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Synthesis of Lurlene, the Sex Pheromone of the Green Flagellate *Chlamydomonas allensworthii*

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Abstract : Lurlene [(4*E*,8*E*,12*E*)-14-[2'-hydroxy-3',4'-dimethyl-5'-(1"- β -D-xylopyranosyloxy)phenyl]-4,8,12-trimethyltetradeca-4,8,12-trienoic acid, **1**], the sex pheromone produced by the female gametes of *Chlamydomonas allensworthii*, was synthesized as a mixture of **1** and its (12*Z*)-isomer, and the mixture was bioactive.

The green flagellate *Chlamydomonas eugametos* and its sexuality were extensively studied by Moewus[1] in 1930's to 1950's, whose work later turned out to be a scientific fraud.[2-4] One of the present authors (K. M.) became interested in this problem since 1951, when he read Kubota's review[5] on this subject. Very recently in 1995, the sex pheromone produced by the female gametes of *Chlamydomonas allensworthii* was isolated, named as lurlene, and identified as **1** (Fig. 1) by Starr, Jaenicke and Marner.[6,7] Lurlene (**1**) attracts the male gametes at a concentration as low as 10^{-12} M.[6] The structure **1** of lurlene suggests its biogenetic relationship with the ubiquitous benzoquinone, plastoquinone 4 (**2**). This letter reports the first synthesis of lurlene (**1**).

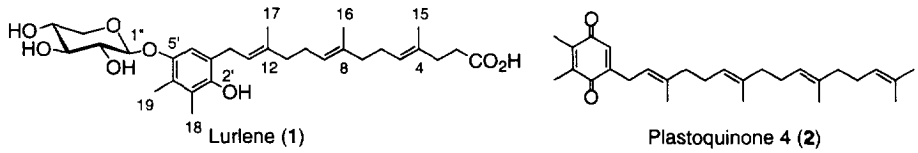

Figure 1. Structures of lurlene and plastoquinone 4

Fig. 2 summarizes the synthesis of **1**. The starting materials were commercially available geranylgeraniol (**3a**), 2,3-dimethyl-*p*-hydroquinone (**7**) and D-xylose. Acetylation of **3a** yielded **3b**, which was converted to the terminal epoxide **4** via the corresponding bromohydrin. Cleavage of **4** with periodic acid furnished the aldehyde **5**.[8] Oxidation of **5** followed by esterification of the resulting acid with diazomethane afforded the acetoxy ester **6**.[9] As to the preparation of the aromatic portion of **1**, **7** was brominated to give **8a**, which was treated with 1.2 eq. of dihydropyran in the presence of *p*-toluenesulfonic acid in THF to give **8b**.[10] The remaining hydroxy group of **8b** was then protected as β -(trimetylsilyl)ethoxymethyl(SEM) ether to give **9**. Treatment of **9** with *n*-butyllithium effected the metal exchange, and the resulting aryllithium was stannylated

with trimethyltin chloride to furnish **10**. The Hegedus-Stille palladium-catalyzed coupling reaction[11] of **6** with **10** in the presence of bis(dibenzylideneacetone)palladium(0) [$Pd(dba)_2$] and lithium chloride in DMF yielded **11a** in 98% yield. The product **11a** was later shown (at the stage of **12**) to be a mixture of the geometrical isomers at C-12.

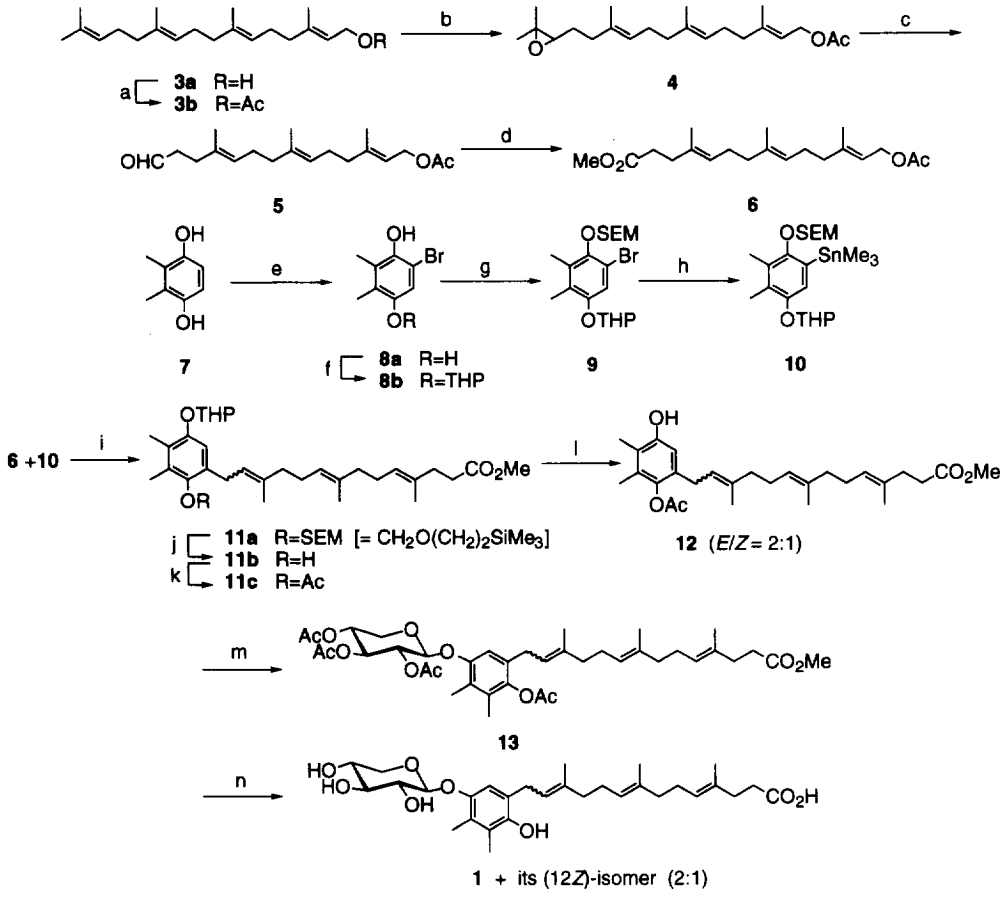

Figure 2. Synthesis of lurlene (**1**)

Reagents: (a) Ac_2O, C_5H_5N (96%). -(b) 1) 1.2 eq. NBS, aq. *t*-BuOH; 2) K_2CO_3, MeOH; 3) Ac_2O, C_5H_5N (52%). -(c) $HIO_4 \cdot 2H_2O$, Et_2O (78%). -(d) 1) Jones CrO_3, Me_2CO; 2) CH_2N_2, Et_2O, (86%). -(e) 1.2 eq. Br_2, THF (76%). -(f) 1.2 eq. DHP, TsOH, THF (72%). -(g) 1.5 eq. SEMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2 (92%). -(h) 1.5 eq. *n*-BuLi; 1.5 eq. Me_3SnCl, THF (73%). -(i) 0.05 eq. $Pd(dba)_2$, 3 eq. LiCl, DMF (98%). -(j) 9 eq. CsF, HMPA (60%). -(k) Ac_2O, C_5H_5N (89%). -(l) TsOH, MeOH (85%). -(m) 3 eq. 2,3,4-tri-*O*-acetyl- α -D-xylopyranosyl fluoride, 3 eq. 1,1,3,3-tetramethylguanidine, 8 eq. $BF_3 \cdot OEt_2$, MeCN. -(n) 1) NaOH, $MeOH/H_2O$; 2) $AcOH/H_2O$ (45% based on **12**).

Three-step-conversion of **11a** to **12** was necessary so as to enable the glycosidation of the phenolic hydroxy group at C-5'. Accordingly, **11a** was treated with cesium fluoride in HMPA[12] to give **11b**, which

was acetylated to afford **11c**. Removal of the THP protective group of **11c** with acidic methanol gave the desired aglycone **12** as a mixture of the geometrical isomers at C-12 (*E*/*Z* = 2:1) as revealed by the NMR analysis.[13] The mixture **12** was submitted to the glycosidation reaction, because the separation of the isomers was difficult. After a number of trials, we adopted Yamaguchi's glycosidation method[14] by employing 2,3,4-tri-*O*-acetyl- α -D-xylopyranosyl fluoride[15] as the glycosyl donor. Thus, boron trifluoride etherate was added to a mixture of **12**, the fluoro sugar and 1,1,3,3-tetramethylguanidine in acetonitrile to give **13**. Treatment of **13** with sodium hydroxide in aqueous methanol hydrolyzed the methyl ester and removed the acetyl protective groups to give a 2:1 mixture of lurlene (**1**) and its (12*Z*)-isomer. The overall yield of the mixture of lurlene (**1**) and its (12*Z*)-isomer was 6.7% based on **3a** (10 steps) or 7.4% based on **7** (8 steps).

Lurlene (**1**) could not be separated from its (12*Z*)-isomer, and therefore the physical and biological properties of the stereoisomeric mixture were examined in detail. The ^{1}H- and ^{13}C-NMR spectra of the synthetic **1** containing its (12*Z*)-isomer exhibited all of the signals observable in the authentic spectra of the naturally occurring lurlene kindly sent to us by Prof. Jaenicke.[16] Some additional signals were observed in the spectra of our synthetic material, indicating the presence of the (12*Z*)-isomer of **1**.[16] The mass spectrum of the synthetic sample exhibited the ion due to $M^{+}-H_2O$ ($C_{30}H_{42}O_7$).[16] The pheromone activity of the synthetic mixture of **1** and its (12*Z*)-isomer was assayed by Profs. Starr and Jaenicke against the sperms of *Ch. allensworthii*. The threshold concentration of the synthetic sample to show the attractancy was about 10^{-13} M. The activity of our synthetic material was therefore slightly stronger than that of the isolated lurlene (10^{-12} M). It thus seems that the geometry of the double bond at C-12 is not crucial and the wrong (12*Z*)-isomer does not inhibit the pheromone activity of **1**.

In conclusion, the structure **1** proposed for lurlene was confirmed by its synthesis. We are currently improving the coupling step (**6+10**) to avoid the isomerization of the double bond at C-12. Full details of this work as well as the synthesis of lurlene analogs will be reported in *Liebigs Annalen*.

Acknowledgment : We thank Prof. L. Jaenicke (Universität zu Köln), Prof. R. C. Starr (University of Texas at Austin) and Dr. F.-J. Marner (Universität zu Köln) for sending to us the copies of the ^{1}H- and ^{13}C-NMR spectra of lurlene and performing the bioassay. Our thanks are due to Kuraray Company and Takasago International Corporation for their gifts of geranylgeraniol.

References and Notes

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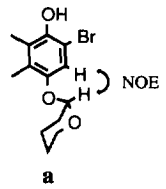
9. All the new compounds were characterized by spectroscopic (IR and NMR) and elemental (combustion or HRMS) analyses.
10. The structure **8b** was confirmed by the NOE experiment to reveal the proximity of the aromatic proton to the THP proton as depicted in **a**.



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13. Properties of **12** : colorless oil; IR (film) vmax. 3448 (m, OH), 1759 (s, CO), 1738 (s, CO), 1440 (m), 1368 (m), 1192 (s), 1079 (m), 1012 (w), 904 (w), 851 (w) cm^{-1}; ^{1}H-NMR (270 MHz, $CHCl_3$) δ = 1.60 (br. s, 6H, 15-H, 16-H), 1.64 (s, 1H, -OH), 1.66 (s, 2H, 17-H), 1.72 (s, 1H, 17-H), 1.90-2.20 (m, 8H, 6, 7, 10, 11-H), 2.04 (s, 3H, 18-H or 19-H), 2.13 (s, 3H, 18-H or 19-H), 2.31 (br. s, 5H, acetyl, 3-H), 2.41 [br. t, *J* (2,3) = 5 Hz, 2H, 2-H], 3.12 [d, *J* (13,14) = 7 Hz, 2H, 14-H], 3.67 (s, 3H, -OMe), 5.07-5.30 (m, 3H, 5, 9, 13-H), 6.50 (s, 1H, 6'-H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ = 11.9 (C-18 or C-19), 13.2 (C-18 or C-19), 15.9 (C-15), 16.0 (C-16), 16.1 (C-17), 20.6 ($\underline{C}H_3CO$), 23.4 (C-17), 26.27 (C-10), 26.38 (C-6), 26.43 (C-10), 28.6 (C-14), 31.9 (C-11), 33.1 (C-2), 34.7 (C-3), 39.5 (C-7), 39.7 (C-11), 51.6 ($O\underline{C}H_3$), 113.3 (C-6'), 113.4 (C-6'), 121.4 (C-4'), 121.5 (C-4'), 121.7 (C-13), 122.4 (C-13), 124.2 (C-9), 124.3 (C-9), 125.1 (C-5), 125.2 (C-5), 129.9 (C-1'), 130.0 (C-1'), 131.1 (C-3'), 133.17 (C-4), 133.22 (C-4), 134.8 (C-8), 135.0 (C-12), 136.6 (C-12), 141.0 (C-2'), 141.1 (C-2'), 151.4 (C-5'), 151.5 (C-5'), 169.7 (acetyl C=O), 174.3 (C-1).; HRMS : $C_{28}H_{40}O_5$ calcd. 456.2876, found 456.2883. This compound is a mixture of (12*E*)- and (12*Z*)-isomers (2:1). The underlined NMR signals are due to the minor (12*Z*)-isomer.
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16. Properties of the synthetic mixture of lurlene (**1**) and its (12*Z*)-isomer : waxy solid; $[\alpha]_D^{24}$ = -3.2 (c = 0.12, MeOH); *Rf* = 0.65 (*i*-BuOH/MeOH/H_2O = 8:1:1) <ref.[7] *Rf* = 0.65>; IR (film) vmax. 3390 (s, OH), 1713 (m, CO), 1556 (w), 1446 (m), 1239 (m), 1051 (s), 844 (w) cm^{-1}; ^{1}H-NMR (270 MHz, CD_3OD) δ = 1.59 (s, 6H, 15-H, 16-H), 1.71 (s, 2H, 17-H), 1.75 (s, 1H, 17H), 1.95-2.40 (m, 12H, 2, 3, 6, 7, 10, 11-H), 2.14 (s, 3H, 18-H or 19-H), 2.16 (s, 3H, 18-H or 19-H), 3.15-3.47 (m, 5H, 3", 2", 14, 5"ax.-H), 3.55 [ddd, *J* (4", 3") = 7, *J* (4", 5"ax.) = 11, *J* (4", 5"eq.) = 5 Hz, 1H, 4"-H], 3.87 [dd, *J* (5"eq., 4") = 5, *J* (5"eq., 5"ax.) = 11 Hz, 1H, 5"eq.-H], 4.59 [d, *J* (1", 2") = 7 Hz, 1H, 1"-H], 5.07-5.21 (m, 2H, 5, 9-H), 5.32 [br. t, *J* (13, 14) = 7 Hz, 1H, 13-H], 6.71 (s, 1H, 6'-H); ^{13}C-NMR (67.8 MHz, CD_3OD) δ = 12.7 (C-18 or C-19), 12.9 (C-18 or C-19), 16.1 (C-15), 16.15 (C-16), 16.21 (C-16), 16.3 (C-17), 23.8 (C-17), 27.6 (C-6), 27.7 (C-10), 29.5 (C-14), 32.9 (C-11), 34.6 (C-2), 36.0 (C-3), 40.7 (C-7), 40.9 (C-11), 66.9 (C-5"), 71.1 (C-4"), 75.0 (C-2"), 78.0 (C-3"), 105.1 (C-1"), 116.5 (C-6'), 124.0 (C-13), 124.5 (C-13), 125.5 (C-9), 126.0 (C-5), 126.2 (C-3'), 126.6 (C-4'), 127.7 (C-1'), 127.9 (C-1'), 134.8 (C-4), 136.0 (C-8), 136.1 (C-8), 137.2 (C-12), 137.4 (C-12), 148.9 (C-2'), 150.6 (C-5'), 177.6 (C-1). The underlined NMR signals are due to the minor (12*Z*)-isomer. The original assignments[7] of the ^{13}C-NMR signals due to C-6, C-7, C-10 and C-11 of **1** were in error.; MS (*m/z*) : 532 (M+, 1%), 514 (7%), 496 (2%), 450 (2%), 400 (41%), 189 (100%), 151 (67%), 81 (27%); HRMS : $C_{30}H_{42}O_7$ (M+-H_2O) calcd. 514.2930, found 514.2942.

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