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Stereoselective synthesis of methyl branched chiral deoxypropionate units: a new route for synthesis of insect pheromone (−)-lardolure and (2*R*,4*R*,6*R*,8*R*) 2,4,6,8-tetramethylundecanoic acid

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ABSTRACT

(−)-Lardolure and (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundecanoic acid have been synthesized via lipase catalyzed desymmetrization strategy to create two methyl chiral centers. Other key steps involved in the synthesis are Wittig reaction, Evan's asymmetric alkylation, Grignard reaction, Pd-catalyzed isomerization of primary allylic alcohol to corresponding saturated aldehyde, and PhNO/proline catalyzed MacMillan α-hydroxylation.

Polydeoxypropionate chains have been found in numerous biologically relevant compounds and are of great interest for the last few decades in respect of their stereocontrolled synthesis.[1] A syn/syn-deoxypropionate unit can be found in many natural products, such as lardolure (**1**), (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundecanoic acid (**2**), siphonareinal (**3**), siphonarienone (**4**), pectinatone (**5**), siphonarienolone (**6**), and supellapyrone (**7**). Mite pheromones have been intensively investigated predominantly by Kuwahara's group.[2,3] They isolated (−)-lardolure (**1**) as the aggregation pheromone of the acarid mite, *Lardoglyphus konoi*, identified as the primary pest for stored products with high protein content in 1982.[4] The relative and absolute stereochemistry of (−)-lardolure was confirmed by Mori and Kuwahara.[5] Extensive studies in 1960s on the preen gland waxes of water fowl revealed the chemotaxonomic utility of waxes. During the studies (2*R*,4*R*,6*R*,8*R*) 2,4,6,8-tetramethylundecanoic acid (**2**) was isolated as preen secretion of graylag goose anser anser by Murray[6] and Odham[7] independently. The structure and stereochemistry was established synthetically by Mori et al.[8] and absolute configuration was proposed by Odham[7] (Fig. 1).

There are four reports[9] for the total synthesis of (−)-**1** so far including iterative conjugate addition of MeMgBr to α,β-unsaturated thioesters and interconversion of **1** to **2** and vice versa.[10] Recently, we have demonstrated enzymatic desymmetrization strategy for

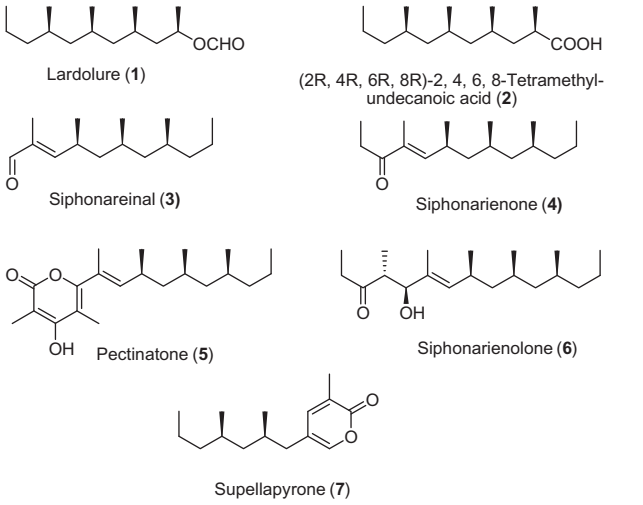

Figure 1. Chemical structures of lardolure (**1**), acid (**2**), and some related natural products containing deoxypropionates.

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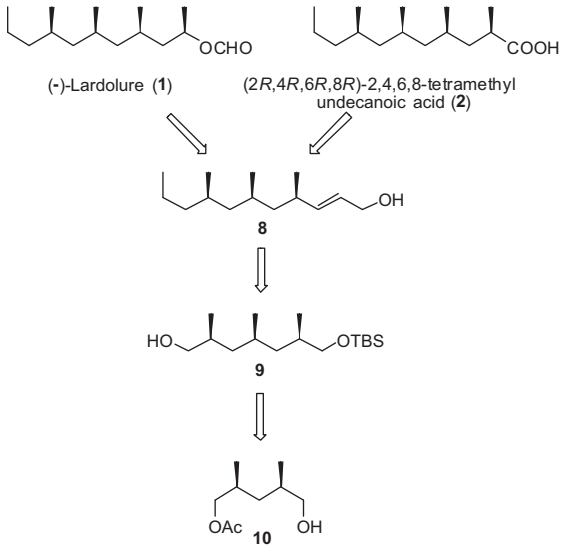


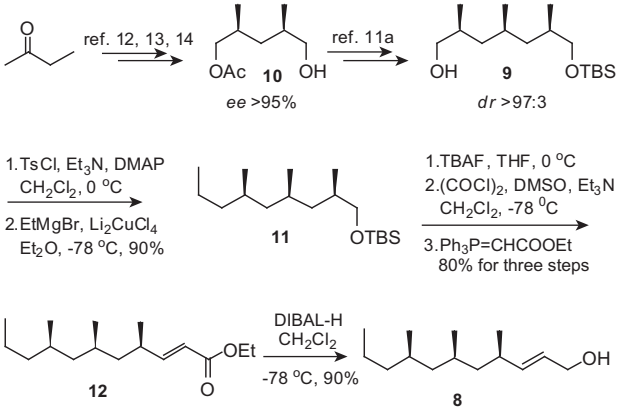
Scheme 1. Retrosynthetic analysis of (−)-lardolure (**1**) and (2*R*,4*R*,6*R*,8*R*)- 2,4,6,8-tetramethylundecanoic acid (**2**).

the total synthesis of biologically active natural products containing polydeoxypropeonates.[11]

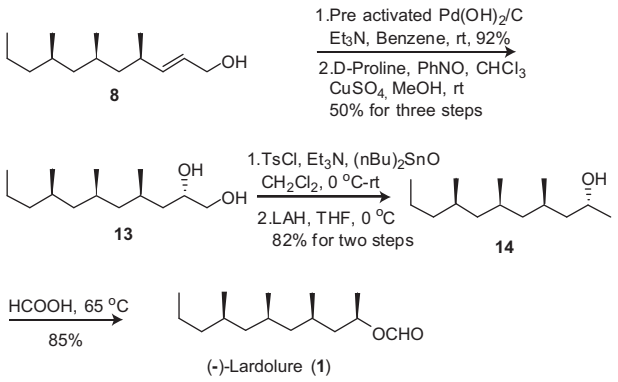
To further highlight the synthetic utility of the protocol, herein, we report the syntheses of both the pheromone **1** and **2** of preen gland waxes from a common methyl branched chiral allylic alcohol intermediate **8**.

The retrosynthetic path (Scheme 1) shows that the targeted molecules **1** and **2** could be easily synthesized from the common allylic alcohol intermediate **8** which has three chiral methyl groups. Furthermore, **8** could be obtained from the known primary alcohol **9**, which was synthesized earlier in our group using a known precursor **10** by means of Wittig reaction and Evan's alkylation reaction.[11a]

Our synthesis began with the known precursor **10** which was synthesized in four steps starting from *cis*-4,6-dimethyl cyclohexan-1,3-dione following a known protocol.[12–14] Primary alcohol **9** was synthesized from **10** by following a reported protocol developed in our group.[11a] Primary hydroxyl group present in **9** was protected as its tosyl derivative by TsCl/Et_3N in the presence of catalytic amount of DMAP. It was then subjected to Grignard reaction[15] with EtMgBr in Et_2O in the presence of 5 mol % Li_2CuCl_4 to afford **11** in 90% yield. Silyl deprotection of **11** by TBAF yielded long chain alcohol which was subjected to Swern oxidation followed by



Scheme 2. Synthesis of allylic alcohol intermediate **8**.



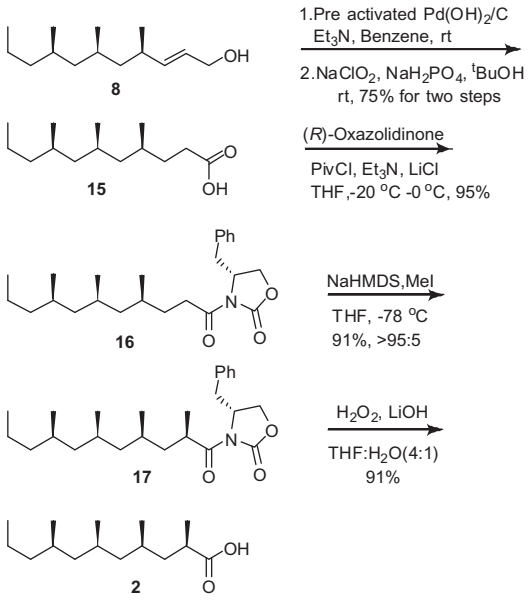
Scheme 3. Synthesis of (−)-lardolure (**1**).

Wittig reaction to obtain α,β-unsaturated ester **12** in 80% yield over three steps. The ester **12** was reduced with DIBAL-H in CH_2Cl_2 to afford the corresponding common allylic alcohol intermediate **8** in 90% yield (Scheme 2).

At first we targeted the total synthesis of **1** from the common intermediate **8** (Scheme 3). $Pd(OH)_2/C$ in benzene was used for the conversion of allylic alcohol **8** to the saturated aldehyde[16] (which was not isolated) and subsequent α-hydroxylation with PhNO and 10 mol % D-proline afforded the desired diol **13** as a major diastereomer[17] with 50% yield in three steps (d.r., >99%, as determined by HPLC analysis). Selective tosyl protection of the primary alcohol of 1,2-diol **13** was achieved by TsCl, Et_3N and the catalytic amount of Bu_2SnO and then $LiAlH_4$ reduction of the tosylate yielded secondary alcohol **14** in 82% yield over two steps. Secondary alcohol **14** was formylated by mixing **14** with formic acid at 65 °C to furnish the targeted pheromone (−)-lardolure (**1**) in 85% yield. The NMR (^1H and ^{13}C) analysis and optical rotation ($[\alpha]_D^{25} = -3.2$) of **1**[18] were in good agreement with the literature value.[9]

Next we initiated the total synthesis of (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethyl undecanoic acid **2** starting from the common allylic alcohol intermediate **8** (Scheme 4).

Accordingly, the allylic alcohol **8** was subjected to Pd-mediated oxidation as mentioned earlier,[16] followed by transformation of



Scheme 4. Synthesis of (2*R*,4*R*,6*R*,8*R*)-2,4,6,8- tetramethylundecanoic acid (**2**).

aldehyde to the corresponding acid **15** under Pinnick conditions using $NaClO_2$, NaH_2PO_4, in $^tBuOH/H_2O$ (2:1) with 75% yield in two steps. Coupling of acid **15** with Evan's (*R*)-oxazolidinone using pivaloyl chloride in the presence of Et_3N and LiCl furnished the required compound **16** in 95% yield. Methylation of the Na-enolate of compound **16** with MeI afforded compound **17** in 91% yield. Finally, treatment of compound **17** with $LiOH/H_2O_2$ in THF/H_2O (4:1) furnished the desired (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundecanoic acid (**2**)[7,8,18] in 91% yield and >99% d.r. and ee (as determined by HPLC analysis).

In conclusion, concise total syntheses of (−)-lardolure and (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundecanoic acid have been accomplished from a common intermediate. The key reactions involved for the syntheses of **1** and **2** are enzymatic desymmetrization of *meso*-diol, Wittig reaction, Evan's alkylation, palladium hydroxide catalyzed isomerization of primary allylic alcohol to aldehyde, and α-hydroxylation.

Acknowledgements

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18. The ^1H and ^{13}C NMR spectral data and optical rotation, of the synthetic compounds **1** and **2** are identical with the reported values. Spectroscopic data for selected compounds are given below.
Compound **11**: colorless oil, $[\alpha]_D^{25}$ = +0.8 (*c* = 0.6, $CHCl_3$); IR (KBr): υ_{max} = 2956, 2929, 2958, 1466, 1254, 1073, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.43 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.33 (dd, *J* = 9.6, 6.2 Hz, 1H), 1.72–1.46 (m, 3H), 1.38–0.97 (m, 8H), 0.89 (s, 9H), 0.89–0.82 (m, 12H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 68.1, 45.4, 41.3, 39.0, 33.2, 29.8, 27.6, 26.0, 21.0, 20.4, 20.0, 18.3, 17.9, 14.4, -5.4; Compound **8**: colorless oil, $[\alpha]_D^{25}$ = –9.1 (*c* = 0.57, $CHCl_3$); IR (KBr): υ_{max} = 3327, 2957, 2923, 2870, 1725, 1460, 1376, 1088, 972, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.58 (dt, *J* = 15.3, 5.6 Hz, 1H), 5.45 (dd, *J* = 15.5, 7.7 Hz, 1H), 4.05 (d, *J* = 5.5 Hz, 2H), 2.32–2.17 (m, 1H), 1.55–1.44 (m, 3H), 1.39–1.03 (m, 8H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 139.0, 127.3, 63.8, 45.5, 44.3, 39.2, 33.9, 29.6, 27.5, 21.5, 20.2, 20.1, 20.0, 14.4; Compound **13**: yellow oil, $[\alpha]_D^{25}$ = −5.4 (*c* = 0.95, $CHCl_3$). IR (KBr): υ_{max} = 3446, 2957, 2925, 1633, 1458, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.82-3.74 (m, 1H), 3.65-3.56 (m, 1H), 3.41–3.35 (m, 1H), 1.82–1.44 (m, 5H), 1.35–1.14 (m, 8H), 0.97–0.82 (m, 6H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.85 (t, *J* = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 69.9, 67.4, 45.8, 45.5, 41.4, 39.8, 27.7, 27.2, 26.2, 22.2, 20.4, 19.8, 18.6, 14.4; Mass (ESI–MS) *m*/*z*: 253 [M + Na]$^+$; Compound **1**: yellow oil, $[\alpha]_D^{25}$ = −3.2 (*c* = 0.25, Hexane). IR (KBr): υ_{max} = 3424, 2957, 2924, 2854, 1723, 1461, 1376, 1260, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.06 (s, 1H), 5.19–5.09 (m, 1H), 1.75–1.68 (m, 1H), 1.63-1.55 (m, 1H), 1.52–1.45 (m, 2H), 1.40–0.85 (m, 12H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 160.9, 69.1, 45.4, 45.2, 42.9, 38.9, 29.6, 27.2, 26.4, 20.9, 20.5, 20.4, 20.2, 19.9, 14.4; HRMS (ESI): calcd for $C_{15}H_{30}O_2$ 242.22403, found 242.28444; Compound **17**: yellow oil, $[\alpha]_D^{25}$ = −30.9 (*c* = 0.8, $CHCl_3$). IR (KBr): υ_{max} = 3448, 2956, 2923, 2853, 1784, 1698, 1634, 1459, 1383, 1099, 972, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 7.3, 2H), 7.20 (t, *J* = 6.5 Hz, 1H), 7.14 (d, *J* = 7.3, 2H), 4.65–4.59 (m, 1H), 4.15–4.08 (m, 2H), 3.86–3.79 (m, 1H), 3.18 (dd, *J* = 13.7, 3.2 Hz, 1H), 2.69 (dd, *J* = 13.7, 9.7 Hz, 1H), 1.88–1.79 (m, 1H), 1.61–1.38 (m, 4H), 1.30–1.09 (m, 8H), 1.15 (d, *J* = 7.3 Hz, 3H), 0.89–0.75 (m, 6H), 0.81 (t, *J* = 6.5 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 177.3, 162.8, 135.2, 129.4, 128.9, 127.3, 65.9, 55.2, 46.5, 45.5, 45.3, 45.2, 40.4, 40.3, 29.6, 28.0, 27.2, 20.7, 20.5, 20.4, 20.0, 18.7, 14.4; Mass (ESI–MS) *m*/*z*: 424 [M + Na]$^+$; Compound **2**: yellow oil, $[\alpha]_D^{25}$ = −28 (*c* = 0.25, $CHCl_3$). IR (KBr): υ_{max} = 2959, 2925, 1707, 1461, 1378, 1227, 944, 889 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.63–2.52 (m, 1H), 2.01–1.61 (m, 3H), 1.61–1.44 (m, 2H), 1.37–1.00 (m, 8H), 1.18 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.0 Hz, 3H), 0.87 (d, *J* = 6.0 Hz, 3H), 0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 183.4, 46.0, 45.2, 40.8, 39.1, 37.3, 29.7, 29.5, 28.5, 20.2, 20.1, 20.0, 19.4, 17.9, 14.4; HRMS (ESI): calcd for $C_{15}H_{31}O_2$ 243.23186, found 243.21023.