Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

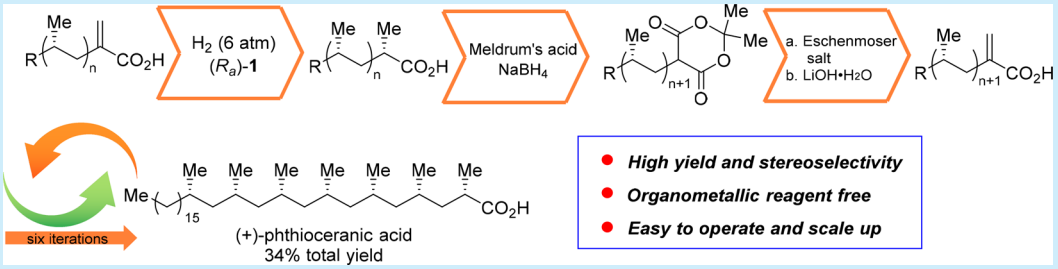
pubs.acs.org/OrgLett

# Iterative Synthesis of Polydeoxypropionates Based on Iridium-Catalyzed Asymmetric Hydrogenation of α-Substituted Acrylic Acids

Wen Che,[†] Danyang C. Wen,[†] Shou-Fei Zhu,*[,†] and Qi-Lin Zhou*[,†,‡]

[†]State Key Laboratory and Institute of Elemento-organic Chemistry, College of Chemistry, and [‡]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Nankai University, Tianjin 300071, China

Supporting Information




**ABSTRACT:** A novel iterative protocol for the synthesis of polydeoxypropionates was developed based on iridium-catalyzed asymmetric hydrogenation of α-substituted acrylic acids. The catalyst loading can be as low as 0.01 mol %, and the overall yield for one iterative cycle is >76%. The reaction conditions are mild, and no organometallic reagents or chromatography steps are required. Using this protocol, (+)-phthioceranic acid and the polydeoxypropionate motifs of ionomycin and borrelidin were synthesized in high yield.

Polydeoxypropionates consisting of an array of 1,3-methyl groups and multiple stereogenic centers are common substructures in polyketides isolated from bacteria, fungi, and plants.[1] Polydeoxypropionates show strong biological activity relevance, including antitumor, antibiotic, cytostatic, and pheromone activities. Therefore, considerable research attention has been devoted to their synthesis. One attractive approach for synthesizing molecules with repeating subunits is iterative homologation.[2] The established procedures for asymmetric iterative homologation mainly rely on either chiral auxiliaries or chiral reagents.[3] Recently, Aggarwal's assembly line synthesis protocol pushed this strategy to a new level.[4] Among the most promising tools for iterative synthesis of polydeoxypropionates is asymmetric catalysis, and a few successful examples have been documented. For example, Negishi and co-workers[5] reported an iterative synthesis of polydeoxypropionates by means of zirconium-catalyzed asymmetric carboalumination of alkenes (Scheme 1a). However, this method has disadvantages that include using an air- and moisture-sensitive organometallic reagent ($AlMe_3$) and requiring column chromatography to increase the diastereomeric purity of the intermediates. Feringa et al.[6] synthesized polydeoxypropionates by means of iterative copper-catalyzed asymmetric conjugate addition reactions of Grignard reagents to α, β-unsaturated thioesters (Scheme 1b); this method also requires the use of organometallic reagents. Burgess and co-workers[7] used iridium-catalyzed asymmetric hydrogenation of trisubstituted alkenes for iterative synthesis of polydeoxypropionates (Scheme 1c). Because the *Z*/*E* geometry of the double bond strongly influences the stereoselectivity of the hydrogenation reaction, the geometry must be carefully controlled to achieve the desired *syn* or *anti* selectivity.[7b,c] Owing to the limitations of the above-described methods, new strategies for catalytic enantioselective iterative synthesis of polydeoxypropionates are desired. Herein, we report an efficient, practical protocol for iterative synthesis of polydeoxypropionates by means of iridium-catalyzed asymmetric hydrogenation of α-substituted acrylic acids (Scheme 1d). The protocol features a high yield (>76% per cycle) and a low catalyst loading (as low as 0.01 mol %); in addition, the protocol is operationally simple and scalable because the $H_2$ pressure is low, and neither organometallic reagents nor chromatography is required.

We recently developed a highly enantioselective iridium-catalyzed hydrogenation of α-substituted acrylic acids.[8] This method allows for the construction of a methyl-substituted tertiary stereogenic center at the α-position of carboxylic acids. However, we have not studied whether the catalyst can give high diastereoselectivity when the substrates have additional stereogenic centers.

We hypothesized that this reaction could be used for the iterative synthesis of compounds with 1,*n*-methyl arrays such as those in polydeoxypropionates. To test this hypothesis, we began by investigating the iridium-catalyzed hydrogenation of acrylic acid **2** to introduce the first methyl-substituted stereogenic center (Table 1). First, several chiral spiro iridium catalysts developed in our laboratory were tested. Although the chiral spiro P,O-ligand modified iridium catalyst **1a**[8b] was

**Received:** April 15, 2018

DOI: 10.1021/acs.orglett.8b01193
Org. Lett. XXXX, XXX, XXX−XXX

**Scheme 1. Iterative Synthesis of Polydeoxypropionates through Catalytic Asymmetric Reactions**

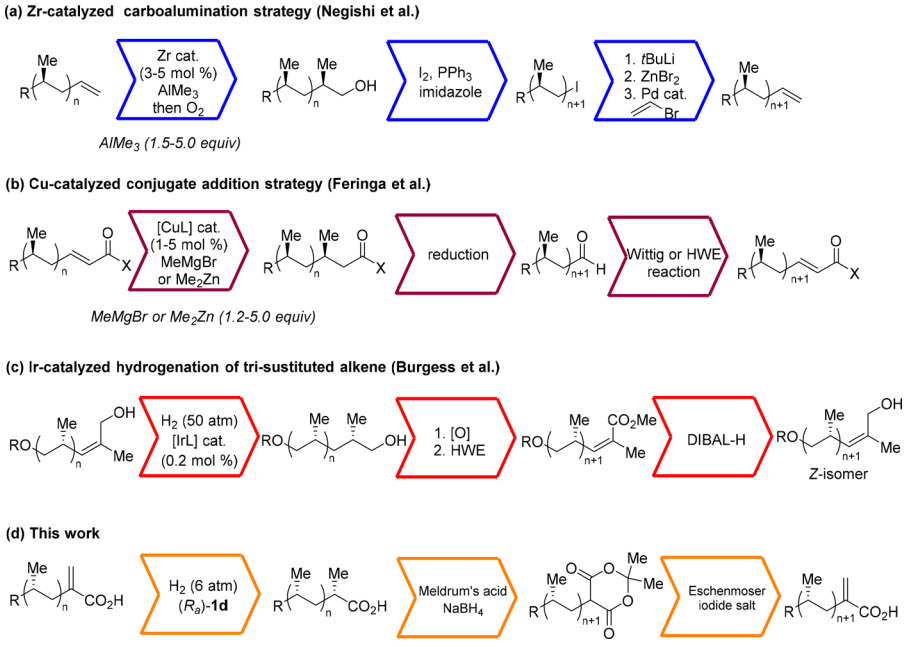
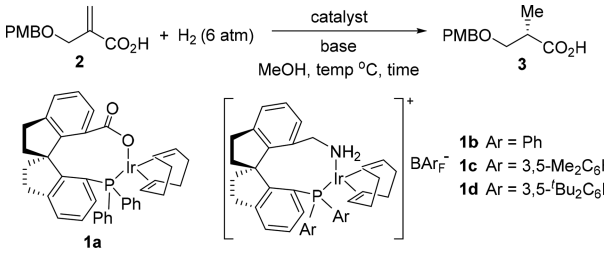



**Table 1. Asymmetric Hydrogenation of 2-(((4-Methoxybenzyl)oxy)methyl)acrylic Acid**[a]



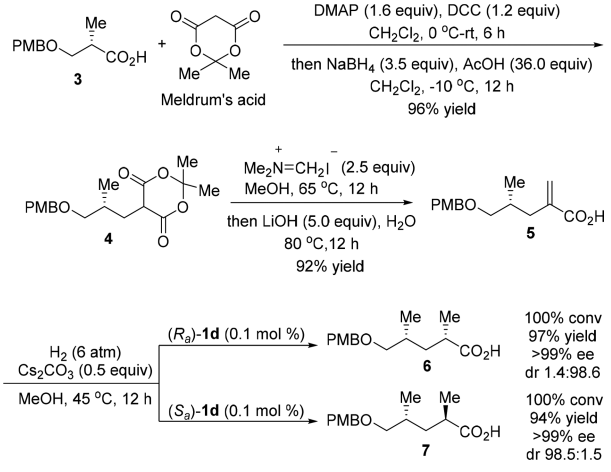

| entry | catalyst | S/C[b] | base (equiv) | temp (°C) | time (h) | conv (%) | ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | ($R_a$)-**1a** | 1000 | $Cs_2CO_3$ (0.5) | 45 | 2.0 | 0 | – |
| 2 | ($S_a$)-**1b** | 1000 | $Cs_2CO_3$ (0.5) | 45 | 2.0 | 100 | 90 |
| 3 | ($R_a$)-**1c** | 1000 | $Cs_2CO_3$ (0.5) | 45 | 2.0 | 100 | 90 |
| 4 | ($R_a$)-**1d** | 1000 | $Cs_2CO_3$ (0.5) | 45 | 2.0 | 100 | 97 |
| 5 | ($R_a$)-**1d** | 1000 | $NEt_3$ (0.5) | 45 | 0.5 | 100 | 97 |
| 6[d] | ($R_a$)-**1d** | 1000 | $NEt_3$ (5.0) | 45 | 1.5 | 100 | 96 |
| 7[d] | ($R_a$)-**1d** | 5000 | $NEt_3$ (5.0) | 45 | 1.5 | 100 | 95 |
| 8 | ($R_a$)-**1d** | 10000 | $NEt_3$ (5.0) | 60 | 3.0 | 100 | 93 |

[a]Substrate 500 mg, PMB = *para*-methoxybenzyl. [b]Substrate to catalyst ratio. [c]Determined by HPLC of the corresponding amide using a Chiralpak AD-H column. [d]Substrate 5.0 g.

inactive for the hydrogenation of **2** (entry 1), the chiral spiro P,N-ligand modified iridium catalysts **1b–d** were proven to be suitable catalysts for the reaction (entries 2–4). Specifically, the catalyst **1d** having bulky Ar groups was very efficient, giving the desired product **3** in quantitative yield with 97% ee under mild conditions (6 atm $H_2$) (entry 4). The use of $NEt_3$ instead of $CsCO_3$ can accelerate the reaction rate (entry 5). The reaction could be performed on a multigram scale (entries 6, 7) and at a low catalyst loading (0.01 mol %, entry 8) with a slight decrease in enantioselectivity.

We established an iterative cycle by exploring transformations of the carboxylic acid group of hydrogenation product **3**. First, we prepared compound **4** (96% yield) by reacting carboxylic acid **3** with Meldrum's acid (Scheme 2)[9]

**Scheme 2. First Iteration To Introduce the Second Methyl Group (DMAP = 4-Dimethylaminopyridine; DCC = Dicyclohexylcarbodiimide)**



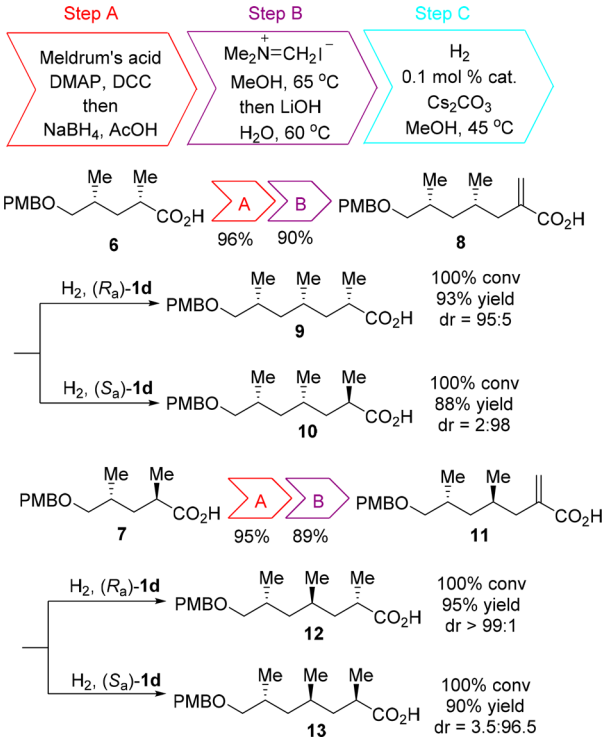

(for optimization of reaction conditions, see Table S1 in the Supporting Information (SI) for details). Compound **4** was then transformed to $\alpha$-substituted acrylic acid **5** by a Mannich-type reaction with Eschenmoser's salt and subsequent hydrolysis (92% yield). Because **5** is a terminal olefin, we could avoid the geometry problem, which is an advantage of this process. Hydrogenation of **5** with catalyst ($R_a$)-**1d** or its enantiomer ($S_a$)-**1d** stereoselectively afforded dimethyl dyads (2*S*,4*R*)-**6** (97% yield, diastereomeric ratio [dr] 98.6:1.4) and (2*R*,4*R*)-**7** (94% yield, dr 98.5:1.5) in excellent yield. That ($R_a$)-**1d** and ($S_a$)-**1d** exhibited essentially the same level of diastereoselectivity in the hydrogenation of **5** indicates that the stereochemistry at the second stereogenic center was


DOI: 10.1021/acs.orglett.8b01193
Org. Lett. XXXX, XXX, XXX–XXX

controlled by the catalyst and not the substrate. Thus, we established a novel iterative protocol for the synthesis of the deoxypropionate building block by means of three steps: (1) carboxymethylation with Meldrum's acid, (2) alkenylation with Eschenmoser's salt, and (3) asymmetric hydrogenation catalyzed by ($R_a$)-**1d** or ($S_a$)-**1d**. In addition to the high overall yield (>83%), low catalyst loading, and excellent dr, another advantage of this protocol is that it does not require column chromatography; the impurities can be removed during the workup of the subsequent hydrolysis step.

Then, we used the above-described protocol for the iterative synthesis of triads (Scheme 3), which are common structures in

**Scheme 3. Second Iteration to Introduce Third Methyl Group**

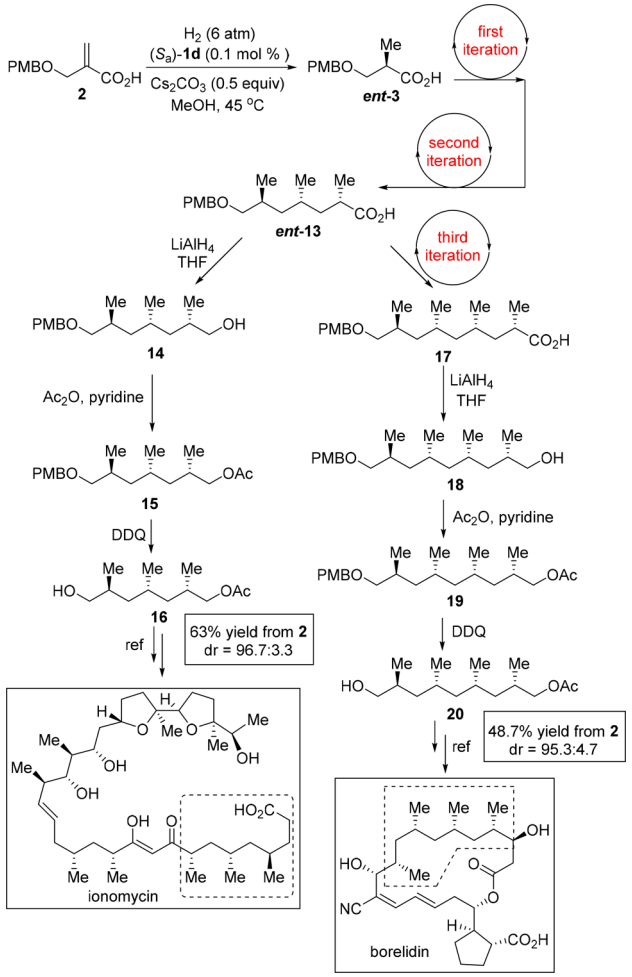



various natural products. By subjecting (2*S*,4*R*)-**6** and (2*R*,4*R*)-**7** to the three basic steps of the first iteration, we were able to obtain all the diastereomers of the triads (2*S*,4*S*,6*R*)-**9** (93% yield, dr 95:5), (2*R*,4*S*,6*R*)-**10** (88% yield, dr 2:98), (2*S*,4*R*,6*R*)-**12** (95% yield, dr >99:1), and (2*R*,4*R*,6*R*)-**13** (90% yield, dr 3.5:96.5) in high yields with excellent dr values.

To demonstrate the synthetic potential of our iterative protocol, we used it to synthesize polydeoxypropionates **16** and **20** (Scheme 4), which are key intermediates in the syntheses of natural products ionomycin[10] and borrelidin,[11] respectively. Starting from $\alpha$-substituted acrylic acid **2**, we synthesized **16** in 63% overall yield with 96.7:3.3 dr by means of two iterations of the protocol, and compound **20** was synthesized in 48.7% overall yield with 95.3:4.7 dr by means of three iterations.[12]

Finally, we synthesized (+)-phthioceranic acid ((+)-**28**, Scheme 5), a side chain of sulfolipid-1, a cell-wall lipid of the bacillus *Mycobacterium tuberculosis*.[13] Because sulfolipid-1 is reported to be a promising candidate for a vaccine against *Mycobacterium tuberculosis*,[14] a practical, efficient synthesis of polydeoxypropionate structures might facilitate the development of potential tuberculosis vaccines. To achieve the first

**Scheme 4. Synthesis of Polydeoxypropionate Intermediates of Ionomycin and Borrelidin**



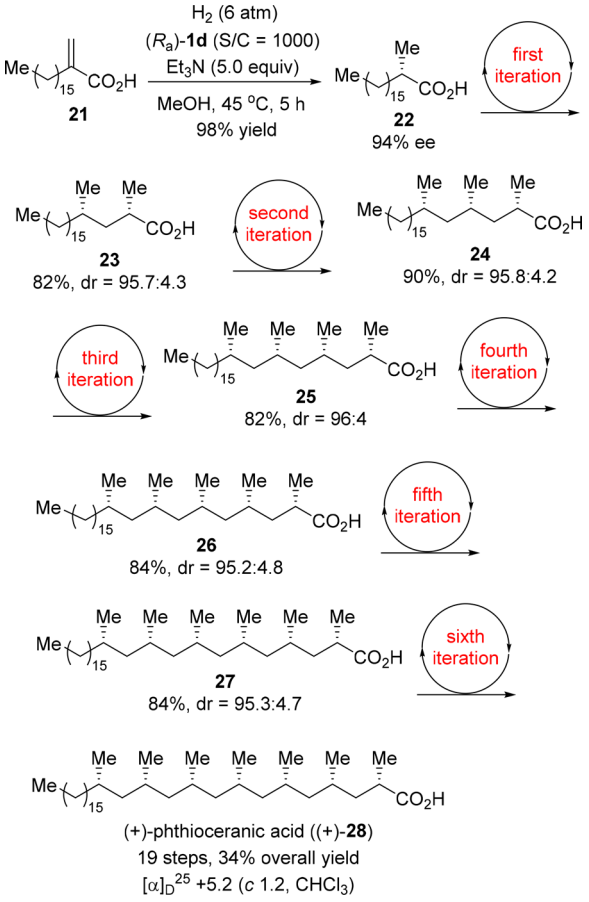

synthesis of (+)-**28**, Feringa, Minnaard, and co-workers[15] used an iterative strategy involving copper-catalyzed asymmetric conjugate addition (24 steps, 4.9% yield). Schneider[16] used a convergent strategy to synthesize (+)-**28** (25 total steps, 20 steps for the longest linear sequence, 21% yield) by means of a palladium-catalyzed Suzuki–Miyaura coupling and an iridium-catalyzed diastereoselective hydrogenation. Negishi and co-workers[17] also reported a convergent synthesis of (+)-**28** (19 total steps, 8 steps for the longest linear sequence, 18.6% yield) using zirconium-catalyzed asymmetric carboalumination of an alkene as a key step. Our iterative synthesis of **28** was started from the chiral carboxylic acid **22**, which was obtained in 98% yield with 94% ee by ($R_a$)-**1d**-catalyzed asymmetric hydrogenation of **21**. After six iterations, we obtained (+)-**28** in an unprecedentedly high overall yield of 34%.

In summary, we have developed a highly diastereo- and enantioselective iterative protocol for construction of polydeoxypropionates by means of iridium-catalyzed asymmetric hydrogenation of $\alpha$-substituted acrylic acids. Using this protocol, we readily synthesized the polydeoxypropionates motifs of natural products ionomycin and borrelidin, as well as (+)-phthioceranic acid, with high efficiency and high stereoselectivity. Because the protocol involves only three simple operations—(1) carboxymethylation with Meldrum's acid, (2) alkenylation with Eschenmoser's salt, and (3) iridium-catalyzed asymmetric hydrogenation—it is practical and scalable. This



DOI: 10.1021/acs.orglett.8b01193
*Org. Lett.* XXXX, XXX, XXX–XXX

**Scheme 5. Total Synthesis of (+)-Phthioceranic Acid**




novel protocol may be applicable to the synthesis of other natural products containing 1,3-polymethyl structures.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01193.

Experimental procedures and characterization data for the intermediates and products (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Authors

*E-mail: sfzhu@nankai.edu.cn.
*E-mail: qlzhou@nankai.edu.cn.

### ORCID

Shou-Fei Zhu: 0000-0002-6055-3139
Qi-Lin Zhou: 0000-0002-4700-3765


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21790332, 21532003, 21625204), the "111" project (B06005) of the Ministry of Education of China, and the National Program for Support of Top-notch Young Professionals for financial support.

## ■ REFERENCES


(1) For reviews, see: (a) Birch, A. J. *Science* **1967**, *156*, 202. (b) Khosla, C. *Chem. Rev.* **1997**, *97*, 2577.

(2) For a review, see: (a) Zheng, K.; Xie, C.; Hong, R. *Front. Chem.* **2015**, *3*, 32. (b) Recently, Nozaki et al. reported a one-step oligomerization of propylene to construct all-*syn* deoxypropionate. However, it is difficult to control the number and configuration of the methyl-branched stereocenter in this protocol. Ota, Y.; Murayama, T.; Nozaki, K. *Proc. Natl. Acad. Sci. U. S. A.* **2016**, *113*, 2857.

(3) For a review, see: Hanessian, S.; Giroux, S.; Mascitti, V. *Synthesis* **2006**, *7*, 1057.

(4) (a) Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. *Nature* **2014**, *513*, 183. (b) Balieu, S.; Hallett, G. E.; Burns, M.; Bootwicha, T.; Studley, J.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 4398.

(5) (a) Negishi, E.-i.; Tan, Z.; Liang, B.; Novak, T. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5782. (b) Magnin-Lachaux, M.; Tan, Z.; Liang, B.; Negishi, E.-i. *Org. Lett.* **2004**, *6*, 1425. (c) Novak, T.; Tan, Z.; Liang, B.; Negishi, E.-i. *J. Am. Chem. Soc.* **2005**, *127*, 2838. (d) Liang, B.; Novak, T.; Tan, Z.; Negishi, E.-i. *J. Am. Chem. Soc.* **2006**, *128*, 2770. (e) Zhu, G.; Negishi, E.-i. *Org. Lett.* **2007**, *9*, 2771. (f) Zhu, G.; Liang, B.; Negishi, E.-i. *Org. Lett.* **2008**, *10*, 1099. (g) Negishi, E.-i.; Xu, S. *Proc. Jpn. Acad., Ser. B* **2015**, *91*, 369. (h) Xu, S.; Negishi, E.-i. *Acc. Chem. Res.* **2016**, *49*, 2158. (i) Xu, S.; Li, H.; Komiyama, M.; Oda, A.; Negishi, E.-i. *Chem. - Eur. J.* **2017**, *23*, 149.

(6) (a) Des Mazery, R.; Pullez, M.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 9966. (b) ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2007**, *0*, 489. (c) ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2007**, *9*, 3013. (d) Casas-Arce, E.; ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Chem. - Eur. J.* **2008**, *14*, 4157. (e) ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2010**, *46*, 2535. (f) Geerdink, D.; Buter, J.; van Beek, T. A.; Minnaard, A. J. *Beilstein J. Org. Chem.* **2014**, *10*, 761. (g) Lum, T.-K.; Wang, S.-Y.; Loh, T.-P. *Org. Lett.* **2008**, *10*, 761. For the iterative synthesis of deoxypropionates by means of copper-catalyzed conjugate addition of a dimethylzinc reagent, see: (h) Drissi-Amraoui, S.; Schmid, T. E.; Lauberteaux, J.; Crévisy, C.; Baslé, O.; de Figueiredo, R. M.; Halbert, S.; Gérard, H.; Mauduit, M.; Campagne, J.-M. *Adv. Synth. Catal.* **2016**, *358*, 2519.

(7) (a) Zhou, J.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1129. (b) Zhou, J.; Ogle, J. W.; Fan, Y.; Banphavichit, V.; Zhu, Y.; Burgess, K. *Chem. - Eur. J.* **2007**, *13*, 7162. (c) Zhou, J.; Zhu, Y.; Burgess, K. *Org. Lett.* **2007**, *9*, 1391.

(8) (a) Zhu, S.-F.; Yu, Y.-B.; Li, S.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8872. (b) Yang, S.; Che, W.; Wu, H.-L.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Sci.* **2017**, *8*, 1977. (c) Xie, J.-H.; Zhou, Q.-L. *Huaxue Xuebao* **2014**, *72*, 778.

(9) Hin, B.; Majer, P.; Tsukamoto, T. *J. Org. Chem.* **2002**, *67*, 7365.

(10) (a) Hanessian, S.; Cooke, N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276. (b) Yadav, J. S.; Yadav, N. N.; Reddy, B. V. S. *Tetrahedron* **2015**, *71*, 7539.

(11) (a) Hanessian, S.; Yang, Y.; Giroux, S.; Mascitti, V.; Ma, J.; Raeppel, F. *J. Am. Chem. Soc.* **2003**, *125*, 13784. (b) Vong, B. G.; Kim, S. H.; Abraham, S.; Theodorakis, E. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3947. (c) Madduri, A. V. R.; Minnaard, A. J. *Chem. - Eur. J.* **2010**, *16*, 11726. (d) Yadav, J. S.; Yadav, N. N. *RSC Adv.* **2013**, *3*, 4024.

(12) Negishi and co-workers synthesized compound **16** in 16% overall yield with high dr (20:2:1.7:1) and compound **20** in 12% overall yield with good dr (14:1.4:1.4:1.4:1) using their iterative synthetic strategy based on zirconium-catalyzed asymmetric carboalumination of alkene; ref 5c.

(13) (a) Goren, M. B.; Brokl, O.; Das, B. C.; Lederer, E. *Biochemistry* **1971**, *10*, 72. (b) Goren, M. B.; Brokl, O.; Roller, P.; Fales, H. M.; Das, B. C. *Biochemistry* **1976**, *15*, 2728. (c) Minnikin, D. E.; Kremer, L.; Dover, L. G.; Besra, G. S. *Chem. Biol.* **2002**, *9*, 545. (d) Geerdink, D.; ter Horst, B.; Lepore, M.; Mori, L.; Puzo, G.; Hirsch, A. K. H.; Gilleron, M.; de Libero, G.; Minnaard, A. J. *Chem. Sci.* **2013**, *4*, 709.




DOI: 10.1021/acs.orglett.8b01193
*Org. Lett.* XXXX, XXX, XXX−XXX

(14) (a) de Libero, G.; Mori, L. *Nat. Rev. Immunol.* **2005**, *5*, 485. (b) Lin, T.-W.; Melgar, M. M.; Kurth, D.; Swamidass, S. S.; Purdon, J.; Tseng, T.; Gago, G.; Baldi, P.; Gramajo, H.; Tsai, S.-C. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 3072.
(15) ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Org. Lett.* **2007**, *9*, 3013.
(16) (a) Pischl, M. C.; Weise, C. F.; Müller, M.-A.; Pfaltz, A.; Schneider, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 8968. (b) Pischl, M. C.; Weise, C. F.; Haseloff, S.; Müller, M.-A.; Pfaltz, A.; Schneider, C. *Chem. - Eur. J.* **2014**, *20*, 17360.
(17) Xu, S.; Oda, A.; Bobinski, T.; Li, H.; Matsueda, Y.; Negishi, E.-i. *Angew. Chem., Int. Ed.* **2015**, *54*, 9319.



DOI: 10.1021/acs.orglett.8b01193
*Org. Lett.* XXXX, XXX, XXX−XXX