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Natural Product Synthesis |*Hot Paper*|

A Highly Stereoselective and Flexible Strategy for the Convergent Synthesis of Long-Chain Polydeoxypropionates: Application towards the Synthesis of the Glycolipid Membrane Components Hydroxyphthioceranic and Phthioceranic Acid

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Abstract: A highly stereocontrolled and flexible access to biologically relevant polydeoxypropionates in optically pure form has been developed. Taking advantage of our previously established strategy for the asymmetric and stereodivergent synthesis of trideoxypropionate building blocks, we have now been able to assemble large polydeoxypropionate chains with defined configuration in a highly convergent manner. Central steps of this approach include two Suzuki–Miyaura cross-coupling reactions with subsequent highly diastereoselective hydrogenations to join three advanced synthetic intermediates in excellent yield and with full stereochemical control. We have applied this strategy successfully towards the asymmetric synthesis of glycolipid membrane components phthioceranic acid and hydroxyphthioceranic acid, the latter of which was synthesized on a half-gram scale.

Introduction

Within the large natural product class known as polyketides, the branched deoxypropionate subunit is a common structural motif in various members produced by animals, plants, bacteria, and fungi.[1] They are characterized by an alkyl chain substituted with methyl groups at every second carbon atom, differing from the related polypropionates by the lack of hydroxyl groups at the other carbon atoms. The general biosynthetic pathway to their assembly is characterized by type I fatty acid synthases (FSS) of multi-cellular animals,[2] which are closely related to the modular type I polyketide synthases (PKS) located in plants, fungi, and bacteria.[3] Therefore, the construction of polyketides and fatty acids includes the same biosynthetic transformations, differing in an additional dehydration/reduction sequence for the fatty acid motif to deoxygenate the initially formed propionate structure. The biological activities of polydeoxypropionates are diverse and representative examples of this product class include the pectinatone,[4] the pheromones vittatalactone[5] and 4,6,8,10,16,18-hexamethyldocosane,[6] the cytotoxic natural products borrelidine[7] and doliculide,[8] as well as the long-chain aliphatic hydroxyphthioceranic acid (Scheme 1).[9]

In light of the multitude of biological activities associated with deoxypropionates, substantial research efforts have been undertaken to develop synthetic tools for their stereoselective assembly. Almost all known asymmetric syntheses towards deoxypropionates are inspired by the principle of "biosynthesis", that is, building up the complete carbon chain with each iterative chain elongation. Until today numerous efficient synthetic strategies have been developed for their highly stereoselective formation.[10] The most common method is the 1,4-conjugate addition of a methyl nucleophile toward a reactive α,β-unsaturated acid derivative. The configuration of this carbon–carbon bond-forming event is controlled either by a chiral metal catalyst (e.g., the Minnaard/Feringa approach),[11] through the chirality of the substrate (e.g., the Hanessian and Breit approaches),[12] or by a covalently attached chiral auxiliary (e.g., the Oppolzer and Williams approaches).[13] The application of chiral auxiliaries is also often employed in asymmetric (aza)-enolate alkylation reactions as demonstrated by Enders, Evans, Masamune, and Myers.[14] A zinc-catalyzed, stereospecific cross-coupling reaction of lactate-derived triflates with Grignard reagents has been developed by Breit et al.[15] Another method for the stereoselective synthesis of deoxypropionate subunits employs allylic alkylation reactions of alkyl halides (the groups of Breit and Spino).[16] A hydrogenation-based approach was established by Burgess and Zhou on the basis of chiral Ir–*C,N*-catalyst, which converted prochiral, trisubstituted olefins into methyl-branched alkyl chains with high levels of stereocontrol.[17] Negishi et al. developed the zirconium-catalyzed asymmetric carboalumination (ZACA) reaction of styrene and

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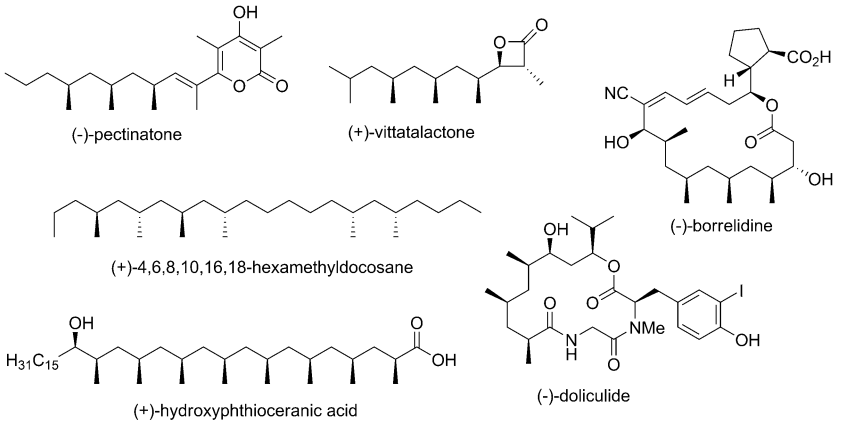


Scheme 1. Representative examples of deoxypropionate-containing natural products.

used it iteratively to access polydeoxypropionates.[18] Finally, Ghosh took advantage of a cyclopropanation–fragmentation protocol to access polydeoxypropionate motifs.[19]

As a general characteristic feature, all these methods follow a linear-iterative strategy: The new deoxypropionate subunits are added to the growing alkyl chain one after another. However, for the conversion of the product of the previous cycle into the substrate for the next cycle, additional transformations have to be performed. This typically lowers the overall yield and efficiency of the processes. The only exception in this respect is a report by Micalizio et al. in 2012, who successfully completed the asymmetric synthesis of smaller deoxypropionates through a convergent alkyne/allylic alcohol cross-coupling reaction with subsequent substrate-controlled asymmetric hydrogenation.[5g] By using this methodology, the pheromone (−)-vittatalactone produced by the striped cucumber beetle was obtained in only five additional steps.

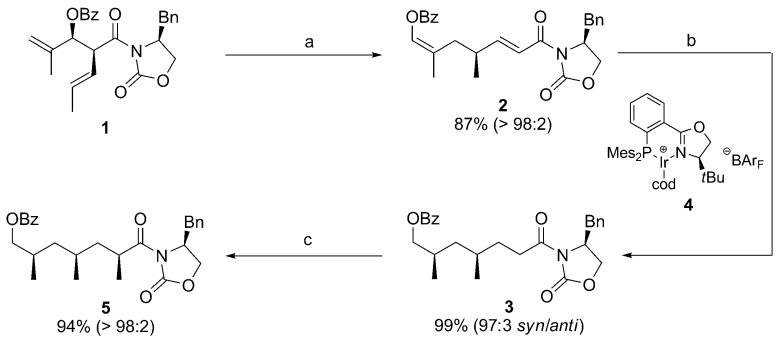
Recently, we reported the first highly convergent total synthesis of the glycolipid components phthioceranic acid and hydroxyphthioceranic acid.[20a,b] Subsequently, Aggarwal's group developed another convergent enantioselective synthesis using a traceless lithiation–borylation–protodeboronation strategy.[20c] Central to the success of our approach was the development of a sequential and highly stereoselective Suzuki–Miyaura cross-coupling–hydrogenation strategy to join three advanced synthetic intermediates in excellent yield and with full stereochemical control. We now report the full details and show that the flexibility associated with this strategy, which allowed us to prepare the various stereoisomeric products easily.

Results and Discussion

Large-scale synthesis of trideoxypropionate 5

We have recently developed a new and highly flexible strategy for the non-iterative synthesis of trideoxypropionate building blocks in an optically pure form. Starting from readily available chiral aldol products, the trideoxypropionates were obtained in good overall yields and with excellent stereocontrol by using only three synthetic steps: A thermal oxy-Cope rearrangement, an iridium-catalyzed hydrogenation, and an enolate methylation.[21] Depending upon the substrates and catalysts employed in this Scheme, all four stereochemical permutations were easily accessible (*syn/syn*, *syn/anti*, *anti/syn*, and *anti/anti*). In addition, their differently functionalized termini allow for flexible and selective modifications as we were able to demonstrate in the course of syntheses of the pheromones (+)-vittatalactone and (+)-norvittatalactone isolated from the striped cucumber beetle *Acalymma vittatatum*.[21]

Inspection of the configuration within polydeoxypropionate-based natural products reveals that the majority among them carries an all-*syn* configuration along the carbon chain with all of the branching methyl groups pointing in the same direction. This observation suggests that the *syn*,*syn*-configured stereoisomer **5** constitutes the most versatile intermediate for natural product synthesis and for a synthesis of the glycolipid components hydroxyphthioceranic acid (**9**) and phthioceranic acid (**10**) in particular. Thus, our first attention was devoted to the large-scale synthesis of **5** (Scheme 2). The oxy-Cope rearrangement of benzoylated aldol product **1** was easily scaled up even to 37 grams of substrate without any problems, which gave the isolated product in 87% yield and as a single diastereomer (vs. 95% in small-scale reactions). However, the hydrogenation conditions had to be slightly adjusted: By using only 1.6–1.8 mol% of our previously optimized chiral iridium-Mes-PHOX catalyst **4** and 85 bar hydrogen pressure in a 500 mL autoclave with a special glass inlet, we were able to run the hydrogenation on large scale. Thus, upon ensuing enolate

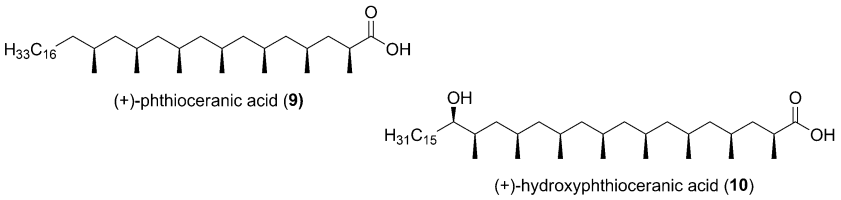


Scheme 2. Large-scale synthesis of *syn*,*syn*-deoxypropionate **5**. a) Toluene, 185 °C, 5 h, 87%; b) Compound **4** (1.8 mol%), CH_2Cl_2, H_2, 85 bar, RT, 1 d, 99%; c) NaHMDS, MeI, THF, −78 °C, 3 h, 94%.

methylation, we obtained 26 grams (80% overall yield) of the desired *syn,syn*-trideoxypropionate **5**.

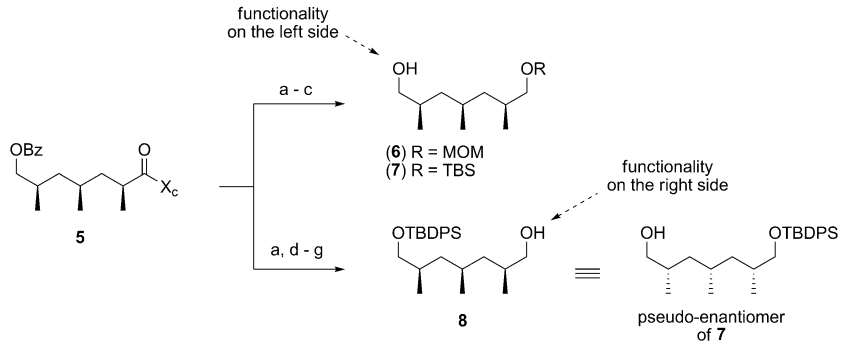
With sufficient quantities of trideoxypropionate **5** in our hands, we turned our attention to a reliable conversion into a broadly applicable synthetic intermediate for natural product synthesis. Our first synthesis of the pheromone (+)-vittatalactone, in which we had converted **5** into the corresponding hydroxy ester through base-catalyzed transesterification, occasionally suffered from partial epimerization at the carbon center adjacent to the carbonyl group. To avoid this detrimental side reaction, which we expected to be even more pronounced on a larger scale, we opted for a safer and more reliable alternative. Thus, applying a three-step sequence comprising reductive cleavage of the chiral auxiliary, protection of the liberated hydroxy group as either methoxymethyl (MOM)- or *tert*-butyldimethylsilyl (TBS) ethers, and mild hydrolysis of the benzoate furnished **6** and **7**, respectively, in excellent overall yields (Scheme 3). Both products carried the free and readily manipulated alcohol moiety on the left side of the molecule. In addition, after reductive cleavage of the chiral auxiliary in **5**, carbamoylation with *t*BuNCO, cleavage of the benzoate moiety, silylation with *tert*-butyl(chloro)diphenylsilane (TBDPSCl), and selective cleavage of the carbamate group on the other end of the molecule, we were able to prepare the pseudo-enantiomer of **7** as well. This not only further expands the versatility of this building block, but also opens more options for subsequent coupling reactions.

this strategy might be implemented into a synthesis of larger deoxypropionate chains. Being among the most challenging target compounds we intended to approach the glycolipid components phthioceranic acid (**9**) and hydroxyphthioceranic acid (**10**), which have been shown to display significant biological activity as immune-stimulating agents against *Mycobacterium tuberculosis* (Scheme 4).



Scheme 4. Phthioceranic acid (**9**) and hydroxyphthioceranic acid (**10**).

Inspection of their structure reveals that they each contain seven deoxypropionate subunits and that compound **10** incorporates an additional propionate unit. For the assembly of a long alkyl chain with seven branching methyl groups one of the trideoxypropionates had to be converted into a tetradeoxypropionate before coupling of the two would furnish the desired heptadeoxypropionate. As the most promising way for coupling, we envisioned a strategy that took advantage of a palladium-catalyzed Suzuki–Miyaura cross coupling reaction of an alkyl metal reagent and a vinyl iodide followed by stereoselective hydrogenation of the resulting trisubstituted olefin. The vinyl iodide in turn should easily be available from a trideoxypropionate aldehyde through alkynylation, hydrozirconation, and iodination.

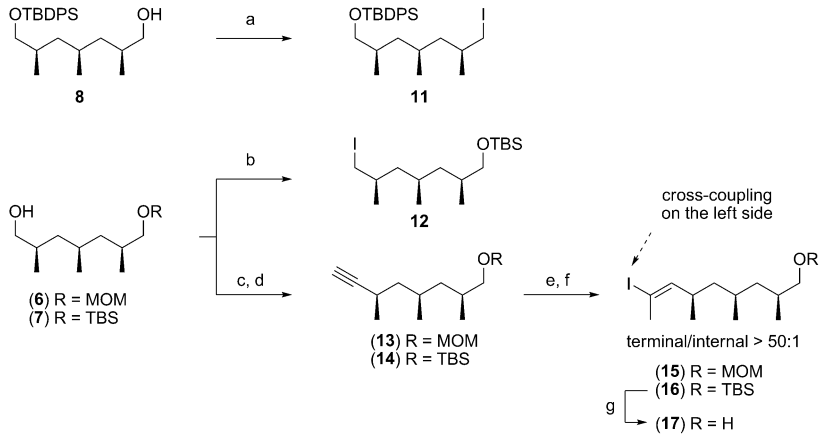


Scheme 3. Further conversion of **5** into the central trideoxypropionate intermediates **6**–**8**. a) $NaBH_4$, THF/H_2O, 0 °C, 16 h, 94%; b) MOMCl, *N,N*-diisopropylethylamine (DIPEA), CH_2Cl_2, RT, 1 d, quant.; b) TBSCl, ImH, DMAP, CH_2Cl_2, 30 min, 0 °C, 99%; c) K_2CO_3, MeOH, RT–35 °C, 7 h–1 d, 93–98%; d) *t*BuNCO, TMSCl, CH_2Cl_2, RT, 1 h; quant.; e) K_2CO_3, MeOH, RT, 1 d, 97%; f) TBDPSCl, ImH, CH_2Cl_2, RT, 1 h, quant.; g) Diisobutylaluminium hydride (DIBAL-H), THF, 0 °C, 3 h, 93%.

To put these plans into practice, we started from our central trideoxypropionate intermediates **6**–**8** (Scheme 5). Iodination of the two trideoxypropionates **7** and **8** produced the corresponding pseudo-enantiomeric alkyl iodides **11** and **12** in almost quantitative yields, which were intended to serve later as the immediate precursors for the corresponding alkyl metal reagents through halogen–metal exchange processes. As second coupling partner vinyl iodides **15** and **17** were prepared from **6** and **7** through a sequence comprising 2-iodoxybenzoic acid (IBX) oxidation, alkynylation with the Bestmann–Ohira reagent,[22] methylation of the resulting terminal alkyne, and finally, hydrozirconation/iodination with the Schwartz reagent. The final vinyl iodides were obtained in 75 (compound **15**) and 71% (compound **17**) overall yields as single regioisomers (>50:1). It should be noted that increasing both the reac-

Total synthesis of phthioceranic acid (9)

At this stage, we wondered how we could merge two of the building blocks **5** most economically and selectively and how



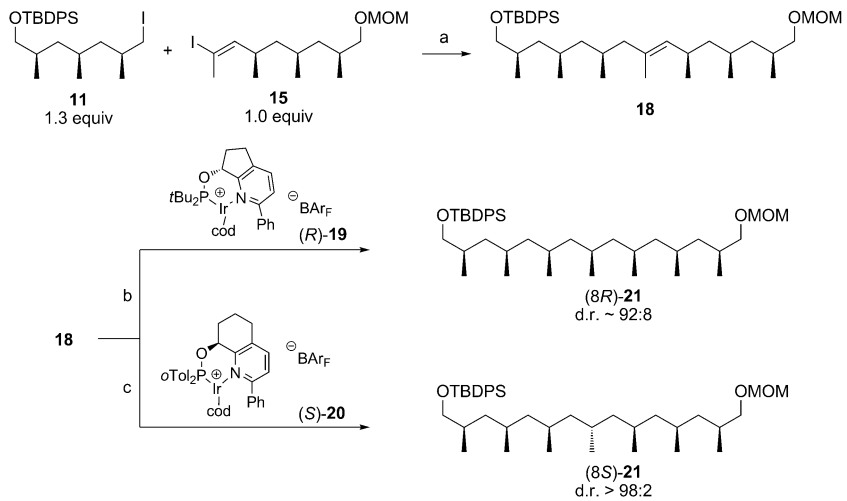
Scheme 5. Synthesis of the coupling partners **15** and **17** for the Suzuki–Miyaura reaction. a) PPh_3, I_2, ImH, Et_2O/CH_3CN, 0 °C, 1 h, 98%; b) PPh_3, I_2, ImH, Et_2O/CH_3CN, 0 °C, 30 min, 98%; c) IBX, DMSO/THF, RT, 2 h, 96%–quant.; d) 1) Bestmann–Ohira reagent, NaOMe, THF/MeOH, −78 °C, 30 min; 2) then aldehyde, −78 °C to RT, 2 h, 88%; e) 1) *n*BuLi, THF, −78 °C, 1 h; 2) MeI, DMPU, −78 °C to RT, 1 d, 97–98%; f) 1) Cp_2ZrHCl, THF, RT, 1 d; 2) I_2, THF, RT, 30 min, 86%; g) Tetra-*n*-butylammonium fluoride (TBAF), THF, RT, 4 h, 98%.

tion time and the amount of the Schwartz reagent had a beneficial effect on the regioselectivity of the hydrozirconation, presumably as a result of a reversible addition to the alkyne.[23]

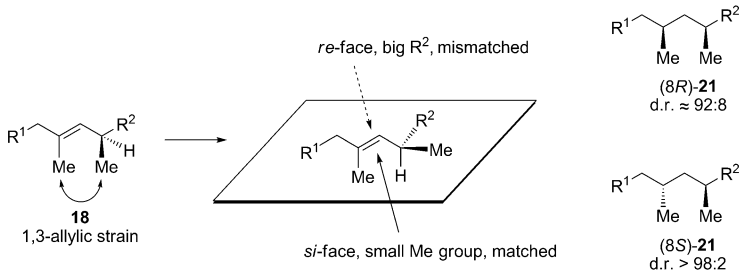
With the requisite coupling partners for the critical Suzuki–Miyaura cross-coupling reaction in our hands we felt that conditions, which were originally developed by the groups of Marshall and Lee for sp^2–sp^3 couplings and later employed by Rychnovsky et al. in similar settings, were most promising for our endeavor as well.[24] Thus, iodide **11** was first converted into a reactive alkyl lithium-boranate complex through halogen–metal exchange with *t*BuLi and subsequent reaction with *B*-OMe-9-BBN (9-BBN = 9-borabicyclo[3.3.1]nonane).[25] This reactive alkyl metal compound was then treated with MOM-protected vinyl iodide **15** (1.3 equiv) in the presence of 5 mol% [$PdCl_2$(dppf)] (1,1′-bis(diphenylphosphino)ferrocene) and K_3PO_4 in DMF at room temperature to afford the trisubstituted olefin **18** in 92% yield under very mild conditions (Scheme 6).

To establish the last stereogenic center in the carbon backbone of phthioceranic acid, olefin **21** needed to be hydrogenated with high stereoselectivity. We had previously shown that similar trisubstituted olefins can be efficiently hydrogenated with excellent enantioselectivity with certain iridium–pyridine-phosphinite catalysts and used this strategy in the asymmetric synthesis of α-tocotrienyl acetate.[26] Therefore, our first hydrogenation experiments of the MOM-protected alkene **18** were performed accordingly with various iridium catalysts.[26,27] Under standard conditions all experiments, however, resulted in complex mixtures of products. In our search for the origin of this failure we came across studies by the groups of Andersson and Burgess on iridium-catalyzed hydrogenations, which showed that Ir–H species generated in situ were typically so acidic that enol ethers decomposed in the course of the hydrogenations.[28] These findings suggested that the addition of finely powdered $NaHCO_3$ should buffer the solution effectively and prevent any acid-catalyzed decomposition of the MOM-protecting group both in the substrate and product. Gratifyingly, under the modified conditions with added $NaHCO_3$ we were able to isolate the hydrogenation product (8*R*)-**21** in excellent yield and with 92:8-diastereoselectivity (Scheme 6). More importantly, with the quasi-enantiomeric catalyst (*S*)-**20** the diastereomer (8*S*)-**21** was obtained in 94% yield as a single diastereomer proving the catalyst-controlled stereoselectivity in this reaction. The use of $NaHCO_3$ apparently had an effect on catalyst efficiency, however, and we had to use 3 mol% of catalyst twice to drive the hydrogenation to completion.

The difference in diastereoselectivity observed in the two reactions suggested a minor substrate influence and a matched and mismatched scenario, which may be explained by consid-



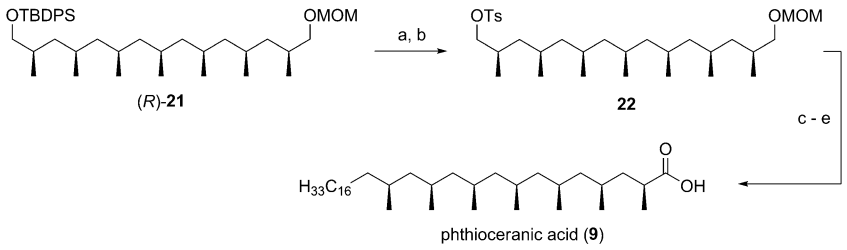
Scheme 6. First Suzuki–Miyaura cross-coupling of two trideoxypropionates. Determination of the diastereoselectivity of both diastereomers (8*R*)-**21** and (8*S*)-**21** after selective hydrogenation with the pyridyl-phosphinite complex (*R*)-**19** and (*S*)-**20**. a) 1) Compound **11**, *t*BuLi, *B*-OMe-9-BBN, Et_2O/THF, −78 °C to RT, 2,5 h; 2) then **15**, aq. 3 M K_3PO_4, [$PdCl_2$(dppf)]·CH_2Cl_2 (5 mol%), DMF, RT, 18 h, 92%; b) 2×3 mol% (*R*)-**19**, CH_2Cl_2, 60 bar, H_2, $NaHCO_3$, RT, 3 h + 2 h, 91%; c) 2×3 mol% (*S*)-**20**, CH_2Cl_2, 60 bar, H_2, $NaHCO_3$, RT, 3 h + 2 h, 94%.



Scheme 7. Proposed rationale for the diastereofacial selectivity of hydrogenation.

ering A(1.3)-strain effects on the preferred conformation of **18** (Scheme 7). In the lowest-energy conformation of **18** the allylic C–H bond is oriented coplanar to the C–Me bond on the alkene with the allylic Me group pointing to the front and the larger R^2-substituent pointing to the back. For steric reasons, the iridium-hydride addition to the olefin should now occur from the front side over the smaller allylic substituent furnishing the *anti*-diastereomer (8*S*)-**21** with a diastereomeric ratio (d.r.) of $>98:2$ in a matched situation. With the quasi-enantiomeric catalyst (*R*)-**19** the opposite diastereomer (8*R*)-**21** is formed preferentially albeit in a slightly diminished selectivity of 92:8 d.r. in a mismatched scenario because the backside attack is somewhat retarded by the larger allylic substituent.

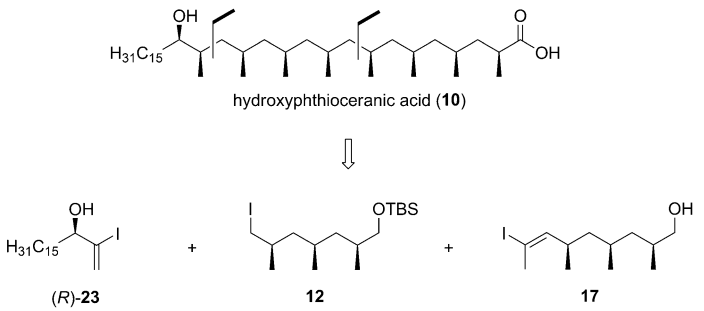
To complete the synthesis of phthioceranic acid (**9**) heptadeoxypropionate (8*R*)-**21** was converted into tosylate **22** within two chemical steps and the terminal C_{15}-alkyl chain was introduced through a copper-catalyzed cross-coupling with the requisite Grignard reagent as the third building block. Finally, MOM-deprotection and oxidation of the primary alcohol to the acid[29] afforded phthioceranic acid (**9**) in 62% yield over the three steps (Scheme 8).



Scheme 8. Total synthesis of the phthioceranic acid (**9**). a) TBAF, THF, RT, 4 h, 95%; b) TsCl, DMAP, CH_2Cl_2/pyridine 1:1, RT, 1 d, 92%; c) 8 mol% Li_2CuCl_4, $C_{15}H_{31}MgBr$, Et_2O, RT, 1 d, 76%; d) cat. HCl, MeOH/DCE, 70 °C, 40 min, 96%; e) $RuCl_3$, $NaIO_4$, $CH_3CN/CCl_4/H_2O$, RT, 3 h, 85%.

Total synthesis of hydroxyphthioceranic acid (10)

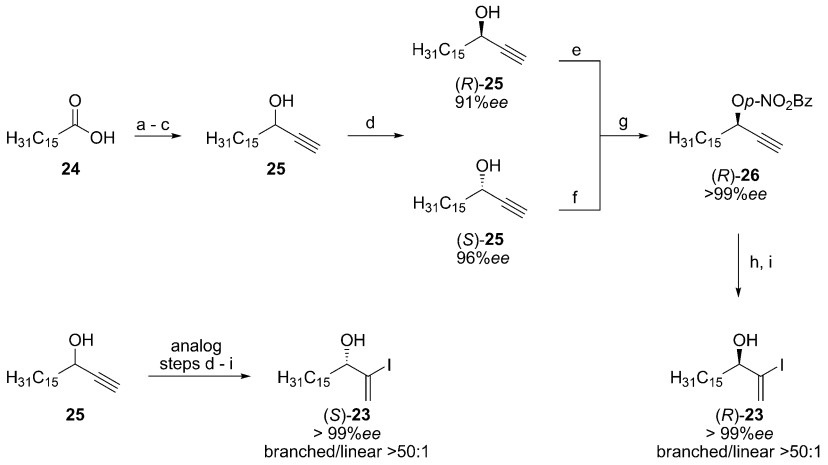
The design plan for the synthesis of hydroxyphthioceranic acid (**10**) had to be carefully adjusted mainly to incorporate the additional propionate unit. In principle, the same order of events as shown previously in the phthioceranic acid synthesis was planned here as well, in particular, the sequential Suzuki–Miyaura cross-coupling–hydrogenation strategy is the central element; however, we decided to assemble the propionate-containing left fragment of **10** first. Specifically, we intended to start from commercially available palmitic acid as the long-chain C_{16}-source, which was to be converted through a number of steps into the iodo-substituted allylic alcohol (*R*)-**23** as the left fragment (Scheme 9), which in turn was planned to be coupled to our first trideoxypropionate building block **12** through a first cross-coupling hydrogenation sequence. After some protecting group manipulations, the coupling product should



Scheme 9. Design plan for the convergent assembly of hydroxyphthioceranic acid (**10**).

be further elongated to the complete carbon backbone of hydroxyphthioceranic acid through a second cross-coupling hydrogenation sequence with vinyl iodide **17**.

To put these plans into practice, we started from racemic propargylic alcohol **25**, which was conveniently obtained in good yield through Grignard addition of ethynylmagnesium bromide to palmitic aldehyde, further obtained by reduction–oxidation reaction of commercially available palmitic acid (**24**). For the sake of practicality and the production of large amounts of material, we opted for an enzymatic kinetic resolution strategy over alternative enantioselective protocols. Thus, *Candida antarctica* lipase B (CAL-B)-catalyzed esterification of the racemic mixture of **25** with vinyl acetate yielded 54% of *R*-configured, recovered alcohol (*R*)-**25** with an enantiomeric excess (*ee*) of 91%, and, upon hydrolysis, 40% of *S*-configured (*S*)-**25** with 96% *ee* (Scheme 10). Both enantiomers were separately converted into the homogenous, *R*-configured *para*-nitrobenzoate (*R*)-**26** through classical and Mitsunobu esterifications, respectively, and the final product was successfully recrystallized to $>99\%$ *ee*. Following this convenient strategy we were able to convert 70% of racemic propargylic alcohol **25** into enantiomerically pure *para*-nitrobenzoate (*R*)-**26** on large scale (10–20 gram batches). At the same time,



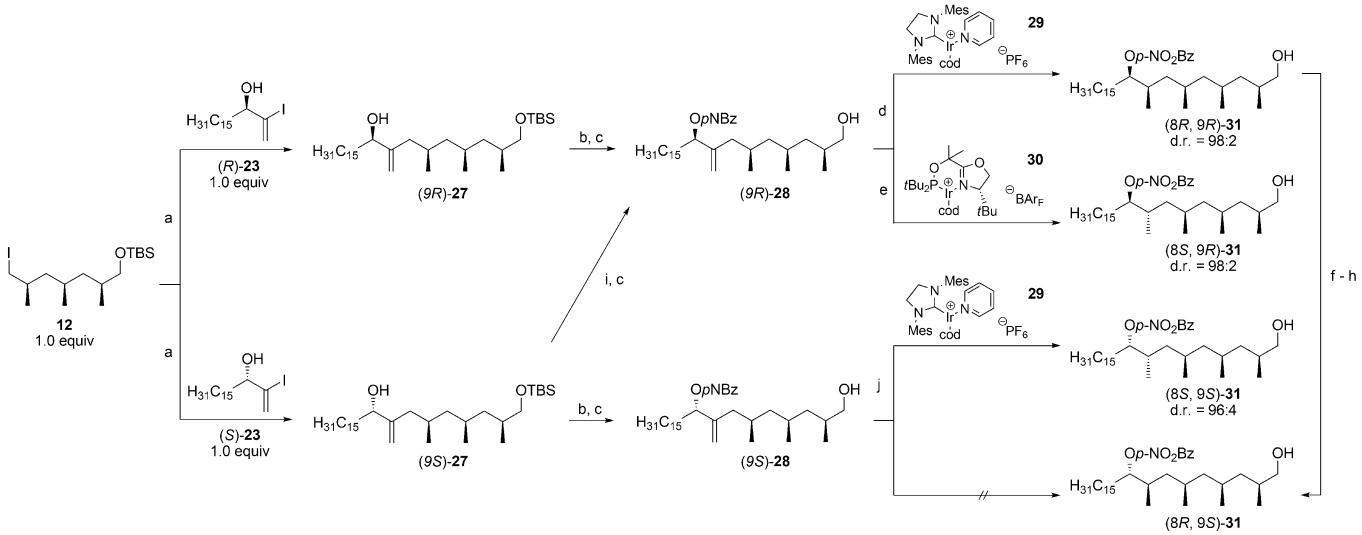
Scheme 10. Synthesis of the aliphatic chain containing building blocks (*R*)-**23** and (*S*)-**23** for the Suzuki–Miyaura cross-coupling reactions. a) $NaBH_4$, I_2, THF, reflux, 1 h, 96%; b) IBX, DMSO/THF, RT, 1 d, 92%; c) ethynylmagnesium bromide, THF, 0 °C, 30 min, 81%; d) 1) CAL-B, vinyl acetate, hexane, RT, 3 h; 2) acetyl-(*S*)-enantiomer, NaOH, MeOH/H_2O, reflux, 1 h, 54% of (*R*)-**25** and 40% of (*S*)-**25**; e) *p*-NO_2BzCl, pyridine, CH_2Cl_2, 0 °C, 1 h, 96%; f) *p*-NO_2BzOH, PPh_3, DIAD, THF, 0 °C to RT, 4 h, 84%; g) Crystallization from hexane, 73%; h) NaOH, MeOH/H_2O, reflux, 94%; i) 1) MeLi, THF, −20 °C to RT; $Cp_2ZrHCl/ZnCl_2$, THF, 40 °C; 2) I_2, THF, 0 °C, 70%.

this strategy provided us with a convenient access to the enantiomeric product (*S*)-**26**.

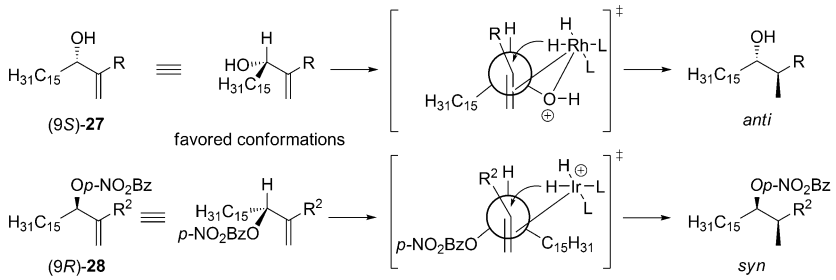
Upon hydrolysis of (*R*)-**26** and (*S*)-**26**, a highly regioselective, substrate-controlled hydrozirconation of the free propargylic alcohols (*R*)-**25** and (*S*)-**25** was accomplished according to the protocol of Ready et al.[31] With the assistance of a $Cp_2ZrHCl/ZnCl_2$ complex (Cp_2 = bis(cyclopentadienyl)) and subsequent iodination, the branched vinyl iodides (*R*)-**23** and (*S*)-**23** were obtained in good yields and with >99% *ee* (branched/linear > 50:1).

With both enantiomers of allylic alcohol (*R*)-**23** and (*S*)-**23**, respectively, in our hands we set out to couple them with the central trideoxypropionate building block **12** applying slightly adjusted conditions compared with the phthioceranic acid synthesis. Thus, conversion of alkyl iodide **12** into the corresponding reactive alkyl-lithium-boranate complex with reduced amounts of both *t*BuLi and *B*-OMe-9-BBN and subsequently palladium-catalyzed Suzuki–Miyaura reaction with both enantiomers of vinyl iodide **23** delivered olefins (9*R*)-**27** and (9*S*)-**27**, respectively, in excellent yield in each case (Scheme 11). It is noteworthy (and saved substantial material) that equimolar amounts of both starting materials were sufficient here to realize this elaborate transformation successfully.

The task ahead was now to hydrogenate the *exo*-methylene group with high stereocontrol. Initially, we considered this situation to be an ideal scenario for acyclic stereocontrol through A(1.2)-strain effects in which the methylene substituent R would eclipse the allylic C–H bond in the lowest-energy conformation (Scheme 12). Precoordination of the catalyst to the free hydroxyl group of allylic alcohol (9*S*)-**27** was then expected to give rise to a transition state in which the hydrogenation would now occur from the backside to furnish the *anti*-stereo-



Scheme 11. Flexible synthesis of the *exo*-methylens (9*S*)-**28** and (9*R*)-**28** and synthesis of all four diastereomers of **31**. a) 1) Compound **12**, *t*BuLi, Et_2O, *B*-OMe-9-BBN, THF, −78 °C to RT, 2 h; 2) then (*R*)-**23** or (*S*)-**23**, aq. 3 M K_3PO_4, 5 mol% $[PdCl_2(dppf)]\cdot CH_2Cl_2$, DMF, RT, 2 h, 79–82%; b) *p*-NO_2BzCl, Pyr, CH_2Cl_2, 0 °C, 2 h, 89–97%; c) 10 mol% $TBABr_3$, MeOH, RT, 4 h, 97%; d) Compound **29** (2 mol%), CH_2Cl_2, H_2, 90 bar, RT, 1 d, 98%; e) Compound **30** (5 mol%, CH_2Cl_2, H_2, 90 bar, RT, 3 h, 84%; f) TBSCl, ImH, DMAP, CH_2Cl_2, RT, 30 min, 98%; g) MeOH, K_2CO_3, reflux, 6 h, 94%; h) 1) PPh_3, DIAD, *p*-NO_2BzOH, THF, RT, 5 h; 2) 20 mol% $TBABr_3$, MeOH, RT, 4 h, 55%; i) PPh_3, DIAD, *p*-NO_2BzOH, THF, 0 °C, 1 h, 88%; j) Compound **29** (2 mol%), CH_2Cl_2, H_2, 1 bar, RT, 1 d, 85%.



Scheme 12. Expected products of the asymmetric hydrogenation of (9*S*)-**27** and (9*R*)-**28** with achiral metal-catalysts: Top: Hydroxy-directed hydrogenation of the free alcohol (9*S*)-**27**; Bottom: Hydrogenation of the sterically hindered derivative (9*R*)-**28** to the Cram- and Felkin–Anh model.

isomer selectively. As consequence of the synthesis of hydroxyphthioceranic acid, we would have to start from the "wrong" enantiomer of **23** to set the correct configuration at C(16) and subsequently invert the allylic C(17)-configuration, for example, through a Mitsunobu reaction. Alternatively, we envisioned that a suitably O-protected substrate might be stereoselectively hydrogenated in a Felkin–Anh-type transition state and directly afford the desired *syn* diastereomer (8*R*, 9*R*)-**31** (Scheme 12). The second option would obviously obviate the need for subsequent inversion of the carbinol stereocenter.

Initial attempts using the free allylic alcohol and the catalyst $[Rh(nbd)(dppb)]^+[BF_4]^-$ (nbd = norbornadiene; dppb = 1,4-bis-(diphenylphosphino)butane) in varying amounts ranging between 1–20 mol%, however, were accompanied by a high degree of isomerization to the ketone and surprisingly rather low selectivities. Additional experiments with a range of other transition-metal catalysts (e.g., $[Rh(nbd)((R)\text{-BINAP})][BF_4]$, $[Rh(nbd)(dppb)][BAr_F]$, $[Rh(nbd)((R)\text{-BINAP})][BAr_F]$, $[Rh(nbd)((S)\text{-BINAP})][BAr_F]$; BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl); BAr_F = tetrakis(3,5-trifluoromethylphenyl)borate]) did not improve upon these results.[33] Accordingly, we resorted to the second option and converted both diastereomers (9*R*)-**27** and (9*S*)-**27** into the corresponding *para*-nitro benzoates (9*R*)-**28** and (9*S*)-**28**, respectively, which carry a free primary hydroxyl group. First, hydrogenation experiments of (9*R*)-**28** instantly succeeded with the Crabtree catalyst (as its BAr_F^- salt) **32**,[34] which delivered the *syn* isomer (8*R*,9*R*)-**31** in quantitative yield and with 95:5-diastereoselectivity, suggesting that our transition state model shown above was working (Scheme 12). Further investigation revealed that achiral catalysts consistently gave rise to the *syn*-configuration with varying levels of diastereoselectivity (see the Supporting Information). Eventually, the iridium-complex $([Ir(cod)(SIMes)(Pyr)]^+[PF_6]^-$; cod = cycloocta-1,5-diene) **29**[35] carrying a NHC ligand instead of the PCy_3 ligand proved to be the catalyst of choice for our substrates. Thus, using only 2 mol% of catalyst **29**, the product (8*R*,9*R*)-**31** was obtained in almost quantitative yield and with 98:2 *syn*/*anti*-diastereoselectivity. Likewise, epimeric (9*S*)-**28** was converted into (8*S*,9*S*)-**31** in 85% yield and with 96:4 *syn*/*anti* diastereoselectivity.

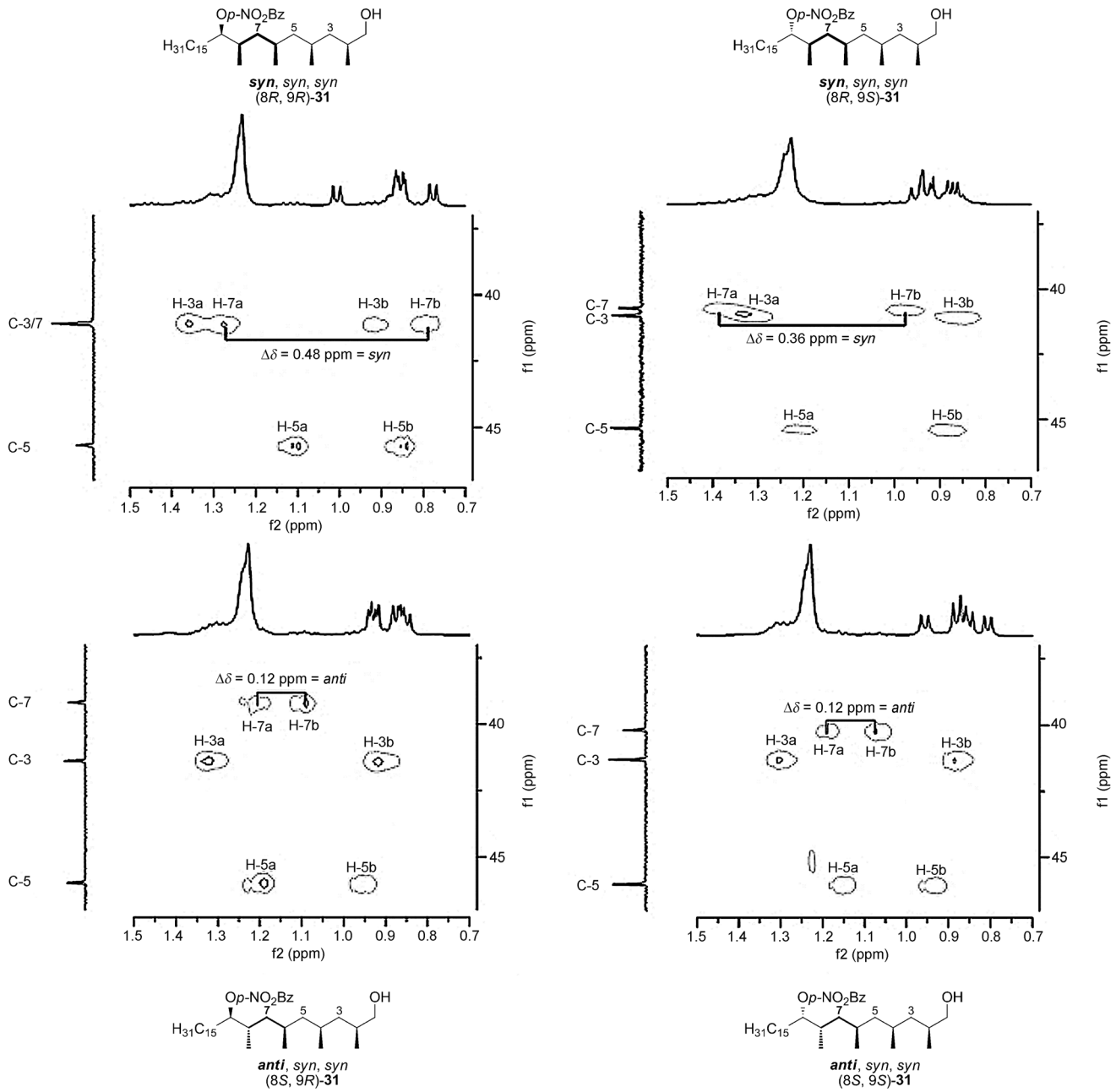
To also access the *anti*-configured *para*-nitro benzoates (8*S*,9*R*)-**31** and (8*R*,9*S*)-**31** and make this approach as versatile and flexible as possible, we extensively screened a broad range of chiral hydrogenation catalysts that were expected to override the inherent facial bias of the substrate (for a full documentation see the Supporting Information). Eventually, it turned out that the Simple-PHOX catalyst **30**[36] hydrogenated the substrate (9*R*)-**28** successfully to produce the desired *anti*-isomer (8*S*,9*R*)-**31** with 84% yield and 98:2 *anti*/*syn*-diastereoselectivity (Scheme 11). Unfortunately, this scenario could not be extended to (9*S*)-**28**, which gave almost no selectivity in the hydrogenation. Instead, compound (8*R*,9*S*)-**31** was conveniently obtained from (8*R*,9*R*)-**31** through a Mitsunobu inversion strategy, which occurred with full inversion of the carbinol configuration.

Assignment of the relative configuration of all four diastereomers of **31** was subsequently carried out by the two-dimensional NMR-spectroscopic method developed by Breit et al. based upon conformational preferences of the deoxypropionate backbone (Scheme 13).[37]

The HSQC NMR-spectra of deoxypropionates (8*R*,9*R*)-**31** and (8*R*,9*S*)-**31** showed two large chemical shift differences for the signals of the 7-CH_2 methylene protons with $\Delta\delta = 0.48$ and 0.36 ppm, respectively, indicating a 6,8-*syn*-configuration each for both compounds. Conversely, two small chemical shift differences of $\Delta\delta = 0.12$ ppm each were observed for the same signals in the case of (8*S*,9*R*)-**31** and (8*S*,9*S*)-**31** suggesting a 6,8-*anti*-configuration for both compounds. These results are in perfect agreement with related data reported by Breit for similar *syn*- and *anti*-configured deoxypropionates leaving no doubt about the configuration of the new C8-stereogenic center.

In an attempt to broaden the scope of this hydrogenation of *exo*-methylene groups, we briefly investigated substrates similar to **28**, which we employed in our hydroxyphthioceranic acid synthesis (Table 1). It turned out that *para*-nitro benzoate **33a**, which is structurally most reminiscent of **28**, as well as acetate **33b**, were hydrogenated with very good *syn* diastereoselectivity by using catalyst **29** (entries 1 and 2, Table 1). The corresponding benzoate **33c** furnished the *syn* stereomer as well albeit with diminished selectivity (entry 3, Table 1). The two phenyl-substituted alkenes **33d** and **33e**, however, did not give rise to significant stereoselectivity suggesting that the Felkin–Anh transition state discussed in Scheme 12 could not be accommodated so easily here due to the larger phenyl group.

To proceed with the second Suzuki–Miyaura cross-coupling reaction for the assembly of the complete carbon backbone of hydroxyphthioceranic acid (**10**) the base-sensitive *para*-nitrobenzoyl group within **31** was exchanged for the more robust TBDPS group and the product was further converted into iodide **35** (Scheme 14). Employing the same conditions, which had proven successful above, the sp^2–sp^3 cross-coupling of

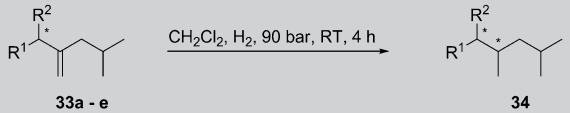


Scheme 13. Determination of the relative configuration by using two-dimensional HSQC NMR spectroscopy. Comparison of the chemical shift difference ($\Delta\delta$) of the methylene protons 7-CH_2 of the propionates (8*R*,9*R*)-**31**, (8*R*,9*S*)-**31**, (8*S*,9*R*)-**31**, and (8*S*,9*S*)-**31**.

alkyl iodide **35** and vinyl iodide **17** also proceeded without any problem, and delivered the product **36** in 85% yield as one single stereoisomer. Once again, an excess of one of the substrates was not necessary. The TBDPS protecting group in **36** was subsequently removed to avoid its partial cleavage in the ensuing hydrogenation. In addition, the reaction could now be performed without the use of $NaHCO_3$, which had been shown to reduce the reactivity of the catalyst in the synthesis of phthioceranic acid (**9**). Thus, the iridium-catalyzed hydrogenation of alkene **37** with only 2.5 mol% of catalyst (*R*)-**19** delivered saturated alkane **38** in excellent yield and as a single diastereomer as judged by ^{1}H- and ^{13}C NMR spectroscopy. Oxidation of hydroxyphthioceranol (**38**) in a two-step process consisting of a 2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) oxidation and a Pinnick oxidation completed the synthesis of hydroxyphthioceranic acid (**10**) in 82% yield over the two steps and produced almost a half-gram of material. Thus, the natural product was produced in 23 steps along the longest linear route and in an excellent 25% overall yield. The spectroscopic and analytical data accurately matched those reported for the natural product.

To assign the relative configuration of hydrogenation product **37** more rigorously we prepared the corresponding TBDPS-protected C8-epimers (8*S*)-**39** and (8*R*)-**39** through hy-

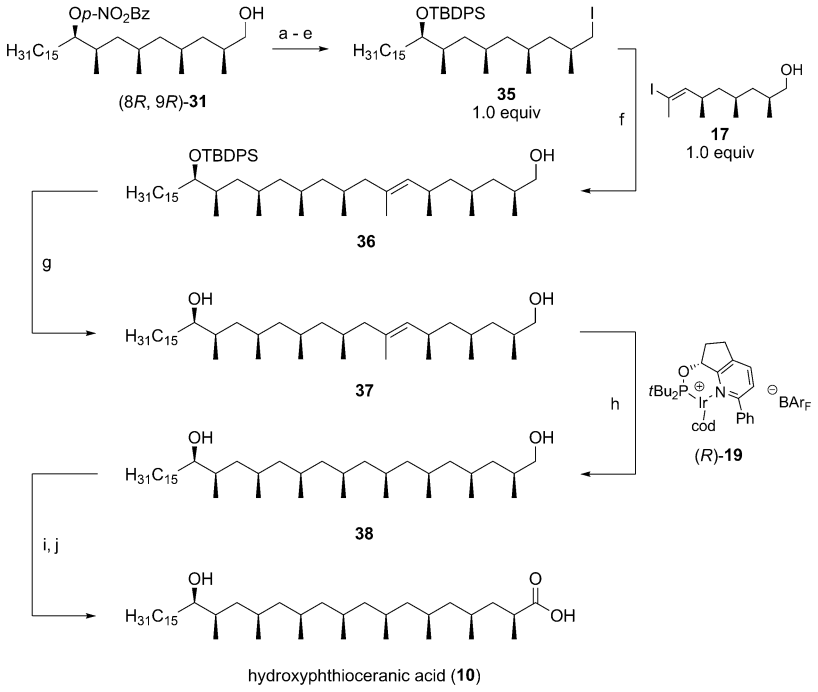
Table 1. Hydrogenation of some *exo*-methylene model substrates **33a–e**.[a]



Entry	Substrate	R^1	R^2	Cat.	Conv. [%][d]	*syn/anti*[d]
1	**33a**	$H_{13}C_6$	*p*-NO_2BzO	**29**	99	92:8
2	**33b**	$H_{13}C_6$	OAc	**29**	99	92:8
3	**33c**	$H_{13}C_6$	OBz	**29**	99	84:16
4	**33d**	Ph	*p*-NO_2BzO	**32**[b]	91	56:44
5	**33e**	Ph	OAc	**32**[c]	99	64:36

[a] Reaction conditions: *exo*-methylene substrate **33** (1.0 equiv), catalyst **29** (5 mol%), CH_2Cl_2 (0.025 M), H_2, 90 bar, RT, 4 h. [b] Compound **32** (15 mol%). [c] Compound **32** (20 mol%). [d] Determined by ^{1}H NMR spectroscopy.

protons 7-CH_2 and 9-CH_2 within the double *anti*-configuration in (8*R*)-**39** was expected to give two small values $\Delta\delta$. Actually, we even obtained three small values between $\Delta\delta = 0.20$ and 0.25 ppm, presumably as a result of additional conformational changes within the product. Notwithstanding this result, the evidence strongly suggested a 6,8- and 8,10-*anti*-configuration within (8*R*)-**39**. Additionally, in the ^{13}C NMR spectrum of epimeric (8*R*)-**39** with the unnatural 8-configuration, there is one signal for a methyl substituent that is shifted significantly away from all other methyl signals to lower frequencies at about $\delta =$ 19 ppm, which indicated an opposite configuration of this 8′-CH_3 group (see the Supporting Information). All other signals for methyl substituents both in (8*S*)-**39** and (8*R*)-**39**, respectively, appear very close together between $\delta = 21$–22 ppm suggesting an all-*syn* configuration between the other methyl groups. Finally, this assignment of the relative configuration of hydrogenation products (8*S*)-**39** and (8*R*)-**39** perfectly matches the results of our enantioselective hydrogenation of γ-tocopheryl acetate.[26] As we have been able to show that hydrogenation of **36** is purely a catalyst-controlled event, a stereochemical influence exerted by the substrate is highly unlikely.

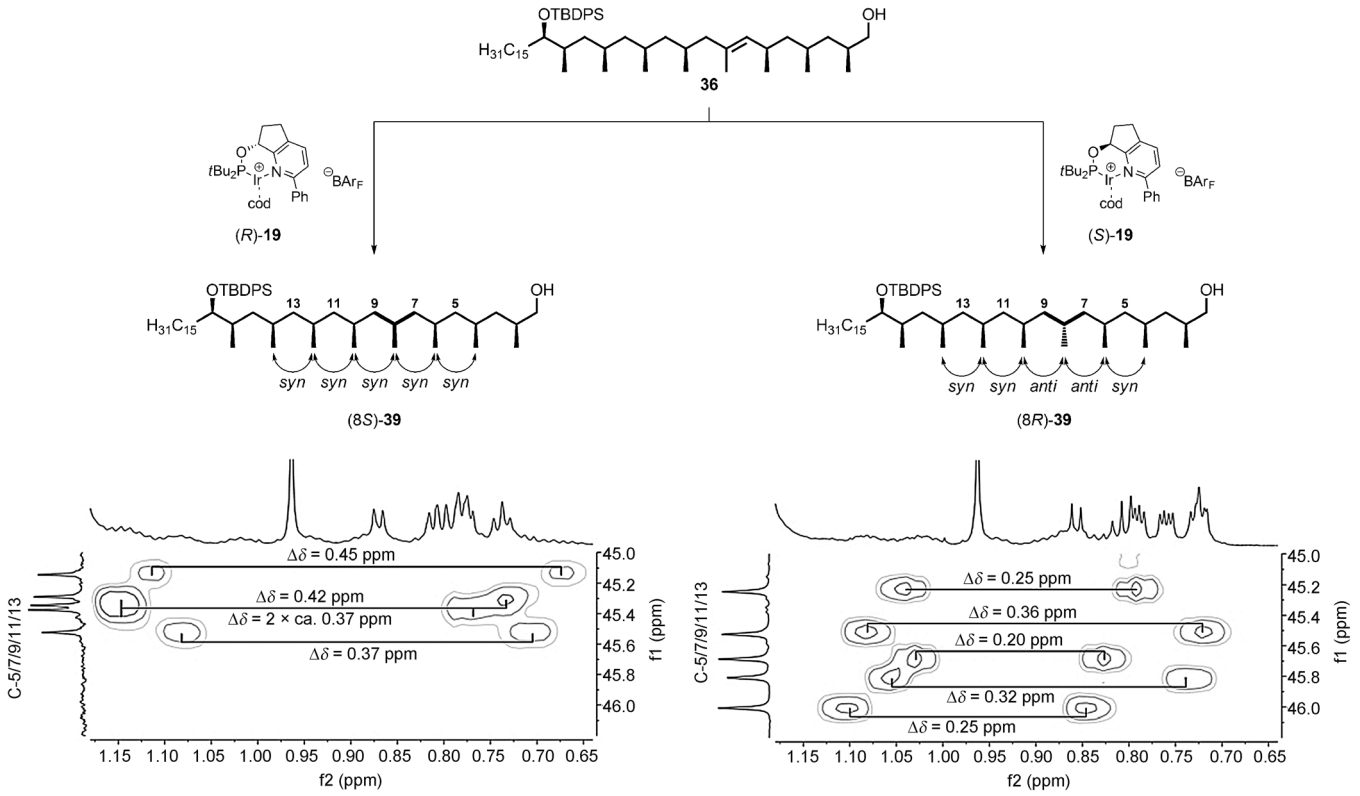


Scheme 14. Completion of the total synthesis of hydroxyphthioceranic acid (**10**). a) TBSCl, ImH, DMAP, CH_2Cl_2, RT, 30 min, 98%; b) MeOH, K_2CO_3, reflux, 6 h, 94%; c) TBDPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 5 h, 98%; d) 30 mol% $TBABr_3$, MeOH/THF, RT, 3 h, 99%; e) PPh_3, ImH, I_2, Et_2O/CH_3CN, RT, 15 min, 99%; f) 1) Compound **35**, *t*BuLi, Et_2O, *B*-OMe-9-BBN, THF, −78 °C to RT, 2 h; 2) then compound **17**, aq. 3 M K_3PO_4, 5 mol% $[PdCl_2(dppf)]\cdot CH_2Cl_2$, DMF, RT, 4 h, 85%; g) TBAF, THF, RT, 6 d, 94%; h) 2.5 mol% (*R*)-**19**, CH_2Cl_2, 60 bar, H_2, 2.5 mol% (*R*)-**19**, RT, 1.5 d, 99%; i) $NaHCO_3$, KBr, NaOCl, 5 mol% TEMPO, CH_2Cl_2 0 °C, 50 min, 93%; j) *t*BuOH/H_2O/isoprene, $NaClO_2$, NaH_2PO_4, RT, 4 h, 88%.

Conclusion

We have developed a new and highly convergent strategy for the stereoselective and fully flexible synthesis of long-chain polydeoxypropionates. Taking advantage of our previously reported trideoxypropionate synthesis, which provides a general access to all stereochemical permutations, we have been able to merge two of these fragments through a Suzuki–Miyaura cross-coupling reaction and subsequent iridium-catalyzed hydrogenation to access heptadeoxypropionate building blocks with excellent stereocontrol. By adding a suitable third fragment, we have completed the synthesis of the glycolipid components phthioceranic acid (**9**) and hydroxyphthioceranic acid (**10**), the latter of which was prepared in an amount of almost half a gram, which documents the applicability of our approach. More importantly, we have shown that this strategy is not limited to the synthesis of the two natural products, but is amenable to the synthesis of almost every other diastereomer by modification of the cross-coupling and hydrogenation conditions. Thus, we have been able to prepare all stereoisomers of the propionate unit in **31** as well as the 8-

drogenation of **36** with enantiomeric iridium catalysts (*R*)-**19** and (*S*)-**19** and analyzed them by using NMR spectroscopy according to the method of Breit et al. (Scheme 15).[37] Again, a clear picture emerged with the stereoisomer (8*S*)-**39** containing the natural configuration showing the expected chemical shift difference of the methylene protons 5/7/9/11/13-CH_2 with large values ranging between $\Delta\delta = 0.37$ and 0.45 ppm indicating an all-*syn*-deoxypropionate. On the contrary, the methylene



Scheme 15. Asymmetric hydrogenation of **51** with the iridium-pyridyl-phosphinite complexes (*R*)-**19** and (*S*)-**19**. Determination of the absolute configuration by two-dimensional HSQC NMR-spectroscopy. Comparison of the chemical shift difference ($\Delta\delta$) of the methylene protons 5/7/9/11/13-CH_2 of the propionates (8*S*)-**39** und (8*R*)-**39**. a) Compound (*R*)-**19** (4×5 mol%), CH_2Cl_2, 90 bar, H_2, 0.8 equiv $NaHCO_3$, RT, 4×1 d, 91%; b) (*S*)-**19** (15+10 mol%), CH_2Cl_2, 90 bar, H_2, 1.5 equiv $NaHCO_3$, RT, 2 d+1 d, 88%.

epimeric precursors (8*S*)-**39** and (8*R*)-**39** for the natural products by using the enantiomeric iridium catalyst. We therefore believe that this strategy will be of great utility for the stereoselective and flexible synthesis of other long-chain deoxypropionates as well.

Experimental Section

General methods

Unless otherwise stated, all reactions were carried out in dry solvents under an argon atmosphere using standard vacuum line techniques. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution using a Varian Gemini 300 spectrometer (300 MHz) and Bruker Avance DRX 400 (400 MHz) and a Bruker Avance 700 (700 MHz). Chemical shifts are reported in ppm and calibrated to residual chloroform peaks ($\delta = 7.26$ ppm, ^1H, 77.16 ppm, ^{13}C), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), and br s (broad singlet). Melting points were determined uncorrected on a Boetius heating table. IR spectra were obtained with an Avatar 360 FTIR of Thermo Nicolet and a 4100 FTIR of Jasco. Optical rotations were measured using a Polarotronic polarimeter (V-630 UV/Vis of Jasco and DU-600 of Beckman). All ESI mass spectra were recorded on a Bruker Daltonics Apex II FT-ICR and the EI mass spectra on a MAT 8230 of Finnigan (70 eV). All GCMS mass spectra were recorded on an Agilent Technologies 6890N/5975B inert GC/MSD, with the capillary GC column HP-5 ms (30 m×0.25 mm x 0.25 μm, 5% diphenyl- 95% dimethylpolysiloxane). HPLC analyses were carried out on a Jasco MD-2010 plus instrument with chiral stationary phase column Chiracel OD-H (250×4.6 mm) and Chiracel AD-H (250×4.6 mm) of Chiral Technologies Europe. Solvents were distilled from the indicated drying reagents: Dichlormethane (CaH_2), tetrahydrofuran (Na, bezophenone), diethyl ether (Na, benzophenone), toluene (Na, benzophenone), *n*-hexane (Na), and acetonitrile ($MgSO_4$, CaH_2). Other solvents were of technical grade and distilled from the indicated drying reagents: Diethyl ether (KOH), methyl-*tert*-butyl ether (KOH), ethyl acetate ($CaCl_2$), *n*-hexane (KOH), and dichloromethane (CaH_2). Triethylamine, diisopropylamine and diisopropylethylamine were directly distilled from CaH_2 before use. Flash column chromatography was performed using Merck silica gel 60 230–400 mesh (0.040–0.063 mm). Abbreviations for solvents are used as follows: Diethyl ether (Et_2O), ethyl acetate (EtOAc), *n*-hexane (Hex), dichloromethane (CH_2Cl_2), methyl-*tert*-butylether (MTBE). Reactions were monitored by thin-layer chromatography on precoated TLC Silica gel 60 F_{254} plates (Merck), were visualized by UV and treated with vanillin staining (5.0 g vanillin, 100 mL acetic acid, 50 mL conc. sulfuric acid, 1 L methanol) solution. Hydrogenation experiments were carried out in a Premex 50 mL MED 1234 at the indicated reaction conditions.

Syntheses

Syntheses and characterizations of compounds **1**–**18, (8*S*)-21**, **22**, (*R*)-**23**, (*R*)-**25**, (*R*)-**26**, (9*R*)-**27**, (9*R*)-**28**, (8*R*,9*R*)-**31**, and **35**--**38**, as well as the remaining spectral data of compounds (*S*)-**23**, have

been reported in the Supporting Information of our previous communication.[20b]

Large scale synthesis of 5: Protected aldol product **1** (45.7 g, 105 mmol) was solved in a 250 mL screw cap round bottom flask in 200 mL toluene ($c = 0.50$ M). The tube was sealed, placed into a heating bath and the reaction mixture was stirred for 5 h at185 °C. After cooling to room temperature, the solvent was removed and the viscous oil was treated with 400 mL of a 1:2 mixture of Et_2O/Hex. After slowly removal of a part of the solvent in vacuum most product was appeared as a white powder in the yellow solution. The solid was filtrated, washed with hexane, and dried in vacuum to give 32.2 g (74.3 mmol, 71%) of beaming white and clean rearrangement product **2**. The mother liquor was treated with 30 g of silica and dried in vacuum. Purification by flash column chromatography (MTBE/Hex 1:2→1:1→2:1→MTBE) gave additional 7.20 g (17 mmol, 16%) rearrangement product **2**. A 250 mL special manufactured glass inlet for the autoclave (500 mL inner volume) was filled with the combined rearrangement product **2** (26.8 g, 61.7 mmol, 1.0 equiv), iridium catalyst **4** (1.82 g, 1.11 mmol, 0.018 equiv), and CH_2Cl_2 (200 mL; $c = 0.30$ M). The glass inlet was placed into the hydrogenation autoclave that was sealed and purged twice with 50 bar of hydrogen. The reaction mixture was stirred at 85 bar hydrogenation pressure for one day. Removel of the solvent under reduced pressure and purification by flash column chromatography (EtOAc/Hex 1:4→1:2→1:1) gave 26.7 g (61.1 mmol, 99%, d.r. = 97/3) product **3** als colorless oil. A solution of 27.1 g (61.9 mmol, 1.0 equiv) hydrogenation product **3** in 250 mL THF ($c = 0.25$ M) was cooled to −78 °C. Sodium bis(trimethylsilyl)amide (NaHMDS; 33 mL, 65 mmol, 1.05 equiv, 2 M in THF) was added through a dropping funnel over a period of 15 min and the solution was stirred for additional 45 min at this temperature. MeI (7.00 mL, 111 mmol, 1.80 equiv) was added at −78 °C within 15 min and the reaction mixture was stirred additional three hours at this temperature. The reaction was stopped by the addition of half saturated NH_4Cl solution (400 mL) at −78 °C and warmed to room temperature. The aqueous phase was extracted with CH_2Cl_2 (5×100 mL). The combined organic extracts were dried over Na_2SO_4. Purification by flash column chromatography (EtOAc/Hex 9:1→7:1→5:1→3:1) gave trideoxypropionate **5** (26.3 g, 58.3 mmol, 94%) as a colorless oil.

Palmitol: $NaBH_4$ (4.43 g, 117 mmol, 2.0 equiv) and 15.0 g (58.8 mmol, 1.0 equiv) palmitic acid were placed in a 250 mL three neck bottom flask with reflux condenser, dropping funnel, and gas delivery pipe. The solvents were suspended in THF (90 mL) and cooled to 0 °C. iodine (16.4 g, 254 mmol, 1.1 equiv; soluted in 30 mL abs. THF) was carefully added through a dropping funnel over a period of two hours ($H_2\uparrow$) followed by stirring under reflux for 1 hour. The mixture was cooled to 0 °C and treated with 2 N HCl (30 mL) and a saturated $Na_2S_2O_3$ solution (30 mL). The mixture was extracted with MTBE (3×50 mL). The combined organic extracts were washed with 3 N NaOH (100 mL) and the aqueous phase was extracted with MTBE (3×50 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash column chromatography (Hex/EtOAc, 1:10) gave palmitol (13.6 g, 56.3 mmol, 96%) as a clear and crystalline solid. $R_f = 0.68$ (Hex/EtOAc 4/1). ^{1}H NMR (300 MHz, $CDCl_3$, 26 °C): $\delta = 3.64$ (dd, $^2J = 10.7$ Hz, $^3J = 6.3$ Hz, 2H, 1-CH_2), 1.67–1.43 (m, 2H, 2-CH_2), 1.43–1.18 (m, 26H, 3–15-CH_2), 0.88 ppm (t, $^3J = 6.7$ Hz, 3H, 16-CH_3).

Palmitic aldehyde: A solution of palmitol (3.00 g, 12.4 mmol, 1.0 equiv) in 60 mL of a 1:1 mixture of THF/DMSO ($c = 0.20$ M) was treated with IBX (5.20 g, 18.6 mmol, 1.5 equiv) and stirred at room temperature over night. The suspension was diluted with Et_2O (30 mL), water (30 mL) and the directly filtrated into a seperatory funnel. The mixture was extracted with Et_2O (3×30 mL) and the combined organic extracts were dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification by flash column chromatography (Et_2O/Hex 1:20) gave 2.73 g (11.4 mmol, 92%) palmitic aldehyde as a clear and crystalline solid. $R_f = 0.66$ (Hex/MTBE 10:1). ^{1}H NMR (400 MHz, $CDCl_3$, 26 °C): $\delta = 9.97$–9.54 (m, 1H, 1-CHO), 2.41 (dt, $^3J = 1.2$, 7.3 Hz, 2H, 2-CH_2), 1.85–1.46 (m, 2H, 3-CH_2), 1.42–1.13 (m, 24H, 4–15-CH_2), 0.87 ppm (t, $^3J = 6.7$ Hz, 3H, 16-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$, 26 °C): $\delta = 203.0$ (1-CHO), 44.05 (2-CH_2), 32.06 (14-CH_2), 29.83/29.81/29.80/29.77/29.72/29.56/29.49/29.31 (4–13-CH_2), 22.83 (3-CH_2), 22.23 (15-CH_2), 14.24 ppm (16-CH_3); GCMS (DB-50_S): $t_R = 6.55$ min, $m/z = 240.3$ $[M]^{\bullet+}$.

Propargylic alcohol 25: Ethynyl magnesium bromide (31 mL, 0.5 M in THF, 15.5 mmol, 1.05 equiv) was added to solution of palmitic aldehyde (3.54 g, 14.7 mmol, 1.0 equiv) in THF (70 mL; $c = 0.2$ M) at 0 °C and stirred for 30 min at this temperature. The reaction mixture was treated with a saturated NH_4Cl solution (30 mL) and was extracted with MTBE (3×30 mL). The combined organic extracts were dried over Na_2SO_4. Purification by flash column chromatography (Hex/MTBE 40:1→30:1→20:1) gave 3.16 g (11.9 mmol, 81%) of propargylic alcohol **25** as a colorless and crystalline solid. Enantiomerically pure (*S*)-**25** was obtained following the previously reported procedure using CAL-B-induced kinetic resolution.[20] Hereby, the racemic mixture (*rac*)-**25** (10.9 g, 40.9 mmol) was transformed into the propargylic alcohol (9*S*)-**25** (6.63 g, 24.9 mmol, 61%, >99% *ee*). $[\alpha]_D^{23} = -4.00$ ($c = 1.00$, $CHCl_3$). The determination of the enantiomeric excess of the free alcohol (*S*)-**25** was performed after conversion into the *para*-nitrobenzoic acid derivative.[20] $[\alpha]_D^{23} = -18.0$ ($c = 1.00$, $CHCl_3$, >99% *ee*); HPLC: Chiralcel OD-H column, Hex/*i*PrOH = 99:1, flow rate = 0.5 mL min^{-1}; (*R*)-enantiomer $t_R = 17.5$ min; (*S*)-enantiomer $t_R = 18.9$ min.

Internal vinyl iodide (*S*)-23: Propargyl alcohol (*S*)-**25** (533 mg, 2.0 mmol, 1.0 equiv, 99% *ee*) was dissolved in THF (5 mL, $c = 0.40$ M) and cooled to −40 °C. Then, methyllithium (1.25 mL, 1.6 M in THF, 2.0 mmol, 1.0 equiv) was added over a period of 10 min and the reaction mixture was stirred for additional 30 min at room temperature. Meanwhile, in a separate Schlenk flask, the Schwartz reagent (1.03 g, 4.0 mmol, 2.0 equiv) was treated at 0 °C with a solution of $ZnCl_2$ (12 mL, 1 M in THF, 12 mmol, 6.0 equiv). After removal of the ice bath, the lithium alkoxide-containing solution was concentrated under reduced pressure till half of its volume and then transferred to the $Cp_2ZrHCl/ZnCl_2$ solution through a cannula, rinsing with 1.0 mL of THF. After stirring 1 h at room temperature, the deep-grey suspension was treated with CH_3CN (1.05 mL, 20.0 mmol, 10 equiv) and stirring was continued for 10 min. The mixture was cooled to −50 °C, then treated with 1.01 g (4.0 mmol, 2.0 equiv) of iodine (dissolved in 4 mL THF) and allowed to reach room temperature over 1 h. The excess of iodine was destroyed with a sat. $NaHSO_3$ solution (20 mL), then diluted with water (20 mL) and extracted with MTBE (3×20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the residue was brought onto 3.5 g of silica (60–200 μm). Flash column chromatography (Hex/MTBE 30:1→20:1) gave 581 mg (1.47 mmol, 74%, internal/terminal > 50:1, >99% *ee*) of vinyl iodide (*S*)-**23** as a colorless solid. $[\alpha]_D^{23} = +10.0$ ($c = 1.00$, $CHCl_3$); HPLC: Chiralcel OJ column, Hex/*i*PrOH = 98:2, flow rate = 0.5 mL min^{-1}; (*S*)-enantiomer $t_R = 10.1$ min; (*R*)-enantiomer $t_R = 11.4$ min.

Hydrogenation product (8*S*)-21: Alkene **18** (40 mg, 0.064 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.5 mL) in a 2 mL reaction vial. Catalyst (*S*)-**28** (3.1 mg (0.035 equiv)) followed by $NaHCO_3$ (tip of a spatula) were added and the vial was placed into the autoclave. The reaction was stirred under hydrogen atmosphere (60 bar) for

3 h. After that time GCMS indicated leftover starting material. Additional catalyst (0.03 equiv) was added and the reaction was stirred for another 2 h under hydrogen atmosphere (60 bar) of hydrogen pressure. The crude reaction mixture was subjected to a column (Et_2O/Hex 0:1→1:20) to give 37.5 mg (0.060 mmol, 94%) of alkane (8*S*)-**20** as a colorless liquid. GC-MS and ^{13}C NMR spectroscopy indicated that the ratio of epimers generated during the hydrogenation was at least d.r. = 98:2. R_f = 0.30 (Et_2O/Hex 1/20); $[\alpha]_D^{22} = +3.5$ (c = 1.80, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 26 °C): δ = 7.71–7.65 (m, 4H), 7.45–7.35 (m, 6H), 4.62 (m_c, 2H), 3.52 (dd, J = 9.8, 5.1 Hz, 1H), 3.46–3.39 (m, 2H), 3.36 (s, 3H), 3.27 (dd, J = 9.3, 7.0 Hz, 1H), 1.89–1.79 (m, 1H), 1.79–1.70 (m, 1H), 1.67–1.49 (m, 5H), 1.42–1.24 (m, 3H), 1.23–1.08 (m, 3H), 1.06 (s, 9H), 0.99–0.77 ppm (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$, 26 °C): δ = 135.8, 135.8, 134.3, 134.3, 129.6, 127.7, 96.74, 73.37, 68.97, 55.22, 46.33, 46.11, 45.68, 45.60, 41.92, 41.67, 33.28, 30.97, 27.62, 27.52, 27.50, 27.48, 27.06, 20.88, 20.83, 20.78, 20.71, 19.48, 19.12, 18.36, 18.23; IR (film): $\tilde{\nu}$ = 3071, 3050, 2956, 2925, 1590, 1511, 1461, 1428, 1379, 1214, 1152, 1111, 1049, 971, 921, 824, 739, 702, 615, 505 cm^{-1}; HRMS (ESI): *m/z* calcd for: $C_{40}H_{68}O_3SiNa$: 647.48299 $[M+Na]^+$; found: 647.48289.

Suzuki–Miyaura cross-coupling product (9S)-27: *t*BuLi (0.50 mL, 0.80 mmol, 2.1 equiv, 1.6 M in pentane) was added slowly to a solution of alkyl iodide **20** (152 mg, 0.38 mmol, 1.0 equiv) in Et_2O (1.4 mL) at −78 °C. After 10 min stirring at −78 °C, the solution was treated with *B*-OMe-9-BBN (0.89 mL, 0.89 mmol, 2.35 equiv, 1.0 M in Hex) and then with THF (1.4 mL). This emulsion was brought to room temperature over a period of 2 h. In a separate flask, vinyl iodide (*S*)-**23** (150 mg, 0.38 mmol, 1.0 equiv) was dissolved in DMF (2 mL) and K_3PO_4 (0.63 mL, 1.90 mmol, 5.0 equiv, 3 M in water) and mixed roughly. The mixture was added at room temperature to the boronate solution with rinsing of 1 mL DMF. Finally, [$PdCl_2$-(dppf)]·CH_2Cl_2 (16 mg, 0.019 mmol, 0.05 equiv) was added and the brown suspension was stirred for 2 h under exclusion of light. The reaction mixture was diluted with MTBE (10 mL) and a sat. NaCl solution (2 mL). The aqueous phase was extracted with MTBE (3× 10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the resulting crude product was purified by flash column chromatography (MTBE/Hex 1:100) to give the coupling product (9S)-**27** (161 mg, 0.30 mmol, 79%) as a colorless oil. R_f = 0.50 (Hex/MTBE 9/1); $[\alpha]_D^{23} = -1.74$ (c = 1.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.06 (s, 1H, 8′-CHH), 4.83 (s, 1H, 8′-CHH), 4.02 (br s, 1H, 9-CH), 3.46 (dd, ^2J = 9.7 Hz, ^3J = 5.0 Hz, 1H, 1-CHH), 3.34 (dd, ^2J = 9.7 Hz, ^3J = 6.5 Hz, 1H, 1-CHH), 2.13 (dd, ^2J = 14.4 Hz, ^3J = 5.3 Hz, 1H, 7-CHH), 1.86–1.14 (m, 35H, -OH, 2/4/6-CH, 7-CHH, 3/5-CHH, 10–23-CH_2), 0.99–0.75 (m, 23H, 3/5-CHH, $SiC(CH_3)_3$, 2′/4′/6′/24-CH_3), 0.03 ppm (s, 6H, 2×$SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.0 (8-C_q), 110.6 (8′-CH_2), 75.54 (9-CH), 68.12 (1-CH_2), 45.57 (5-CH_2), 41.15 (3-CH_2), 39.97 (7-CH_2), 35.75 (10-CH_2), 33.26 (2-CH), 32.08 (22-CH_2), 29.85/29.77/29.52 (12–21-CH_2), 28.89 (6-CH), 27.86 (4-CH), 26.11 ($SiC(CH_3)_3$), 25.88 (11-CH_2), 22.84 (23-CH_2), 21.24 (4′-CH_3), 20.68 (6′-CH_3), 18.50 ($SiC(CH_3)_3$), 18.21 (2′-CH_3), 14.27 (24-CH_3), −5.21 (2×$SiCH_3$); IR (film): $\tilde{\nu}$ = 3365, 2954, 2925, 2854, 2360, 1646, 1463, 1378, 1253, 1095, 1007, 902, 837, 814, 775, 666, 602, 454 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{34}H_{70}O_2SiNa$: 561.50403 $[M+Na]^+$; found: 561.50373; GCMS (DB-100L): t_R = 9.67 min, *m/z* = 520.6 $[M-H_2O]^+$, 481.5 $[M-t\text{Bu}]^+$.

Standard protection of (9S)-27: A solution of 92.0 mg (0.171 mmol, 1.0 equiv) coupling product (9*S*)-**27** in CH_2Cl_2 (0.7 mL, c = 0.25 M) and pyridine (28 μL, 0.342 mmol, 2.0 equiv) was treated at 0 °C with *para*-nitrobenzoyl chloride (48 mg, 0.257 mmol, 1.5 equiv). After stirring for 2 h at 0 °C, the solution was acidified with 2N HCl to pH 1. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. Purification by flash column chromatography (Hex/MTBE, 100:1) afforded 105 mg (0.152 mmol, 89%) of fully protected (9*S*)-product as a slightly yellow, viscous oil. R_f = 0.96 (Hex/MTBE, 9:1); $[\alpha]_D^{23} = +7.84$ (c = 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.31–8.28 (m, 2H, 2×Ar-CH), 8.25–8.21 (m, 2H, 2×Ar-CH), 5.44 (t, ^3J = 6.3 Hz, 1H, 9-CH), 5.11 (s, 1H, 8′-CHH), 4.92 (s, 1H, 8′-CHH), 3.45 (dd, ^2J = 9.7 Hz, ^3J = 5.1 Hz, 1H, 1-CHH), 3.33 (dd, ^2J = 9.7 Hz, ^3J = 6.5 Hz, 1H, 1-CHH), 2.18 (dd, ^2J = 14.0 Hz, ^3J = 3.5 Hz, 1H, 7-CHH), 1.88–1.55 (m, 6H, 2/4/6-CH, 7-CHH, 10-CH_2), 1.44–1.17 (m, 28H, 11–23-CH_2, 3/5-CHH), 1.06–0.77 (m, 23H, 3/5-CHH, $SiC(CH_3)_3$), 2′/4′/6′/24-CH_3), 0.03 ppm (s, 6H, 2×$SiCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.0 (Ar-COO-), 150.7 (Ar-C_q), 146.0 (8-C_q), 136.2 (Ar-C_q), 130.8 (2×Ar-CH), 123.8 (2×Ar-CH), 112.4 (8′-CH_2), 78.30 (9-CH), 68.16 (1-CH_2), 45.61 (5-CH_2), 41.25 (3-CH_2), 40.26 (7-CH_2), 33.40 (2-CH), 32.08 (22-CH_2), 29.84/29.82/29.82/29.78/29.72/29.64/29.51 (10/12–21-CH_2), 28.42 (6-CH), 27.80 (4-CH), 26.10 ($SiC(CH_3)_3$), 25.59 (11-CH_2), 22.84 (23-CH_2), 21.06 (4′-CH_3), 20.43 (6′-CH_3), 18.49 ($SiC(CH_3)_3$), 18.09 (2′-CH_3), 14.27 (24-CH_3), −5.22 (2×$SiCH_3$); IR (film): $\tilde{\nu}$ = 2953, 2925, 2854, 1727, 1608, 1531, 1462, 1378, 1348, 1272, 1114, 1101, 909. 873, 837, 776, 735, 719, 667, 647, 599, 488, 456 cm^{-1}; UV λ_{max} (log ε): 3.69 (260 nm, MeCN); HRMS (ESI): *m/z* calcd for: $C_{41}H_{73}NO_5SiNa$: 710.51522 $[M+Na]^+$; found: 710.51480.

Mitsunobu protection of (9S)-27: A solution of the coupling product (9*S*)-**27** (2.35 g, 4.36 mmol, 1.0 equiv) in THF (22 mL, c = 0.20 M) was treated at 0 °C with triphenyl phosphine (5.61 g, 21.4 mmol, 4.9 equiv), *para*-nitrobenzoic acid (3.21 g, 19.2 mmol, 4.4 equiv), and Diisopropyl azodicarboxylate (DIAD; 4.20 mL, 21.4 mmol, 4.9 equiv). After stirring for 2 h at 0 °C, the orange solution was treated with 20 mL water. The aqueous phase was extracted with CH_2Cl_2 (3×20 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. The solid residue was treated with hexane and filtered through a 5 cm pipette of silica. Purification by flash column chromatography (Hex/MTBE, 50:1) afforded fully protected (9*R*)-product (2.63 g, 3.83 mmol, 88%) as a slightly yellow, viscous oil. $[\alpha]_D^{20} = -7.00$ (c = 1.43, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.32–8.26 (m, 2H, 2×Ar-CH), 8.24–8.18 (m, 2H, 2×Ar-CH), 5.45 (t, ^3J = 6.6 Hz, 1H, 9-CH), 5.16 (s, 1H, 8′-CHH), 4.96 (s, 1H, 8′-CHH), 3.44 (dd, ^2J = 9.7 Hz, ^3J = 5.0 Hz, 1H, 1-CHH), 3.32 (dd, ^2J = 9.7 Hz, ^3J = 6.5 Hz, 1H, 1-CHH), 2.19 (dd, ^2J = 13.8 Hz, ^3J = 4.1 Hz, 1H, 7-CHH), 1.85–1.53 (m, 6H, 2/4/6-CH, 7-CHH, 10-CH_2), 1.44–1.14 (m, 28H, 11–23-CH_2, 3/5-CHH), 0.98–0.74 (m, 23H, 3/5-CHH, $SiC(CH_3)_3$, 2′/4′/6′/24-CH_3), 0.02 ppm (s, 6H, 2×$SiCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1 (Ar-COO-), 150.6 (Ar-C_q), 145.8 (8-C_q), 136.2 (Ar-C_q), 130.8 (2×Ar-CH), 123.7 (2×Ar-CH), 113.9 (8′-CH_2), 79.11 (9-CH), 68.11 (1-CH_2), 45.58 (5-CH_2), 41.01 (3-CH_2), 40.18 (7-CH_2), 33.20 (2-CH), 32.07 (22-CH_2), 29.83/29.81/29.77/29.71/29.63/29.50 (10/12–21-CH_2), 28.76 (6-CH), 27.79 (4-CH), 26.09 ($SiC(CH_3)_3$), 25.64 (11-CH_2), 22.84 (23-CH_2), 21.18 (4′-CH_3), 20.41 (6′-CH_3), 18.48 ($SiC(CH_3)_3$), 18.11 (2′-CH_3), 14.26 (24-CH_3), −5.23 ppm (2×$SiCH_3$).

Alcohol (9S)-28: Tetrabutylammonium tribromide (59.0 mg, 0.188 mmol, 0.1 equiv) was added to a solution of the fully protected (9*S*)-product (1.29 g, 1.88 mmol, 1.0 equiv) in MeOH (9.4 mL, c = 0.20 M). After 4 h stirring at room temperature, TLC indicated full conversion. The reaction mixture was quenched with a half sat. $NaHSO_4$ (20 mL) solution and all volatiles were removed under reduced pressure. The aqueous phase was extracted with EtOAc (3× 20 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. Flash column chromatography (Hex/MTBE, 30:1) gave 1.04 g (1.82 mmol, 97%) of *exo*-methylene alcohol (9*S*)-**28** as a slighly yellow, viscous oil. R_f = 0.21 (Hex/MTBE 9/1); $[\alpha]_D^{23} = +5.76$ (c = 1.21, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.33–8.26 (m, 2H, 2×Ar-CH), 8.26–8.19 (m, 2H, 2×Ar-CH), 5.44 (t, ^3J = 6.3 Hz, 1H, 9-

CH), 5.10 (s, 1H, 8′=CHH), 4.92 (s, 1H, 8′=CHH), 3.52 (m_c, 1H, 1-CHH), 3.38 (m_c, 1H, 1-CHH), 2.17 (d, ^2J=10.5 Hz, 1H, 7-CHH), 1.89–1.52 (m, 6H, 2/4/6-CH, 7-CHH, 10-CH_2), 1.46–1.19 (m, 28H, 11–23-CH_2, 3/5-CHH), 1.09–0.83 (m, 14H, 3/5-CHH, 2′/4′/6′/24-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ=164.1 (Ar-COO-), 150.6 (Ar-C_q), 146.1 (8-C_q), 136.1 (Ar-C_q), 130.8 (2×Ar-CH), 123.7 (2×Ar-CH), 112.4 (8′-CH_2), 78.19 (9-CH), 68.22 (1-CH_2), 45.45 (5-CH_2), 41.21 (3-CH_2), 40.36 (7-CH_2), 33.42 (2-CH), 33.22 (10-CH_2), 32.07 (22-CH_2), 29.81/29.79/29.78/29.75/29.69/29.61/29.48 (12–21-CH_2), 28.53 (6-CH), 27.83 (4-CH), 25.57 (11-CH_2), 22.81 (23-CH_2), 21.09 (4′-CH_3), 20.44 (6′-CH_3), 17.72 (2′-CH_3), 14.24 ppm (24-CH_3); IR (film): $\tilde{\nu}$=3376, 2952, 2924, 2853, 2360, 2341, 1726, 1650, 1608, 1530, 1461, 1409, 1380, 1348, 1320, 1274, 1168, 1116, 1102, 1080, 1037, 1015, 974, 903, 874, 838, 784, 719 cm^{-1}; UV λ_{max} (log ε): 9.01 (261.5 nm, CH_3CN); HRMS (ESI): *m/z* calcd for: $C_{35}H_{59}NO_5Na$: 596.42857 $[M+Na]^+$; found: 596.42837.

Catalyst screening: (see the Supporting Information, Table 1 in Section II): A 2 mL glass inlet, equipped with a magnetic stirrer bar was filled with the catalyst (0.871 μmol, 0.05 equiv) and 0.7 mL (c=0.023 M) of a stock solution of (9*S*)-**28** or (9*R*)-**28** (10 mg, 17.4 μmol, 1.0 equiv) in CH_2Cl_2. Four of the glass inlets were placed into the autoclave, which was sealed and purged twice with 50 bar of hydrogen. The reaction mixture was stirred under hydrogen atmosphere at room temperature with the given parameters (1 bar→15 h, 90 bar→3 h). The solvent was removed under reduced pressure and the residual solid was filtered over 4 cm of a silica pipette with a 1:1-mixture of Hex/MTBE (6 mL) for HPLC analysis.

Synthesis of the diastereomers (8*S*,9*R*)-31, (8*S*,9*S*)-31 and (8*R*,9*S*)-31: The hydrogenation experiments for the diastereomeric pure products (8*S*,9*R*)-**31** (the Supporting Information, Table 1: entry 3) and (8*S*, 9*S*)-**31** (the Supporting Information, Table 1: entry 17) were repeated in a 34.8 μmol scale. The combined fractions were purified with flash column chromatography (Hex/MTBE, 10:1) to complete the analytical data. R_f=0.21 (Hex/MTBE, 9:1); IR (film): $\tilde{\nu}$=3421, 2953, 2924, 2853, 1723, 1608, 1530, 1460, 1379, 1348, 1319, 1274, 1117, 1102, 1038, 1015, 874, 719 cm^{-1}; UV: λ_{max} (log ε): 4.10 (261.5 nm, CH_3CN); HRMS (ESI): *m/z* calcd for: $C_{35}H_{61}NO_5Na$: 598.44422 $[M+Na]^+$; found: 598.44398.

Diastereomer (8*S*,9*R*)-31: Yield: 85%; $[\alpha]_D^{23}=-7.00$ (c=1.75, $CHCl_3$, d.r.=98:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.31–8.26 (m, 2H, 2×Ar-CH), 8.22–8.17 (m, 2H, 2×Ar-CH), 5.16 (m_c, 1H, 9-CH), 3.45 (dd, ^2J=10.4 Hz, ^3J=5.1 Hz, 1H, 1-CHH), 3.32 (dd, ^2J=10.4 Hz, ^3J=6.6 Hz, 1H, 1-CHH), 1.99–1.87 (m_c, 1H, 8-CH), 1.79–1.52 (m, 5H, 2/4/6-CH, 10-CH_2), 1.37–1.17 (m, 29H, 3/5/7-CHH, 11–23-CH_2), 1.14–1.05 (m, 1H, 7-CHH), 0.93 (d, ^3J=6.7 Hz, 3H, 8′-CH_3), 0.92 (d, ^3J=6.7 Hz, 3H, 2′-CH_3), 1.03–0.81 (m, 5H, 3/5-CHH, 24-CH_3), 0.87 (d, ^3J=6.5 Hz, 3H, 4′-CH_3), 0.85 ppm (d, ^3J=6.5 Hz, 3H, 6′-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ=164.7 (Ar-COO-), 150.6 (Ar-C_q), 136.3 (Ar-C_q), 130.8 (2×Ar-CH), 123.7 (2×Ar-CH), 80.68 (9-CH), 68.33 (1-CH_2), 45.98 (5-CH_2), 41.38 (3-CH_2), 39.18 (7-CH_2), 33.99 (8-CH), 33.24 (2-CH), 32.06 (22-CH_2), 30.43 (10-CH_2), 29.82/29.80/29.76/29.71/29.66/29.64/29.49 (12–21-CH_2), 27.68 (4-CH), 27.60 (6-CH), 25.88 (11-CH_2), 22.83 (23-CH_2), 21.02 (6′-CH_3), 20.31 (4′-CH_3), 17.65 (2′-CH_3), 15.48 (8′-CH_3), 14.26 ppm (24-CH_3); HPLC: Chiralcel OD-H column, Hept/*i*PrOH=99.5/0.5, flow rate=0.5 mL min^{-1}; minor diastereomer t_R=56.6 min; major diastereomer t_R=62.6 min.

Diastereomer (8*S*,9*S*)-31: Yield: 84%; $[\alpha]_D^{23}=-18.5$ (c=1.50, $CHCl_3$, d.r.=96:4); ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.32–8.26 (m, 2H, 2×Ar-CH), 8.23–8.18 (m, 2H, 2×Ar-CH), 5.08 (m_c, 1H, 9-CH), 3.50 (dd, ^2J=10.4 Hz, ^3J=5.1 Hz, 1H, 1-CHH), 3.36 (dd, ^2J=10.4 Hz, ^3J=6.7 Hz, 1H, 1-CHH), 1.95–1.85 (m_c, 1H, 8-CH), 1.76–1.49 (m, 5H, H-2/4/6-CH, 10-CH_2), 1.35–1.21 (m, 27H, 3-CHH, 11–23-CH_2), 1.21–1.02 (m, 3H, 3/5/7-CHH), 0.96 (d, ^3J=6.7 Hz, 3H, 8′-CH_3), 0.88 (d, ^3J=6.9 Hz, 3H, 2′-CH_3), 0.98–0.78 (m, 5H, 3/5-CHH, 24-CH_3), 0.85 (d, ^3J=6.6 Hz, 3H, 4′-CH_3), 0.81 (d, ^3J=6.5 Hz, 3H, 6′-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ=164.6 (Ar-COO-), 150.6 (Ar-C_q), 136.3 (Ar-C_q), 130.8 (2×Ar-CH), 123.7 (2×Ar-CH), 80.39 (9-CH), 68.29 (1-CH_2), 46.01 (5-CH_2), 41.30 (3-CH_2), 40.18 (7-CH_2), 33.95 (8-CH), 33.21 (2-CH), 32.06 (22-CH_2), 31.42 (10-CH_2), 29.82/29.80/29.76/29.71/29.67/29.64/29.50 (12–21-CH_2), 27.61 (6-CH), 27.46 (4-CH), 25.88 (11-CH_2), 22.83 (23-CH_2), 21.01 (6′-CH_3), 20.31 (4′-CH_3), 17.65 (2′-CH_3), 14.49 (8′-CH_3), 14.26 ppm (24-CH_3); HPLC: Chiralcel AD-H column, Hept/*i*PrOH=98:2, flow rate=1.0 mL min^{-1}; minor diastereomer t_R=11.8 min; major diastereomer t_R=13.7 min.

Diastereomer (8*R*,9*S*)-31: After TBS-protection and *p*-NO_2Bz-deprotection of product (8*R*,9*R*)-**31**,[9b,20] the resulting alcohol (50.0 mg, 92 μmol, 1.0 equiv) was dissolved in THF (0.5 mL, c=0.20 M) and treated at 0 °C with triphenyl phosphine (119 mg, 0.45 mmol, 4.9 equiv), *para*-nitrobenzoic acid (68.0 mg, 0.45 mmol, 4.4 equiv), and DIAD (0.89 mL, 0.41 mmol, 4.9 equiv). After stirring for 5 h at 0 °C the orange solution was treated with 15 mL water. The aqueous phase was extracted with MTBE (3×10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. The solid residue was treated with hexane and filtered through a 5 cm pipette of silica. Purification by flash column chromatography (Hex/MTBE, 50:1) afforded the protected deoxypropionate (44.0 mg, 63.8 μmol, 69%) of as a slightly yellow, viscous oil. The deoxypropionate was dissolved in MeOH (0.3 mL, c=0.20 M), treated with tetrabutylammonium tribromide (4.0 mg, 12.8 μmol, 0.2 equiv) and stirred for 4 h at room temperature. The reaction mixture was quenched with a half sat. $NaHSO_4$ (5 mL) solution and all volatiles were removed under reduced pressure. The aqueous phase was extracted with MTBE (3×10 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. Flash column chromatography (Hex/MTBE, 10:1) gave (8*R*,9*S*)-**31** (29.3 mg, 50.9 μmol, 80%) as a slighly yellow, viscous oil. $[\alpha]_D^{23}=-8.97$ (c=1.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.29 (m, 2H, 2×Ar-CH), 8.20 (m, 2H, 2×Ar-CH), 5.17–5.05 (m_c, 1H, 9-CH), 3.54 (dd, ^2J=10.4 Hz, ^3J=4.9 Hz, 1H, 1-CHH), 3.37 (dd, ^2J=10.4 Hz, ^3J=6.7 Hz, 1H, 1-CHH), 1.99 (m_c, 1H, 8-CH), 1.78–1.49 (m, 5H, 2/4/6-CH, 10-CH_2), 1.44–1.14 (m, 29H, 3/5/7-CHH, 11–23-CH_2), 1.04–0.81 ppm (m, 18H, 3/5/7-CHH, 2′/4′/6′/8′/24-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ=164.6 (Ar-COO-), 150.6 (Ar-C_q), 136.4 (Ar-C_q), 130.8 (2×Ar-CH), 123.7 (2×Ar-CH), 79.87 (9-CH), 68.16 (1-CH_2), 45.35 (5-CH_2), 41.01 (3-CH_2), 40.72 (7-CH_2), 33.98 (8-CH), 33.26 (2-CH), 32.07 (22-CH_2), 29.83/29.80/29.77/29.71/29.66/29.50/29.46 (10/12–21-CH_2), 28.00/27.90 (4/6-CH), 26.05 (11-CH_2), 22.84 (23-CH_2), 21.33 (4′/6′-CH_3), 17.92 (2′-CH_3), 16.05 (8′-CH_3), 14.26 ppm (24-CH_3); HPLC: Chiralcel AD-H column, Hept/*i*PrOH=98:2, flow rate=1.0 mL min^{-1}; minor diastereomer t_R=13.7 min; major diastereomer t_R=11.8 min.

Hydrogenation product (8*S*)-39: In a 2 mL glass inlet, equipped with a magnetic stirrer bar, were placed alcohol **36** (78.0 mg, 93.4 μmol, 1.0 equiv), sodium hydrogencarbonate (6.3 mg, 74.7 μmol, 0.8 equiv), and catalyst (*R*)-**19** (7.1 mg, 46.7 μmol, 0.05 equiv) in CH_2Cl_2 (0.6 mL, c=0.10 M). The glass inlet was placed into the autoclave, which was sealed and purged twice with 50 bar of hydrogen. The reaction mixture was stirred under hydrogen atmosphere (90 bar) at room temperature for 1 day. After that time ^{1}H NMR spectroscopic analysis indicated leftover starting material. This procedure was then repeated overall three times with the addition of 0.10 equiv catalyst for another 1 d under hydrogen atmosphere (90 bar). The solvent was removed under reduced pressure and flash column chromatography (EtOAc/Hex 1:20) gave the diastereomeric pure alkane (8*S*)-**39** (70.8 mg, 70.5 μmol, 91%) as a colorless oil. TLC: R_f=0.67 (Hex/Et_2O, 1:1); $[\alpha]_D^{22}=+4.00$ (c=1.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.74–7.65 (m, 4H, 4×Ar-CH),

7.44–7.31 (m, 6H, 6×Ar-CH), 3.63–3.51 (m, 2H, 17-CH, 1-CHH), 3.42–3.33 (m, 1H, 1-CHH), 1.80–1.69 (m_c, 1H, 2-CH), 1.04 (s, 9H, $SiC(CH_3)_3$), 0.95 (d, $^3J=6.7$ Hz, 3H, 2′-CH_3), 1.69–0.71 ppm (m, 74H, -OH, 4/6/8/10/12/14/16-CH, 3/5/7/9/11/13/15/18–31-CH_2, 4′/6′/8′/10′/12′/14′/16′/32-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=136.2$ (2×Ar-CH), 136.1 (2×Ar-CH), 135.5 (Ar-C_q), 134.6 (Ar-C_q), 129.5 (Ar-CH), 129.4 (Ar-CH), 127.5 (2×Ar-CH), 127.4 (2×Ar-CH), 76.91 (17-CH), 68.30 (1-CH_2), 45.57/45.44/45.41/45.36/45.21 (5/7/9/11/13-CH_2), 41.55 (15-CH_2), 41.07 (3-CH_2), 34.42 (16-CH), 34.36 (18-CH), 33.28 (2-CH), 32.09 (30-CH_2), 29.87/29.83/29.76/29.65/29.57/29.53 (20–29-CH_2), 27.99/27.89/27.84/27.79 (4/6/8/10/12/14-CH), 27.32 ($SiC(CH_3)_3$), 26.04 (19-CH_2), 22.86 (31-CH_2), 21.86/21.83/21.74/21.55/21.38/21.24 (4′/6′/8′/10′/12′/14′-CH_3), 19.76 ($SiC(CH_3)_3$), 17.91 (2′-CH_3), 14.78 (16′-CH_3), 14.28 (32-CH_3).IR (film): $\tilde{\nu}=3374$, 2954, 2924, 2854, 2360, 2341, 1460, 1427, 1377, 1362, 1111, 1040, 822, 739, 702, 688, 611, 506, 488 cm^{-1}; UV λ_{max} (log ε): 4.29 (200.5 nm, CH_3CN), 3.96 (218.5 nm, CH_3CN), 2.86 (265.0 nm, CH_3CN); HRMS (ESI): *m/z* calcd for $C_{56}H_{100}O_2SiNa$: 855.73848 $[M+Na]^+$; found: 855.73856.

Hydrogenation product (8*R*)-39: In a 2 mL glass inlet, equipped with a magnetic stirrer bar, were placed alcohol **36** (49.0 mg, 60 μmol, 1.0 equiv), $NaHCO_3$ (7.6 mg, 90 μmol, 1.5 equiv), and catalyst (*S*)-**19** (13.7 mg, 90 μmol, 0.15 equiv) in 0.5 mL CH_2Cl_2 ($c=0.10$ M). The glass inlet was placed into the autoclave, which was sealed and purged twice with 50 bar of hydrogen. The reaction mixture was stirred under hydrogen atmosphere (90 bar) at room temperature for 1 day. After that time, ^{1}H NMR spectroscopy indicated leftover starting material. Another 0.10 equiv catalyst were added and the reaction was stirred for another 1 day under a hydrogen atmosphere (90 bar). The solvent was removed under reduced pressure and flash column chromatography (EtOAc/Hex, 1:5) gave 70.8 mg (70.5 μmol, 88%) of diastereomeric pure alkane (8*R*)-**39** as a colorless oil. $[\alpha]_D^{22}=+4.93$ ($c=1.80$, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): $\delta=7.71$–7.66 (m, 4H, 4×Ar-CH), 7.44–7.33 (m, 6H, 6×Ar-CH), 3.61–3.56 (m_c, 1H, 17-CH), 3.54 (dd, $^2J=10.0$ Hz, $^3J=4.8$ Hz, 1H, 1-CHH), 3.38 (dd, $^2J=10.0$ Hz, $^3J=7.1$ Hz, 1H, 1-CHH), 1.73 (m_c, 1H, 2-CH), 1.67–1.54 (m, 6H, 4/6/8/10/12/14-CH), 1.53–1.44 (m, 2H, 16-CH, 15-CHH), 1.39 (m_c, 1H, 18-CHH), 1.04 (s, 9H, $SiC(CH_3)_3$), 0.95 (d, $^3J=6.7$ Hz, 3H, 2′-CH_3), 1.33–0.77 ppm (m, 63H, 18-CHH, 3/5/7/9/11/13/15/19–31-CH_2, 4′/6′/8′/10′/12′/14′/16′/32-CH_3); ^{13}C NMR (176 MHz, $CDCl_3$): $\delta=136.2$ (2×Ar-CH), 136.1 (2×Ar-CH), 135.5 (Ar-C_q), 134.5 (Ar-C_q), 129.5 (Ar-CH), 129.4 (Ar-CH), 127.5 (2×Ar-CH), 127.4 (2×Ar-CH), 76.75 (17-CH), 68.43 (1-CH_2), 46.01/45.81/45.69/45.52/45.25 (5/7/9/11/13-CH_2), 41.56 (15-CH_2), 41.46 (3-CH_2), 34.31 (18-CH), 34.28 (16-CH), 33.19 (2-CH), 32.09 (30-CH_2), 29.87/29.83/29.76/29.65/29.59/29.57/29.54 (20–29-CH_2), 27.68/27.50/27.45/27.38 (4/6/8/10/12/14-CH), 27.30 ($SiC(CH_3)_3$), 26.03 (19-CH_2), 22.86 (31-CH_2), 21.34/21.05/20.99/20.91/20.74 (4′/6′/10′/12′/14′-CH_3), 19.76 ($SiC(CH_3)_3$), 18.98 (8′-CH_3), 17.70 (2′-CH_3), 14.75 (16′-CH_3), 14.30 ppm (32-CH_3).

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