

Highly Efficient, Convergent, and Enantioselective Synthesis of Phthioceranic Acid**

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Abstract: A new strategy for highly concise, convergent, and enantioselective access to polydeoxypropionates has been developed. ZACA-Pd-catalyzed vinylation was used to prepare smaller deoxypropionate fragments, and then two key 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. We employed this strategy for the synthesis of phthioceranic acid, a key constituent of the cell-wall lipid of *Mycobacterium tuberculosis*, in just 8 longest linear steps with full stereocontrol.

Deoxypropionate subunits are common structural motifs found in a broad range of naturally occurring compounds derived from polyketide pathways.^[1] They represent a family of structurally diverse compounds with a broad range of biological activities and pharmacological properties,^[2] e.g., neutral sphingomyelinase inhibitor (+)-scyphostatin,^[3] cytotoxic agents (–)-borrelidin^[4] and (–)-doliculide,^[5] pheromone (+)-4,6,8,10,16,18-hexamethyldocosane,^[6] calcium ionophore ionomycin,^[7] as well as the long-chain aliphatic phthioceranic acid (Figure 1).^[8]

In view of the abundant presence of deoxypropionate-containing natural products with diverse fascinating biological activities, intense efforts for the development of efficient and stereoselective methods for their synthesis have been made.^[9] Since deoxypropionates are devoid of heterofunctional groups that could assist asymmetric C–C or C–H bond formation, most of the currently known and widely used methods for their constructions have to install temporary functional or chiral directing groups that are to be removed later.^[9] These methods construct deoxypropionate units in a linear-iterative fashion: one deoxypropionate unit after another is typically attached to the growing alkyl chain, and one iteration cycle typically requires 3–6 steps to introduce one methyl-branched chiral center. Thus, they suffer from long synthetic steps, low efficiency, and/or use of stoichiometric amount of chiral auxiliaries.

Recently, the first convergent route to smaller deoxypropionates through [CpTi(OiPr)₃] (1.5 equiv)-mediated alkyne–

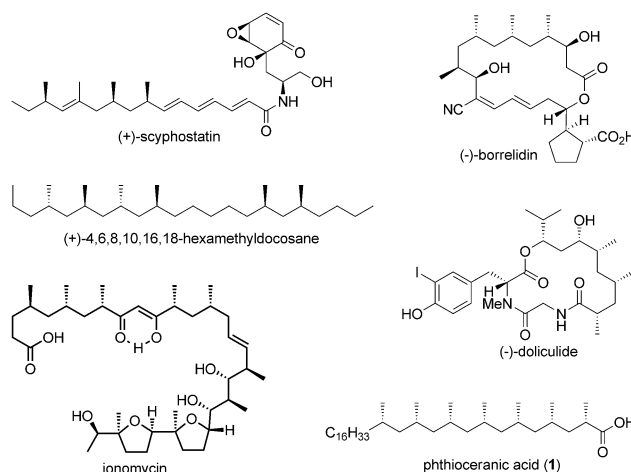


Figure 1. Representative examples of natural products containing deoxypropionate subunits.

allylic alcohol cross-coupling with sequential substrate-controlled asymmetric hydrogenation was established.^[10] Pfaltz, Schneider and their co-workers developed a convergent synthesis of polydeoxypropionates phthioceranic acid and hydroxyphthioceranic acid on the basis of a sequential Pd-catalyzed Suzuki coupling/Ir-catalyzed asymmetric hydrogenation strategy.^[11] Aggarwal et al. reported another convergent stereoselective synthesis using lithiation–borylation followed by protodeboronation.^[12] While these convergent strategies for the syntheses of deoxypropionates are powerful and efficient, their key steps linking fragments together are not suitable for straightforward construction of the deoxypropionate unit, and thus require subsequent transformations, such as hydrogenation where stereoselectivity is typically substrate-dependent. Thus, it is highly desirable to develop novel convergent strategies for the direct formation of deoxypropionates, especially those exhibiting high stereoselectivity.

Phthioceranic acid (**1**) is a component of sulfolipid-1 (SL-1), a main constituent of the cell-wall lipid of virulent human *Mycobacterium tuberculosis* (MTB).^[13] Tuberculosis (TB) remains one of the world's deadliest communicable diseases, which caused 1.5 million people deaths in 2013 alone.^[14] Studies revealed that SL-1 shows significant immunomodulatory activities against various immune cells, and thus it has been considered as a promising component of potential tuberculosis vaccines.^[15] Phthioceranic acid was first synthesized by Feringa and Minnaard^[16] in 27 longest linear steps from ethylene glycol, and also by Pfaltz and Schneider^[11] in 20 longest linear steps from (*S*)-4-benzyl-2-oxazolidinone. Here

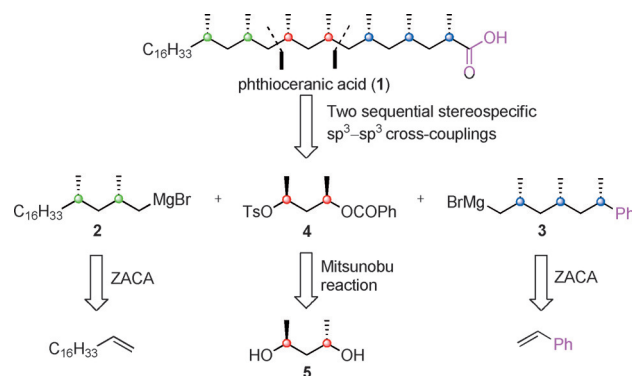
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we report a new strategy for a highly concise, convergent, and enantioselective synthesis of long-chain polydeoxypropionates as exemplified by phthioceranic acid (**1**) in 8 steps (longest linear sequence).

Our synthesis of phthioceranic acid (**1**) makes use of the convergent assembly of three smaller building blocks **2–4** through two sequential stereospecific sp^3 – sp^3 cross-couplings (Scheme 1), inspired by recent advances in the tran-



Scheme 1. Strategy for the highly convergent synthesis of phthioceranic acid (**1**).

sition metal-catalyzed C–C cross-coupling of nonactivated secondary alkyl halides or pseudohalides with alkylmetal nucleophiles.^[17,18] Both fragments **2** and **3** should be readily prepared by Zr-catalyzed asymmetric carboalumination of alkenes (ZACA)–Pd-catalyzed vinylation tandem process from very simple terminal alkenes.^[19] The third fragment **4** should be easily derived from commercially available (2*S*,4*S*)-(+)-pentanediol **5**, which, in turn, is preparable from catalytic asymmetric hydrogenation of acetylacetone in one step.^[20]

The synthesis of the fragment **2** began with the ZACA reaction of 1-octadecene. To our surprise, the methylalumination of 1-octadecene using 1.5 equiv of trimethylaluminum and 3 mol % [(+)-(NMI)₂ZrCl₂]^[21] in anhydrous CH₂Cl₂ at either 0 °C or room temperature resulted only in recovered starting material (Table 1, entry 1). It has been shown that the addition of water (1 equiv) greatly accelerates the methylalumination of terminal alkenes.^[22] Indeed, the methylalumi-

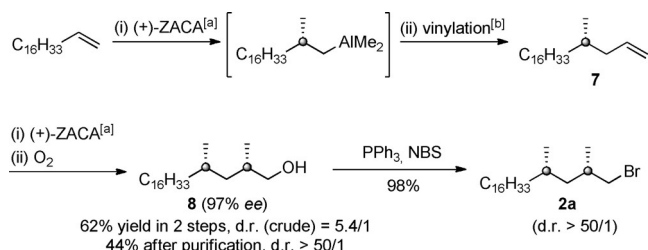
Table 1: Water effect on the ZACA reaction of 1-octadecene.

$\text{C}_{16}\text{H}_{33} \xrightarrow[\text{CH}_2\text{Cl}_2 \text{ (anhydrous), } 0^\circ\text{C, 12 h}]{[(+)\text{-(NMI)}_2\text{ZrCl}_2], \text{Me}_3\text{Al (1.5 equiv), H}_2\text{O}} \text{C}_{16}\text{H}_{33}\text{AlMe}_2 \xrightarrow{\text{O}_2} \text{C}_{16}\text{H}_{33}\text{OH}$				
Entry	[(+)-(NMI) ₂ ZrCl ₂] ^[a]	H ₂ O	Yield [%] ^[b]	ee [%] ^[c]
1	3 mol %	none	0	NA
2	1 mol %	100 mol %	45	40
3	1 mol %	50 mol %	66	52
4	1 mol %	5 mol %	77	73
5	1 mol %	2 mol %	60	77
6	1 mol %	2 mol %	82 ^[d]	77

[a] Freshly prepared. [b] Isolated yield. [c] Determined by ¹H NMR of Mosher ester analysis of the alcohol **6**. [d] Yield obtained after 24 h.

nation of 1-octadecene was completed when water (1 equiv) was added. However, only 45 % of the desired alcohol **6** of 40 % ee was obtained after in situ oxidation with O₂ (entry 2), where the major side reaction was oligomerization. Importantly, we found that a decreased amount of water (2 mol %) significantly improved both enantioselectivity and yield of the desired product, although the reaction occurred at a lower rate (entry 6). Interestingly, the enantioselectivities and product yields in the ZACA reactions of styrene derivatives and proximately heterosubstituted alkenes appeared to be basically unaffected by the amount of water.^[19c,d,22,23] The mechanistic role of water in the ZACA reaction remains unclear at present.

Under suitable conditions for the ZACA reaction of 1-octadecene in hand, we then synthesized the building block **2a** as shown in Scheme 2. Compound (*S*)-**7** was prepared by

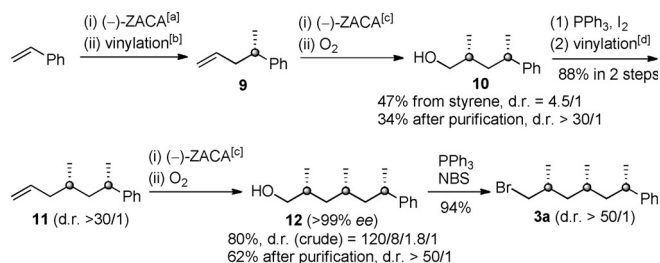


Scheme 2. Synthesis of fragment **2a** by ZACA reaction.

[a] [(+)-(NMI)₂ZrCl₂] (1 mol %), AlMe₃ (1.5 equiv), H₂O (2 mol %), 0 °C. [b] i) Zn(OTf)₂ (1.2 equiv); ii) [PdCl₂(DPEPhos)] (3 mol %), DIBAL-H (6 mol %), vinyl bromide (6 equiv).

(+)-ZACA reaction of 1-octadecene followed by [Pd-(DPEPhos)Cl₂]-catalyzed vinylation of the in-situ generated isoalkylalane promoted by Zn(OTf)₂^[19c] (*S*)-**7** was then converted to alcohol **8** (d.r. = 5.4) by (+)-ZACA-oxidation, which was readily purified by ordinary column chromatography. Bromide **2a** (d.r. > 50) was thus synthesized in 43 % yield over three steps from 1-octadecene.

Trimethyl-branched intermediate **3a** was synthesized by a similar strategy as shown in Scheme 3.^[19c] Alcohol **10** was prepared from styrene by ZACA-vinylation and ZACA-oxidation. After conversion of **10** into **11** in 88 % yield by

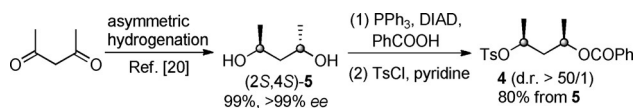


Scheme 3. Synthesis of fragment **3a** by ZACA reaction.

[a] [(−)-(NMI)₂ZrCl₂] (2 mol %), AlMe₃ (3 equiv), H₂O (1 equiv), 0 °C. [b] i) Zn(OTf)₂ (1.2 equiv); ii) [PdCl₂(DPEPhos)] (3 mol %), DIBAL-H (6 mol %), vinyl bromide (6 equiv). [c] [(−)-(NMI)₂ZrCl₂] (2 mol %), AlMe₃ (2 equiv), H₂O (2 mol %), 0 °C. [d] i) *t*BuLi, ii) ZnBr₂, iii) [PdCl₂-(DPEPhos)] (5 mol %), DIBAL-H (10 mol %), vinyl bromide (4 equiv).

iodination and Negishi coupling, another ZACA-oxidation produced **12** in 80 % yield (62 % after chromatographic purification to d.r. > 50), which was further transformed to bromide **3a**.

The third key fragment **4** was synthesized from the commercially available diol **5**, which, in turn, is available in one step from acetylacetone by asymmetric hydrogenation.^[20] Fragment **4** was then synthesized as a single stereoisomer by Mitsunobu reaction^[24] and tosylation (Scheme 4).



Scheme 4. Synthesis of fragment **4**.

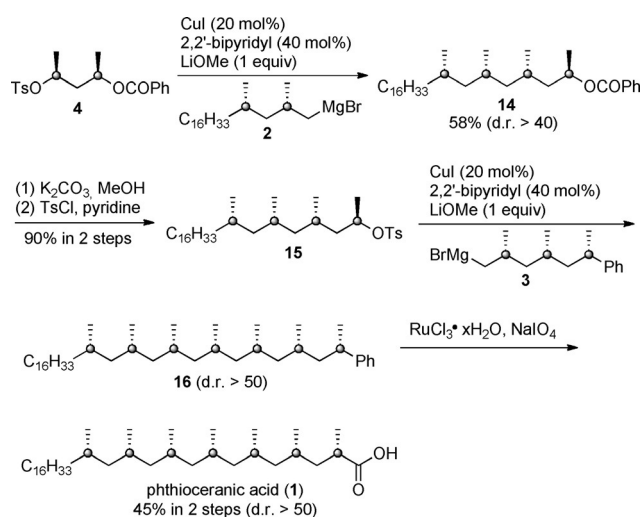
With the key fragments in hand, we were in a position to test the key stereospecific sp^3 – sp^3 cross-coupling, inspired by recent Cu-catalyzed cross-coupling of nonactivated secondary alkyl halides or tosylates by L. Liu.^[18a] By using CuI/TMEDA/LiOMe catalytic system, the desired product **13** was obtained in modest 40 % yield with complete inversion of configuration (d.r. > 50) (Table 2, entry 1). To our delight, changing

Table 2: Optimization of stereospecific Cu-catalyzed cross-coupling of **4**.

Entry	Catalyst	Ligand	X	Yield [%] ^[a]
1	CuI	TMEDA	Br	40
2	CuI	TMEDA	Cl	38
3	CuI	PMDTA	Br	69
4	CuI	HMTETA	Br	67
5	CuI	2,2'-bipyridyl	Br	71
6	CuI	2,2':6',2''-terpyridine	Br	46
7	CuI	1,10-phenanthroline	Br	52
8	CuCl	2,2'-bipyridyl	Br	62
9	CuI ^[b]	2,2'-bipyridyl ^[b]	Br	75

[a] Isolated yields. [b] CuI (20 mol %) and 2,2'-bipyridyl (40 mol %) were used. TMEDA = *N,N,N',N'*-tetramethylethylenediamine, PMDTA = *N,N,N',N'',N''*-pentamethyldiethylenetriamine, HMTETA = 1,1,4,7,10,10-hexamethyltriethylenetetramine.

bidentate *N,N,N',N'*-tetramethylethylenediamine (TMEDA) to tridentate PMDTA (*N,N,N',N'',N''*-pentamethyldiethylenetriamine) significantly improved the yield to 69 % (entry 3). Tetradentate 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) did not further improve the reaction (entry 4). The use of bidentate aromatic 2,2'-bipyridyl increased yield to 71 % (d.r. > 50) (entry 5). However, tridentate aromatic 2,2':6',2''-terpyridine and rigid planar bidentate 1,10-phenanthroline provided lower yields (entries 6 and 7). After using CuI (20 mol %) and 2,2'-bipyridyl (40 mol %), the desired product **13** was obtained in 75 % with essentially perfect stereocontrol (d.r. > 50).



Scheme 5. Highly convergent synthesis of phthioceranic acid (**1**).

Using the modified conditions for Cu-catalyzed stereospecific cross-coupling, we achieved a convergent assembly of phthioceranic acid (**1**). Thus, bromide **2a** was converted to the corresponding Grignard reagent **2** and coupled with fragment **4** providing **14** in 58 % yield (Scheme 5). After hydrolysis and tosylation, tosylate **15** was subjected to another Cu-catalyzed cross-coupling reaction with Grignard reagent **3** and afforded the key intermediate **16** with excellent stereoselectivity (d.r. > 50). Finally, conversion of the phenyl moiety of **16** to the carboxylic acid by oxidative cleavage with $\text{RuCl}_3/\text{NaIO}_4$ completed the synthesis of phthioceranic acid (**1**) in 8 steps in longest linear sequence. With essentially full stereocontrol of Cu-catalyzed cross-coupling, phthioceranic acid was generated as a single stereoisomer. Comparison of the proton and ^{13}C NMR data with those of compounds previously synthesized by other groups^[11,16] showed a perfect match.

In summary, we have developed a highly concise, convergent and enantioselective route to a long-chain polydeoxypropionate phthioceranic acid by an eight-step longest linear sequence involving coupling together three smaller building blocks. Key steps include ZACA-Pd-catalyzed vinylation, and two sequential Cu-catalyzed stereospecific sp^3 – sp^3 cross-coupling reactions proceeding with full inversion of configuration. In view of the practically perfect stereocontrol observed in the Cu-catalyzed cross-coupling, we anticipate that the strategy described herein will provide a general and efficient method for the straightforward construction of enantiomerically and diastereomerically pure polydeoxypropionates without resorting to very difficult late-stage purification of the diastereomeric mixtures.

Keywords: asymmetric synthesis · cross-coupling · natural product synthesis · polydeoxypropionates · ZACA reaction

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