A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

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Accepted Article

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Authors: Andreas Kirschning, Benjamin Schröder, Vanessa Harms, Clara Oberhauser, Katja Seidel, Kimia Ekramzadeh, Sascha Beutel, Jeroen Dickschat, Lukas Lauterbach, and Sven Winkler

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201805526
Angew. Chem. 10.1002/ange.201805526

Link to VoR: http://dx.doi.org/10.1002/anie.201805526
http://dx.doi.org/10.1002/ange.201805526

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10.1002/anie.201805526

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Exploiting the synthetic potential of sesquiterpene cyclases for generating unnatural terpenoids

Clara Oberhauser+,[a] Vanessa Harms+,[a] Katja Seidel,[a] Benjamin Schröder,[a] Kimia Ekramzadeh,[b] Sascha Beutel,[b] Sven Winkler,[c] Lukas Lauterbach,[d] Jeroen S. Dickschat[d] and Andreas Kirschning*[a]

Dedicated to Prof. Ernst Schaumann on the occasion of his 75th birthday.

Abstract: The substrate flexibility of eight purified sesquiterpene cyclases was evaluated using six new heteroatom modified farnesyl pyrophosphates and the formation of six new heteroatom-modified macrocyclic and tricyclic sesquiterpenoids is described. GC-O analysis revealed that tricyclic furan exhibits an ethereal, peppery and camphor-like olfactoric scent.

Terpenes are structurally the most diverse class of secondary metabolites. These complex backbones are generated from a linear precursor - in the case of sesquiterpenes this is farnesyl pyrophosphate (FPP, **17**) - by means of a cascade reaction composed of π-solvolytic steps and Wagner-Meerwein rearrangements. This unique cascade is catalyzed by terpene cyclases (TCs) and is commonly finalized either by proton abstraction or by trapping of the final carbocation with a nucleophile, commonly water.[1] TCs have seen increased interest lately, because several of these enzymes were expressed as functional proteins and served to study the mechanisms of cyclization in detail.[2,3]
In selected biosynthetic studies unnatural substrates, mainly fluoro- and hydroxyl-modified derivatives of FPP, were administered to sesquiterpene cyclases (STCs). E.g. 12-hydroxy-FPP was transformed by the amorphadiene synthase from *Artemisia annua* to yield the artemisinin precursor dihydroartemisinic aldehyde in 34% yield.[4] With the natural substrate **17** the yield could recently be raised to over 90% under continuous flow conditions.[5] These few examples demonstrate that the field of chemo-enzymatic use of TCs is an emerging field of research with prospects to access new terpene derivatives and even new terpenoid backbones.
Oxyfunctionalized mono- and sesquiterpenes are widely applied in the flavor and fragrance industries. However the products of the TCs, so called terpene hydrocarbons, often do not show beneficial olfactoric properties and are therefore commonly separated from the oxidized derivatives.[6] In fact, the growing flavor and fragrance industries constantly demand for new terpenoids with olfactoric potential. Noteworthy, the concept of transforming heteroatom-modified pyrophosphate precursors to new terpenoids using recombinant TCs has not been pursued in the arena of fragrances and flavors so far.

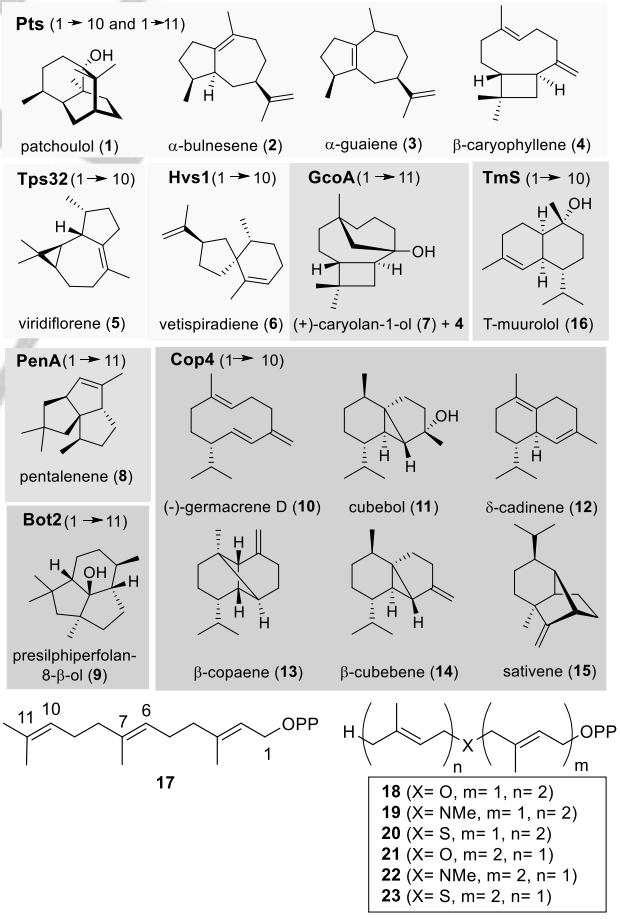


Figure 1. Reported main products **1**-**16** of sesquiterpene cyclases studied here (from plants (light grey): Pts= patchoulol synthase, Tps32= viridiflorene synthase, Hvs1= vetispiradiene synthase; from bacteria (grey): GcoA= caryolan-1-ol synthase, TmS= T-muurolol synthase, PenA= pentalenene synthase; from fungi (dark grey): Bot2= presilphiperfolan-8-β-ol synthase, Cop4= cubebol synthase), FPP **17** and its derivatives **18**-**23** employed in the present studies.

[a] C. Oberhauser, V. Harms, Dr. K. Seidel, Dr. B. Schröder, Prof. Dr. A. Kirschning
Institute of Organic Chemistry and Center of Biomolecular Drug Research (BMWZ)
Leibniz Universität Hannover
Schneiderberg 1B, 30167 Hannover (Germany)
Fax: (+49) 511-762-3011
E-mail: andreas.kirschning@oci.uni-hannover.de
[b] K. Ekramzadeh, Dr. S. Beutel
Institute of Technical Chemistry and Center of Biomolecular Drug Research (BMWZ)
Leibniz Universität Hannover
Callinstr. 5, 30167 Hannover (Germany)
[c] S. Winkler, Symrise AG, Mühlenfeldstrasse 1, 37603 Holzminden, (Germany)
[d] Prof. Dr. J. S. Dickschat, L. Lauterbach
Kekulé-Institute of Organic Chemistry and Biochemistry
University of Bonn
Gerhard-Domagk-Straße 1, 53121 Bonn (Germany)
+ These authors contributed equally.

Supporting information under http://www.angewandte.org or from the authors.

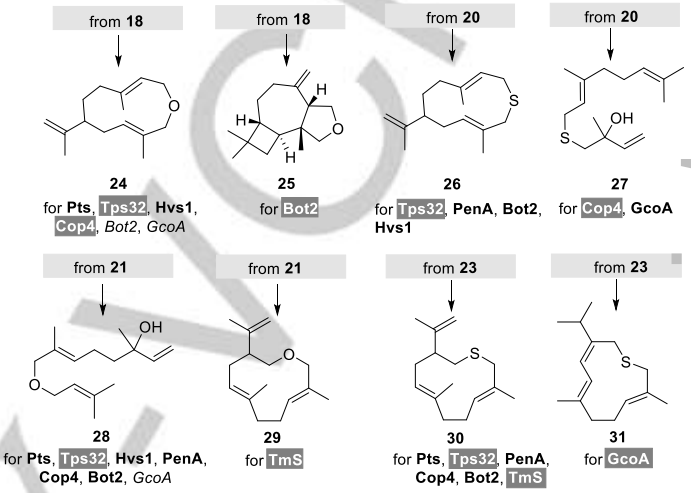
In this report we study the substrate flexibility of eight recombinant and purified STCs with respect to their ability to transform oxygen-, nitrogen- and sulfur-containing unnatural FPPs and additionally disclose preliminary results on the olfactoric properties of selected terpenoids formed. For all STCs chosen, the initial cyclization of FPP proceeds between the positions 1 and 10 or 11, respectively (Figure 1).[7] Three of the chosen TCs are plant-based, two are found in fungi and three cyclases are of bacterial origin. Plant-derived STCs included the patchoulol synthase (Pts) from *Pogostemon cablin* that provides patchoulol (**1**), α-bulnesene (**2**), α-guaiene (**3**) and β-caryophyllene (**4**) as the main products.[8] Additionally, viridiflorene synthase (Tps32, yielding **5**) found in *Solanum lycopersicum*[9] and vetispiradiene synthase (Hvs1, yielding **6**), originating from *Hyoscamus muticus* and a sequence homology of 90% were included.[10] The bacterial caryolan-1-ol-synthase (GcoA) from *Streptomyces griseus* catalyzes the transformation of FPP (**17**) to (+)-caryolan-1-ol (**7**) and (+)-β-caryophyllene (**4**),[11] and (+)-T-muurolol synthase (TmS) from *Roseiflexus castenholzii* catalyzes the conversion of FPP (**17**) into (+)-T-muurolol (**16**).[12] The pentalenene (**8**) synthase (PenA) is obtained from *Streptomyces exfoliatus* UC5319.[13] In addition, the two fungal STCs presilphiperfolan-8-β-ol synthase (Bot2) from *Botrytis cinerea* being responsible for the formation of the tricyclic sesquiterpene alcohol **9**[14] and cubebol synthase (Cop4) that originates from *Coprinus cinereus* and which yields several cyclization products (**10**-**15**) in temperature and pH dependent proportions were employed. Commonly, germacrene D (**10**) and cubebol (**11**) are the main products.[15]

First enzymes were cloned and expressed in *E. coli*. *In vitro* enzyme tests were used to determine enzyme activity and the substrate tolerance. Semipreparative transformations were optimized with respect to temperature, pH-value as well as substrate and enzyme concentration to avoid denaturation and effects of inhibition. Moreover, the solubility of enzyme and substrate in semi-preparative scale were optimized (see SI).

We found that Tps32 yielded vetispiradiene (**6**) instead of viridiflorene (**5**) from **17**. This was confirmed NMR-spectroscopically and by GC-coinjection of the FPP-cyclization products obtained with Tps32 and Hvs1, respectively. In no case variations of conditions (pH, temperature and Mg-concentration) yielded traces of **5**. The mechanistic formation of both terpenes is alike and initiated by a 1→10 cyclization. The resulting carbocation is stabilized by deprotonation either with formation of a terminal alkene (for **6**) or a cyclopropane (for **5**). Then a proton-induced cyclization that either provides a decahydro-azulene (for **5**) or alternatively a decahydronaphthalene (for **6**) backbone occurs. Clearly, subtle conformational changes in the active site lead to substantial structural deviations.

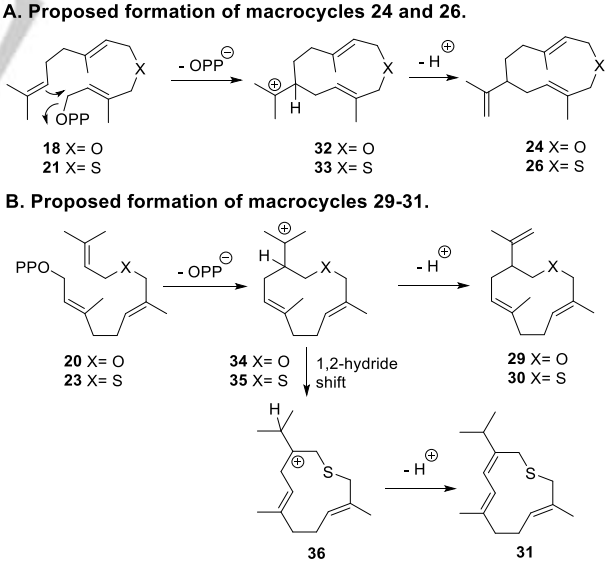
The four new FPP derivatives **18**, **20**, **21** and **23** were prepared from geraniol and after standard preparations of the different building blocks these were merged by means of the Williamson ether synthesis (see SI). The key step for preparing corresponding new amines **19** and **22** was the nucleophilic substitution of the metallated Boc-protected amines with the appropriate bromides. The pyrophosphatyl group was introduced by Appel chlorination of the terminal allylic alcohols followed by substitution with tris(tetra-*n*-butylammonium) hydrogen pyrophosphate (see SI).[15]

An overview on the outcome of the biotransformations for individual enzymes is shown in Scheme 1. The nitrogen functionalized analogues **19** and **22** generally did not serve as substrates for any TC (Pts, Tps32, Hvs1, GcoA, PenA, Cop4 and Bot2). In contrast, ethers **18** and **21** as well as thioethers **20** and **23**, respectively, are well suited to create new heteroatom-containing macrocycles **24**, **26**, **29**-**31** and in one case a tricyclic terpenoid **25** (Scheme 1).



Scheme 1. New terpenoid products **24**-**31** from FPP-derivatives **18**, **20**, **21** and **23** (bold: main product; marked in grey: enzyme used for preparative scale; italic: traces of product).

Also the rearranged tertiary alcohols **27** and **28** are formed from the precursor pyrophosphates **20** and **21**, respectively, noteworthy only under enzyme-catalysis conditions.



Scheme 2. Mechanistic considerations on the formation of new terpenoids **24**, **26** and **29-31.**

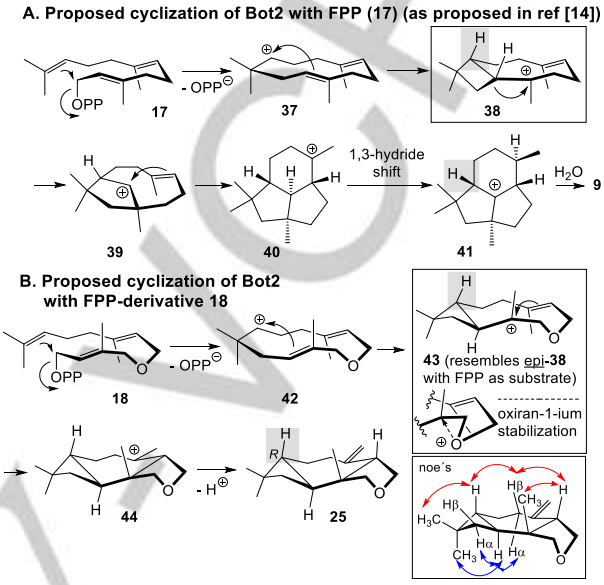
The STCs Pts, Tps32, Hvs1, GcoA, Cop4 and Bot2 are all able to generate macrocyclic ether **24**, despite the fact that they resemble 1→10 as well as 1→11 cyclases. The corresponding

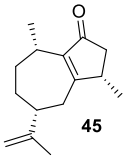
thioether **20** was cyclized by Tps32, PenA and Bot2 to the corresponding macrocyclic thioether **26**.

The isomeric ether **21** and thioether **23** yielded the corresponding macrocycles **29** (catalyzed by TmS) and **30** (catalyzed by Pts, Tps32, PenA, Cop4, Bot2 and TmS). The formation of products **24**, **26**, **29** and **30** is expectable as they are generated after pyrophosphate activation, cyclization via C10 (cationic intermediates **32**-**35**) and formation of the 1,1-disubstituted alkene after deprotonation. In the presence of GcoA **23** was transformed into 1,3-diene **31**, whose formation can be rationalized if one assumes that a 1,2-hydride shift occurs after formation of cation **35** and deprotonation on intermediate allylic cation **36** occurs.

The most remarkable product is the tricyclic cyclobuta[3,4]cyclohepta[1,2-c]furan derivative **25** obtained from ether **18**. Despite the structural differences between presilphiperfolan-8-β-ol (**9**) and the derivative **25** a sensible proposal of its formation is depicted in Scheme 3. The biosynthesis of **9** from FPP (**17**)[14] is initiated by formation of the humulyl cation **37**. Next, a cationic cascade leads to cyclopentaindene **40** via cyclobutane **38**, bicyclic bridged cation **39**, followed by a third cyclization. Tantillo noted, that the 1,2-alkyl shift and cation–alkene cyclization may proceed via a transition state structure more closely resembled by a nonclassical carbocation. A hydride migration provides cation **41** which is finally trapped by water to provide the carbinol moiety in **9**. In a similar manner ether **18** yields cationic cyclobutane intermediate **43** that resembles cation **38** via **42** (Scheme 2, case B). At this stage the two proposed biosynthetic sequences diverge. Instead of a Wagner-Meerwein rearrangement the cation in **43** is trapped by the remaining alkene and the resulting cation **44** yields terpenoid furan **25** after deprotonation. Intermediate **43** is the key intermediate of this route, as unlike for FPP, the extra oxygen atom is able to exert a slightly different substrate fold in the enzyme and furthermore anchimerically can stabilize the cation by formation of an oxiran-1-ium cation. The relative stereochemistry was elucidated by determining selected nuclear Overhauser effects, and these are summarized in Scheme 3. Clearly, the cyclobutane ring is fused to the central seven-membered ring in an anti fashion while the furan ring is attached in a syn manner to the cycloheptane which can be rationalized from the shown conformations of **18** and **42** in Scheme 3B. The mechanistic considerations on the formation of terpenoid **25** also provide information on the likely absolute stereochemistry. The carbon atom labelled in grey is formed during cyclobutane formation and remains unaltered for both mechanistic pathways (leading to **9** and **25**, respectively). The relative as well as the absolute configurations of presilphiperfolan-8-β-ol (**9**) were unequivocally determined spectroscopically[17], by derivatization to silphiperfol-6-enes,[17] by X-ray crystallographic analysis of the p-nitrobenzoate[18] and recently by total synthesis.[19] Therefore, we assume that the C-atom marked in grey in **25** is (*R*)-configured.[20]

Unlike other authors[21] Cane and coworkers proposed that the stereochemistry of the caryophyllenyl cation **38** formation is *cis*.[14] This assumption was based on the use of specifically deuterated FPPs and on the analysis of the deuterated presilphiperfolan-8-β-ols formed with respect to the presence and position of the label. It is further argued that formation of the cyclobutyl carbinyl cation **38** either takes place much faster than conformational reorganization of the humulyl cation **37** and that it is synchronous with the generation of **37**. These stereochemical results contrast our findings for **25**.





Scheme 3. Mechanistic considerations on the formation of presilphiperfolan-8-β-ol **9** (A)[14] and terpenoid **25** (B) catalyzed by Bot2 and noe correlations relevant for determining the relative configuration.The stereogenic center that is identical in **9** and **25** is marked in grey and acts as a reference for the absolute stereochemistry of **25**; α and β refer to the nomenclature used in steroids.

Clearly, the insertion of an extra oxygen atom into the linear precursor leads to subtle conformational alterations when being incorporated into the active site of Bot2, so that the cyclobutane formation may be effected, and additionally the remaining olefinic double bond can act as a nucleophile and induce a new final ring closure.

A GC-O (gas chromatography-olfactometry) olfactory evaluation was conducted for new farnesol derivatives (S7, S16, S20 and S31, see SI) as well as for isolated products **24**-**31**. This analysis revealed, that tricyclic furan **25** shows an ethereal, peppery and camphor scent, a sensory profile that is comparable with the sesquiterpene rotundone **45** in terms of the peppery note. Interestingly, both molecules contain a similar bicyclic ring system that is related to hydroazulene. Rotundone is found in many essential oils such as patchouli oil, agarwood or various pepper oils. Moreover, it can be part of spicy wines.[22]

In conclusion, we report on the use of eight STCs from fungal, bacterial and plant sources for the transformation of six heteroatom functionalized FPP derivatives to create six unnatural heteroatom-modified macrocyclic terpenoids. We encountered that viridiflorene synthase (Tps32) clearly yielded vetispiradiene instead of viridiflorene. Most remarkably, Bot2 furnished a tricyclic product from FPP derivative **18** in 36% yield. The olfactoric analysis revealed an ethereal, peppery and camphoric scent for tricyclic terpenoid **25**. In this work we paved

the way to create new terpenoid backbones to serve as starting point for semisynthetic derivatizations such as oxidations, creating potentially new terpenoids with new olfactoric properties.

Experimental Section

General experimental procedure for biotransformations with unnatural FPPs: Biotransformations were carried out in a fed-batch mode. The initial conditions such as concentrations of enzyme, substrate and magnesium, the pH-value, temperature additives such as Tween, pyrophosphatase (from *S. cerevisiae*) and a hydrophobic adsorber (Amberlite XAD-4) are listed in the SI. The biotransformations were carried out in an orbital shaker while the pyrosphosphate derivatives **18**-**23** were added either portionwise or continuously through a syringe. When biotransformations took longer than 4 hours new portions of enzyme were added at intervals of 3-5 h. Under these circumstances also 1 to 2 portions of pyrophosphatase were added. Then, shaking was elongated for up to 10 h. The biotransformation was terminated by addition of proteinase K (from *Tritirachium album*) and an aqueous solution of $CaCl_2$. After 3-5 h protein precipitation had markedly decreased. Workup was carried out either by multiple extraction with pentane or by removal of the hydrophobic adsorber. This was washed with water before the product was eluted with pentane. The mixture was dried ($MgSO_4$) and concentrated under mildly reduced pressure (900 mbar) followed by a flow of nitrogen gas at -5°C. Results of preparative biotransformations (isolated yields): a) Bot2, pyrophosphate **17**: 46% yield of **9**; b) Bot2, pyrophosphate **18**: 36% yield of **25**; c) Cop4, pyrophosphate **17**: 30% yield of **11**; d) Cop4, pyrophosphate **20**: 27% yield of **27**; e) Tps32, pyrophosphate **17**: 30% yield of **6**; f) Tps32, pyrophosphate **20**: 20% yield of **26**; g) Tps32, pyrophosphate **23**: 18% yield of **30**; h) GcoA, pyrophosphate **17**: 16% yield of **7**; i) GcoA, pyrophosphate **23**: 17% yield of **31**; j) PenA, pyrophosphate **17**: 89% yield of **8**.

Acknowledgements

We thank J. Fohrer (LUH) for support in NMR spectroscopic analyses.

Keywords: biotransformations • farnesyl pyrophosphates • scent • terpene cyclases • terpenoids

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[20] Additionally, we analyzed cyclization products **24**-**26**, **29** and **30** by chiral GC and could not detect the presence of two enantiomers. Chiral GC columnsused: Hydrodex-β-6-TBDM, hydrodex-β-PM and Lipodex-G; for details see SI.

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10.1002/anie.201805526

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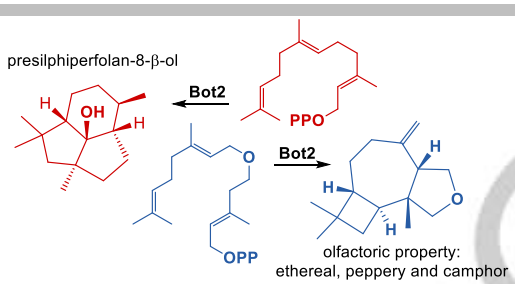
COMMUNICATION

Flexibility for new scents: Eight sesquiterpene cyclases from fungal, bacterial and plant sources were tested to transform 6 heteroatom functionalized farnesylpyrophosphate derivatives. Bot2 yielded a novel tricyclic product in 36 % yield. The olfactoric analysis revealed an ethereal, peppery and camphoric scent.



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Exploiting the synthetic potential of sesquiterpene cyclases for generating unnatural terpenoids