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# One-step Homologation for the Catalytic Asymmetric Synthesis of Deoxypropionates

Shiqing Xu,[†] Haijun Li,[†] Masato Komiyama, Akimichi Oda and Ei-ichi Negishi*

Dedicated to the memory of Professor Jean F. Normant

**Abstract:** A one-step homologation protocol for the synthesis of natural products containing deoxypropionate motif is described by the combination of ZACA–Pd-catalyzed vinylation and ZACA–oxidation reaction. Contrastive to most other synthetic strategies used to date that typically require 3 steps per deoxypropionate unit due to the functional-group interconversions, our one-step homologation strategy promises to provide a general and more efficient synthetic route toward deoxypropionate natural products as exemplified by significant improvements in the syntheses of intermediates and/or final products of mycolipenic acid **1** and its analogue **2**, (–)-rasfonin, *syn*- and *anti*-dicarboxylic acids **5** and **6**.

## Introduction

Deoxypropionate units, alternately methylated alkyl chain containing multiple stereogenic centers, are ubiquitous structural motifs found in a broad range of naturally occurring compounds derived from polyketide pathways.[1] Single deoxypropionate unit (1,3-dimethyl subunit) can be represented by two stereoarrays corresponding to *syn*- and *anti*-orientations of the methyl groups (Figure 1). A wide range of fascinating biological activities and pharmacological properties are associated with these structures, e.g., neutral sphingomyelinase inhibitor (+)-scyphostatin,[2] potent squalene synthase inhibitor zaragozic acid A,[3] antibiotics TMC-151 A,[4] pheromones (+)-4,6,8,10,16,18-hexamethyldocosane[5] and (–)-lardolure[6], glycolipids of Mycobacterium tuberculosis,[7] as well as apoptosis inducer (–)-rasfonin.[8]

In the light of the broad biological activities and abundance of this motif found in natural products, substantial efforts have been made to develop synthetic methods for the stereoselective construction of deoxypropionates.[9] The most common methods used to date are chiral auxiliary-controlled (aza)-enolate alkylations and conjugate additions, as well as substrate-controlled conjugate additions and allylic alkylations.[10] In addition to these stoichiometric approaches, catalytic enantioselective methods have also been introduced. Minnaard and Feringa reported an iterative catalytic route to deoxypropionate subunits by Cu-catalyzed asymmetric conjugate addition of Grignard reagents to α,β-unsaturated thioesters.[11] Burgess developed an iterative route based on

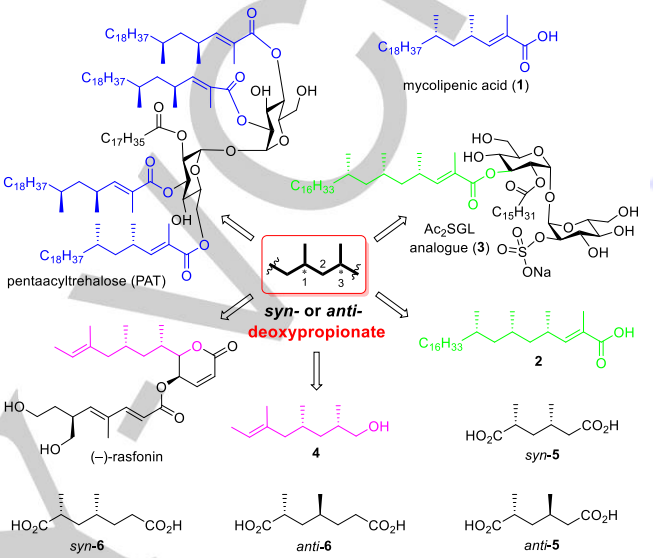


**Figure 1.** Representative examples of natural products and bioactive molecules containing deoxypropionate units.

Ir(I)-catalyzed asymmetric hydrogenation of enantio-enriched and stereodefined trisubstituted allylic alcohols and derivatives.[12] Recently, Aggarwal developed an assembly-line synthesis of deoxypropionates via iterative homologation of boronic esters with chiral lithiated benzoate esters and chloromethyllithium (Scheme 1d).[13] Despite the tremendous progress, the majority of reported methods have to install temporary directing groups or chiral auxiliaries to assist asymmetric C–C bond or C–H bond formation that are to be removed later. Thus, these methods suffer from long synthetic sequences and low efficiency requiring several functional-group interconversions between chain-growing steps (3–6 steps per unit) (Scheme 1a-c). Recently, convergent strategies for the synthesis of the long-chain polydeoxypropionate motif have been reported.[14] Most recently, Nozaki developed a novel one-step construction of deoxypropionate motif by stereo-controlled propylene oligomerization.[15] However, Nozaki's elegant methodology suffers from scope limitation (only all-*syn* deoxypropionate), and difficulty of chain length control leading to multiple oligomers mixtures with different number of deoxypropionate units. Therefore, strategies for highly efficient and stereoselective synthesis of deoxypropionate motif are still highly desirable.

Recently, we reported a highly convergent and enantioselective route to polydeoxypropionates exemplified as phthioceranic acid.[14d] Zr-catalyzed asymmetric carboalumination of alkenes (ZACA)[16]–Pd-catalyzed vinylation was used to prepare smaller deoxypropionate fragments, and then two key

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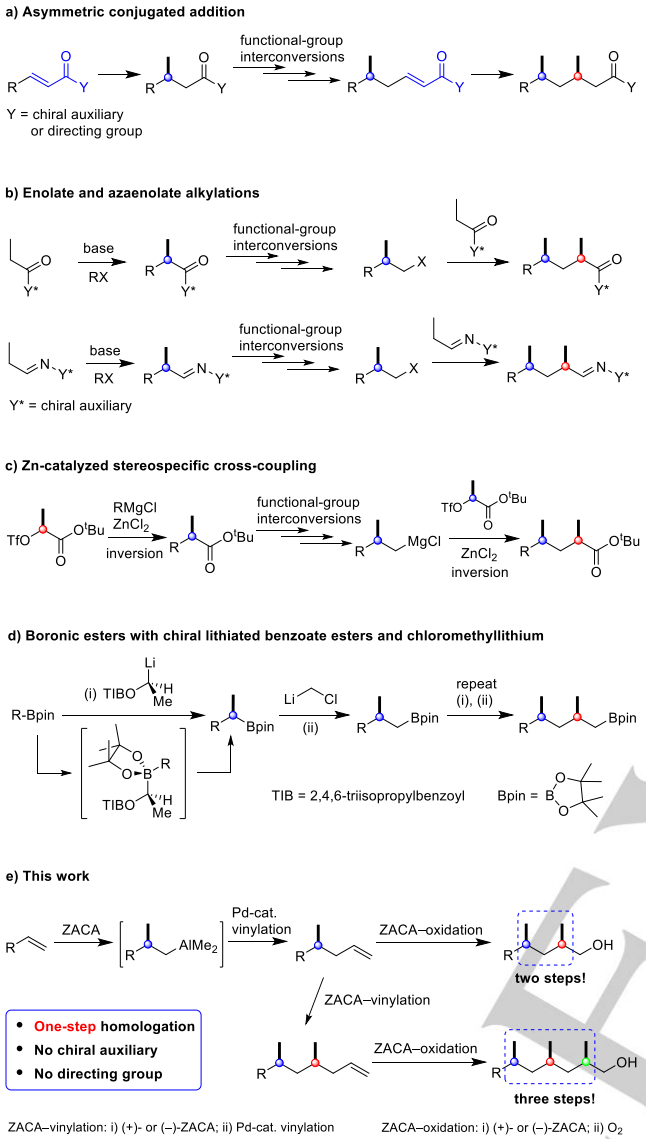



**Scheme 1.** Strategies of the synthesis of deoxypropionate units.

sequential Cu-catalyzed stereocontrolled $sp^3$–$sp^3$ cross-coupling reactions allowed convergent assembly of smaller building blocks to build-up long polydeoxypropionate chains with excellent stereoselectivity. In continuation of our efforts in the development of efficient methods for the construction of deoxypropionates, we report herein a one-step homologation protocol (one step per deoxypropionate unit, Scheme 1e) for highly concise and enantioselective synthesis of deoxypropionate natural products by the combination of ZACA–Pd-catalyzed vinylation and ZACA–oxidation reaction, which is contrastive to most other synthetic methods that require 3–6 steps per unit. This one-step homologation protocol heavily relies on three key features of ZACA reaction: (i) catalytic asymmetric C–C bond formation to introduce stereogenic carbon centers; (ii) many potential transformations of the initially formed alkylalane intermediates (*i.e.* in situ Pd-catalyzed vinylation, and oxidation with $O_2$); (iii) use of alkene substances of one-point-binding without requiring any directing groups (ability to repeat ZACA reaction after one-pot ZACA–Pd-catalyzed vinylation to realize one-step homologation synthesis of deoxypropionate motif). In this paper we show that mycolipenic acid **1** and its analogue **2**, (–)-rasfonin key intermediate **4**, and *syn*- and *anti*-dicarboxylic acids **5** and **6** (Figure 1) can be synthesized with high efficiency and stereoselectivity by using our one-step homologation protocol.

## Results and Discussion

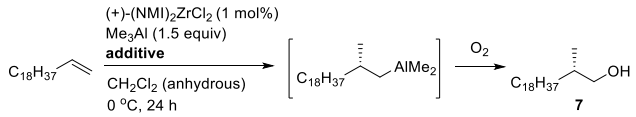
Our first two targets were mycolipenic acid **1** (side chain of pentaacyltrehalose) and its analogue **2** (side chain of an $Ac_2$SGL analogue). Pentaacyltrehalose (PAT),[17] diacylated sulfoglycolipid $Ac_2$SGL,[18] and polyacylated sulfoglycolipid SL-1[19] are three representative examples of cell-wall lipids exclusively found in virulent strains of *Mycobacterium tuberculosis*. Substantial studies revealed that these lipids can not only potentially be used as biomarkers, but also are promising candidates for new tuberculosis vaccines.[17-20] The common structural feature of these lipids is encompassing a trehalose as a central carbohydrate, which is acylated with various long-chain fatty acids, typically polymethylated chiral deoxypropionate chains (Figure 1). However, low availability of these lipids limited their further development as potential tuberculosis vaccines. The main challenge in total synthesis of these lipids is highly efficient and stereoselective synthesis of deoxypropionate side-chains.

Mycolipenic acid **1**, the major acyl residue found in pentaacyltrehalose, has been shown to be a potent inhibitor of leukocyte migration in vitro.[17,20] Mycolipenic acid **1** was first synthesized and characterized by Polgar et al. in 1958 by a lengthy route comprising a kinetic resolution.[21] Minnikin and co-workers synthesized **1** as a racemate in 1992.[22] Recently, Minnaard and Feringa reported a catalytic asymmetric synthesis of mycolipenic acid **1** by using an iterative three-step homologation procedure involving Cu-catalyzed asymmetric conjugate addition of MeMgBr to α,β-unsaturated thioesters (Scheme 1a), which required 14 longest linear steps in 3% overall yield from glycol.[23]

Our synthesis of mycolipenic acid **1** began with the ZACA reaction of 1-eicocene. It has been reported that water as an additive significantly affects reaction rate, enantioselectivity, and yield of ZACA reaction.[14d,24] We decided to survey different additives to optimize ZACA reaction.[25] Consistent with previous results,[14d] ZACA reaction of 1-eicocene did not occur in the absence of an additive (Table 1, entry 1). After addition of 2 mol% of water, ZACA reaction proceeded smoothly and provided desired (*S*)-2-methyl-1-eicosanol **7** of 77% *ee* in 71% yield after in situ oxidation with $O_2$ (entry 2). Similar to water, the addition of MAO (methylaluminoxane) and IBAO (isobutylaluminoxane) produced **7** of 75% *ee* in 72% yield, and 74% *ee* in 68% yield, respectively (entries 3 and 5). EAO (ethylaluminoxane) provided product **7** in 70% yield, but with a decreased enantiopurity of 69% *ee* (entry 4). To our delight, the use of 5 mol% TIBAO (tetraisobutyldialuminoxane) provided the

desired alcohol **7** in 78% yield and 85% *ee* (entry 6). The increased amount of TIBAO (10 mol%) led to a lower enantiopurity of 77% *ee* (entry 7). The exact mechanistic role of water and aluminoxanes remain unclear. Presumably, aluminoxanes can act as Lewis acid activators or co-activators to assist the formation of the active cationic zirconium complex.

**Table 1.** Additive effect on the ZACA reaction of 1-eicocene.

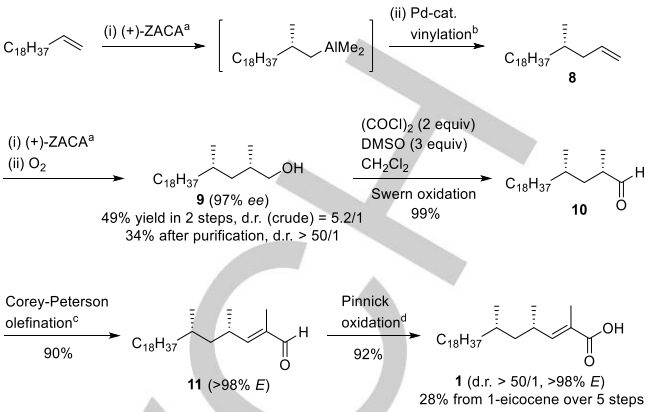



| Entry | Additive | Additive | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|
| 1 | none | none | 0 | NA |
| 2 | $H_2O$ | 2 mol% | 71 | 77 |
| 3 | MAO[c] | 5 mol% | 72 | 75 |
| 4 | EAO[d] | 5 mol% | 70 | 69 |
| 5 | IBAO[e] | 5 mol% | 68 | 74 |
| **6** | **TIBAO[f]** | **5 mol%** | **78** | **85** |
| 7 | TIBAO[f] | 10 mol% | 79 | 77 |

[a] Isolated yield. [b] Determined by $^1$H NMR of Mosher ester analysis of alcohol **7**. [c] Methylaluminoxane. [d] Ethylaluminoxane. [e] Isobutylaluminoxane. [f] Tetraisobutyldialuminoxane.

With the optimized reaction conditions in hand, we began the total synthesis of mycolipenic acid **1** as shown in Scheme 2. The key intermediate **9** was synthesized by ZACA-based one-step homologation strategy. 1-Eicocene was subjected to ZACA reaction in the presence of (+)-$(NMI)_2ZrCl_2$ (1 mol%),[26] $Me_3Al$ (1.5 equiv), and TIBAO (5 mol%), providing a chiral isoalkylalane intermediate. This isoalkyldimethylalane, generated by ZACA reaction, was directly used for Pd-catalyzed Negishi coupling with vinyl bromide in the presence of $Zn(OTf)_2$ and catalytic Pd(DPEphos)$Cl_2$/*i*-$Bu_2AlH$ with DMF as the solvent. This one-pot ZACA–Pd-catalyzed vinylation process produced alkene (*S*)-**8** in 70% GC yield after fast flash chromatography with hexane. Without further purification, crude alkene **8** was subjected to a second (+)-ZACA reaction followed by in situ oxidation with $O_2$ to afford the desired alcohol **9** (d.r. = 5.2/1) in 49% isolated yield. After purification by ordinary silica gel column chromatography, (2*S*,4*S*)-2,4-dimethyl-1-docosanol **9** (d.r. > 50/1, 97% *ee*) was obtained in 34% yield over 2 steps from 1-eicocene (Scheme 2). It should be noted that the previous synthesis of **9** required 11 longest linear steps (11% overall yield) from glycol.[23]

Swern oxidation[27] of **9** produced aldehyde **10** in almost quantitative yield. The crudely obtained aldehyde **10** was subjected to Corey-Peterson olefination[28] with $Et_3SiCLi(Me)CH{=}NCy$ (in situ generated by treating *N*-cyclohexyl(2-triethylsilylpropylidene)imine with $^s$BuLi at –78 °C). After treatment with $CF_3CO_2H$, the desired aldehyde **11** of >98% *E* was obtained in 90% yield. In the previously reported synthesis of mycolipenic acid **1**, aldehyde **10** was converted to the corresponding enoate ester by Wittig reaction with the formation of 10% *Z*-isomer.[23] Finally, conversion of aldehyde **11**




**Scheme 2.** Synthesis of mycolipenic acid **1**. Reaction conditions: [a] (+)-$(NMI)_2ZrCl_2$ (1 mol%), $AlMe_3$ (1.5 equiv), TIBAO (5 mol%), DCM, 0 °C. [b] i) $Zn(OTf)_2$ (1.2 equiv), DMF; ii) $PdCl_2$(DPEPhos) (3 mol%), DIBAL-H (6 mol%), vinylbromide (6 equiv). [c] i) $Et_3SiCLi(Me)CH{=}NCy$ (1.3 equiv), –20 °C; ii) $CF_3COOH$ (2 equiv), 0 °C; iii) $H_2O$, 0 °C. [d] $NaClO_2$ (1.4 equiv), $NaH_2PO_4{\cdot}H_2O$ (1.1 equiv), 2-methyl-2-butene (10 equiv), $H_2O$/$^t$BuOH, 23 °C.

to carboxylic acid by Pinnick oxidation[29] under very mild conditions completed the total synthesis of mycolipenic acid **1** in 28% overall yield over 5 steps from 1-eicocene. There was no sign of epimerization throughout these steps. Its spectral data as well as $[\alpha]_D^{26}$ = + 17.79° (c = 2.08, $CHCl_3$) are in good agreement with those reported previously.[23]

To further demonstrate the utility of our ZACA-based one-step homologation strategy for the synthesis of deoxypropionates, we executed the synthesis of trimethyl-branched **2** as summarized in Scheme 3. (+)-(4*S*,6*S*,8*S*,*E*)-2,4,6,8-Tetramethyltetracos-2-enoic acid **2** is the key side-chain of an $Ac_2SGL$ analogue **3** which showed the most promising T-lymphocyte-activation activity among a series of analogues (Figure 1).[30] The chain length has been shown to be of utmost importance for high antigenicities. The previously reported synthesis of **2** used an iterative hydrazone lithioenamine (azaenolate) alkylation of four-step homologation protocol (Scheme 1b).[30] Its major drawback is the use of stoichiometric amounts of the expensive chiral auxiliary three times as well as long synthetic sequences. In our synthesis, the preparation of the key trimethyl-branched intermediate **14** was achieved only in three steps from 1-octadecene as shown in Scheme 3. 1-Octadecene was subjected to two rounds of (+)-ZACA–Pd-catalyzed vinylation followed by a third (+)-ZACA reaction and in situ oxidation with $O_2$. The crude alcohol **14** was thus obtained in 35% yield over three steps from 1-octadecene containing minor amounts of other diastereomers (d.r. = 18.6/1.6/2/1). This crude alcohol **14** could be purified by ordinary column chromatography to give a pure **14** (>99% *ee*, d.r. > 40/1) in 15% yield from 1-octadecene. After Swern oxidation, Corey-Peterson olefination, and Pinnick oxidation, trimethyl-branched deoxypropionate **2** was thus synthesized in 12% yield over six steps from 1-octadecene.

In order to explore the scope of our ZACA-based one-step homologation strategy, a key intermediate **4** in recently reported syntheses of (–)-rasfonin[31] was chosen. (–)-Rasfonin was isolated from the fermented mycelium of Taleromyces species

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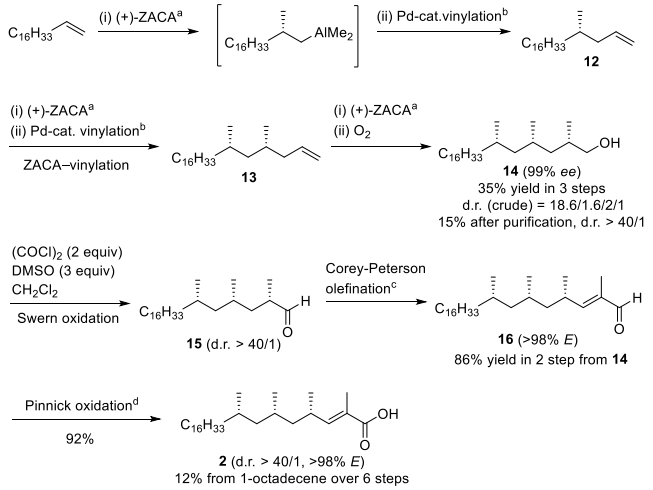
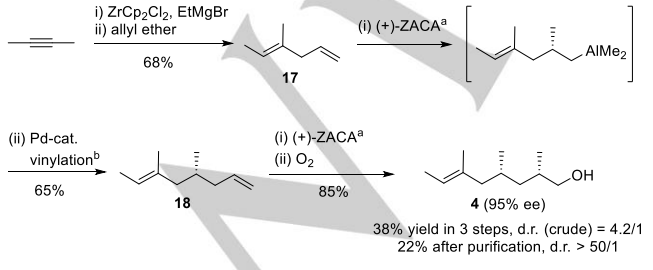


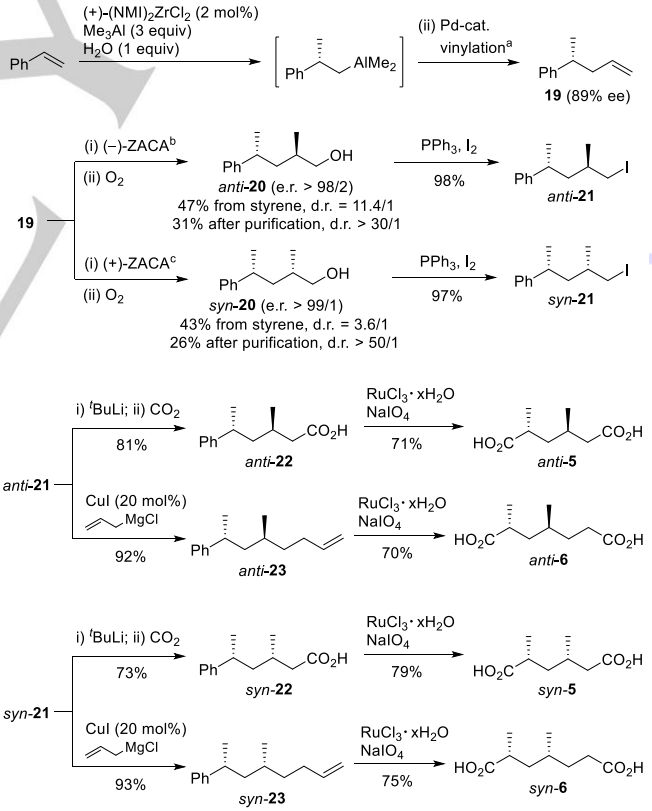

**Scheme 3.** Synthesis of mycolipenic acid analogue **2**. Reaction conditions (a–d) are the same as described in Scheme 2.

3565-A1.[31] Recent studies have indicated that (–)-rasfonin is an active apoptosis inducer in *ras* dependent cells, having potential use for the development of novel cancer chemotherapeutics.[32,33] Compound **4** was synthesized as an intermediate for the total synthesis of (–)-rasfonin in 2006 by Boeckman based on the use of camphor lactam chiral auxiliaries in 12 steps (longest linear sequence) from (–)-camphoric acid,[31a] and in 2012 by Minnaard in 12 steps from glycol,[31b] respectively. Our synthesis of **4** is very simple as summarized in Scheme 4. Carbozirconation reaction of 2-butyne with $ZrCp_2Cl_2$ and EtMgBr, followed by in situ treatment with allylic ether, provided 1,4-diene **17** in 68% yield.[34] The ZACA reaction of 1-alkene **17** containing a proximal π-bond was slower compared to those of alkenes without any other functional groups, such as 1-eicocene and 1-octadecene. Such difficulty was solved by the use of promotor MAO (5 mol%), increased amount of (+)-$(NMI)_2ZrCl_2$ catalyst (3 mol%), and higher temperature (23 °C). Then after in situ Pd-cataylzed vinylation, alkene **18** was subjected to a second (+)-ZACA reaction followed by oxidation providing **4** (d.r = 4.2/1) in 85% yield. The undesired diastereomer of **4** was removed by ordinary column chromatography. Thus, **4** (d.r > 50) was synthesized in 22% yield over just 3 steps from 2-butyne.




**Scheme 4.** Synthesis of (–)-rasfonin key intermediate **4**. Reaction conditions: [a] (+)-$(NMI)_2ZrCl_2$ (3 mol%), $AlMe_3$ (1.5 equiv), MAO (5 mol%), DCM, 23 °C, 16 h. [b] i) $Zn(OTf)_2$ (1.2 equiv), DMF; ii) $PdCl_2$(DPEPhos) (3 mol%), DIBAL-H (6 mol%), vinylbromide (6 equiv).

To further demonstrate its synthetic utility, one-step homologation strategy was applied to the synthesis of *syn*- and *anti*-dicarboxylic acids **5** and **6**, identified as the metabolites in human blood and urine,[35] and the fatty components of Pollen Typhae (a traditional Chinese herbal medicine widely used to treat the hemorrhagic diseases both by external and oral application)[36]. The synthesis of *syn*- and *anti*-dicarboxylic acids **5** and **6** was summarized in Scheme 5. The (+)-ZACA reaction of styrene proceeded smoothly with the addition of 1 equivalent of water, followed by Pd-catalyzed vinylation, providing alkene (*S*)-**19**. Alkene (*S*)-**19** was subjected to (–)-ZACA and (+)-ZACA reaction by using different enantiomer of $(NMI)_2ZrCl_2$ catalyst, producing *anti*-pamplefleur **20** (d.r = 11.4/1) and *syn*-pamplefleur **20** (d.r. = 3.6/1) in 47% and 43% yield from styrene, respectively Both crude *anti*- and *syn*-pamplefleur **20** can be purified by ordinary column chromatography to remove the minor diastereomer. It should be noted that the odor response of pamplefleur isomers **20** is rather unusual in the realm of chiral fragrances.[37] All the four stereoisomers of pamplefleur **20** were synthesized by using lipase-catalyzed kinetic resolution of racemic primary alcohols from 2-phenyl-1-propanol in 6–8 steps and extremely low overall yield (<1%) due to the poor enantioselectivity of the kinetic resolutions.[37]

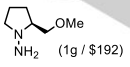



**Scheme 5.** Synthesis of *syn*- and *anti*- dicarboxylic acids **5** and **6**. Reaction conditions: [a] i) $Zn(OTf)_2$ (1.2 equiv), DMF; ii) $PdCl_2$(DPEPhos) (3 mol%), DIBAL-H (6 mol%), vinylbromide (6 equiv). [b] (–)-$(NMI)_2ZrCl_2$ (2 mol%), $AlMe_3$ (1.5 equiv), TIBAO (5 mol%), DCM. [c] (+)-$(NMI)_2ZrCl_2$ (2 mol%), $AlMe_3$ (1.5 equiv), TIBAO (5 mol%), DCM.

*Anti*- and *syn*-pamplefleur **20** were converted to their corresponding iodide **21**. *Anti*-**21** was treated with 2.1 equivalents of $^{t}$BuLi followed by the addition of dry ice providing carboxylic acid *anti*-**22** in 81% yield, which was further converted to dicarboxylic acid *anti*-**5** by oxidative cleavage of phenyl group with $RuCl_3/NaIO_4$.[38] The synthesis of *anti*-**6** was achieved by CuI-catalyzed allylation of iodide *anti*-**21** with allylmagnesium chloride to produce alkene *anti*-**23** in 92% yield. $RuCl_3$-catalyzed oxidation of both phenyl ring and terminal double bond of **23** to the carboxylic acid groups completed the synthesis of *anti*-**6**. The dicarboxylic acids *syn*-**5** and *syn*-**6** were efficiently synthesized in the similar route from iodide *syn*-**21**. Through the comparison of the NMR spectra of *anti*- and *syn*-**5**, as well as *anti*- and *syn*-**6**, no epimerization was observed during the transformations.

A comparison of current and previous syntheses of natural products containing deoxypropionate motif was summarized in Table 2, which clearly indicates the substantial improvements accomplished in our synthesis by using ZACA-based one-step homologation protocol. Thus, this one-step homologation strategy promises to provide a facile general and more efficient synthetic route toward natural products containing the deoxypropionate motif.

**Table 2.** Comparison of current and previous syntheses of deoxypropionates.

| Compound | Major author | No. of steps | Overall yield (%) | Starting compound | Ref. (year) |
|---|---|---|---|---|---|
| **9** | **current work** | **2** | **34** | **1-eicocene** | |
| **9** | Minnaard and Feringa | 11 | 11 | glycol | 23 (2010) |
| **1** | **current work** | **5** | **28** | **1-eicocene** | |
| **1** | Minnaard and Feringa | 14 | 3 | glycol | 23 (2010) |
| **2** | **current work** | **6** | **12** | **1-octadecene** | |
| **2** | Prandi | >12 | N.A. |  (1g / $192) | 30 (2008) |
| **4** | **current work** | **3** | **22** | **2-butyne** | |
| **4** | Boeckman | 12 | 18 | (–)-camphoric acid | 31a (2006) |
| **4** | Minnaard and Feringa | 12 | 35 | glycol | 31b (2012) |
| *anti*-**20** | **current work** | **2** | **31** | **styrene** | |
| *anti*-**20** | Brenna | 8 | <1 | 2-phenyl-1-propanol | 37 (2005) |
| *syn*-**20** | **current work** | **2** | **26** | **styrene** | |
| *syn*-**20** | Brenna | 7 | <1 | 2-phenyl-1-propanol | 37 (2005) |
| *anti*-**5**, **6** *syn*-**5**, **6** | **current work** *(no previous asymmetric synthesis)* | | | | |

## Conclusions

In summary, a general approach to deoxypropionate natural products through ZACA-based one-step homologation protocol is described by the combination of ZACA–Pd-catalyzed vinylation and ZACA–oxidation reaction. Both *syn*- and *anti*-deoxypropionate motif, found in a number of natural products, can be constructed by altering different enantiomer of $(NMI)_2ZrCl_2$ catalyst. Our one-step homologation strategy heavily relies on three key features of ZACA reaction: (i) catalytic asymmetric C–C bond formation, (ii) many potential transformations of the initially formed alkylalane intermediates and, (iii) use of alkene substances of one-point-binding without requiring any directing groups. Although there is room for further improvements, especially of the modest enantioselectivity of ZACA reaction which would limit the yields of isomerically pure products. The one-step homologation protocol presented herein promises to provide a general, efficient, and satisfactory route to deoxypropionates as exemplified by significant improvements in the syntheses of intermediates and/or final products of mycolipenic acid **1** and its analogue **2**, (–)-rasfonin, and *syn*- and *anti*-dicarboxylic acids **5** and **6**.

## Experimental Section

**General information:** All reactions were run under a dry Argon atmosphere. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25-mm Merck silica gel plates (60F-254) or by GC analysis of reaction aliquots. Flash chromatographic separations were carried out on 230-400 mesh silica gel. $^{1}$H and $^{13}$C NMR spectra were recorded on Varian-Inova-300, Bruker-ARX-400 or Bruker Avance-III-800 Optical rotations were measured on an Autopol III automatic polarimeter. THF and ether was dried by distillation under argon from sodium/benzophenone. $CH_2Cl_2$ was dried by distillation under argon from $CaH_2$. (–)-$(NMI)_2ZrCl_2$ and (+)-$(NMI)_2ZrCl_2$[26] were prepared as reported in the literature. Other commercially available solvents and reagents were of reagent grade and used without further purification.

**(4*S*)-4-Methyl-docos-1-ene (8).** To a solution of (+)-$(NMI)_2ZrCl_2$ (268 mg 0.4 mmol, 1 mol%) in $CH_2Cl_2$ (120 mL) at 23 °C were added $Me_3Al$ (6 mL 60 mmol, 1.5 equiv) under argon. Then the resultant solution was cooled to 0 °C, and tetraisobutyldialuminoxane solution (TIBAO) (10 wt. % in toluene, 6.9 mL, 2 mmol, 5 mol%) was added dropwise at 0 °C. The reaction mixture was stirred at 0°C for 15 min, and 1-eicosene (11.6 g, 13.7 mL, 40 mmol) was added dropwise. After the mixture was stirred at 0 °C for 24 h, the solvent as well as excess $Me_3Al$ were evaporated *in vacuo*. Then flamed-dried $Zn(OTf)_2$ (17.5 g, 48 mmol, 1.2 equiv) in 120 mL of DMF was added dropwise at 0 °C, and the mixture was stirred for 2 h at 70 °C. In another flask, Pd(DPEphos)$Cl_2$ (0.86 g, 1.2 mmol, 3 mol%) was dissolved in THF (20 mL) followed by dropwise addition of a solution of DIBAL-H in hexanes (1 M, 2.4 mL, 2.4 mmol, 6 mol%). After 10 min, vinyl bromide (16.9 mL, 240 mmol, 6.0 equiv) was added to the above the Pd catalyst solution under 0 °C, which then was transferred to the above DMF solution at 0 °C. After stirring for 12 h at 0 °C and another 2 h under room temperature, the reaction was quenched with 2*N* HCl, filtered through celite, extracted with hexanes, washed with saturated aqueous $NaHCO_3$ solution and Brine, dried over anhydrous $Na_2SO_4$, concentrated, and purified by column chromatography (silica gel, hexanes as eluent) to afford the crude title product without further purification (70% yield).

**(2*S*,4*S*)-2, 4-Dimethyl-docosan-1-ol (9).** To a solution of (+)-$(NMI)_2ZrCl_2$ (201 mg, 0.3 mmol) in $CH_2Cl_2$ (100 mL) at 23 °C were added $Me_3Al$ (4.5 mL, 45 mmol) under argon. Then the resultant solution was cooled to 0 °C, and TIBAO (10 wt. % in toluene, 5.2 mL, 1.5 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, and (4*S*)-4-methyl-docos-1-ene **8** (crude product from 40 mmol of 1-eicosene) in 20 mL of $CH_2Cl_2$ was added dropwise. After stirring at 0 °C for 24 h, the reaction mixture was treated with a vigorous stream of $O_2$

bubbled through a needle at 0 °C for 4 h. The reaction was then quenched with 2*N* HCl, extracted with $Et_2O$, washed with saturated aqueous $NaHCO_3$ solution and Brine, dried over anhydrous $Na_2SO_4$, concentrated, and purified by column chromatography (silica gel, 9/1 of hexanes/ethyl acetate) to afford the title product (6.9 g, 49% from 1-eicosene, d.r. = 5.2/1). The product was further purified by column chromatography (silica gel, 0 to 2% gradient ethyl acetate in hexanes) to give the title product (4.8 g, 34% from 1-eicosene, d.r. > 50/1, 97% *ee*). $[\alpha]_D^{26.4}$ = –7.71° (c = 1.40, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): δ 0.86–0.93 (m, 9 H), 1.00–1.10 (m, 1 H), 1.12–1.40 (m, 35 H), 1.40–1.57 (m, 1 H), 1.63–1.80 (m, 1 H), 3.35–3.55 (m, 2 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 14.08, 17.30, 20.33, 22.68, 26.90, 29.38, 29.72, 30.05, 31.93, 33.10, 36.68, 41.11, 68.27. HRMS calcd for $C_{24}H_{50}ONa$ $[M+Na]^+$: 377.3759, found 377.3745.

**(2*S*,4*S*)-2,4-Dimethyldocosanal (10).** To a stirred solution of oxalyl chloride (0.35 mL, 4.0 mmol) in 10 mL of $CH_2Cl_2$ at –78 °C was added dropwise DMSO (0.43 mL, 6.0 mmol) in 5 mL of $CH_2Cl_2$ *via* cannula. After 30 min stirring at –78 °C, (2*S*,4*S*)-2,4-dimethyl-docosan-1-ol **9** (709 mg, 2.0 mmol) in 20 mL of $CH_2Cl_2$ was added slowly and dropwise. The resulting white heterogeneous mixture was stirred at –78 °C for 2 h, and $Et_3N$ (1.12 mL, 8.0 mmol) was added. After 30 min at –78 °C, the mixture was warmed to 23 °C for 4 h and 10 mL of $H_2O$ was added. The aqueous layer was extracted with $Et_2O$ three times. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The title product was obtained as orange oil (699 mg, 99%) and used directly to the next reaction without further purification. $^1$H NMR (300 MHz, $CDCl_3$): δ 0.83–0.87 (m, 6 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 1.08–1.36 (m, 36 H), 1.65–1.72 (m, 1 H), 2.36–2.45 (m, 1 H), 9.55 (d, *J* = 2.4 Hz, 1 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 13.9, 14.0, 19.7, 22.6, 26.7, 29.3, 29.6, 29.8, 30.3, 31.8, 36.6, 38.2, 44.0, 205.0. HRMS calcd for $C_{24}H_{48}ONa$ $[M+Na]^+$: 375.3603, found 375.3591.

**(4*S*,6*S*,*E*)-2,4,6-Trimethyltetracos-2-enal (11).** $^s$BuLi (1.85 mL, 1.4 M in cyclohexane, 2.6 mmol) was added dropwise to a solution of 2-triethylsilylpropionaldehyde-*N*-cyclohexylimine (0.76 g, 3.0 mmol) in 20 mL of THF at –78 °C. After stirring at –78 °C for 1 h, (2*S*,4*S*)-2,4-dimethyldocosanal **10** (699 mg, 1.98 mmol) in THF (20 mL) was added dropwise. The solution was immediately warmed to –20 °C, maintained at this temperature for 4 h, quenched with $H_2O$, and extracted three times with $Et_2O$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. The oil thus obtained was dissolved in 20 mL of dry THF and cooled to 0 °C, where upon $CF_3CO_2H$ (0.31 mL, 4.0 mmol) was added slowly with stirring. The reaction mixture was stirred at 0 °C for 2 h, quenched with 10 mL of $H_2O$, maintained at 0 °C for 12 h, and poured into saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over $Na_2SO4$, and concentrated. The residue was purified by flash chromatography (1/20 EtOAc/hexane) to provide the title product (710 mg, 90% yield over 2 steps from **9**). $[\alpha]_D^{26.7}$ = +2.61° (c = 1.69, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): δ 0.88 (d, *J* = 4.4 Hz, 3 H), 0.92 (t, *J* = 4.8 Hz, 3 H), 1.08 (d, *J* = 4.4 Hz, 3 H), 1.22–1.34 (m, 36 H), 1.42–1.45 (m, 1 H), 1.80 (s, 3 H), 2.81–2.89 (m, 1 H), 6.25 (d, *J* = 6.4 Hz, 1 H), 9.43 (s, 1 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 9.1, 13.9, 19.4, 20.2, 22.6, 26.8, 29.3, 29.6, 29.8, 30.7, 31.0, 31.8, 37.4, 44.3, 137.7, 160.1, 194.9. HRMS calcd for $C_{27}H_{52}ONa$ $[M+Na]^+$: 415.3916, found 415.3900.

**Mycolipenic acid (1).** A solution of 80% chemically pure $NaClO_2$ (158 mg, 1.4 mmol) and $NaH_2PO_4{\cdot}H_2O$ (155 mg, 1.1 mmol) in $H_2O$ (5 mL) was added dropwise to a rapidly stirred solution of aldehyde **11** (392 mg, 1.0 mmol) and 2-methyl-2-butene (1.07 mL, 10 mmol) in *tert*-butanol (5 mL) at 23 °C. The resultant solution was stirred for 12 h at 23 °C. Then the reaction mixture was quenched with 2*N* HCl and extracted four times with ether. The extracts were washed with brine and water, dried over $Na_2SO_4$, concentrated and purified by flash silica gel column chromatography to give the title compound (1/10 EtOAc/hexane) in 92% isolated yield (376 mg). $[\alpha]_D^{26.6}$ = +17.79° (c = 2.08, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): δ 0.87 (d, *J* = 4.4 Hz, 3 H), 0.92 (t, *J* = 4.8 Hz, 3 H), 1.03 (d, *J* = 4.4 Hz, 3 H), 1.11–1.16 (m, 1 H), 1.17–1.21 (m, 1 H), 1.28–1.36 (m, 34 H), 1.38–1.43 (m, 1 H), 1.89 (s, 3 H), 2.65–2.70 (m, 1 H), 6.70 (d, *J* = 6.8 Hz, 1 H), 12.36 (bs, 1 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 11.9, 14.0, 19.5, 20.3, 22.6, 26.8, 29.3, 29.7, 29.9, 30.7, 31.0, 31.9, 37.5, 44.4, 125.4, 150.9, 174.1. HRMS calcd for $C_{27}H_{52}O_2Na$ $[M+Na]^+$: 431.3865, found 431.3850.

**(2*S*,4*S*,6*S*)-2,4,6-Trimethyldocosan-1-ol (14).** To a solution of (+)-$(NMI)_2ZrCl_2$ (152 mg, 0.23 mmol, 1 mol%) in $CH_2Cl_2$ (100 mL) at 23 °C were added $Me_3Al$ (3.4 mL, 34.2 mmol) under argon. Then the resultant solution was cooled to 0 °C, TIBAO (10 wt. % in toluene, 3.93 mL, 1.14 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, and crude (4*R*,6*S*)-4,6-dimethyldocos-1-ene **13** (product from 30.8 mmol of (*S*)-4-methylicos-1-ene **12**) in 20 mL of $CH_2Cl_2$ was added dropwise. After stirring at 0 °C for 24 h, the reaction mixture was treated with a vigorous stream of $O_2$ bubbled through a needle for 4 h at 0 °C. The reaction was then quenched with 2*N* HCl, extracted with $Et_2O$, washed with saturated aqueous $NaHCO_3$ solution and Brine, dried over anhydrous $Na_2SO_4$, concentrated, and purified by column chromatography (silica gel, 9/1 of hexanes/ethyl acetate) to afford the title product (5.16 g, 35% from 1-eicosene, d.r. = 18.6/1.6/2/1). The crude product was further purified by column chromatography (silica gel, 0 to 1 % gradient ethyl acetate in hexanes) to give the title product (2.2 g, 15% from 1-octadecene, d.r. > 40/1, *ee* >99%). $[\alpha]_D^{26.4}$ = –12.12° (c = 1.60, $CHCl_3$).$^1$H NMR (300 MHz, $CDCl_3$): δ 0.83–0.94 (m, 12 H), 0.97–1.02 (m, 1 H), 1.18–1.32 (m, 33 H), 1.47–1.50 (m, 1 H), 1.55–1.60 (m, 1 H), 1.69–1.76 (m, 1 H), 3.33–3.38 (m, 1 H), 3.51–3.55 (m, 1 H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 14.0, 17.5, 20.4, 20.8, 22.6, 26.8, 27.5, 29.3, 29.6, 29.9, 30.0, 31.8, 33.0, 36.4, 41.2, 45.1, 68.1. HRMS calcd for $C_{25}H_{52}ONa$ $[M+Na]^+$: 391.3916, found 391.3902.

**(4*S*,6*S*,8*S*,*E*)-2,4,6,8-Tetramethyltetracos-2-enoic acid (2).** A solution of 80% chemically pure $NaClO_2$ (79.2 mg, 0.7 mmol) and $NaH_2PO_4{\cdot}H_20$ (77.5 mg, 0.55 mmol) in water (3 mL) was added dropwise to a rapidly stirred solution of aldehyde **16** (204 mg, 0.5 mmol) and 2-methyl-2-butene (0.54 mL, 5 mmol) in *tert*-butanol (3 mL) at room temperature. The resultant solution was stirred for 12 h at room temperature, then it was quenched with 2*N* HCl and extracted four times with ether. The extracts were washed with brine and water, dried over $Na_2SO_4$, concentrated and purified by flash silica gel column chromatography to give the desired compound (1/10 EtOAc/hexane) in 92% isolated yield (196 mg). $[\alpha]_D^{26.7}$ = +21.80° (c = 2.00, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$): δ 0.85 (d, *J* = 4.4 Hz, 3 H), 0.87 (d, *J* = 4.0 Hz, 3 H), 0.92 (t, *J* = 4.8 Hz, 3 H), 1.03 (d, *J* = 4.4 Hz, 3 H), 1.10–1.15 (m, 1 H), 1.18–1.35 (m, 33 H), 1.39–1.45 (m, 1 H), 1.49–1.52 (m, 1 H), 1.90 (s, 3 H), 2.65–2.74 (m, 1 H), 6.70 (d, *J* = 6.8 Hz, 1 H); $^{13}$C NMR ( 101 MHz, $CDCl_3$) δ 12.1, 14.1, 20.0, 20.4, 20.5, 22.7, 27.0, 28.2, 29.4, 29.7, 29.9, 30.0, 31.1, 31.9, 37.1, 44.2, 45.6, 125.5, 151.0, 174.1. HRMS calcd for $C_{28}H_{54}O_2Na$ $[M+Na]^+$: 445.4022, found 445.4004.

**(2*S*,4*R*,*E*)-2,4,6-Trimethyloct-6-en-1-ol (4).** To a solution of (+)-$(NMI)_2ZrCl_2$ (64 mg, 0.095 mmol) in $CH_2Cl_2$ (7.9 mL) at 23 °C were added $Me_3Al$ (0.46 mL, 4.77 mmol) under argon. After 5 min, the resultant solution was cooled to 0 °C, and the crude **18** (3.18 mmol) in $CH_2Cl_2$ (7.9 mL) was added dropwise. The reaction mixture was allowed to warm up to 23 °C and stirred for 24 h. Then 10% methylaluminoxane in toluene (0.11 mL, 0.16 mmol) was added at 0 °C. The resultant mixture was warmed up to 23 °C and stirred for additional 18 h. The reaction mixture was treated with a vigorous stream of $O_2$ bubbled through a needle for 3 h at 0 °C. The reaction was then quenched with 2 *N* HCl, extracted with $CH_2Cl_2$, washed with saturated aqueous $NaHCO_3$ solution and Brine, dried over $MgSO_4$, concentrated, and purified by column chromatography (silica gel, 8 % ethyl acetate in hexanes) to afford the title product (460 mg, 85% yield, d.r. = 4.2/1) as a colorless oil.

The product was further purified by column chromatography (silica gel, 0 to 8 % gradient ethyl acetate in hexanes) to give the title product (265 mg, d.r. > 50/1, 95% *ee*). $[\alpha]_D^{23}$ = –8.82° (c 0.23, $CH_2Cl_2$). $^1$H NMR (800 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.2 Hz, 3 H), 0.90–0.96 (m, 4 H), 1.24–1.30 (m, 2 H), 1.56 (s, 3 H), 1.58 (d, *J* = 6.7 Hz, 3 H), 1.63–1.70 (m, 2 H), 1.70–1.78 (m, 1H), 2.01 (q, *J* = 9.6 Hz, 1 H), 3.35–3.42 (m, 1 H), 3.49–3.57 (m, 1 H), 5.18 (qd, *J* = 6.7, 1.2 Hz, 1 H). $^{13}$C NMR (201 MHz, $CDCl_3$) δ 13.36, 15.56, 17.44, 20.21, 28.13, 33.17, 40.94, 47.60, 68.30, 119.87, 134.58. HRMS calcd for $C_{11}H_{23}O$ $[M+H]^+$ : 171.1749, found 171.1743.

**(2*R*,4*R*)-2-Methyl-4-phenylpentan-1-ol (*anti*-20).** To a solution of (–)-$(NMI)_2ZrCl_2$ (230 mg, 0.34 mmol, 2 mol%) in $CH_2Cl_2$ (24 mL) at 23 °C was added $Me_3Al$ (2.47 mL, 25.8 mmol) under argon. After 5 min, the resultant solution was cooled to 0 °C, and to the solution was added tetraisobutylaluminoxane (0.86 mmol) in $CH_2Cl_2$ (6.9 mL). The reaction mixture was stirred for 10 min, and (*R*)-pent-4-en-2-ylbenzene **19** (17.2 mmol) in $CH_2Cl_2$ (3.4 mL) was added dropwise. After stirring at 0 °C for 20 h, the reaction mixture was treated with a vigorous stream of oxygen bubbled through a needle for 3 h at 0 °C. The reaction was then quenched with 2*N* HCl, extracted with $CH_2Cl_2$, washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, concentrated, and purified by column chromatography (silica gel, 8 % ethyl acetate in hexanes) to afford the title product (2.67 g, 87%, d.r. = 11.4/1) as a colorless oil. The product was further purified by column chromatography (silica gel, 0 to 8 % gradient ethyl acetate in hexanes) to give the title product (1.79 g, 58%, d.r. > 30/1, e.r. > 98/2) as colorless oil. $[\alpha]_D^{23}$ = –0.42° (c 2.9, $CH_2Cl_2$). $^1$H NMR (800 MHz, $CDCl_3$) δ 0.90 (d, *J* = 6.7 Hz, 3 H), 1.22 (d, *J* = 6.9 Hz, 3 H), 1.31 (s, 1 H), 1.39–1.46 (m, 1 H), 1.57–1.67 (m, 2 H), 2.78–2.85 (m, 1 H), 3.42 (dd, *J* = 10.5, 6.2 Hz, 1 H), 3.50 (dd, *J* = 10.5, 5.1 Hz, 1 H), 7.14–7.22 (m, 3 H), 7.26–7.31 (m, 2 H).$^{13}$C NMR (201 MHz, CDCl3) δ 16.95, 22.23, 33.52, 37.18, 41.97, 68.15, 125.93, 126.91, 128.42, 147.92.

**(3*R*,5*R*)-3-Methyl-5-phenylhexanoic acid (*anti*-22).** To a solution of ((2*R*,4*R*)-5-iodo-4-methylpentan-2-yl)benzene *anti*-**21** (173 mg, 0.60 mmol) in Pentane / $Et_2O$ = 3/2 (3 mL) at –78 °C was added 1.7 M *t*BuLi in pentane (0.74 mL, 1.26 mmol) under argon. After 5 min, the resultant solution was transferred into dry ice (132 mg, 3 mmol) in pentane / $Et_2O$ = 3 / 2 (3.0 mL) at –78 °C, followed by quickly adding the same amount of dry ice (132 mg, 3 mmol). The reaction mixture was allowed to warm up to 23 °C, stirred for 1 h, and quenched through the addition of half saturated $NaHCO_3$ aq. until the aqueous pH around 8. The aqueous layer was separated, and the organic layer was extracted with half saturated $NaHCO_3$ aq. twice. The combined aqueous layer was acidified with 6*N* HCl dropwise at 0 °C, extracted with EtOAc three times. The combined organic layer was washed with brine, dried over $MgSO_4$, concentrated, and used in the next step without further purification (101 mg, 81%). $[\alpha]_D^{24}$ = +4.9° (c 3.4, $CDCl_3$). $^1$H NMR (800 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.7 Hz, 3 H), 1.23 (d, *J* = 6.9 Hz, 3 H), 1.48–1.53 (m, 1 H), 1.53–1.60 (m, 1 H), 1.91–1.97 (m, 1 H), 2.15 (dd, *J* = 15.1, 8.3 Hz, 1 H), 2.37 (dd, *J* = 15.1, 5.5 Hz, 1 H), 2.73–2.82 (m, 1 H), 7.15–7.20 (m, 3 H), 7.26–7.30 (m, 2 H), 11.58 (s, 1 H).

**(2*R*,4*R*)-2,4-dimethylhexanedioic acid (*anti*-5).** To a solution of (3*R*,5*R*)-3-methyl-5-phenylhexanoic acid *anti*-**22** (0.49 mmol) in MeCN (2.5 mL), $CCl_4$ (2.5 mL), and water (5.0 mL) at 0 °C were added sodium periodate (1.57 g, 7.32 mmol) and Ruthenium(III) chloride hydrate (25 mg, 0.10 mmol) under argon. After vigorously stirring at 0 °C for 6 h and 8 °C for 14 h, the resulting mixture was filtered through a sheet of filter paper, and washed with water (2.5 mL) and $CH_2Cl_2$ (10 mL). The aqueous layer was extracted with EtOAc (10 mL) three times. To the combined organic layer was added sat. $NaHCO_3$ aq. (1.9 mL) and $H_2O$ (1.9 mL) to adjust the pH to 8. After vigorously stirring for 15 min, the mixture was filtered through celite pad, and washed with water (7.5 mL). The organic layer was extracted with mixture of sat. $NaHCO_3$ aq. (0.94 mL) and $H_2O$ (8.4 mL) twice. To the combined aqueous layer was added 6*N* HCl aq. (0.81 mL) to adjust the pH to 1 at 0 °C. The aqueous layer was extracted with EtOAc (10 mL) four times. The combined organic layer was dried over $MgSO_4$, concentrated, and purified by column chromatography (silica gel, 30 to 70 % gradient EtOAc with 1% AcOH in hexanes) to afford the title product (61 mg, 71%) as a white solid. $[\alpha]_D^{24}$ = +2.4° (c 2.8, $CH_2Cl_2$). $^1$H NMR (800 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.7 Hz, 3 H), 1.19 (d, *J* = 7.0 Hz, 3 H), 1.41–1.49 (m, 1 H), 1.61–1.70 (m, 1 H), 2.01–2.12 (m, 1 H), 2.22 (dd, *J* = 15.3, 7.8 Hz, 1 H), 2.39 (dd, *J* = 15.4, 5.9 Hz, 1 H), 2.50–2.59 (m, 1 H), 11.45 (s, 2 H). $^{13}$C NMR (201 MHz, $CDCl_3$) δ 16.71, 19.33, 27.85, 37.07, 39.92, 41.39, 179.53, 183.47. HRMS calcd for $C_8H_{14}O_4Na$ $[M+Na]^+$ :197.0790, found 197.0786.

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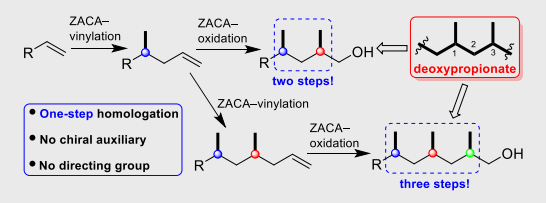


A one-step homologation strategy for the construction of deoxypropionate motif is described via the combination of ZACA–Pd-catalyzed vinylation and ZACA–oxidation reaction. The power of this one-step homologation protocol has been demonstrated by the highly efficient synthesis of intermediates and/or final products of mycolipenic acid **1** and its analogue **2**, (–)-rasfonin, and *syn*- and *anti*-dicarboxylic acids **5** and **6**.

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**One-step Homologation for the Catalytic Asymmetric Synthesis of Deoxypropionates**