2004**, *239*, 1−50.

(2) Butenandt, A.; Beckmann, R.; Stamm, D.; Hecker, E. *Z. Naturforsch.* **1959**, *14b*, 283−284.

(3) Deschka, G.; Dimić, N. *Acta Ent. Jugosl.* **1986**, *22*, 11−23.

(4) (a) Svatoš, A.; Kalinová, B.; Hoskovec, M.; Kindl, J.; Hovorka, O.; Hrdý, I. *Tetrahedron Lett.* **1999**, *40*, 7011−7014. (b) Francke, W.; Franke, S.; Bergmann, J.; Tolasch, T.; Subchev, M.; Mircheva, A.; Toshova, T.; Svatoš, A.; Kalinová, B.; Karpati, Z.; Szocs, G.; Toth, M. *Z. Naturforsch.* **2002**, *57c*, 739−752.

(5) (a) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660−6662. For asymmetric versions of this reduction, see: (b) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108−110. (c) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32−33.

(6) For elegant examples involving catalytic reactions, see: (a) Burke, S. D.; Müller, N.; Beaudry, C. M. *Org. Lett.* **1999**, *1*, 1827−1829. (b) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573−575. (c) van Summeren, R. P.; Reijmer, S. J. W.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2005**, 1387−1389. (d) Sun, B.; Peng, L.; Chen, X.; Li, Y.; Lia, Y.; Yamasaki, K. *Tetrahedron: Asymmetry* **2005**, *16*, 1305−1307. (e) Ikishima, H.; Sekiguchi, Y.; Ichikawa, Y.; Kotsuki, H. *Tetrahedron* **2006**, *62*, 311−316. (f) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193−4195.

(7) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245−2258.

(8) Randl, S.; Connon, S. J.; Blechert, S. *Chem. Commun.* **2001**, 1796−1797.

(9) Anhydrous glutaraldehyde **1a** ($n = 1$) was prepared from its 50% aqueous solution: (a) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061−1070. **1b** and **1d** ($n = 2, 4$) were obtained by periodate cleavage of the corresponding cyclo-1,2-diols: Lopez, S.; Fernandez-Trillo, F.; Midon, P.; Castedo, L.; Saa, C. *J. Org. Chem.* **2005**, *70*, 6346−6352. **1c** and **1e** were obtained from IBX oxidation of the corresponding diols: (b) Lafont, D.; Chevalier, Y.; Grumel, V.; Cassel, S.; Rollin, P. *Synth. Commun.* **2002**, *32*, 2919−2930.

(10) We have stored this material in the freezer over several weeks without any detectable decomposition. (a) Iriye, R.; Toya, T.; Makino, J.; Aruga, R.; Doi, Y.; Handa, S.; Tanaka, H. *Agric. Biol. Chem.* **1988**, *52*, 989−996.

(11) (a) Xiong, H.; Huang, J.; Ghosh, S. K.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694−12695. (b) Duffy, P. E.; Quinn, S. M.; Roche, H. M.; Evans, P. *Tetrahedron* **2006**, *62*, 4838−4843. (c) Lu, K.; Huang, M.; Xiang, Z.; Liu, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2006**, *8*, 1193−1196.

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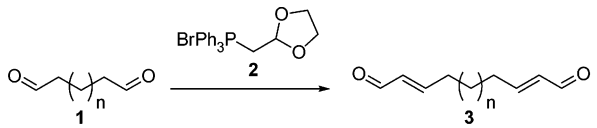
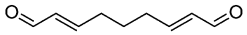
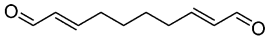
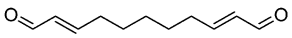
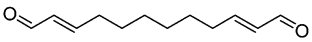
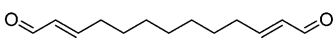
TABLE 1. Double Wittig Reaction of Dialdehydes[a]

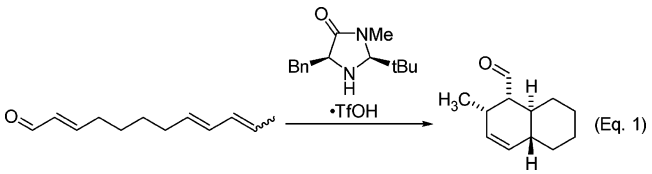


entry	dienedialdehyde **3**		yield
1		**3a** (n=1)	87%
2		**3b** (n=2)	76%
3		**3c** (n=3)	86%
4		**3d** (n=4)	91%
5		**3e** (n=5)	81%

[a] Reaction conditions: **2** (2.3 equiv), KO^{t}Bu (2.3 equiv), THF, 0 °C, 6 h, then 10% aq oxalic acid, room temperature, 12 h.

and co-workers.[5a] Some representative pheromones **5**[12] that were accessible by our strategy are summarized in Table 2.

The selectivity for the desired *nE*,(*n* + 2)*Z*-alkanals was always greater than 9:1 as indicated by NMR spectroscopy. Interestingly, the intermediacy of an α,*β*-unsaturated iminium ion during the reduction step opens a Diels−Alder pathway for the minor *E*,*E*,*E*-diene isomer, which could be used for a kinetic enrichment of desired *E*,*Z*-diene. Because the *E*,*Z*-diene moiety does not adopt an *s-cis* conformation, it is inert, whereas the minor *E*,*E*,*E*-isomer can participate in an intramolecular Diels−Alder reaction as shown by MacMillan and co-workers (eq 1).[13]

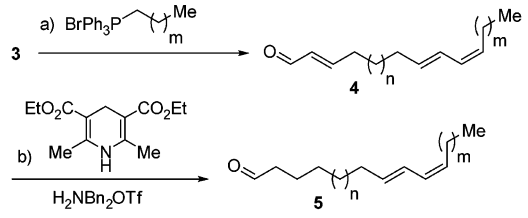


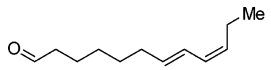
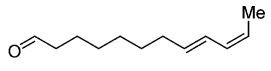
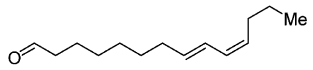
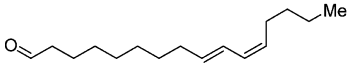
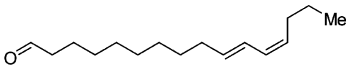
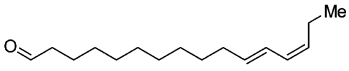
(Eq. 1)

Alternatively, several groups have used tetracyano ethylene as a dienophile[4b] or urea inclusion complexes to remove minor *E*,*E*-diene impurities.[14]

Elaboration of the aldehyde functionality into alcohol and acetate groups may give rise to other lepidopteran pheromones as exemplified for the synthesis of bombykol and two other pheromones (Scheme 1). The aldehydes **5a** and **5e** were reduced to **6a** (*Lobesia botrana*)[15] and bombykol **6e**[16] using $NaBH_4$ in methanol. Subsequently, **6a** was acetylated with acetic anhydride in pyridine to yield **7a**[17] (*Matsumuraeses falcana*) in 95% yield.[16]

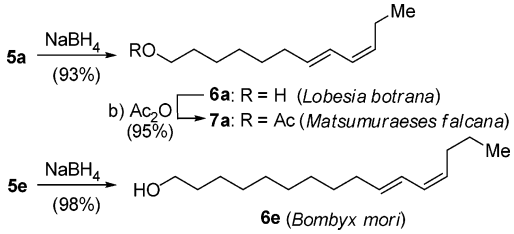
TABLE 2. Wittig Olefination/Conjugate Reduction[a]



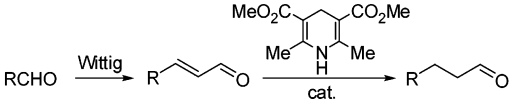
entry	**5**		yield[b]
1	 (*Idaea biselata*)	**5a**	**74%** (45%)
2	 (*Acria ceramitis*)	**5b**	**82%** (41%)
3	 (*Cameraria ohridella*)	**5c**	**81%** (46%)
4	 (*Acrobasis nuxvorella*)	**5d**	**78%** (39%)
5	 (*Coloradia Pandora*)	**5e**	**84%** (41%)
6	 (*Notodonta dromedarius*)	**5f**	**73%** (37%)

[a] Reaction conditions: (a) phosphonium salt (0.8 equiv), NaHMDS (0.8 equiv), THF, −10 °C, then **3** (1 equiv). (b) $HNBn_2$·TFA (0.2 equiv), Hantzsch ester (4 equiv), THF, 25 °C. [b] Yields for the conjugate reduction (**4**→**5**); the yield in parentheses refers to the Wittig reaction (**3**→**4**).

SCHEME 1. Functionalization of the Terminus



Wittig/transfer hydrogenation sequence



(Eq. 2)

We have described a novel strategy for the synthesis of an important class of lepidopteran sex pheromones starting from simple dialdehydes. The two-step combination of a Wittig reaction and an organocatalytic reduction (eq 2) comprises a

(12) **5a**: (a) Ando, T.; Koike, M.; Uchiyama, M.; Kuroko, H. *Agric. Biol. Chem.* **1987**, *51*, 2691−2694. **5b**: (b) Ando, T.; Katagiri, Y.; Uchiyama, M. *Agric. Biol. Chem.* **1985**, *49*, 413−422. **5c**: ref 4. **5d**: (c) Santangelo, E. M.; Coracini, M.; Witzgall, P.; Correa, A. G.; Unelius, C. R. *J. Nat. Prod.* **2002**, *65*, 909−915. (d) Passaro, L. C.; Webster, F. X. *Synthesis* **2003**, 1187−1190. **5e**: (e) Cabezas, J. A.; Oehlschlager, A. C. *Synthesis* **1999**, 107−111. **5f**: (f) Michelot, D. *Synthesis* **1983**, 130−134.

(13) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616−11617.

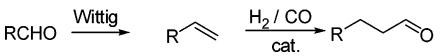
(14) Mozuraitis, R.; Buda, V.; Liblikas, I.; Unelius, C. R.; Borg-Karlson, A.-K. *J. Chem. Ecol.* **2002**, *28*, 1191−1208.

(15) El-Sayed, A. M.; Gödde, J.; Witzgall, P.; Arn, H. *J. Chem. Ecol.* **1999**, *25*, 389−400.

(16) (a) Alexakis, A.; Jachiet, D. *Tetrahedron* **1989**, *45*, 381−389. (b) Uenishi, J.; Kawahama, R.; Izaki, Y.; Yonemitsu, O. *Tetrahedron* **2000**, *56*, 3493−3500.

very useful sequence for the nontrivial two-carbon homologation of aldehydes. Because of the iminium-type activation, other double bonds remain unaffected. This offers some advantages over the alternative methylenation/hydroformylation approach (eq 3),[18] where regioselectivity issues (linear vs branched) arise.[19]

Wittig/hydroformylation sequence



(Eq. 3)

The pheromone products were accessed in three synthetic steps by two consecutive Wittig reactions and a conjugate reduction which could be rendered diastereoselective upon slight modification of the reduction protocol. Diversity was introduced by the chain lengths of the starting dialdehydes and the alkyl chain of the phosphonium salts as well as by functionalization of the termini.

Experimental Section

Synthesis of the α,β-Dialdehydes 3 from the Corresponding Dialdehydes 1. To a cooled (0 °C) and magnetically stirred suspension of phosphonium salt **2** (53.1 mmol, 22.8 g) in THF (200 mL) was added KO^{t}Bu (51.6 mmol, 5.78 g) upon which the suspension turned deep yellow. After 30 min, a solution of the aldehyde **1** (20 mmol) in THF (50 mL) was added over 20 min. The now light yellow solution was stirred for 6 h at ambient temperature and then hydrolyzed by addition of aqueous oxalic acid (42 g in 400 mL of H_2O). After stirring for another 8 h, the mixture was extracted with Et_2O (4 × 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to 1/3 of the initial volume. The concentrate was filtered through silica gel and concentrated in vacuo. Flash chromatography of the residue on silica gel afforded the known title compounds, which were used directly or stored in benzene at −20 °C.

Synthesis of the Trienals 4 from the Corresponding α,β-Unsaturated Dialdehydes 3. To a cooled (−10 °C) and magnetically stirred suspension of the required alkylphosphonium salt (0.8 mmol) in THF (14 mL) was added NaHMDS (0.8 mmol, 0.8 mL, solution 1 N in THF) upon which the suspension turned deep yellow. After 30 min at this temperature, a solution of the α,β-unsaturated dialdehyde **3** (1 mmol) in THF (3.4 mL) was added in one portion. The resulting light yellow solution was stirred for 1 h at −10 °C. Workup was performed by quenching with ice water (14 mL) and extraction with Et_2O (4 × 28 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The concentrate was purified by flash chromatography on silica gel (pentane/diethyl ether 10:1) to afford the required trienals, which were used directly or stored in benzene at −20 °C. **4c:** Colorless oil; R_f 0.31 (diethyl ether/pentane 1:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (d, J = 8.0 Hz, 1H), 6.84 (dt, J = 15.4, 6.9 Hz, 1H), 6.31 (ddq, J = 15.1, 11.0, 1.4 Hz, 1H), 6.12 (ddt, J = 15.7, 8.0, 1.6 Hz, 1H), 5.95 (t, J = 11.0 Hz, 1H), 5.62 (dt, J = 15.1, 6.9 Hz, 1H), 5.32 (dt, J = 10.7, 7.7 Hz, 1H), 2.34 (qd, J = 6.9, 1.4 Hz, 2H), 2.19−2.02 (m, 4H), 1.54−1.33 (m, 6H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 158.5, 133.5, 132.9, 130.2, 128.4, 126.1, 32.6, 32.5, 29.8, 28.9, 27.4, 22.9, 13.8; IR (capillary) 2929, 2860, 1692, 980 cm^{-1}; MS (EI) *m*/*z* (%) 206 (10, M^+), 177 (19), 124 (19), 123 (24), 107 (23), 95 (34), 91 (26), 79 (54), 67 (100). Anal. calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.79; H, 11.01.

Synthesis of the Pheromones 5 via Conjugate Reduction from the Corresponding Trienals 4. To a solution of the trienal (0.5 mmol) and dibenzylammonium trifluoroacetate (0.1 mmol) in anhydrous THF (7 mL) was added the Hantzsch ester (2.2 mmol) at room temperature. The yellow suspension was stirred at this temperature for 3 h. Column chromatography on silica gel without previous workup (pentane/ether 15:1) afforded the required pheromones.

Acknowledgment. We are grateful to the Fonds der Chemischen Industrie for a Liebig fellowship (M.C.), the Deutsche Forschungsgemeinschaft (Priority Program 1179 "Organocatalysis"), and Prof. Dieter Enders for his encouragement and support. We thank Dr. Csóka György for allowing us to use his picture of *Cameraria ohridella*.

Supporting Information Available: Additional procedures, characterization of new compounds, and copies of ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0620415

(17) Negishi, E.; Yoshida, T.; Abramovitch, A.; Lew, G.; Williams, R. M. *Tetrahedron* **1991**, *47*, 343−356.

(18) (a) Ojima, I.; Tsai, C.-Y.; Tzamarioudaki, M.; Bonafoux, D. *Org. React.* **2000**, *56*, 1. (b) Breit, B.; Seiche, W. *Synthesis* **2001**, 1.

(19) For an efficient access to the linear products, see: Petricci, E.; Mann, A.; Schoenfelder, A.; Rota, A.; Taddei, M. *Org. Lett.* **2006**, *8*, 3725−3727.