Preprint Title	Synthesis of deoxypropionates using a combination of enzymatic desymmetrisation and substrate controlled conjugate addition
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Publication Date	05 Nov. 2024
Article Type	Full Research Paper
Supporting Information File 1	supporting info file.docx; 14.0 MB
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Synthesis of deoxypropionates using a combination of enzymatic desymmetrisation and substrate controlled conjugate addition

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Abstract

The all-*syn* deoxypropionate motif can be efficiently constructed using a combination of enzymatic desymmetrization and substrate-controlled conjugate addition of lithium dimethylcopper. This strategy was used to prepare mycocerosic acid, from *Mycobacterium tuberculosis,* and the sex pheromone of *Margarodes prieskaensis* (Jakubski), both in 10% overall yield.

Keywords

Conjugate addition; deoxypropionates; enzymatic desymmetrisation; mycocerosic acid; pheromones.

Introduction

In nature, (poly)deoxypropionates are synthesized by repetitive Claisen condensation of propionyl CoA forming a β-keto ester, keto reduction, elimination and alkene reduction. If the methyl substituents point in the same direction, upon drawing the chain in the zigzag conformation, the term *syn*-deoxypropionates is used.

Deoxypropionates are present in many natural products including pheromones and bacterial lipids.[1–4] Examples of *syn*-methyl deoxypropionates are (-)-lardolure **1**,[5–12] the pheromone of *Margarodes prieskaensis* **2**,[9,13] (+)-phthioceranic acid **3**,[14–18] (+)-hydroxyphthioceranic acid **4**,[15,16,19,20] and mycocerosic acid **5** (Figure 1).[21–23]

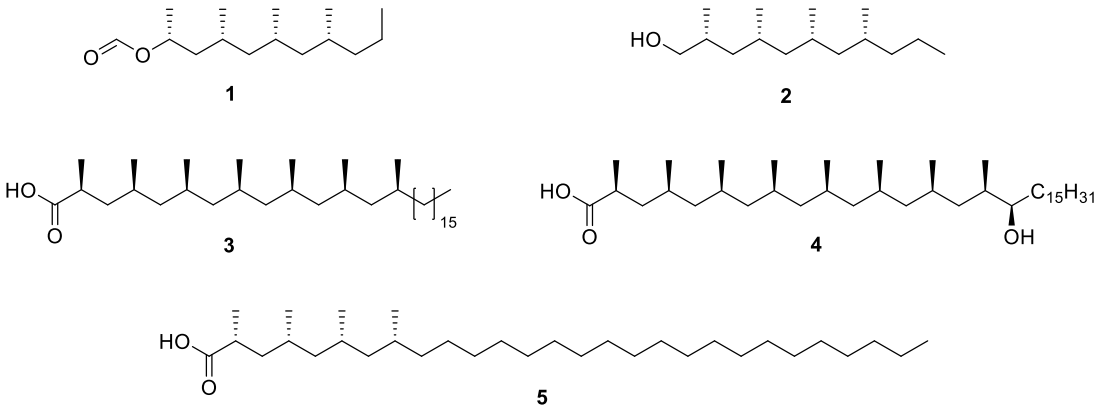


Figure 1: Examples of natural products containing a *syn*-deoxypropionate motif.

Mycocerosic acid **5** is located in the cell wall of *M. tuberculosis*[24] and has previously been prepared using catalytic asymmetric conjugated addition (ACA).[22] An alternative approach using the alkylation of a vinylketene silyl N,O-acetal followed by asymmetric hydrogenation has also been reported.[23] The ACA approach uses an α,β-unsaturated thioester as substrate with methylmagnesium bromide and a copper bromide/Josiphos catalyst to introduce the methyl substituent in the desired position

and stereochemistry. Iterative ACA provides the desired number of methyl substituents in high yield and high selectivity. Although this method is highly selective and robust, it requires a considerable number of reaction steps and we decided to explore a more scalable and cost-effective route to mycocerosic acid **5**, and *syn*-deoxypropionates in general. We also took the opportunity to prepare the sex pheromone of *Margarodes prieskaensis* **2**, as the insect (commonly named “ground pearls”) is a pest in vineyards.[25] The pheromone has not been prepared before, although an ester analogue has been extracted from the uropygial gland of the domestic goose, *Anser anser domesticus.*[9,13] The females produce (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethylundecan-1-ol **2**, which attracts the males. The pheromone may, if available in sufficient quantities, be used to control the population of this pest insect and consequently reduce harvest loss.[13]

We decided to combine the enzymatic desymmetrisation of meso-diol **7** which is well-described in literature,[26–31] with the substrate-controlled conjugate addition of lithium dimethylcopper developed by the group of Hanessian.[32–34] We recently applied the desymmetrisation of **7** in an efficient synthesis of mycolipanolic acid.[35]

Hanessian *et al.* studied in detail the diastereoselectivity of the conjugate addition of lithium dimethylcopper to conjugated esters. The presence of a chelating group at the chain terminus, a “director group” and the nature of the alkyl residue of the ester all influence the stereoselectivity of the conjugate addition reaction. In addition, the presence of methyl substituents in a 1,3-array, forces the substrate to adopt a conformation in which the *syn*-pentane interactions are minimized (Figure 2).[36–38]

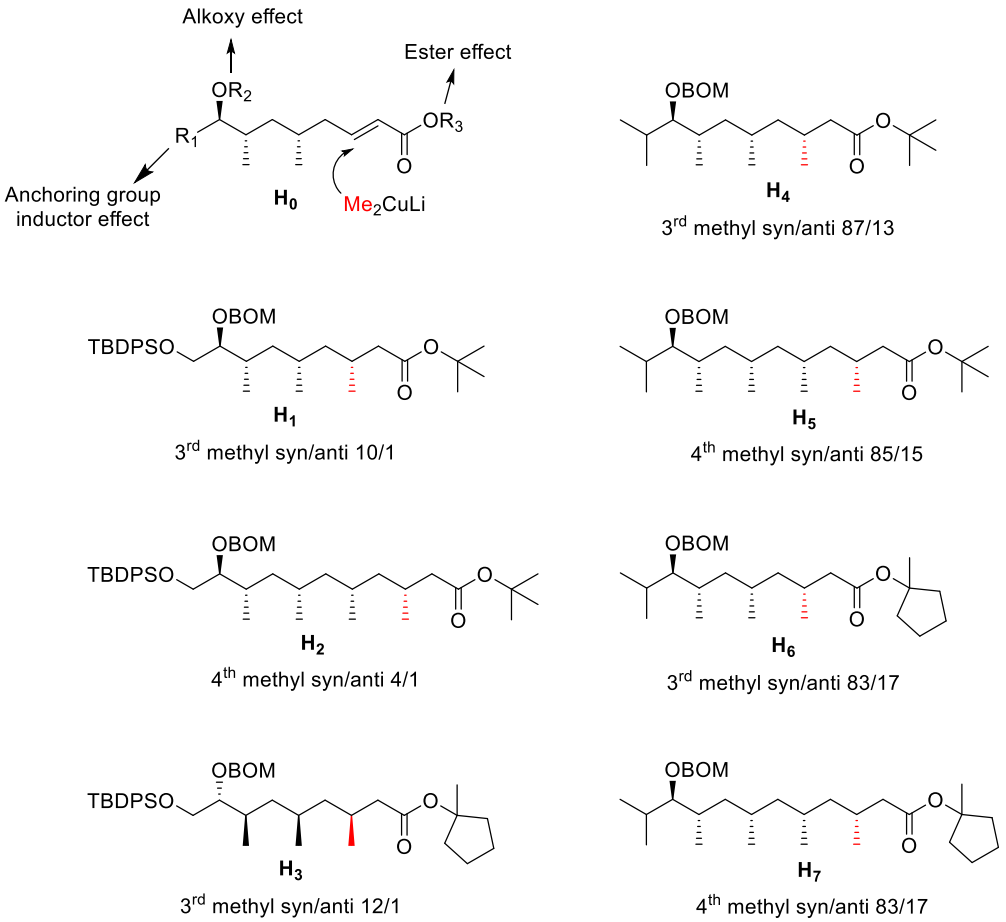


Figure 2: Influence of the various anchoring groups and ester groups on the *syn/anti* ratio in the conjugate addition reaction to substrates that possess already 2 or 3 methyl substituents. *Anti*-isomers are not shown. (Adapted from Hanessian *et al.*[32–34])

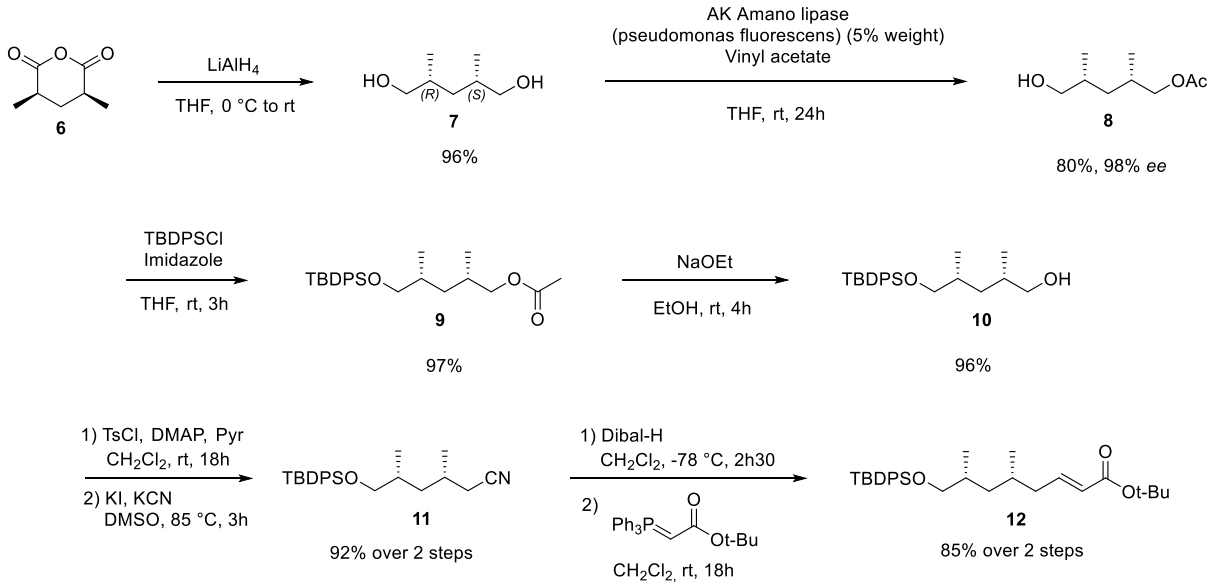
We expected this combination of methodologies to streamline the synthesis of *syn*-deoxypropionates and allow readily scale up.

Results and Discussion

The synthesis started from *cis*-2,4-dimethylglutaric anhydride **6** (Scheme 1). **6** is prepared in two steps from low-cost diethyl methylmalonate and ethyl α-bromoisobutyrate,[39] and subsequently reduced with lithium aluminium hydride to give the *meso*-diol **7**. The enzymatic desymmetrisation of *meso*-diol **7** has been well-

studied.[26] Tsuji *et al.* demonstrated the acetylation of the *meso*-diol **7** with vinyl acetate (1.5 eq) catalysed by lipase P from *Pseudomonas fluorescens* to give the desired monoacetate **8** (98% *ee* and 82% yield) at rt in 6 h.[27] Lin and Xu used porcine pancreatic lipase in wet THF but obtained just 50% yield,[28] whereas Fujita and Mori applied lipase AK 20 in THF and obtained 98% *ee* and 72% yield at 0 °C in 5 days.[29] The procedure of Tsuji *et al.* has become less practical, as lipase P is not commercially available any more. We therefore selected AK Amano lipase, a pro-*S* selective enzyme. Other lipases were tried as well (porcine pancreatic lipase and *Candida rugosa* lipase)[30,31] but these gave lower enantioselectivities in our hands. The procedure of Fujita and Mori using AK Amano lipase was successful, but the reaction time was very long (5 days). The procedure was improved by adding less vinyl acetate (1.01 eq) and carrying out the reaction at room temperature instead of zero degrees. This shortened the reaction time from five days to one day, without using an excess of vinyl acetate. The improved procedure was scalable to 10 g of **7** and provided **8** in 80% yield and an excellent enantiomeric excess of 98% *ee*.[40]

TBDPS-protection of **8** gave **9**, followed by a transesterification under basic conditions with NaOEt to give alcohol **10** in 96% yield. Chain extension was carried out in two steps. First, a one carbon homologation was performed via tosylation and cyanation, leading to **11** in 92% over 2 steps. Second, a two carbon extension was achieved using a Wittig reaction in order to prepare the acyclic α,β-unsaturated ester **12**. This was effected by reduction of nitrile **11** to the aldehyde, and using *tert*-butyl(triphenylphosphoranylidene)acetate to give *E*-isomer **12** in 85% yield over 2 steps.

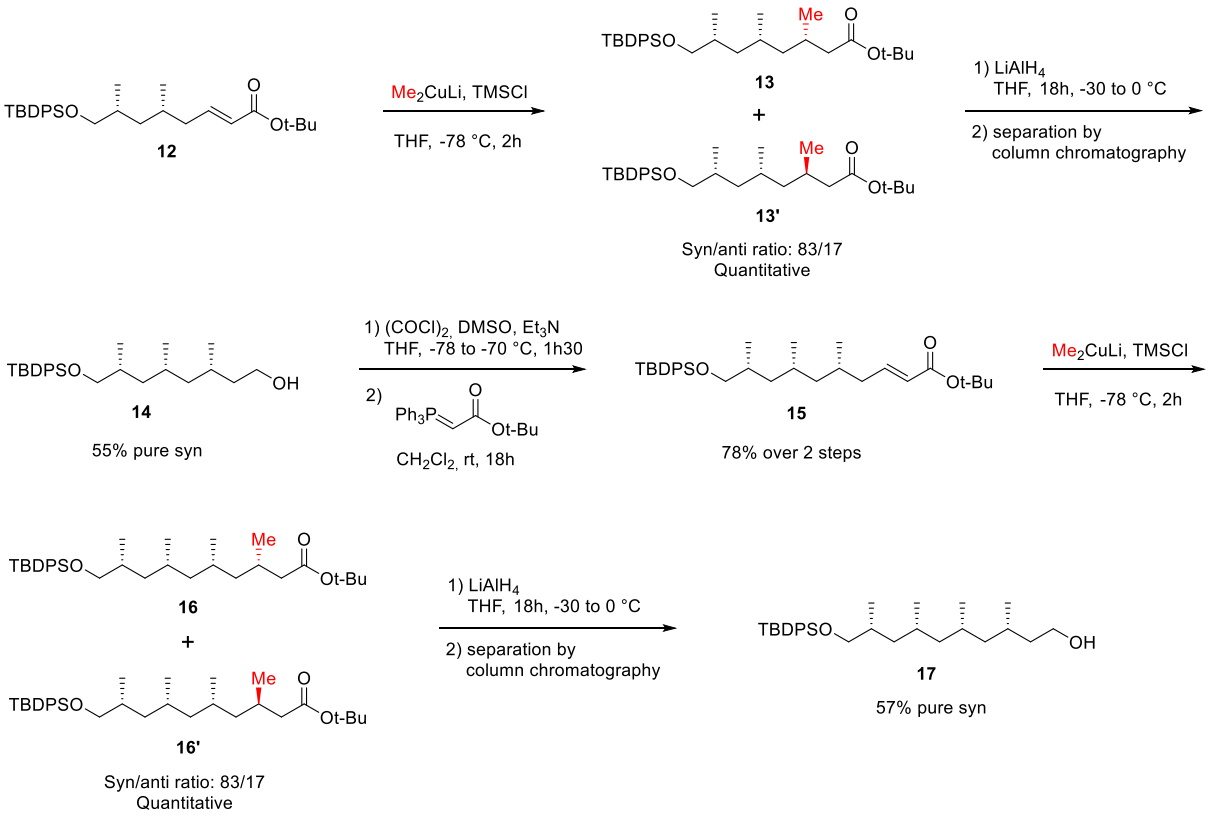


Scheme 1: First part of the synthesis including the enzymatic desymmetrisation.

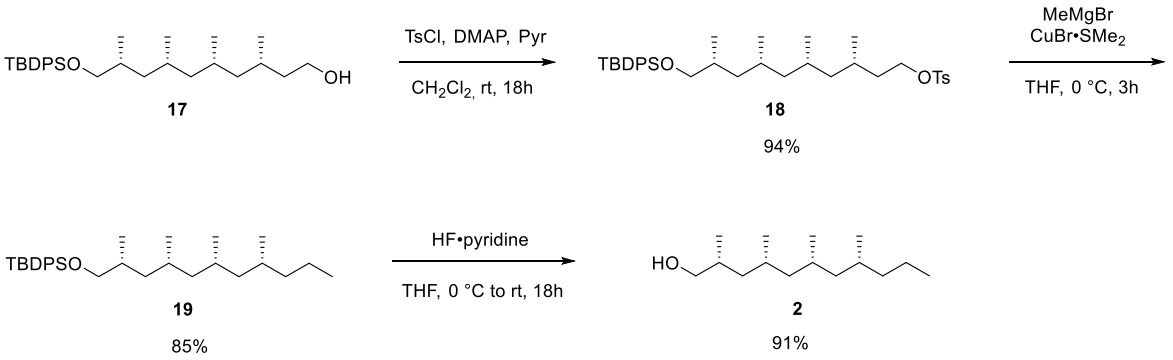
The next key step in our strategy was to install the third methyl substituent via conjugate addition with a Gilman reagent (lithium dimethylcopper) using Hanessian's methodology.[32] Formation of the organocuprate (Me_2CuLi) at low temperature from methyllithium and copper iodide, was followed by the addition of chlorotrimethylsilane, as an activator of ester **12**, to give the esters **13** and **13'**.[41] According to Hanessian *et al*., the difference in chemical shift of the diastereotopic hydrogens of the methylene group between the methyl substituents in the ^{1}H-NMR spectrum can be used to determine the ratio of **13** and **13'**.[32–34] This provided a *syn/anti* ratio of 83:17. Breit *et al*., used a similar method applying 2D-HSQC NMR.[42]

At this stage, separation of the diastereomers via column chromatography was unsuccessful. Fortunately, the diastereomers were separable after reduction of the ester with $LiAlH_4$ and the desired *syn* product **14** was isolated in 55% yield (Scheme 2). Swern oxidation of alcohol **14** led to the corresponding aldehyde, and a subsequent Wittig reaction with *tert*-butyl(triphenylphosphoranylidene)acetate gave *E*-isomer **15** in 78% yield over two steps. To introduce the fourth methyl substituent, again a Gilman

reaction was performed, yielding ester **16** and **16'** in again a *syn/anti* ratio of 83:17. $LiAlH_4$ reduction gave **17** in 57% yield as the pure all-*syn* alcohol after separation. Subsequently, alcohol **17** was converted to tosylate **18** in 94% yield (Scheme 3). Alkylation was performed with MeMgBr and copper(I) bromide dimethyl sulphide complex ($CuBr•SMe_2$) to give **19** in 85% yield. Although deprotection with TBAF was successful, this led to siloxane impurities which were inseparable from the product. Therefore, **19** was deprotected with HF•pyridine to give the pheromone **2** in 91% yield. The spectral data including optical rotation are in agreement with literature values, so this concludes the first synthesis of this natural product.[9]

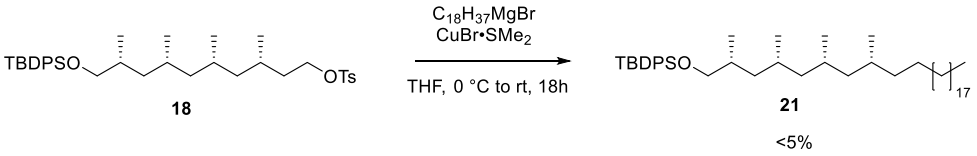


Scheme 2: Synthesis of the tetramethyl-building block **17**.



Scheme 3: Completion of the synthesis of pheromone **2**.

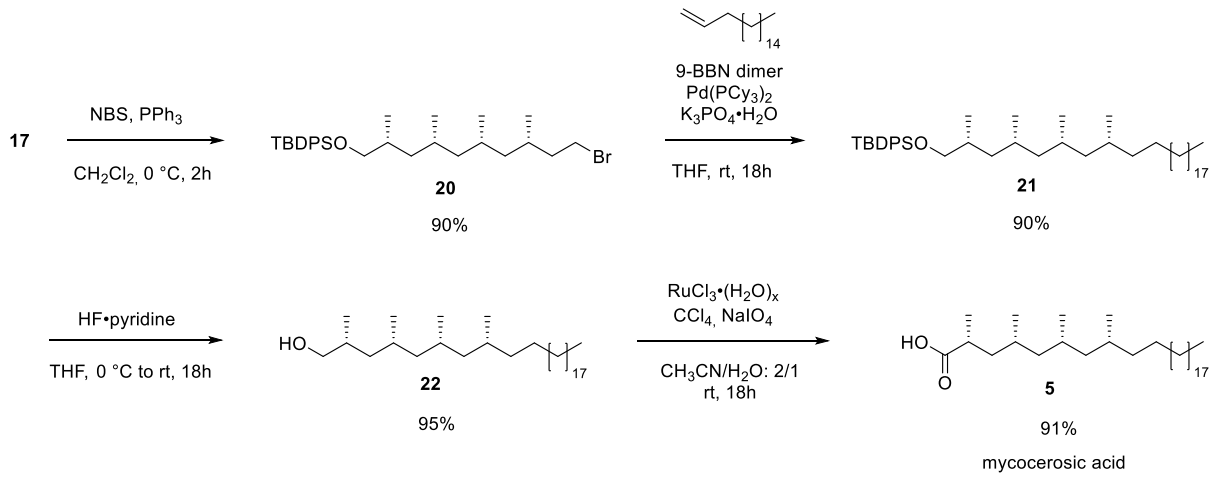
To synthesize mycocerosic acid **5**, our intention was to use the same route as above-mentioned, now with octadecylmagnesium bromide ($C_{18}H_{37}MgBr$) as the Grignard reagent. Unfortunately, the expected product **21** was formed in a very poor yield (< 5%) and the tosylate had been substituted by bromide to yield **20** as a major side product (Scheme 4). Quenching of an aliquot of the Grignard reagent with 1 M HCl, followed by GC-MS analysis showed octadecane as the major product (>90%), so the formation of the Grignard reagent had occurred. Although on small scale this reaction incidentally gave satisfactory yields, all attempts to scale up the reaction met with failure. These results remain largely unexplained, all the more so because a very similar reaction using hexadecylmagnesium bromide ($C_{16}H_{33}MgBr$), had been successful.[43]



Scheme 4: Unsuccessful copper catalysed coupling reaction.

As an alternative strategy, we switched to an sp^3-sp^3 Suzuki-Fu cross-coupling.[44] Alcohol **17** was converted to bromide **20** with *N*-bromosuccinimide (NBS) and

triphenylphosphine (PPh_3) (Scheme 5). Hydroboration of 1-octadecene followed by cross coupling, catalyzed by bis(tricyclohexylphosphine)palladium and tribasic potassium phosphate hydrate, gave **21** in a very good yield (90%). Deprotection with HF•pyridine led to **22** in 95% yield, followed by ruthenium-catalyzed oxidation to give mycocerosic acid **5** in 91% yield. The spectral data including optical rotation are in agreement with literature values.[22] Despite the small amount of Ru(III) chloride hydrate used in the reaction, removal from the product was very troublesome because the transition metal (complex) co-eluted with the product on the silica column. The addition of ammonium pyrrolidine dithiocarbamate, however, formed an insoluble precipitate which was readily removed by centrifugation followed by column chromatography.[45]



Scheme 5: Completion of the synthesis of mycocerosic acid **5.**

Conclusion

Mycocerosic acid and the pheromone of *Margarodes prieskaensis* have been prepared in a robust route comprising of enzymatic desymmetrisation and diastereoselective conjugate addition of lithium dimethylcopper. The alkyl chain in mycocerosic acid was

introduced by a highly efficient Suzuki-Fu cross-coupling reaction. The chemistry is scalable and suitable for large scale preparation.

Supporting Information

Supporting Information File 1. Experimental procedures and characterization data of compounds (^{1}H and ^{13}C NMR spectra, HRMS, HPLC).

Acknowledgments

The Netherlands Science Foundation NWO is acknowledged for funding.

Author Contributions

G L C: investigation, writing the original draft. M D W: conceptualization, supervision, data curation. A J M: conceptualization, writing, supervision.

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Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information to this article.

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