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Methyl-Shifted Farnesyldiphosphate Derivatives Are Substrates for Sesquiterpene Cyclases

Vanessa Harms,[§] Benjamin Schröder,[§] Clara Oberhauser, Cong Duc Tran, Sven Winkler, Gerald Dräger, and Andreas Kirschning*

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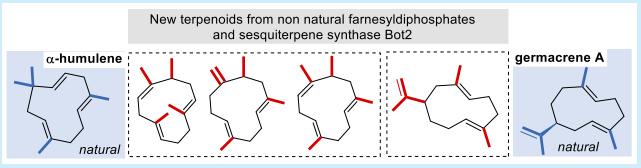
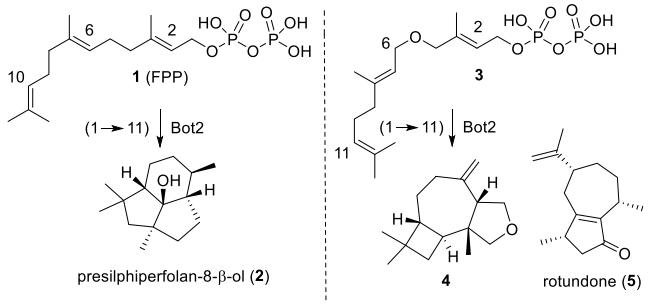
ABSTRACT: New sesquiterpene backbones are accessible after biotransformation of presilphiperfolan-8β-ol synthase (BcBOT2), a fungal sesquiterpene synthase, with non-natural farnesyldiphosphates in which methyl groups are shifted by one position toward the diphosphate terminus. One of the macrocycles formed, a new germacrene A derivative, undergoes a Cope rearrangement to iso-β-elemene. Three of the new terpenoids show olfactoric properties that range from an intense peppery note to a citrus, ozone-like, and fruity scent.



One unique synthetic feature of terpene biosynthesis is linked with terpene cyclases (TCs). These utilize linear unsaturated methyl-branched precursors activated as terminal diphosphate esters to yield a diverse range of (oligo)cyclic products, called monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), and sesterpenes (C25). The mechanistic features of these catalytic transformations are cationic cascade reactions. These cascades are composed of cyclizations, hydride shifts, and Wagner−Meerwein rearrangements. Proton abstraction or trapping of the final carbocation with a nucleophile, commonly water, terminates these sequences.[1] So far, the chemo-, regio-, and stereoselectivity for each step have not been matched by chemical transformations intended to mimic TCs.[2]

In recent years, the substrate specificity of TCs, especially of mono- and sesquiterpene cyclases, has been championed[3] mainly by testing unnatural geranyl- and farnesyldiphosphate derivatives as substrates.[4−7] Commonly, oxygen, sulfur, and halogen functionalizations have been included in the backbone of the natural precursor farnesyldiphosphate (FPP **1**; PP = pyrophosphate) when sesquiterpene cyclases (STCs) have been probed (Scheme 1). A telling example is presilphiperfolan-8β-ol synthase (BcBOT2), a fungal sesquiterpene cyclase from *Botrytis cinerea*, which is responsible for the formation of the tricyclic sesquiterpene presilphiperfolan-8β-ol (**2**) from FPP **1**.[8] When BcBOT2 was exposed to ether derivative **3**, the tricyclic terpenoid **4**, whose scent resembles that of rotundone (**5**), was isolated in 36% yield instead.[5] It has to be noted that for the formation of **2** and **4** the cascade is initiated by a ring closure between carbon atoms 1 and 11. Dickschat et al. reported on isopentenyl diphosphates with an additional methyl group at C4 that were enzymatically transformed into methylated terpenes.[4h] The same group also carried out studies on the formation of 2-methylisoborneol in myxobacterium *Nannocystis exedens*.[9a] *S*-Adenosyl methionine (SAM) was

Scheme 1. Structures of Diphosphate Precursors 1 and 3, Cyclization Products 2 and 4 Formed by the Sesquiterpene Cyclase BcBOT2, and Rotundone 5



proposed to be the source of the extra methyl group. Independently, the groups of Cane and Ikeda identified members of the actinomycetes family that use a combination of a terpene synthase and a C-methyl transferase for the generation of 2-methylisoborneol.[9b9c]

On the basis of these findings, Kampranis and co-workers showed that the chemical code of terpene biosynthesis can be expanded to C11 building blocks, namely 2-methyl-geranyldiphosphate [2me-GPP (**7**)], by engineering the GPP methyltransferase from *Pseudanabaena limnetica* into a *Saccharomyces cerevisiae* strain AM94 (Figure 1).[9d] 2-Methylisoborneol (**8**) is a noncanonical bacterial product

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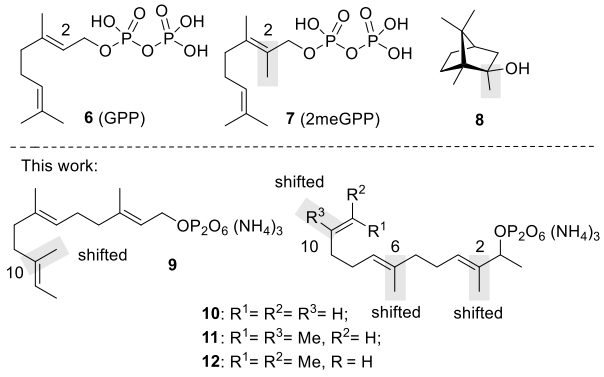


Figure 1. Structures of geranyl- and 2-methylgeranyl diphosphates **6** and **7**, methylisoborneol (**8**), and new FPPs **9**−**12** with shifted methyl groups.

that contributes to the musty-earthy fragrant notes of Brie and Camembert cheeses.[10] C11 precursor **7** is generated under the control of a dedicated methyltransferase that acts at C2 of geranyldiphosphate **6** (GPP). It was noted that the cyclization process is unique, because hardly any other C11 terpenoid has been reported as a major metabolite in bacteria.[11,12] The authors found that for broadening the substrate tolerance of monoterpene synthases to 2-methyl-branched GPP derivatives bearing 11 carbon atoms, only a single-residue switch in the TC was necessary.[9d]

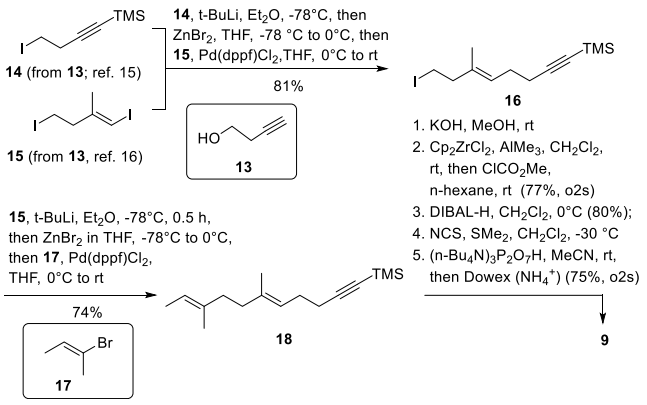
In 2me-GPP **7**, the additional methyl group is located one position closer to the diphosphate group, which should cause steric congestion in the key step, Mg-promoted ionization of the allyldiphosphate moiety, and cyclization.[11c] So far, 2-methyl-branched analogues of FPP **1** have rarely been tested in biotransformations with STCs.[13]

In this report, we describe the synthesis of four new FPP derivatives **9**−**12** bearing one or more methyl groups that are shifted by one position toward the diphosphate terminus. This also includes position 2 similar to that of GPP derivative **7**. In diphosphates **10**−**12**, the terminal alkene moiety displays different patterns of substitution. These serve as substrates for recombinant and purified BcBOT2, which in our hands shows promiscuous behavior toward a variety of FPP derivatives.[5] The major products formed were commonly isolated by preparative GC. Preliminary results on their olfactoric properties were also collected.

In FPP derivative **9**, one methyl group is shifted from C11 to C10 compared to natural FPP **1**. Our synthesis relied on two sp^2−sp^3 Negishi coupling reactions (Scheme 2).[14] Homopropargyl alcohol **13** was used to prepare both building blocks **14**[15] and **15**,[16] which were coupled after transforming iodide **14** into the organozinc species using $Pd(dppf)Cl_2$ as a precatalyst. Then, the resulting alkyl iodide **16** underwent a second Negishi cross-coupling reaction with the organozinc species derived from vinyl bromide **17**[17] to yield yne-diene **18**.[18] After desilylation and methyl metalation of the alkyne group, the trapping of the active organometallic species with $ClCO_2Me$ provided the α,β-unsaturated methylester intermediate. This was reduced to the allyl alcohol, which was further transformed into diphosphate **9** via the corresponding allyl chloride.[19]

The underlying synthetic concept toward FPP derivatives **10**−**12** is based on the idea of moving the diphosphate moiety to the opposite terminus of GPP. The original hydroxyl group in geraniol **19** then served to introduce different new C-

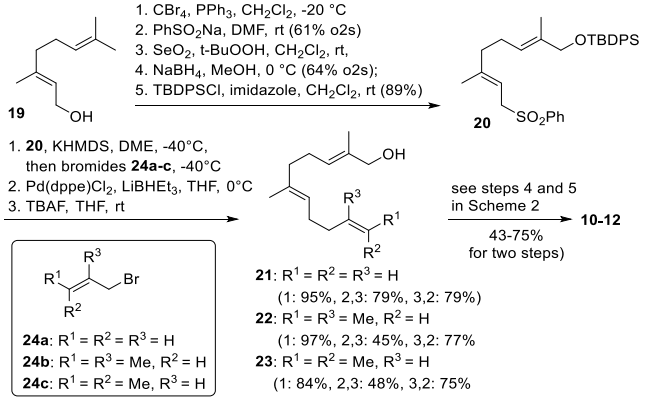
Scheme 2. Synthesis of New Farnesyldiphosphate Derivative 9[a]



[a]TMS = trimethylsilyl. cp = cyclopentadienyl. dppf = (diphenylphosphino)ferrocene. NCS = *N*-chlorosuccinimide.

termini. Thus, a set of standard reactions (bromination, sulfone introduction, Riley oxidation, reduction of the intermediate aldehyde, and O-silylation) yielded sulfone **20** starting from geraniol **19** (Scheme 3). At this stage, the syntheses diverged

Scheme 3. Synthesis of New Farnesyldiphosphate Derivatives 10−12[a]



[a]TBDPS = *tert*-butyldiphenylsilyl. dppe = 1,2-bis(diphenylphosphino)ethane. KHMDS = potassium bis(trimethylsilyl)amide. TBAF = tetra-*n*-butylammonium fluoride. NCS = *N*-chlorosuccinimide.

toward allyl alcohols **21**−**23** by alkylation of deprotonated sulfone **20** with different allyl bromides **24a**−**c** followed by O-desilylation. The corresponding diphosphates **10**−**12** were obtained via the corresponding allyl chlorides according to an established protocol.[19]

Next, BcBOT2 was cloned and expressed in *Escherichia coli*. *In vitro* enzyme tests for determining enzyme activity and for optimizing substrate tolerance were conducted on small scales (150 μM substrate and 0.01 mg/mL enzyme) using natural precursor FPP **1** (see the Supporting Information). The key parameters to be optimized were the temperature and the pH value. To study possible inhibitory effects or denaturation, substrate and enzyme concentrations were also part of this study (see the Supporting Information). Interestingly, non-natural FPP derivatives **9**−**12** require higher temperatures for achieving the best yields of new biotransformed products (*vide supra*). This can be ascribed to the increased conformational

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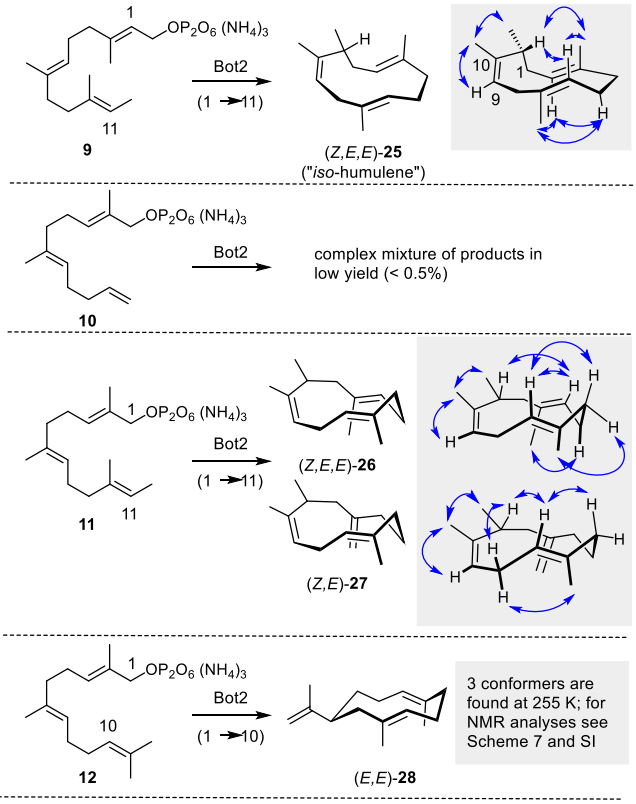
flexibility of the protein allowing the easier fit of unnatural substrates.[20]

The outcome of biotransformations with FPP derivatives **9**–**12** with BcBOT2 is summarized in Scheme 4. Derivative **10**

Scheme 4. Formation of Cyclization Products 25–28[a]



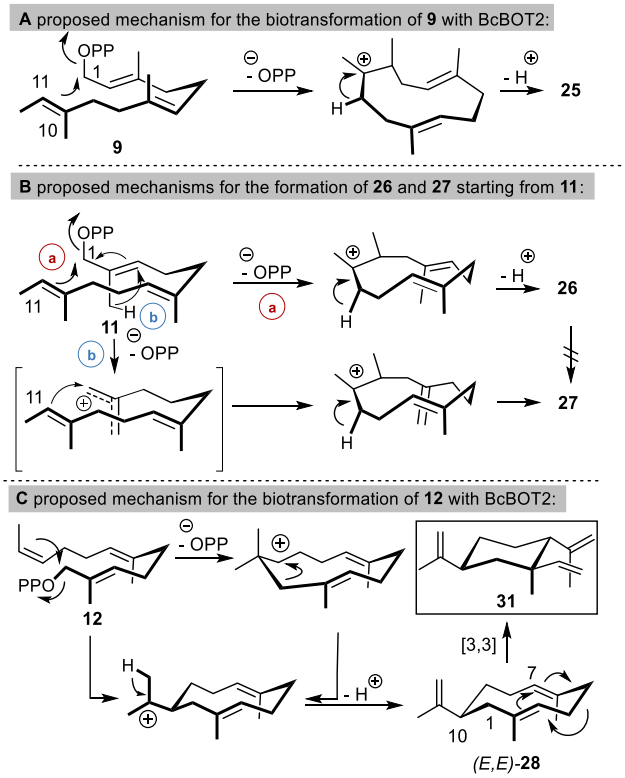
[a]NOE correlations for (*Z*,*E*,*E*)-**25** and isomeric macrocycles **26** and **27** are given. Cyclization product **28** was commonly accompanied by small amounts of Cope product **31**.

that lacks any methyl group at the terminal alkene (C10–C11) gave a complex mixture with no major product that could be detected by GC-MS. However, the other three FPP derivatives **9**, **11**, and **12** yielded defined cyclization products **25**–**28** in amounts sufficient for isolation and structural elucidation (**25**, 13%; **26** and **27**, 33%; **28**, 31%).

Each of the two FPP derivatives, **9** and **12**, yielded one major product. In contrast, substrate **11** is transformed into two main isomeric macrocycles **26** and **27** along with five unidentifiable byproducts. The two isomers **26** and **27** were separated by preparative GC. Our work revealed that BcBOT2 commonly initiates a C1 → C11 macrocyclization with FPP **1**, including all unnatural FPP derivatives studied so far (see also **1** → **4**).[5] Likewise, new FPP derivative **9** supports this observation. Deprotonation at C9 leads to macrocycle **25** [70.9% purity (GC-FID) before pGC] (Scheme 5A). The formation of a (*Z*)-configured olefinic double bond was proven by determining a NOE correlation between the methyl group at C10 and 9-H. Other NOE correlations provided insight into the preferred conformation of the macrocycle in C_6D_6.

FPP derivative **11** bears three methyl groups that are shifted by one position. It yielded macrocycles **26** (92.8% purity after pGC) and **27** (86.5% purity after pGC). The two isomers differ in the position of one of the three olefinic double bonds. The cationic cascade also starts with a C1 → C11

Scheme 5. Proposed Mechanisms for the BcBOT2-Promoted Formation of Macrocyclic Terpenoids 25–28 from FPP Derivatives 9, 11, and 12 (cases A–C, respectively)[a]



[a]The configurations of the double bonds were determined by NOESY experiments.

macrocyclization followed by deprotonation at C9 to yield **26** (Scheme 5B). The formation of isomer **27** could be the result of a monoprotic intramolecular hydrogen transfer either initially for **11** or at a late stage with isomer **26**. Precedence for such a hydride transfer was reported for sesquiterpene cyclase pentalenene synthase (PenA) and the diterpene taxadiene cyclase (TDC1).[21] When pure terpenoid **26** was exposed to BcBOT2, GC-MS analysis revealed no formation of **27** so that its late stage formation can be excluded.[22]

Here, FPP derivative **12** behaves remarkably. It is the first example of an unnatural FPP derivative that is transformed by BcBOT2 into a 10-membered macrocycle, although the substitution patterns of the terminal alkene in FPP **1** and derivative **12** are identical. It is remarkable that the shift of the two methyl groups (at C3 and C7) by one position closer to the diphosphate terminus has a profound influence on the type of cyclization. The possibility that the system first undergoes a 1 → 11 cyclization[8] followed by a Wagner–Meerwein rearrangement cannot be ruled out (Scheme 5C).

A common feature of the cyclodecadiene ring system of germacrenes is its fit in two preferred conformations. The conformation of germacrene A (**29**) shown in Scheme 6 finds the propenyl group in a pseudo-equatorial orientation. It is established that this conformation is subject to a facile [3,3]-sigmatropic Cope rearrangement, which leads to the 1,2-divinylcyclohexane elemene (**30**).[23] The new germacrene A derivative **28** behaves in a similar manner yielding what we call here "iso-*β*-elemene" (**31**) as a single diastereoisomer. This can

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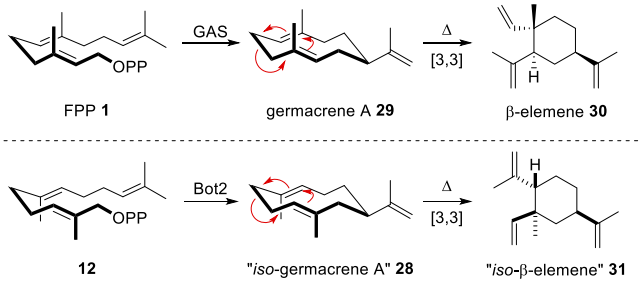
Scheme 6. Considerations of Germacrene A (29) (top) and "Iso-germacrene A" (28) (bottom) Conformations for Cope Rearrangements to β-Elemene 30 and "Iso-β-elemene A" 31, Respectively[a]



[a]GAS = germacrene A synthase. For analysis of other conformers, see Scheme 7.

be rationalized if one assumes that the conformation of **28** depicted in Scheme 6 is the preferred one.[24−28] The first evidence of this Cope rearrangement was obtained during GC analysis of "iso-germacrene A" (**28**) (for details about GC analyses, see the Supporting Information). "Iso-β-elemene" (**31**) was collected when the pGC was operated in a hot-injection mode that initiated quantitative (98.4%) rearrangement to **31**.[26,27]

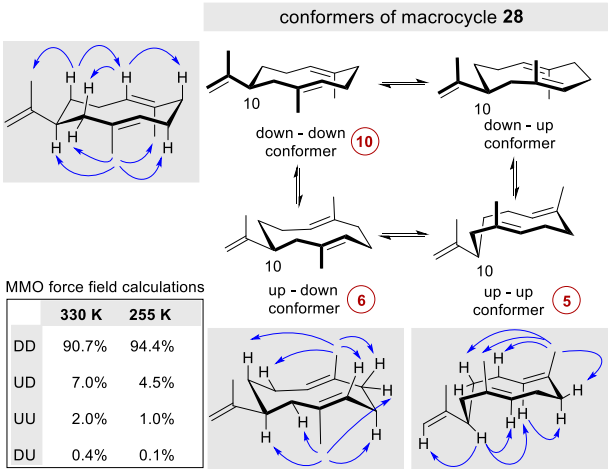
The (*E*,*E*)-germacrenes, including **29**,[29−32] have widely been studied in solution with respect to their conformational dynamics around the cyclodecandiene core. Stable conformers are interconverted through rotation of the two double bonds and the C7−C9 segment. These conformers can be studied at lower temperatures by NMR spectroscopy.[30,32,33] It was found that the iso-propenyl group commonly is positioned in an equatorial or pseudo-equatorial orientation,[26,30] and that this prerequisite can result in four distinct conformations, commonly labeled DD, UU, UD, and DU (with respect to the orientation of the methyl groups, D = down and U = up).

Also, the isolated "iso-germacrene A" (**28**) exists in different stable conformers as judged by several cross-couplings and saturation transfers in the NOESY and NOE. Although NMR spectra were poorly resolved at rt, the carbon backbone of **28** was identified for the major conformer by COSY and HMBC spectroscopy.

At 255 K in toluene-d_8, three sets of well-resolved signals in a ratio of 10:6:5 were visible in the ^{1}H NMR spectrum that refer to three conformations (Scheme 7). The relative orientations of the methyl groups (three groups each with three signals that differed in signal intensities) were determined from selected one-dimensional NOE correlation experiments.

The relative orientation of the proton at C10 was established by reference to the relative configuration of the Cope-rearranged product iso-β-elemene (**31**) that had formed as a single diastereoisomer via a chairlike transition state from the DD isomer **28**, similar to that reported for the rearrangement of germacrene A (**29**) to β-elemene (**30**) (Scheme 6).[26,29] The stereochemical course of such Cope rearrangement, which proceeds through a chairlike transition state of the DD conformer, was recently elegantly confirmed using stereospecifically deuterated probes.[34] Our analyses revealed that the main conformer of **28** is down−down (DD) (see Scheme 7 and the Supporting Information). The second most abundant

Scheme 7. Possible and Found Stable Conformations of "Iso-germacrene A" (28) and Key NOE Correlations (blue arrows)[a]



[a]Encircled numbers in red refer to the relative abundance at 255 K (for further details about NMR analyses, including NOESY and NOE correlations, see the Supporting Information). Relative abundances of four conformers (DD, UD, UU, and DU) obtained by computational analysis in toluene (MM3 force field).

conformer has an up−down (UD) orientation, and the up−up conformer (UU) was also unequivocally determined.

Thus, "iso-germacrene A" (**28**) preferentially adopts two crossed alkene conformations (DD and UU, 71.4%) and one with a parallel orientation of the two alkenes (UD, 28.6%) at low temperatures. The relative preference was supported by MM3 force field calculations at 300 and 255 K (Scheme 7). In contrast, germacrene A (**29**) parallel and crossed conformations are distributed in a nearly equal ratio.[30]

Chromatography with a chiral stationary phase was performed for "iso-β-elemene" **31** with a heptakis(6-*O*-TBDMS-2,3-di-*O*-Me)-β-CD column, known to separate the enantiomers of β-elemene. The analysis revealed only one signal, indicating the presence of one enantiomer.[26,35] Due to the stereospecificity of the Cope rearrangement, it is reasonable to propose that also "iso-germacrene A" was formed as a single enantiomer.

Finally, the sensoric profile of new terpenoids was determined by GCO analysis (Table 1). Macrocycle **25** exerts

Table 1. Olfactoric Properties of New Terpenoids 25−28[36]

compound	olfactoric analysis
25	intensive, peppery
26	no profile
27	no profile
28	citrus, ozone-like, fruity
31	citrus, ozone-like

an intense peppery smell comparable to that of terpenoid rotundone (**5**). Isomers **26** and **27** did not reveal any sensory properties. Finally, "iso-β-elemene" (**31**) was found to show a citrus and ozone-like odor, whereas the olfactoric property of the thermal precursor "iso-germacrene A" (**28**) is similar to that of **31**, except that it additionally shows a fruity note.

In summary, we demonstrate that sesquiterpene cyclases like BcBOT2 can accept and transform FPP derivatives with an

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altered methyl group substitution pattern compared to that of farnesyl diphosphate (**1**). Remarkably, a shift of the methyl group from C3 to C2 does not suppress activation of the diphosphate moiety and initiation of cyclization cascades. Olfactoric analyses revealed the practical opportunities of employing unnatural substrates in biotransformations with terpene synthases.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01345.

Detailed experimental procedures and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Andreas Kirschning − *Institute of Organic Chemistry and Center of Biomolecular Drug Research (BMWZ), Leibniz Universität Hannover, 30167 Hannover, Germany;* orcid.org/0000-0001-5431-6930; Email: andreas.kirschning@oci.uni-hannover.de

Authors

Vanessa Harms − *Institute of Organic Chemistry and Center of Biomolecular Drug Research (BMWZ), Leibniz Universität Hannover, 30167 Hannover, Germany*

Benjamin Schröder − *Institute of Organic Chemistry and Center of Biomolecular Drug Research (BMWZ), Leibniz Universität Hannover, 30167 Hannover, Germany*

Clara Oberhauser − *Institute of Organic Chemistry and Center of Biomolecular Drug Research (BMWZ), Leibniz Universität Hannover, 30167 Hannover, Germany*

Cong Duc Tran − *Institute of Organic Chemistry and Center of Biomolecular Drug Research (BMWZ), Leibniz Universität Hannover, 30167 Hannover, Germany*

Sven Winkler − *Symrise AG, 37603 Holzminden, Germany*

Gerald Dräger − *Institute of Organic Chemistry and Center of Biomolecular Drug Research (BMWZ), Leibniz Universität Hannover, 30167 Hannover, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01345

Author Contributions

[§]V.H. and B.S. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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