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A Unified Strategy for the Stereospecific Construction of Propionates and Acetate–Propionates Relying on a Directed Allylic Substitution

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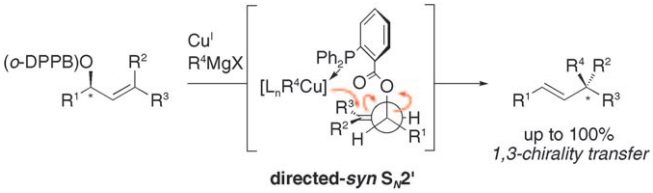
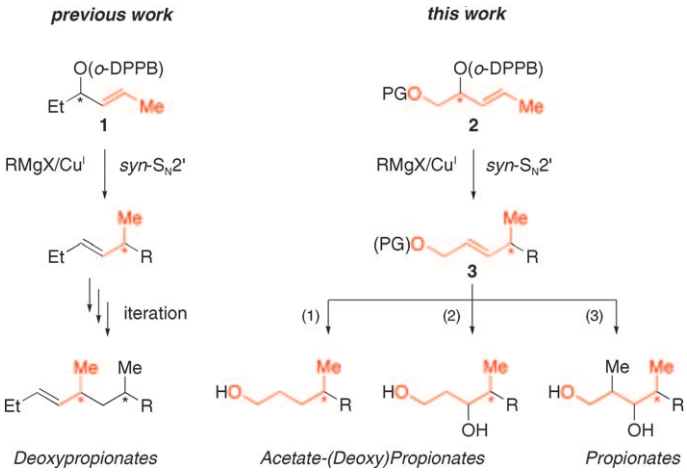
Carbon–carbon bond-forming reactions that allow the predictable, flexible, and stereospecific construction of a desired carbon skeleton are valuable transformations in organic synthesis. In this context we recently reported on the development of the *o*-DPPB-directed allylic substitution with Grignard-derived organocopper reagents that occurs with complete control of the chemo-, regio-, and stereochemistry, and delivers the corresponding S_N2' substitution products with either a tertiary or a quarternary stereogenic center with perfect *syn*-1,3-chirality transfer (Scheme 1).[1,2] A particular value of this reaction is that only a stoichiometric amount of the Grignard reagent is required to achieve quantitative transformation, which allows the economic use of functionalized valuable Grignard reagents and may be employed even in a fragment coupling step in the course of a total synthesis.[3]



Scheme 1. *o*-DPPB-directed allylic substitution with Grignard-derived organocopper reagents (*o*-DPPB: *ortho*-diphenylphosphanyl benzoate).

Furthermore, based on the directed allylic substitution a new methodology for the iterative construction of deoxypropionates has been developed (see Scheme 2, left side).[4,5]



Scheme 2. Concept of a unified strategy for the flexible and stereospecific construction of major polyketide structural elements based on the *o*-DPPB-directed allylic substitution.

Here, the enantiomerically pure allylic *o*-DPPB esters **1** served as the key building blocks for iterative propionate insertion. The strength and reliability of this methodology has been proved in the course of a pheromone synthesis, which led to the deduction of its absolute configuration.[6]

We herein report on a new strategy for the flexible and stereospecific preparation of propionates, acetate propionates and acetate deoxypropionate structural motifs relying on the *o*-DPPB-directed allylic substitution (see Scheme 2, right side). The key building block in this strategy is the new allylic *o*-DPPB ester **2**, which contains an additional oxygen functionality in the homoallylic position. Thus, the product of a directed S_N2' reaction becomes an allylic alcohol derivative **3**. Hydrogenation of its alkene function would furnish acetate deoxypropionates (Scheme 2, route (1)). The process should be iterable and would allow the stereoselective construction of 1,5-skipped oligomethyl chains of isoprenoid or polyketide origin. Asymmetric Sharpless epoxidation of allylic alcohol **3** followed by an epoxide ring opening with a hydride nucleophile would furnish acetate–propionate structures (Scheme 2, route (2)), whereas ring opening of the

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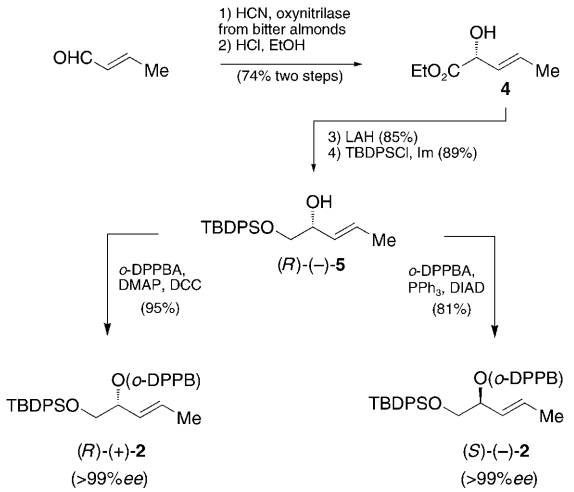
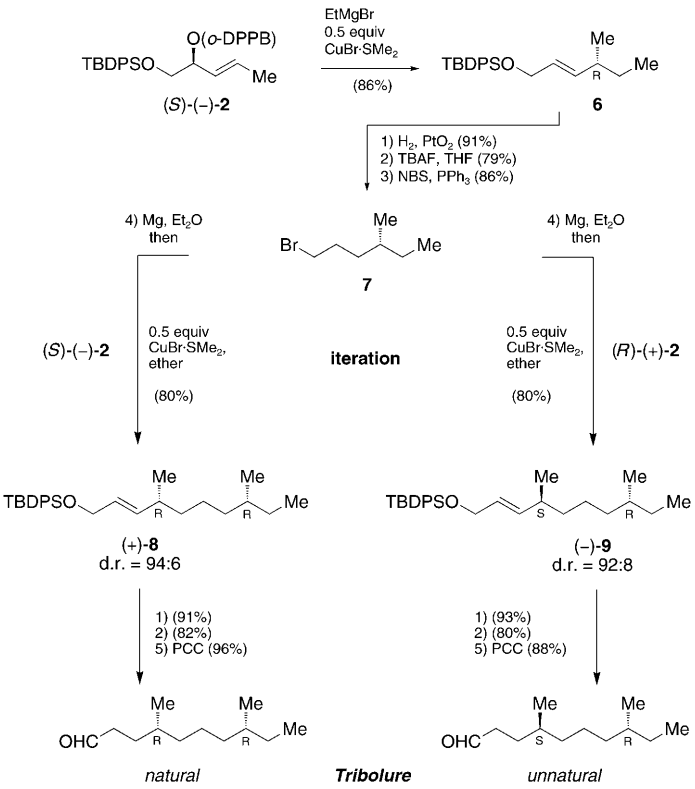
same epoxide with a methyl nucleophile would allow propionate construction (Scheme 2, route (3)).

For implementation of this synthesis strategy we required an efficient enantioselective access towards both optical antipodes of allylic *o*-DPPB ester **2**. Thus, crotonaldehyde was treated with HCN in the presence of the oxynitrilase[7] from bitter almonds to furnish the (*R*)-cyanohydrin with high levels of enantioselectivity (>96% *ee*). The nitrile function was transformed into the ethyl ester **4** following a Pinner reaction protocol (Scheme 3).[8] Ester reduction and protection



Scheme 3. Preparation of key allylic *o*-DPPB esters (*R*)-**2** and (*S*)-**2**. LAH = lithium aluminum hydride; DMAP = 4-dimethylaminopyridine; DCC = dicyclohexylcarbodiimide; DIAD = diisopropyl azodicarboxylate.



Scheme 4. Acetate–deoxypropionate (and isoprenoid) iterative construction: Stereodivergent synthesis of a natural and an unnatural stereoisomer of tribolure—an aggregation pheromone of the red flour beetle. PCC = pyridinium chlorochromate.

of the primary alcohol as the *tert*-butyldiphenyl silyl ether (TBDPS) furnished (*R*)-**5** on a multigram scale.[9] Steglich esterification[10] with *ortho*-diphenylphosphanylbenzoic acid (*o*-DPPBA) led quantitatively to the (*R*)-*o*-DPPB ester **2**. To access the optical antipode (*S*)-**2**, we wondered whether a Mitsunobu reaction[11] of allylic alcohol (*R*)-**5** employing *o*-DPPBA as the nucleophile could be an option. Since *o*-DPPBA is a carboxylic acid as well as a triarylphosphine we expected this to be a nontrivial task since the reagent triphenylphosphine, as well as *o*-DPPBA may react with the DIAD electrophile. However, we were pleased to find that the Mitsunobu reaction of the allylic alcohol (*R*)-**4** with *o*-DPPBA proceeded cleanly to furnish the corresponding (*S*)-allylic *o*-DPBB ester **2** with complete inversion of configuration. A simple recrystallization provided both esters **2** in essentially enantiomerically pure form, which could be stored for months without notable decomposition.

For the implementation of an iterative acetate–deoxypropionate (and isoprenoid) construction we selected the skeleton of tribolure, which is an aggregation pheromone of the red flour beetle (Scheme 4).[12] Indeed, the 1,5-skipped dimethyl chain has been shown to be of polyketide origin, while such structural elements are also typical for isoprenoids.[13,14] The synthesis began with a directed allylic substitution employing EtMgBr. The allylic substitution product **6** was obtained in good yield as a single stereoisomer. Catalytic alkene reduction, silyl ether cleavage, and a Mukaiayma redox condensation[15] furnished bromide **7**. The sequence becomes iterable through transformation of **7** into the corresponding Grignard reagent, and subjection to the conditions of the directed allylic substitution. Thus, reaction with (*S*)-**2** and (*R*)-**2** gave the diastereomers (+)-**8** and (−)-**9** in good yield and stereocontrol, respectively. Alkene reduction, silyl ether deprotection and oxidation to the aldehyde gave the natural (*R*,*R*) stereoisomer, and the unnatural (*S*,*R*) stereoisomer of tribolure, thus highlighting the stereochemical flexibility of this strategy. Interestingly, allylic *o*-DPPB esters **2** may also be regarded as a chiral isoprenoid building block for a stereospecific C5 chain extension.

We next turned towards the preparation of the acetate-propionate structural motif (Scheme 5). Thus, starting from the allylic substitution product **6**, silyl deprotection furnished allylic alcohol **10**. Sharpless asymmetric epoxidation[16] with (−)-DET led to the *syn*-epoxide **11**, while employing (+)-diethyl tartrate ((+)-DET) provided *anti*-epoxide **12** in good yields and diastereoselectivities, respectively. Reductive epoxide opening with Red-Al[17] furnished *syn*-acetate–propionate **13** and *anti*-**14**, respectively.

Thus, through choice of the absolute configuration of the allylic electrophile **2**, and through selection of the configuration of the Sharpless epoxidation catalyst all four stereoiso-

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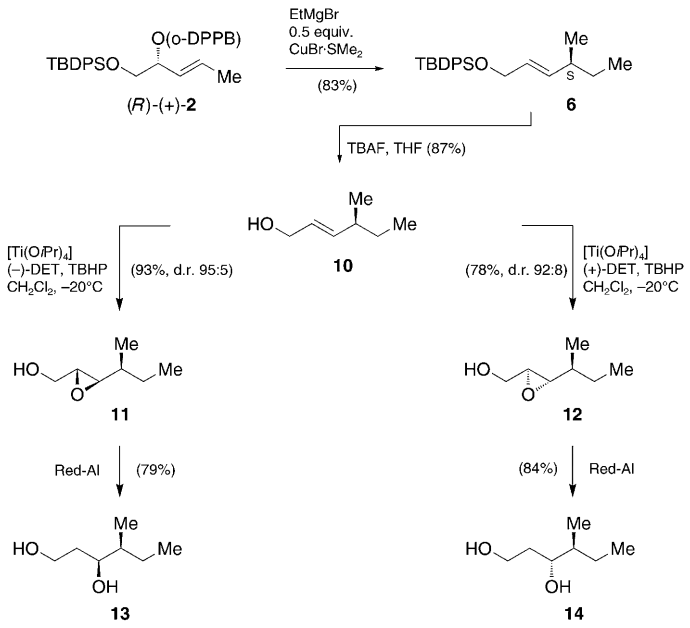
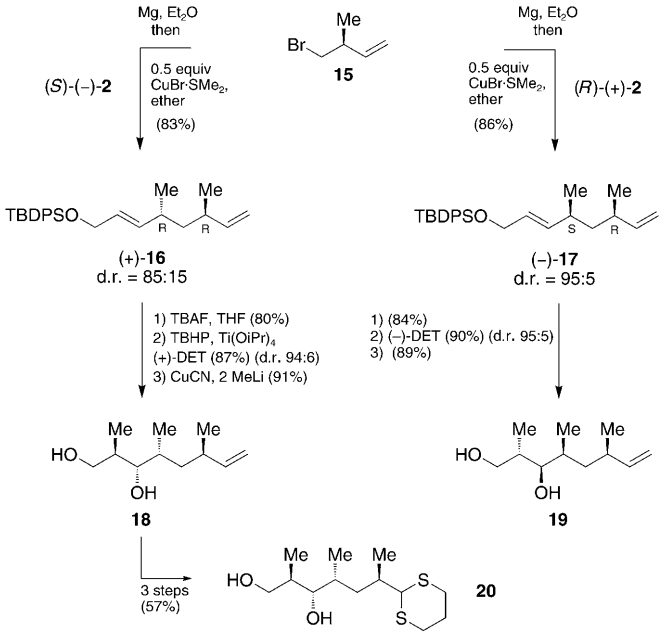


Scheme 5. Acetate–propionate construction. TBHP = *tert*-butyl hydroperoxide.

meric acetate–propionate building blocks are available stereoselectively. This again highlights the stereochemical flexibility of this strategy for acetate–propionate construction.

Based on a similar strategy propionates are accessible as well. To implement the polypropionate synthesis strategy we selected as targets the diastereomers **18** and **19** (Scheme 6). The four stereogenic centers in **18** have the correct absolute and relative configuration to those found for the ionophore calcimycin,[18] while **19** has the correct relative and absolute configuration of the C11–C22 unit of the anticancer macrolide dictyostatin.[19] Furthermore both building blocks are propionate–deoxypropionate motifs. Thus, in addition to the implementation of propionate construction these targets allow simultaneously to demonstrate the flexible combination with a deoxypropionate structural motif that is encountered in many natural products of polyketide origin.



Scheme 6. Propionate construction: Stereodivergent synthesis of a C14–C20 building block **15** of the ionophore calcimycin, and a C11–C23 building block **14** of the macrolide dictyostatin.

Thus, reaction of the Grignard reagent derived from bromine **15** with (*S*)-**2** and (*R*)-**2** furnished the *anti*- and *syn*-deoxypropionates **16** and **17**, respectively (Scheme 6). Deprotection, Sharpless epoxidation with (+)- or (−)-DET gave the corresponding epoxides in excellent stereoselectivity. Introduction of the missing methyl group[20] occurred upon reaction with $Me_2CuCNLi_2$[21] to give the desired diastereomeric propionate–deoxypopionate building blocks in excellent yield and stereoselectivity. Furthermore, **18** was transformed in three further steps[22] into the known thioacetal **20**, which has served as an intermediate in a total synthesis of calcimycin, thus representing a formal total synthesis.[23]

In conclusion, herein we have implemented a new and unified strategy for the stereospecific and flexible construction of many major structural motifs of the polyketide class of natural products relying on the *o*-DPPB-directed allylic substitution with Grignard-derived organocopper reagents as a key step. The key building block of this unified strategy was the multifunctional allyl-*o*-DPPB ester **2**. Both optical antipodes are readily available by combining an enzymatic cyanohydrin synthesis with a Mitsunobu inversion that employs the *o*-DPPBA as an unusual nucleophile. Thus, acetate–deoxypropionates, acetate–propionates, and propionates are readily available in enantiomerically pure form. Hence, this strategy provides an interesting alternative towards established aldol and enolate alkylation chemistry.

Experimental Section

General methods and further reactions are given in the Supporting Information.

Representative procedure for the *o*-DPPB-directed allylic substitution: Copper bromide dimethyl sulfide (196 mg, 0.95 mmol, 0.50 equiv) was added in one portion to a solution of *o*-DPPB ester (*S*)-(−)-**2** (1.20 g, 1.91 mmol, 99 % *ee*) in diethyl ether (40 mL) and the resulting yellow suspension was stirred for 10 min at room temperature. A solution of ethylmagnesium bromide (2.48 mL, 2.48 mmol, 1.30 equiv, 1 M in diethyl ether) was added over 15 min and the bright yellow suspension was stirred for a further 3 h at room temperature. The reaction was quenched by successive addition of a saturated aqueous NH_4Cl solution (10 mL) and an aqueous ammonia solution (10 mL, 12.5 %) followed by the addition of diethyl ether (20 mL). The organic phase was separated and the aqueous phase was extracted with three further portions of dichloromethane (20 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed in vacuo. Column chromatography (cyclohexane/ethyl acetate 10:1) furnished (*R*)-**6** (578 mg, 1.64 mmol, 86 %, 99 % *ee*) as a colorless oil. Analytical data for (*R*)-**6**: Chiral-GC: (deprotected allylic alcohol): Hydrodex-β-TBDAc, 25.0 m × 0.25 mm × 15 μm, injector: 200 °C: 60 °C (isotherm), 0.7 mL min^{-1} He, (*S*)-**4**: t_R = 41.6 min, (*R*)-**4**: t_R = 43.0 min; $[\alpha]_D^{20}$: −7.3 (*c* = 1.5 in chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, ^3J(H,H) = 7.4 Hz, 3H), 0.98 (d, ^3J(H,H) = 6.8 Hz,

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3H), 1.08 (s, 9H), 1.32 (m_c, 2H), 2.05 (m_c, 1H), 4.19–4.20 (m, 2H), 5.52–5.54 (m, 2H), 7.37–7.46 (m, 6H), 7.70–7.73 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.8$, 19.3, 20.1, 27.0 (3C), 29.7, 38.0, 64.9, 127.1, 127.7 (4C), 129.6 (2C), 134.1 (2C), 135.7 (4C), 137.1 ppm; elemental analysis calcd (%) for $C_{23}H_{32}OSi$: C 78.36, H 9.05, found: C 78.35, H 9.15.

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Keywords: allylic substitution · asymmetric synthesis · organocopper reagents · polyketides · synthesis strategy

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