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Synthesis of the *Janus integer* pheromone (4*R*,9*Z*)-9-octadecen-4-olide☆

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Abstract—The synthesis of (4*R*,9*Z*)-9-octadecen-4-olide **1**, the female sex pheromone of *Janus integer* is reported using a Zipper isomerization reaction as the key step.

(4*R*,9*Z*)-9-Octadecen-4-olide **1**, the female sex pheromone of the female currant stem girdler, *Janus integer*, an occasional pest of red currant in North America, was isolated by Cosse et al.[1] in 2001. Lactone **1** was isolated as a single enantiomer and its absolute configuration was proposed as *R* by a bioassay of synthetic samples.[2] Even though, **1** is in great demand in the USA for practical field test, there are not many reports[3] on its synthesis. As part of our continuing interest in the synthesis of bioactive natural lactones,[4] we herein report a synthesis of (4*R*,9*Z*)-9-octadecen-4-olide **1** (Fig. 1) from the known epoxide **2**,[5] wherein a zipper isomerization reaction was employed as the key step.

The 2,3-epoxychloride **2** was converted to alkylated chiral acetylenic alcohol **3** in 70% yield as reported in our earlier communications,[5] in one-pot, by subjecting it to base induced ring opening with Li metal in liquid NH_3 in THF followed by treatment with 1-bromobutane at −78 °C. Next, compound **3** was subjected to a zipper isomerization[6] by treatment with 1,3-diaminopropane and sodium amide at 60 °C for 6 h to afford the desired terminal alkyne **4**[7a] in 60% yield. The secondary hydroxyl group in **4** was protected as its MOM ether using 2.5 equiv of Hunig's base and 2 equiv of MOMCl in dry CH_2Cl_2 at rt. Alkylation of **5** with *n*-butyllithium and 1-bromooctane furnished **6** in 70% yield. THP deprotection of **6** using PPTS in MeOH afforded primary alcohol **7**[7b] which was oxidized to the corresponding acid by a two-step process, firstly to an aldehyde using iodoxybenzoic acid and then perchlorite oxidation using $NaClO_2/NaH_2PO_4{\cdot}2H_2O$ to the acid **8**. Cyclization of **8** was accomplished by reaction with PTSA in MeOH at rt for 12 h to give the cyclized compound **9** in 80% yield. Finally, partial hydrogenation of **9** over Lindlar's catalyst (Pd–$CaCO_3$/quinoline) in EtOAc at −5 to 0 °C under H_2 at atmospheric pressure provided the target lactone, (4*R*,9*Z*)-9-octadecen-4-olide **1**[7c] in 90% yield (Scheme 1).

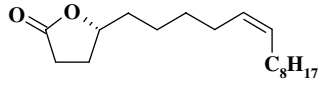

Figure 1. (4*R*,9*Z*)-9-Octadecen-4-olide **1**.

In conclusion, we have accomplished the synthesis of the female sex pheromone of *J. integer*, (4*R*,9*Z*)-9-octadecen-4-olide **1** in eight steps.

Keywords: Pheromone; *Janus integer*; Lactone; Zipper isomerization.
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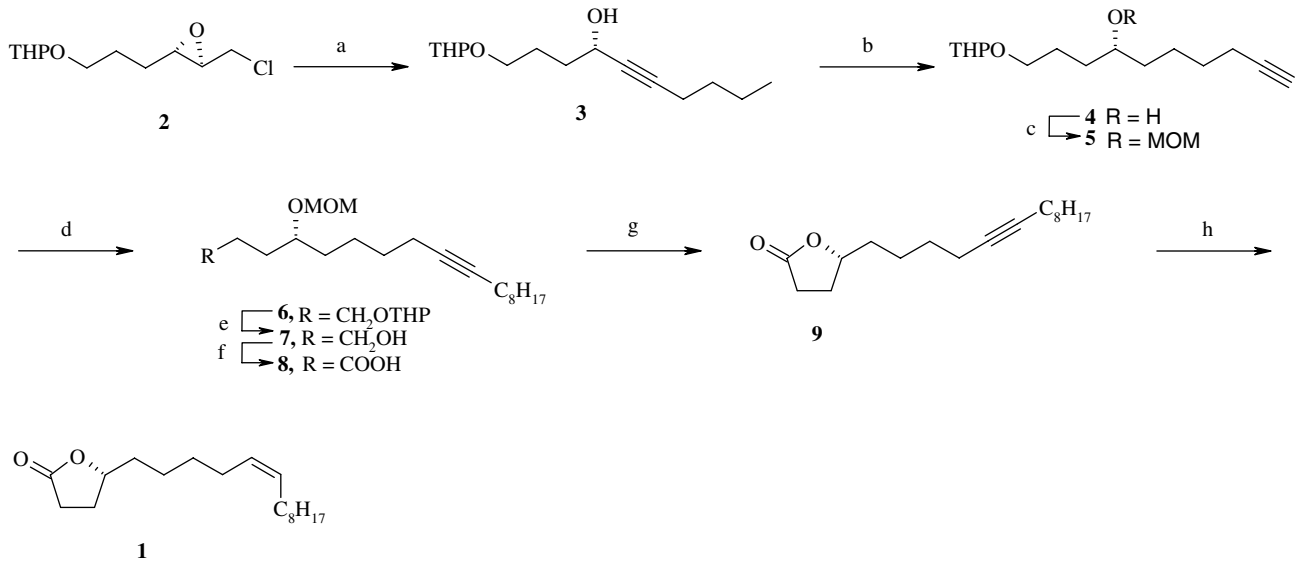

Scheme 1. Reagents and conditions: (a) (i) Li/Liq NH_3, $Fe(NO_3)_3$ (catalyst), −78 °C, dry THF, 2 h; (ii) C_4H_9Br, dry THF, 4 h, 70%; (b) $NaNH_2$, dry 1,3-diaminopropane, 60 °C, 6 h, 60%; (c) MOMCl, Hunig's base, CH_2Cl_2, 0 °C–rt, 2 h, 85%; (d) *n*-BuLi, (1.6 M hexane), $C_8H_{17}Br$, dry THF, −78 °C 2 h, 70%; (e) PPTS, MeOH, 12 h, rt, 72%; (f) (i) IBX, dry DMSO, dry DCM, rt, 2 h, 80%; (ii) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, aq DMSO, rt, 1 h, 74%; (g) PTSA, MeOH, 12 h, 80%; (h) Lindlar catalyst, H_2, quinoline, EtOAc, 2 h, 90%.

References and notes

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7. (a) *Spectral data for compound* **4**: $[\alpha]_D^{25}$ −1.5 (*c* 1, $CHCl_3$); IR (neat): 3461, 3316, 2928, 2857, 2215, 1123, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.81–1.94 (m, 17H), 1.23 (s, 1H), 2.50 (t, 2H, $J = 7.1$ Hz), 3.28–3.50 (m, 2H), 3.61–3.83 (m, 2H), 4.51 (t, 1H, $J = 3.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.3, 18.2, 19.5, 21.6, 24.3, 25.3, 26.3, 30.2, 30.4, 61.5, 63.1, 66.2, 67.1, 83.1, 98.4; ESIMS: *m*/*z* 273 (M^++Na).
(b) *Spectral data for compound* **7**: $[\alpha]_D^{25}$ −8.5 (*c* 1, $CHCl_3$); IR (neat): 3450, 2925, 2240, 1287, 1126, 1114, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, 3H, $J = 6.9$ Hz), 1.26–1.63 (m, 22H), 2.06–2.15 (m, 4H), 3.36 (s, 3H), 3.61 (m, 3H), 4.62 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 18.7, 22.6, 24.5, 26.4, 27.2, 27.9, 28.3, 28.9, 29.1, 29.2, 30.6, 31.8, 33.7, 55.5, 62.9, 76.5, 80.4, 95.4, 96.1; ESIMS: *m*/*z* 349 (M^++Na).
(c) *Spectral data for compound* **1**: $[\alpha]_D^{25}$ +23.3 (*c* 1, $CHCl_3$); lit.[3a] $[\alpha]_D^{25}$ 24 (*c* 0.50, $CHCl_3$) IR (neat): 2925, 2854, 1777, 1644, 1459, 1351, 1176, 1017, 912, 721 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.89 (t, $J = 6.8$ Hz, 3H), 1.24–1.77 (m, 19H), 1.79–1.90 (m, 1H), 1.95–2.07 (m, 4H), 2.30 (ddt, $J = 6.7$, 7.5, 13 Hz, 1H), 2.49 (dd, $J = 1.5$, 7.5 Hz, 1H), 4.44 (quint, $J = 6.0$ Hz, 1H), 5.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz); 14.1, 22.6, 24.7, 26.8, 27.2, 27.9, 28.7, 29.1, 29.2, 29.3, 29.4, 29.7, 31.8, 35.4, 80.9, 129.1, 130.13, 177.1.; ESIMS: *m*/*z* 281 (M^++1).