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Single-step construction of the *anti*-deoxypropionate motif from propylene: Formal total synthesis of the cuticular hydrocarbons isolated from *Antitrogus parvulus*

Toshiki Murayama and Kyoko Nozaki*

Abstract: Herein we report the single-step construction of *anti*-configured deoxypropionate motif by syndiospecific propylene oligomerization catalyzed by C_S-symmetric zirconocene complex. After oligomerization, oxidation of the oligomers by oxygen afforded oligopropylene alcohols in a single step. This strategy was applied to the single-step preparation of *rel*-(2*R*,4*S*,6*R*,8*S*)-2,4,6,8-tetramethylundecan-1-ol, the racemic mixture of the synthetic fragment of the cuticular hydrocarbons isolated from the cane beetle *Antitrogus parvulus*.

The deoxypropionate motif (i.e., 1,3,...,(*n*−1)-polymethylalkyl chain) is a common structure found in natural products synthesized by bacteria, fungi, and plants (Fig. 1a).[1] Because of the abundance of this motif in natural products and the range of biological activities they are related to, its synthesis has received a great amount of attention.[2,3] To construct the structure consisting of repeating units containing stereocenter but no functionalities, the majority of the conventional syntheses of the deoxypropionate motif employ iterative stereoselective reactions including functional group interconversions. The examples include enolate alkylation,[4,5] carboalumination,[6] organocuprate displacement,[7] homologation of boronic esters,[8] and conjugate addition.[9] Although these reactions proceed with high stereoselectivity, long reaction sequences of 3–6 steps per repeating unit are typically necessary. Consequently, long reaction routes toward the natural products are required.

To construct the deoxypropionate motif in a single step, we previously reported asymmetric isospecific propylene oligomerization catalyzed by optically active C_2-symmetric zirconocene complex in the presence of diethylzinc (Fig. 1b).[10] This strategy utilized coordinative chain transfer polymerization,[11] where excess amount of alkylmetal species is used as a chain transfer agent in order to control the chain length. In the previous paper, 2000–5000 equivalents of diethylzinc was added to the system as a chain transfer agent, which result in selective formation of oligopropylenes, maintaining high isospecificity. We demonstrated the three-step synthesis of a natural product (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethyldecanoic acid (**1**), which as previously reported,[6,9] was conventionally synthesized over at least ten steps. However, the product was limited to *syn*-configured deoxypropionate motif owing to the isospecificity provided by C_2-symmetric zirconocene catalyst. Although the significant majority of the deoxypropionate motifs found in natural products have *syn*-configuration to minimize the number of unstable conformations,[12] there are several naturally occurring examples featuring the *anti*-configured deoxypropionate motif. Therefore, the expansion of our methodology into *anti*-configured deoxypropionate motif is indeed important.

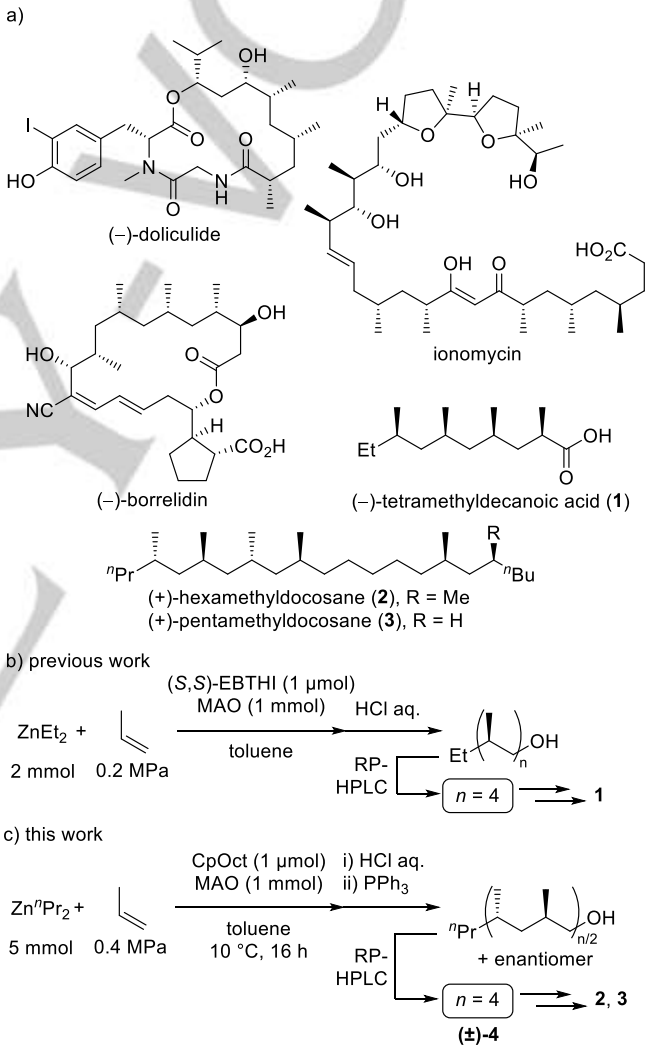

Figure 1. a) Selected examples of natural products containing deoxypropionate motif. b) Asymmetric isospecific propylene oligomerization and total synthesis of **1**.[10] c) Syndiospecific propylene oligomerization and formal total synthesis of **2** and **3** (this work). EBTHI, Dichloro[ethanediylbis(4,5,6,7-tetrahydro-1*H*-inden-1-yl)]zirconium. RP-HPLC, reversed phase high performance liquid chromatography. CpOct, Dichloro[(cyclopentadienyl)(diphenylmethylene)(1,2,3,4,7,8,9,10-octahydro-1,1,4,4,7,7,10,10-octamethyl-12*H*-dibenzo[*b*,*h*]fluoren-12-yl)zirconium dichloride.

Herein we expand our strategy to construct the *anti*-configured deoxypropionate motif, utilizing *C*s-symmetric zirconocene complex in the presence of dialkylzinc (Fig. 1c). This strategy was applied to the facile formal total synthesis of the major

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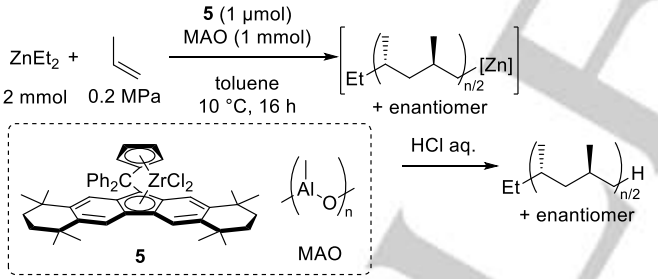
cuticular hydrocarbons isolated from the cane beetle *Antitrogus parvulus*, (4*S*,6*R*,8*R*,10*S*,16*R*,18*S*)-4,6,8,10,16,18-hexamethyldocosane (**2**) and (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane (**3**).[13,14] The racemic mixture of the common synthetic intermediate of **2** and **3**, *rel*-(2*R*,4*S*,6*R*,8*S*)-2,4,6,8-tetramethylundecan-1-ol (**(±)-4**),[15–19] was successfully obtained in a single step.

We chose the C_s-symmetric zirconocene complex **5**[20] as an oligomerization catalyst since it exhibited high activity and stereoregularity in syndiospecific propylene polymerization (Table 1 and Figure 2). In a similar manner to the previous report of isospecific propylene oligomerization,[10] reaction was carried out at 1 μmol Zr scale in the presence of 1000 equivalents of methylaluminoxane (MAO) as a cocatalyst, 2000 equivalents of diethylzinc as a chain transfer agent under 0.2 MPa of propylene. Reaction was carried out at 10 °C for 16 hours and quenched with hydrochloric acid. Analysis of the reaction mixture was carried out by GC and GC-MS. The yield of each oligomer was calculated based on peak area of GC trace on mass basis. We found that Zirconocene **5** successfully catalyzed syndiospecific oligomerization with high stereoregularity (entry 1); the percentage of the main diastereomer of hexamer was calculated to be 92% (by GC). This high diastereoselectivity was further confirmed by comparison with the oligomerization catalyzed by bis(cyclopentadienyl)zirconium dichloride **6**, which produces atactic polypropylenes.[21] GC trace of the reaction mixture of entry 1 showed virtually single peaks for each oligomer (Figure 3, bottom), whereas the use of **6** resulted in the formation of multiple peaks (Figure 3, top).[10]

Table 1. Syndiospecific propylene oligomerization in the presence of diethylzinc.[a]



Entry	Variation	d.p./%[b]
1	n/a	92
2	0.4 MPa	88
3	0.4 MPa, 5 mmol Zn	94
4	0.4 MPa, 10 mmol Zn	95
5	−20 °C	95
6	Same as entry 3, ×5 scale	90
7	Same as entry 3, 1-hexene, 4.0 mL	74

[a] Reaction conditions: **5** (1.0 mL, 1.0 mM in toluene, 1.0 μmol), MAO (0.30 g, 8.9 wt% Al in toluene, 1.0 mmol Al), diethylzinc (2.0 mL, 1.0 M in toluene, 2.0 mmol), propylene (0.2 MPa) at 10 °C for 16 h. After quenched by hydrochloric acid, organic phase was analyzed by GC to determine the yield and the diastereomer percentages. See Supporting Information for the yield of each oligomer and Figure 2 for the yield distribution. [b] Percentage of the main diastereomer of hexamer determined by GC analysis.

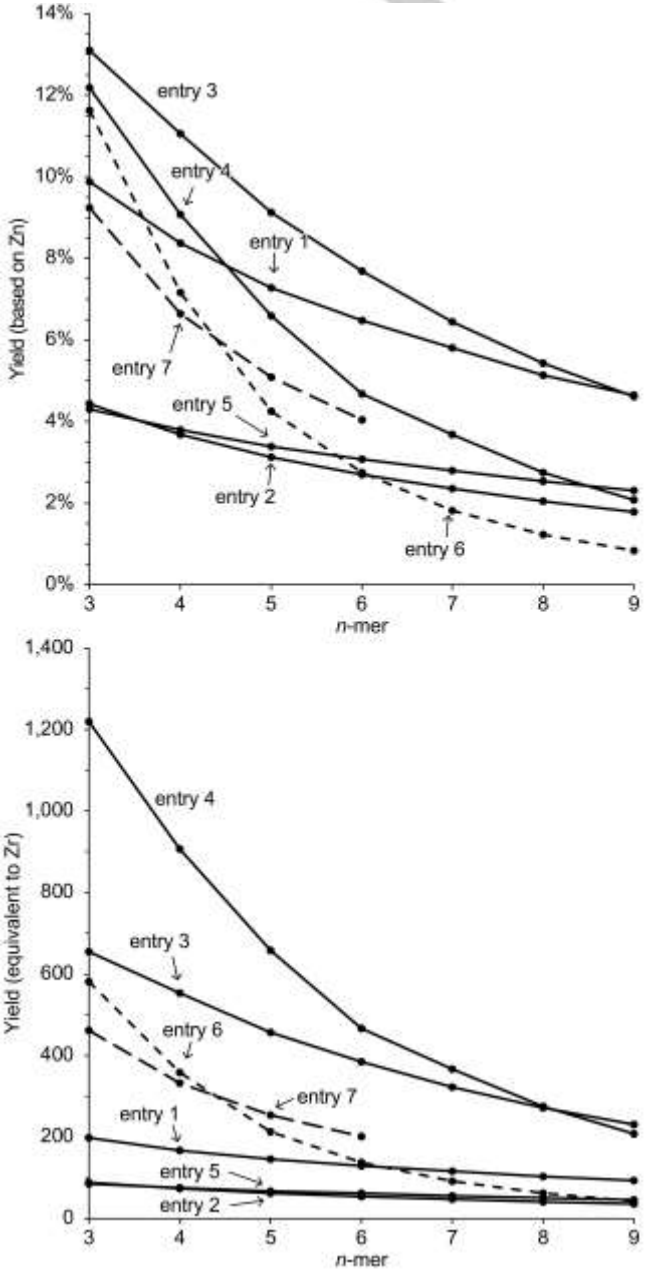


Figure 2. Yield distribution of the main diastereomer of each oligomer in the oligomerization in the presence of diethylzinc (top: percentage based on diethylzinc; bottom: equivalent to **5**). Yield of 7-, 8-, 9-mer in entry 7 was not determined.

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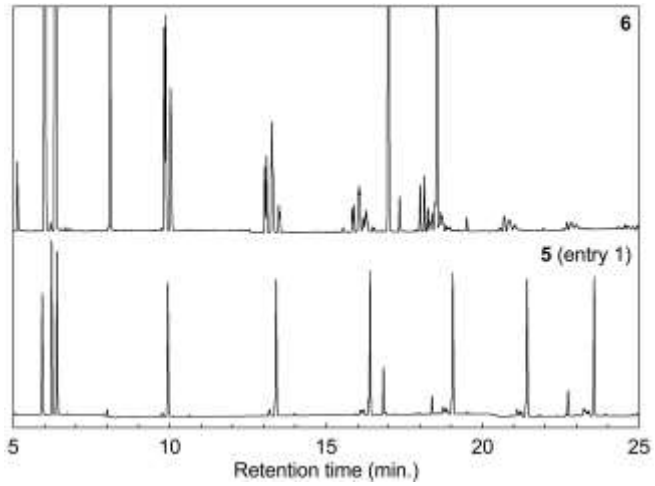

Figure 3. GC traces of the oligomerization products catalyzed by **6**[10] (top) and **5** (bottom, Table 1, entry 1).

Following up on these results, we optimized reaction conditions. Contrary to expectations, increase in propylene pressure from 0.2 MPa to 0.4 MPa (entry 2) led to steep decrease in oligomer yields. We attributed such dependence to rapid propagation rates, leading to the increased probability to form longer oligomers. To oppose rapid propagation rate via an increase in the rate of chain transfer, the ratio of diethylzinc to **5** was raised from 2000 to 5000 or 10000 (entries 3 and 4, respectively). Gratifyingly, oligomer yields, together with the diastereoselectivity were improved. We also found that decreasing the reaction temperature down to −20 °C (entry 5) has virtually no effect on diastereoselectivity, rather only decreased oligomer yields were observed. We concluded that entry 3 was the best condition for the production of oligopropylenes in combined view of both oligomer yield and diastereoselectivity. To investigate the scalability of this reaction, the oligomerization was carried out at 5 times larger scale under the same condition as entry 3 (entry 6). As a result, oligopropylenes were successfully obtained with negligibly lower yield and diastereoselectivity. This strategy was also applicable to α-olefins other than propylene. When 4 mL of 1-hexene was used as a monomer, oligohexenes were obtained (entry 7).

After optimizing the reaction conditions in the **5**/MAO/$ZnEt_2$ system, we switched our focus to the natural product synthesis in order to demonstrate the synthetic utility of our new strategy. The target alcohol **(±)-4**, which was previously synthesized over at least 11 steps,[15,16,18,19] can be synthesized in a single step by syndiospecific propylene oligomerization using di(*n*-propyl)zinc as a chain transfer agent and subsequent oxidation after oligomerization.

When 1.0 M solution of di(*n*-propyl)zinc in toluene was used as a chain transfer agent, although good selectivity for short oligomers and no solid polymers were observed under previously optimized reaction conditions (Table 2 and Figure 4, entry 1), diastereoselectivity was significantly lower compared to the case of diethylzinc.

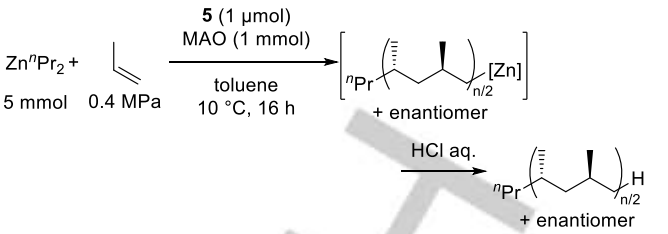

Table 2. Syndiospecific propylene oligomerization in the presence of di(*n*-propyl)zinc.[a]

Entry	Variation	d.p./%[b]
1	n/a	65
2	2 mmol Zn	58
3	10 mmol Zn	90
4	−20 °C	74
5	Neat di(*n*-propyl)zinc, 5 mmol	94

[a] Reaction conditions: **5** (1.0 mL, 1.0 mM in toluene, 1.0 μmol), MAO (0.30 g, 8.9 wt% Al in toluene, 1.0 mmol Al), di(*n*-propyl)zinc (5.0 mL, 1.0 M in toluene, 5.0 mmol), propylene (0.4 MPa) at 10 °C for 16 h. After quenched by hydrochloric acid, organic phase was analyzed by GC to determine the yield and the diastereomer percentages. See Supporting Information for the yield of each oligomer and Figure 3 for the yield distribution. [b] Percentage of main diastereomer of hexamer.

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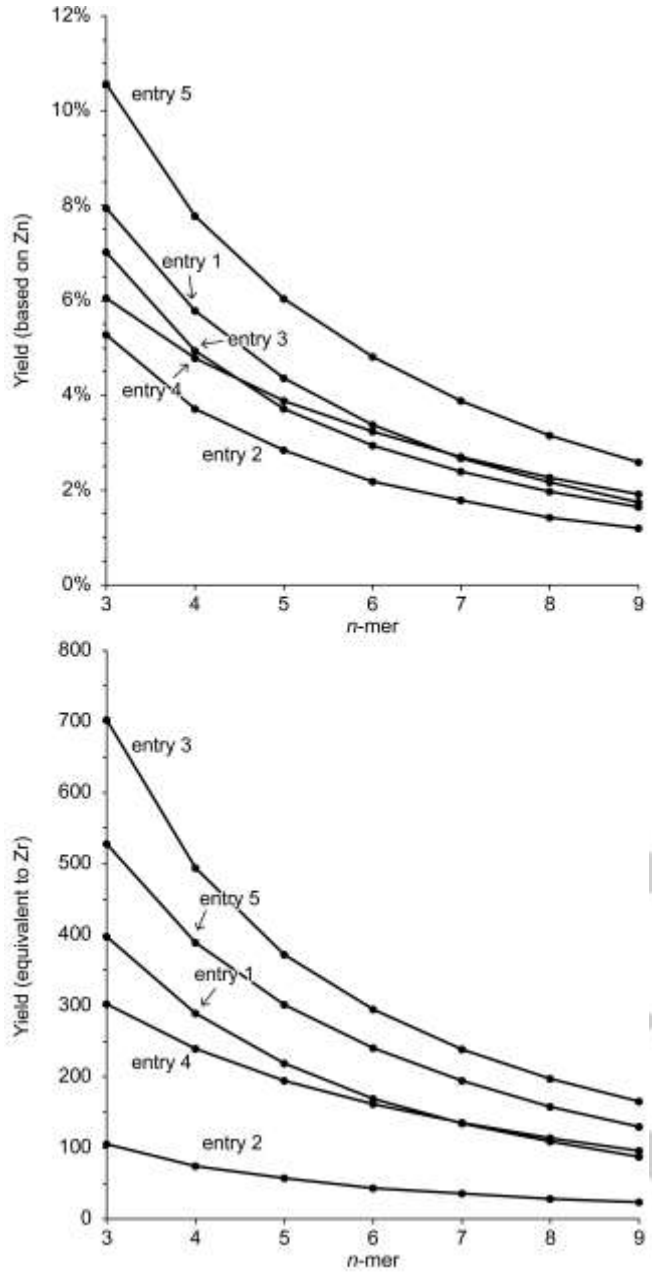
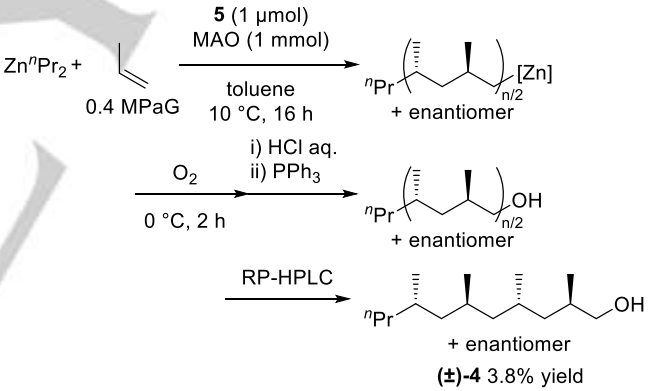


Figure 4. Yield distribution of the main diastereomer of each oligomer in the oligomerization in the presence of di(*n*-propyl)zinc (top: percentage based on di(*n*-propyl)zinc; bottom: equivalent to **5**).

Thus, it was necessary to optimize reaction conditions to obtain oligomers with comparable diastereoselectivity to that obtained when using diethylzinc. We first examined the variation in the ratio of di(*n*-propyl)zinc to **5**. In the presence of 2000 equivalents of di(*n*-propyl)zinc, diastereoselectivity remained almost the same (entry 2). With increased amount of 10000 equivalents of di(*n*-propyl)zinc, diastereoselectivity was improved (entry 3). However, in both cases, yield was lower than entry 1. Lower reaction temperature of −20 °C resulted in lower yield and diastereoselectivity (entry 4). Among various reaction conditions tested with different concentrations of di(*n*-propyl)zinc, the best result with improved oligomer yield and diastereoselectivity was observed when di(*n*-propyl)zinc was added as neat liquid (entry 5) instead of 1.0 M solution in toluene. Since the concentration of dissolved propylene in solvent is constant (Henry's Law), a possible reason for the higher yield of short oligomers is that smaller amount of the solvent decreased the ratio of concentrations of propylene to di(*n*-propyl)zinc.

Finally, propylene oligomerization in the presence of di(*n*-propyl)zinc and oxidation were carried out in series (Scheme 1). After oligomerization reaction under the optimized condition, propylene was vented and a mixture of oligopropylene zinc species was subjected to oxidation by oxygen stream at 0 °C for 2 hours. Reaction was then quenched with hydrochloric acid, and the separated organic layer was treated with triphenylphosphine to convert any remaining alkyl hydroperoxide into alcohol. GC analysis of the reaction mixture revealed that conversion of the oxidation reaction was 76%. Alkanes deriving from unoxidized oligopropylene zinc species, triphenylphosphine, and triphenylphosphine oxide were removed by silica gel column chromatography, and mixture of oligopropylene alcohols were successfully separated by reversed-phase liquid chromatography to afford the tetramer alcohol, which is the target alcohol **(±)-4**, in 3.8% yield based on di(*n*-propyl)zinc. The product was characterized by ^{1}H and ^{13}C NMR analyses. Thus, single-step synthesis of **(±)-4** is achieved and this sequence is the shortest ever reported. Consequently, the formal total syntheses of **2** (over 11 steps with longest linear sequence of 9 steps)[15,16] and **3** (over 12 steps with longest linear sequence of 9 steps)[18,19] were also achieved. It is worth noting that both sequences are the shortest ever reported.



Scheme 1. One-step synthesis of **(±)-4**.

In conclusion, we have successfully utilized syndiospecific oligomerization of propylene followed by oxidation to afford hydroxy-terminated *anti*-configured deoxypropionate motif in a single step. C_s-symmetric zirconocene complex **5** catalyzed propylene oligomerization in highly syndiospecific manner, and resultant oligomers were converted into alcohols by oxygen stream. A mixture of oligopropylene alcohols were separated by reversed-phase HPLC to afford Single-step synthesis of *rel*-(2*R*,4*S*,6*R*,8*S*)-2,4,6,8-tetramethylundecan-1-ol **(±)-4**, the racemic mixture of the synthetic fragment of cuticular hydrocarbons isolated from the cane beadle *Antitrogus parvulus*. Combined with our previous report on the single-step synthesis of *syn*-configured deoxypropionate motif by isospecific propylene oligomerization,[10] these results prove the broad scope of deoxypropionate motif synthesis by propylene oligomerization, further demonstrating the successful application

of polymerization catalysts to synthetic chemistry, which has been an active field of research .[22] Installation of a functional moiety into the initiating group and the use of alternative chain-end functionalization are currently being investigated in our laboratory towards realization of cyclic natural products.

Experimental Section

***Rel*-(2*R*,4*S*,6*R*,8*S*)-2,4,6,8-tetramethylundecan-1-ol ((±)-4)**[16–19] A mixture of **5**[20] (1.0 mL, 1.0 mM in toluene, 1.0 µmol), MAO (0.30 g, 8.9 wt% Al in toluene, 1.0 mmol Al), di(*n*-propyl)zinc[23] (0.75 g, 5.0 mmol) was stirred under propylene (0.40 MPa) in a 50-mL stainless steel autoclave for 16 h at 10 °C. Following propylene venting, the reaction vessel was cooled to 0 °C. Additional toluene (10 mL) was added to the reaction mixture, and oxygen stream was applied for 2 h at 0 °C. Reaction was then quenched with hydrochloric acid, and triphenylphosphine was added to the separated organic phase. The mixture was concentrated for purification by silica gel column chromatography (Hex/EtOAc = 10:1 v/v), and then by reversed phase HPLC (MeOH) to afford 43.6 mg (3.8% yield from di(*n*-propyl)zinc) of **(±)-4** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): **δ**=3.48 (dd, ^2J(H,H)=10.4 Hz, ^3J(H,H)=5.7 Hz, 1H; 1-CH_2), 3.40 (dd, ^2J(H,H)=10.4 Hz, ^3J(H,H)=6.7 Hz, 1H; 1-CH_2), 1.78–1.68 (m, 1H; 2-CH), 1.65–1.54 (m, 2H; CH), 1.53–1.44 (m, 1H; CH), 1.38–0.97 (m, 11H; CH_2 and OH), 0.90 (d, ^3J(H,H)=6.7 Hz, 3H; 2′-CH_3), 0.88 (t, ^3J(H,H)=7.3 Hz, 3H; 11-CH_3), 0.82 (d, ^3J(H,H)=6.5 Hz, 3H; CH_3), 0.82 (d, ^3J(H,H)=6.6 Hz, 3H; CH_3), 0.80 ppm (d, ^3J(H,H)=6.5 Hz, 3H; CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): **δ**=69.07, 46.53, 45.50, 41.32, 40.22, 33.20, 29.71, 27.29, 27.16, 20.09, 19.60, 19.52, 19.39, 16.45, 14.40 ppm.

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Keywords: deoxypropionate motif • propylene • oligomerization • natural product synthesis

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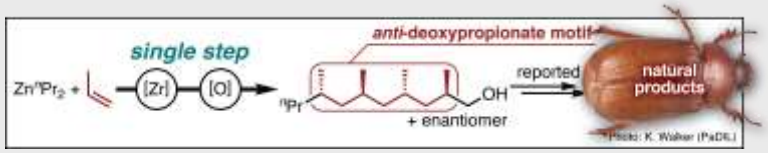

One giant leap: Herein we report the single-step construction of *anti*-configured deoxypropionate motif by syndiospecific propylene oligomerization. This strategy was applied to the single-step preparation of *rel*-(2*S*,4*R*,6*S*,8*R*)-2,4,6,8-tetramethylundecan-1-ol, the racemic mixture of the synthetic fragment of the cuticular hydrocarbons isolated from the cane beadle *Antitrogus parvulus*.

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