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# Prins and RCM protocols for the synthesis of the pheromones of the giant white butterfly *Idea leuconoe*

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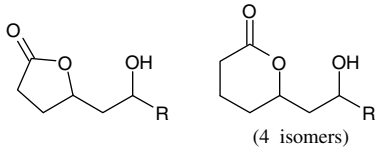
ABSTRACT

The total syntheses of (6*R*)-6-[(2*R*)-2-hydroxyhexyl]tetrahydro-2*H*-2-pyranone and 7-hydroxy-5-dodecanolide are described utilizing a Prins reaction and ring closing metathesis reaction sequence.



Males of the giant white butterfly *Idea leuconoe* hairpencils release a complex mixture of compounds such as dihydropyrrolizines, terpenoids, aromatics, lactones, and hydrocarbons amongst others during courtship.[1] Among them, β- and δ-lactones with two chiral centers are considered as important components of the pheromone system. The chain lengths of lactones, such as 6-hydroxy-4-alkanolides **1** and 7-hydroxy-5-alkanolides **2,** vary between $C_{10}$ and $C_{13}$. δ-Lactones **2** are the minor components of the hairpencil secretion, and occur as mixtures of all the possible enantiomers. Among these, the *anti*-enantiomers predominate. Hairpencil components also produce a warning signal against predators,[2] besides their courtship function. To date, a single report has appeared[3] on the synthesis of these lactones, which uses an enantioselective hydrogenation of a dioxoalkanoate precursor. The development of efficient Prins cyclizations for the synthesis of natural products[4] has prompted us to explore its utility further. In this connection and in continuation of our interest on the synthesis of bioactive naturally occurring lactones,[5] we herein report a concise synthesis of lactones **2a** and **2b** utilizing a Prins cyclization coupled with RCM (ring closing metathesis) (Fig. 1).

The synthesis commenced from the *R*-(+)-benzyl glycidyl ether **4,** obtained by the Jacobsen resolution[6] of racemate **3** using (*S*,*S*)-(salen) Co(II) precatalyst, AcOH and $H_2O$ (0.5 equiv) for 12 h. Regioselective opening of epoxide **4** with the vinyl Grignard reagent formed by the addition of vinyl bromide to Mg in THF in the presence of CuCN in THF afforded homoallylic alcohol **5** in 92% yield.




**1a**; R = $C_4H_9$
**1b**; R = $C_5H_{11}$
**1c**; R = $C_6H_{13}$

**2a**; R = $C_4H_9$
**2b**; R = $C_5H_{11}$
**2c**; R = $C_6H_{13}$

**Figure 1.**

This intermediate **5** can be utilized for the synthesis of both **2a** and **2b** using $C_4H_9CHO$ and $C_5H_{11}CHO$, respectively (Schemes 1 and 2). Accordingly, Prins cyclization of **5** with $C_4H_9CHO$ in the presence of TFA followed by hydrolysis of the resulting trifluoroacetate yielded the desired trisubstituted pyran **7a**. Silyl protection of the 2° alcohol with TBSCl and imidazole in the presence of a catalytic amount of DMAP afforded **8a** in 92% yield, which underwent debenzylation by hydrogenation at atmospheric pressure, in EtOAc in the presence of 10% Pd/C as the catalyst to produce primary alcohol **9a**. Alcohol **9a,** on exposure to TPP, iodine, and imidazole in refluxing diethyl ether and acetonitrile (3:1) converted into the corresponding iodide **10a** in 24 h. The iodo compound **10a** on exposure to activated Zn in refluxing EtOH furnished the key ring opened compound **11a** with the *anti*-1,3-diol system. The secondary alcohol was protected as a benzyl ether and a subsequent removal of the TBDMS group provided **12a**. The alkene **12a** was converted readily into acrylate **13a** upon exposure to acryloyl

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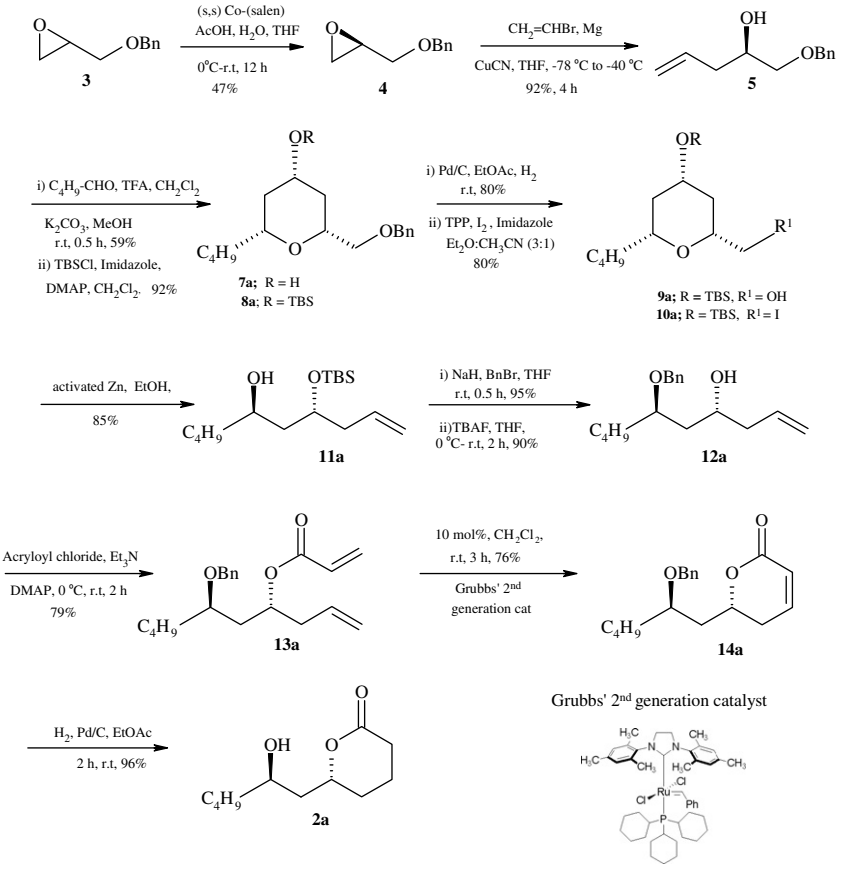
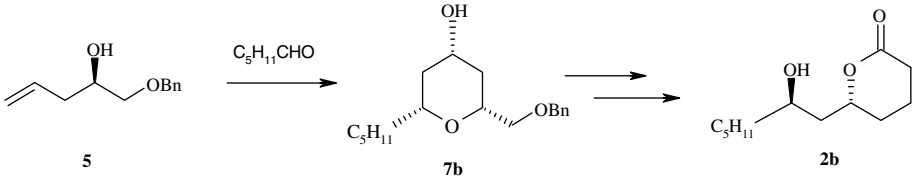



**Scheme 1.**




**Scheme 2.**

chloride, $Et_3N$, and DMAP in 79% yield. Next, the ring closing metathesis reaction was implemented easily by the exposure of a DCM solution of the diene to Grubbs' 2nd generation catalyst (10 mol %), which resulted in clean cyclization to dihydropyran-2-one **14a** in 76% yield.

Removal of the benzyl protecting group with concomitant reduction of the double bond was accomplished by hydrogenation at atmospheric pressure, in EtOAc in the presence of 10% Pd/C as the catalyst to afford target molecule **2a** in 96% yield.

Using the abovementioned synthetic approach, optically active 7-hydroxy-5-dodecanolide **2b** (Scheme 2) was accessed readily from **5** and $C_5H_{11}CHO$ in 6.4% overall yield.

In conclusion, we have achieved a total synthesis of two pheromones of giant white butterfly *I. leuconoe*.

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## References and notes

1. Schulz, S.; Nishida, R. *Bioorg. Med. Chem.* **1996**, *4*, 341–349.
2. Nishida, R.; Schulz, S.; Kim, C. S.; Fukami, H.; Kuwahara, Y.; Honda, K.; Hayashi, N. *J. Chem. Ecol.* **1996**, *22*, 949–972.
3. Stritzke, K.; Schulz, S.; Nishida, R. *Eur. J. Org. Chem.* **2002**, 3884–3892.
4. (a) Yadav, J. S.; Reddy, M. S.; Rao, P. P.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4397–4401; (b) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 2133–2136; (c) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4995–4998; (d) Yadav, J. S.; Rao, P. P.; Reddy, M. S.; Rao, N. V.; Prasad, A. R. *Tetrahedron Lett.* **2007**, *48*, 1469–1471.
5. (a) Sabitha, G.; Sudhakar, K.; Reddy, N. M.; Rajkumar, M.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 6567–6570; (b) Sabitha, G.; Narjis, F.; Swapna, R.; Yadav, J. S. *Synthesis* **2006**, *17*, 2879–2884; (c) Sabitha, G.; Reddy, E. V.; Yadagiri, K.; Yadav, J. S. *Synthesis* **2006**, *19*, 3270–3274; (d) Sabitha, G.; Sudhakar, K.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 8599–8602; (e) Sabitha, G.; Bhaskar, V.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 8179–8181; (f) Sabitha, G.; Swapna, R.; Reddy, E. V.; Yadav, J. S. *Synthesis* **2006**, *24*, 4242–4246; (g) Sabitha, G.; Bhikshapathi, M.; Yadav, J. S. *Synth. Commun.* **2007**, 561–569; (h) Sabitha, G.; Gopal, P.; Yadav, J. S. *Synth. Commun.* **2007**, 1495–1502; (i) Sabitha, G.; Yadagiri, K.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 1651–1652; (j) Sabitha, G.; Yadagiri, K.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 8065–8068.
6. Tokunaga, M.; Larrow, J. F.; Kukiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. Spectral data. *(2R)-1-(Benzyloxy)-4-penten-2-ol* (**5**): $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.33 (m, 5H), 5.83 (m, 1H) 5.11 (dt, $J$ = 5.2 Hz, 2H), 4.56 (s, 2H), 3.85 (m, 1H), 3.49 (dd, $J$ = 3.7, 9.0 Hz, 1H), 3.39–3.32 (dd, $J$ = 7.5, 9.0 Hz, 1H), 2.23 (t, $J$ = 6.7 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 137.9, 134.1, 128.4, 127.7, 127.6, 117.6, 73.9, 73.4, 69.6, 37.8; LCMSD: 215 [M+23]; HRMS 215.1040 [M+23], $C_{12}H_{16}O_2Na$; IR (neat): 3436, 3071, 3031, 2921, 2860, 1718, 1640, 1495, 1452, 1363, 1275, 1209, 997, 743, 698, 608, 468 cm$^{-1}$; $[\alpha]_D^{25}$ −4.98 (*c* 1, $CHCl_3$).
*(2R,4R,6R)-2[(Benzyloxy)- methyl]-6-butyltetrahydro-2H-4-pyranol* (**7a**): $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.33 (m, 5H), 4.55 (q, $J$ =12.0 Hz, 2H), 3.82–3.68 (m, 1H),

3.55–3.22 (m, 4H), 1.93 (td, $J$ = 2.2, 4.5, 12.8 Hz, 4H), 1.50–1.03 (m, 6H), 0.90 (t, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 138.3, 128.3, 127.6, 127.5, 75.8, 74.9, 73.3, 73.2, 68.1, 41.0, 37.9, 35.6, 27.7, 22.6, 13.9; LCMSD: 279 [M+1]; $[\alpha]_D^{25}$ +23.8 ($c$ 0.75, $CHCl_3$).

*((2R,4R,6R)-2-[(Benzyloxy)methyl]-6-butyltetrahydro-2H-4-pyranyloxy)(tert-butyl)-dimethylsilane* (**8a**): $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.35–7.29 (m, 5H), 4.6–4.52 (ABq, $J$ = 12.0, 18.5 Hz, 2H), 3.98–3.94 (m, 1H), 3.81–3.71 (m, 1H), 3.54–3.38 (m, 3H), 1.77 (td, $J$ = 4.5, 12.0 Hz, 1H), 1.62–1.11 (m, 7H), 0.98–0.87 (m, 14H), 0.11–0.04 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz): 138.1, 128.0, 127.4, 127.2, 75.6, 73.1, 74.7, 72.0, 70.7, 41.2, 38.2, 35.5, 27.5, 25.4, 22.5, 20.5, 13.8, −4.5; LCMSD: 393 [M+1]; HRMS: 393.2809 [M+1] $C_{23}H_{41}O_3Si$; $[\alpha]_D^{25}$ +2.3 ($c$ 1.21, $CHCl_3$).

*((2R,4R,6R)-6-Butyl-4-[1-(tert-butyl)-1,1-dimethylsilyl]oxytetrahydro-2H-2-pyranyl)methanol* (**9a**): $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 3.85–3.66 (m, 1H), 3.62–3.14 (m, 4H), 1.95–1.07 (m, 13H), 0.87 (s, 12H), 0.04 (m, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz): 75.89, 75.75, 68.61, 66.10, 41.72, 37.42, 35.71, 27.77, 25.83, 22.70, 18.06, 14.03, −4.59; LCMSD: 325 [M+Na]; HRMS 325.2165 [M+Na], $C_{16}H_{34}O_3NaSi$; $[\alpha]_D^{25}$ −2.9 ($c$ 1.4, $CHCl_3$).

*(4R,6R)-6-(Benzyloxy)-1-decen-4-ol* (**12a**): $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.44–7.12 (m, 5H), 5.93–5.66 (m, 1H), 5.17–5.10 (d, $J$ = 12.50 Hz, 2H), 4.67–4.41 (m, 2H), 3.99–3.83 (m, 1H), 3.77–3.59 (m, 1H), 3.48–3.43 (br s, 1H), 2.24–2.14 (t, $J$ = 6.2 Hz, 2H), 1.74–1.16 (m, 8H), 0.98–0.82 (t, $J$ = 6.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz): 138.3. 134.9, 128.4, 127.8, 117.4, 76.2, 71.1, 67.7, 42.1, 39.3, 33.1, 29.6, 27.5, 22.7, 13.9.; LCMSD: 263 [M+1]; $[\alpha]_D^{25}$ −8.9 ($c$ 2.25, $CHCl_3$).

*(6R)-6-[(2R)-2-(benzyloxy)hexyl]-5,6-dihydro-2H-2-pyranone* (**14a**): $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.34–7.22 (m, 5H), 6.85–6.77 (t, $J$ = 4.5 Hz, 1H), 6.01–5.94 (td, $J$ = 9.0 Hz, 1H), 4.70–4.51 ($AB_q$, $J$ = 11.3, 4.4 Hz, 2H), 4.43 (d, $J$ = 11.3 Hz, 1H), 3.86–3.75 (m, 1H), 2.32–2.26 (td, $J$ = 4.5, 6.0, 1.5 Hz, 2H), 1.93–1.18 (m, 8H), 0.88 (td, $J$ = 1.7, 7.0 Hz, 3H,); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 164.4, 145.2, 138.5, 128.3, 127.8, 127.6, 121.3, 74.9, 74.7, 71.8, 40.5, 33.8, 29.9, 29.6, 26.9, 22.8, 14.0; LCMSD: 301 [M+Na]; HRMS 289.1799 [M+1] $C_{18}H_{23}O_3$; $[\alpha]_D^{25}$ −15.7 ($c$ 1.75, $CHCl_3$).

*(6R)-6-[(2R)-2-Hydroxyhexyl]tetrahydro-2H-2-pyranone* (**2a**): $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 4.58 (t, $J$ = 9.5 Hz, 1H), 4.05–3.85 (m, 1H), 2.68–2.24 (m, 2H), 2.00–1.82 (m, 2H), 1.81–1.20 (m, 10H), 0.91 (t, $J$ = 6.5 Hz, 3H). $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 171.9, 77.3, 67.4, 43.2, 37.6, 29.5, 28.3, 27.6, 22.6, 18.4, 13.9; IR (neat): 3441, 2926, 1731, 1457; LCMSD: 223 [M+Na]; HRMS: 223.1310; $[\alpha]_D^{25}$ −12.5 ($c$ 0.2, $CHCl_3$), −16.5 ($c$ 0.5, diethyl ether).

*(2R,4R,6R)-2-[(Benzyloxy)methyl]-6-pentyltetrahydro-2H-4-pyranol* (**7b**): $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.36–7.22 (m, 5H), 4.56 (q, $J$ = 12.0 Hz, 2H), 3.98–3.70 (m, 1H), 3.56–3.37 (m, 4H), 1.93 (td, $J$ = 4.5, 12.0 Hz, 2H), 1.64–1.06 (m, 11H), 0.97–0.87 (t, $J$ = 6.7 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 138.2, 126.3, 127.6, 127.5, 75.7, 73.6, 73.2, 73.0, 68.0, 40.8, 37.8, 35.7, 31.8, 25.1, 22.5, 13.9; LCMSD: 315 [M+Na]; $[\alpha]_D^{25}$ +6.9 ($c$ 1.65, $CHCl_3$).

*7-Hydroxy-5-dodecanolide/(6R)-6-[(2R)-2-hydroxyheptyl]tetrahydro-2H-2-pyranone* (**2b**): $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 4.60 (t, $J$ = 9.8 Hz, 1H), 3.97 (m, 1H), 2.60 (m, 1H), 2.44 (m, 1H), 1.86–1.99 (m, 2H), 1.53–1.79 (m, 2H), 1.44 (m, 2H), 1.36–1.26 (m, 9H), 0.92 (t, $J$ = 6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 171.9, 77.3, 67.4, 43.3, 38.0, 31.7, 29.5, 28.4, 25.1, 22.6, 18.5, 13.9; LCMSD: 237 [M+Na], HRMS 237.1466 (M+Na); IR (neat): 3448, 2925, 1637, 1458 cm$^{-1}$; $[\alpha]_D^{25}$ −22.5 ($c$ 0.3, $CHCl_3$); −28.0 ($c$ 0.15, diethyl ether), [lit.:[3] −26.5 ($c$ 2.4, diethyl ether)].