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Synthesis of oxygenated sesquiterpenoids enabled by combining metabolic engineering and visible-light photocatalysis

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Abstract: The diversification of natural products to expand biologically relevant chemical space for drug discovery can be achieved by combining complementary bioprocessing and chemical transformations. Herein, we combined genetically-engineered *Escherichia coli* fermentation to produce amorphadiene and valencene, and metal-free photocatalysis transformations to further access nootkatone, *cis*-nootkatol and two hydration derivatives. In fermentation, using a closed, anaerobic condition avoided the use of organic overlay, increased the productivity, and simplified the work-up process. Metal-free photocatalysis hydration and allylic C-H oxidation were designed and implemented to make the whole process greener. We also elucidated that the *anti*-Markovnikov selectivity of photocatalyzed alkene hydration could be reversed by stereo-electronic and steric effects existing in complex natural products. The combination of bioprocessing and photocatalysis may provide an efficient and greener way to expand the chemical space for pharmaceutical, flavor and fragrance industry.

Introduction

A variety of drug molecules are derived from natural products or their derivatives, such as artemisinin, paclitaxel, sinecatechins, rosuvastatin, due to natural products' unique biocompatibility, novel skeletal structure, and extensive pharmacological activity.[1] Rapid assembly of natural products or their core skeletons would provide a platform for diversity-oriented synthesis or late-stage functionalization to greatly expand the chemical space for drug discovery.[2,3] Currently, the majority of natural products are obtained through extraction of plant materials. This supply method is in general inefficient due to the low content of natural products in their native matrix. The supply chain is also prone to be influenced by market supply fluctuations due to the long cycle needed to grow the host plants. As a result, organic synthesis, microbial synthesis and other alternative ways are important and attractive to produce natural products.

Compared with chemical methods requiring multistep synthesis and purifications, metabolic engineering (ME) is capable of accessing complex skeletons of the natural compounds via one-pot fermentation process, highlighting the excellent stereochemistry control, step-economy, and environmental greenness.[4] However, there are limitations associated with the microbial process: a) Heterologous expression of some key enzymes such as cytochrome P450s (CYP450s) remained challenging in engineered bacteria due to their complex cellular mechanisms, which leads to inefficient production of functionalized isoprenoids;[5] b) Although structural diversification of natural products plays an important role for drug discovery – exemplified by artesunate originated from artemisinin with better water solubility and docetaxel derived from paclitaxel with improved efficacy[6,7] – such meaningful but nonnatural modifications may not be efficiently achieved through biosynthetic

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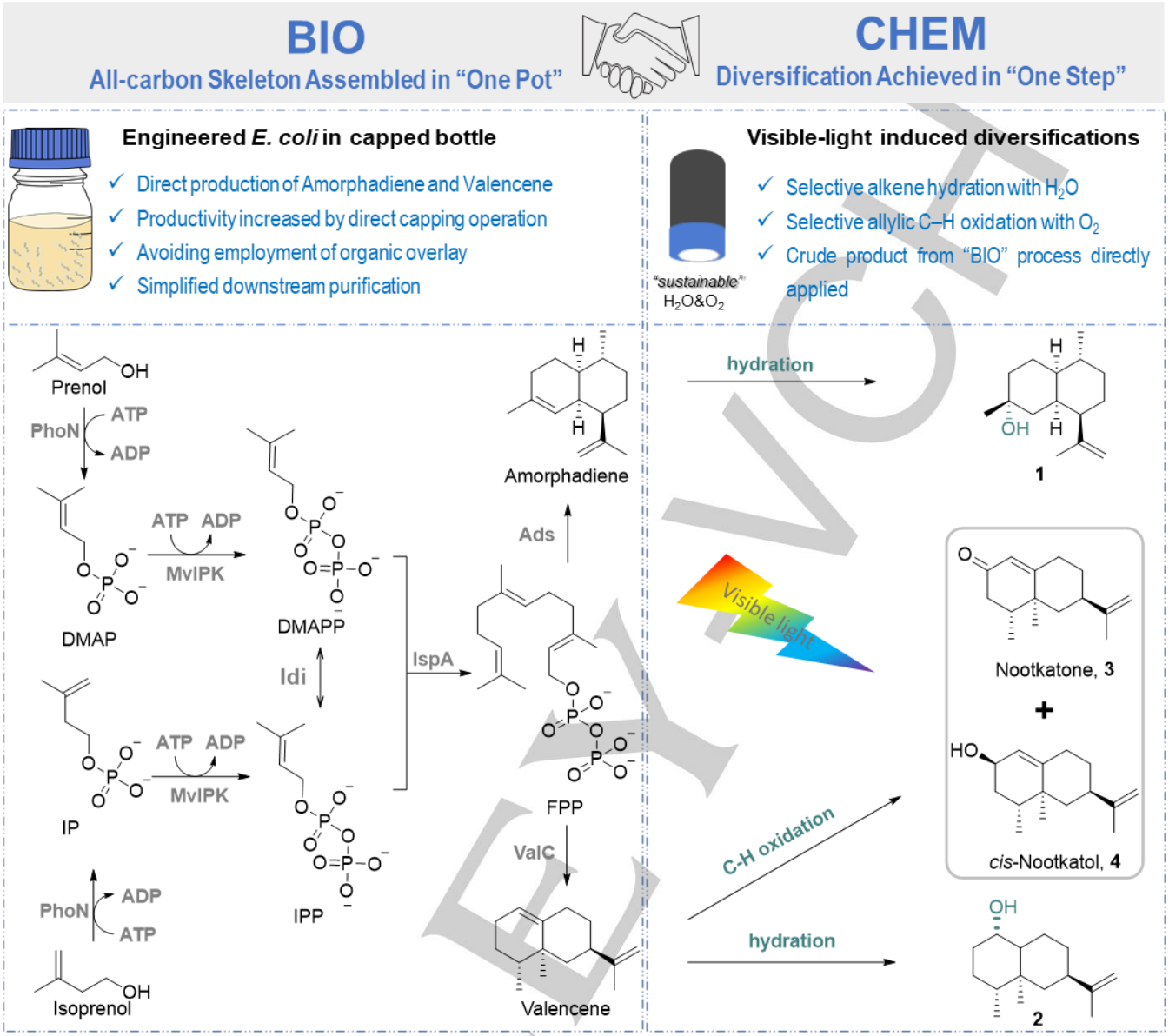

Figure 1. Biocatalysis merged with photoredox catalysis for producing sesquiterpenes and derivatives: Left, Metabolic pathway used for producing amorphadiene and valencene in *E. coli*; Right, Visible light induced derivatization of amorphadiene and valencene. PhoN: Xanthomonas translucens alcohol kinase; MvIPK : Methanococcus vannielii isopentenyl phosphate kinase; IPP: Isopentenyl diphosphate; DMAP: Dimethyl allyl phosphate; IP: isopentenyl phosphate; DMAPP: Dimethylallyl diphosphate; Idi: IPP isomerase; FPP: Farnesyl diphosphate; IspA: *E. coli* FPP synthase; Ads: Artemisia annua amorphadiene synthase; ValC: Chamaecyparis nootkatensis valencene synthase; ADP: Adenosine di-phosphate; ATP: Adenosine tri-phosphate.

pathways, which could involve tedious enzyme screening and engineering efforts.[8]

The emerging visible-light promoted photoredox catalysis provides a convenient way to access highly active open shell radical species, realizing conventionally inaccessible reaction patterns, exemplified well by its application to create densely functionalized intermediates in natural products synthesis.[9] We proposed that ME and photoredox catalysis could be combined in a complementary manner to efficiently expand biologically relevant chemical space. ME can directly assemble all-carbon skeletons with full stereo-control from simple starting materials. The subsequent photoredox chemical transformations provide diversification of these natural skeletons to further expand the chemical space. As a proof-of-concept study, we merged *Escherichia coli* fermentation with metal-free visible-light photoredox transformations in sequence. The *E. coli* fermentation featured the efficient one-pot process to convert prenol and isoprenol into two sesquiterpenes that are tedious to prepare by chemical synthesis (amorphadiene and valencene, Figure 1, left). In this fermentation process, we found that other than adopting organic solvent (dodecane) as an overlay, direct capping the reaction bottle not only led to an enhanced production but also circumvented the problematic downstream purification of two sesquiterpenes from dodecane with a high boiling point (216 °C). With the easy access to the two sesquiterpenes, we then utilized visible-light photoredox catalysis to enable diversification of these natural compounds (Figure 1, right). Under the irradiation of visible light, 9-mesityl-10-methylacridinium perchlorate (Mes-

$Acr^+ClO_4^-$) was applied to oxidize tri-substituted alkene selectively in the presence of *di*-substituted alkenes, where the hydration selectively happened at the double bonds in the ring structure of amorphadiene and valencene respectively. Then a light-induced hydrogen atom transfer (HAT) catalysis was employed to ensure a selective allylic C–H oxidation to convert valencene to *cis*-nootkatol and nootkatone, which has found wide applications in the pharmaceutical, flavour and fragrance industry.[10]

Results and Discussion

Engineered *Escherichia coli* in capped bottle enabling efficient and green production of amorphadiene and valencene

We used an engineered *E. coli* strain (IUP-ads, full genotype provided in Table S1) to produce amorphadiene through Isopentenol Utilization Pathway (Figure 1, left).[11] By conducting two-stage 50 mL fermentation (the growth stage in shake flask and the production stage in Duran bottle [see the fermentation methods in the supporting information]), the strain was able to produce 548 mg/L amorphadiene with a 15% *v/v* dodecane overlay (Figure 2 and S5a). Amorphadiene was synthesized by using prenol and isoprenol as the substrate, and the energy was supplied by sugar (*L*-arabinose). However, despite a routine operation in bioengineering labs, using dodecane as the organic overlay would complicate product purification that is needed for the subsequent chemical transformations: the produced amorphadiene was trapped in dodecane and cannot be easily separated due to the high boiling point of dodecane. Short chain alkanes and esters with lower boiling points than that of dodecane cannot be used due to their high toxicity to the cells.[12] When no organic overlay was applied, the amorphadiene titer was reduced dramatically to 37 mg/L (Figure 2) due to evaporation. Capping the Duran bottle should prevent the evaporation but it would lead to an anaerobic environment after the depletion of the small quantity of oxygen existing in the system. Such condition has not been systematically explored for producing this class of natural products (isoprenoids). To our delight, by tightly screwing the cap of the cell culture vessel (Duran bottles) to form an anaerobic, closed system, the amorphadiene titer (794 mg/L) was even higher than the conventional methods (dodecane overlay, aerobic conditions), which may be due to that a fraction of amorphadiene escaped from the dodecane phase to open space under the aerobic condition. Under the anaerobic conditions, the energy can still be derived from *L*-arabinose, through transforming it into a mixture of organic acids (lactate, acetate, formate and succinate). More importantly, we confirmed that amorphadiene can be easily purified from the dodecane-free culture through liquid-liquid extraction and silica gel column chromatography purification. This novel fermentation process should be useful in producing and harvesting other volatile isoprenoids, which are a large class of valuable natural products.[13]

We arbitrarily chose a 50% loading in the above experiment (each 100 mL bottle was filled with 50 mL of aqueous culture). After we confirmed that a relatively good titer can be achieved under these conditions, we investigated the effect of the loading ratio on amorphadiene production in a 100 mL Duran bottle with tightly sealed cap and without any organic overlay. Our intention was to maximize the total product quantity which would reduce

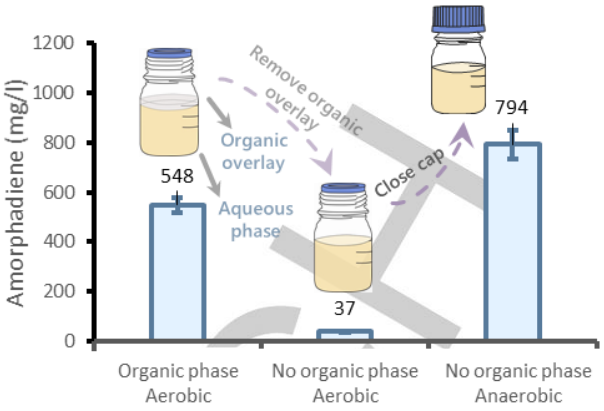

Figure 2. Higher production of amorphadiene enabled by the operation of capping the fermentation bottle.

footprint of the process. It was observed that a larger headspace (10 mL culture in 100 mL bottle; loading ratio: 10%) led to higher amorphadiene titer (1,044 mg/L, Figure S1a). When the loading ratio was increased to 25% and above, lower and similar amorphadiene titer was obtained (~750 mg/L, Figure S1a). More *L*-arabinose was consumed and less organic acids were produced with 10% loading than with 25% or more loading (Figure S1b), because a larger headspace to culture ratio (at 10% loading) provided more oxygen to the microbes, which would increase *L*-arabinose assimilation rate and the energy production efficiency (in terms of ATP per *L*-arabinose). By tabulating carbon mass balance for the loading of 10%, it was found that 30% of carbon from *L*-arabinose taken up by cells did not accumulate in by-products, which could be released in the form of CO_2. In the rest of this study, we used 50% loading based on two considerations: 1) we chose a higher loading to reduce footprint of the process (based on Figure S1a, producing one gram of amorphadiene would require 10 L and 2.8 L of reactor volume when the loading was 10% and 50%, respectively); 2) a loading higher than 50% was not chosen to avoid high headspace pressure due to production of CO_2.

We further increased the amorphadiene titer to 1,024 mg/L from 737 mg/L by tripling cell density under optimum culture condition (Figure S2 and S3). We also scaled up the amorphadiene production from 50 mL to 1 L under the anaerobic conditions. By using the same method, another sesquiterpene (valencene) could be produced at the titer of 60 mg/L.

Visible-light induced hydration of Amorphadiene and Valencene

The rapid access to amorphadiene and valencene paved the way for visible light induced chemical conversions to incorporate functionalities into these skeletons, which would further expand the chemical space.

Mes-$Acr^+ClO_4^-$ was first utilized as a photocatalyst, which could oxidize *tri*- substituted alkenes into radical cations under blue light irradiation without activating the *di*-substituted alkenes.[14] The site selectivity was consistent with literature report[14b] and the hydration reactions occurred on trisubstituted alkenes to afford two sesquiterpenoids in 58% and 65% isolated yields respectively, in both of which the alkenes in the side chains remained intact (Figure 3). Moreover, the robustness of this photo-induced protocol was further validated by the result

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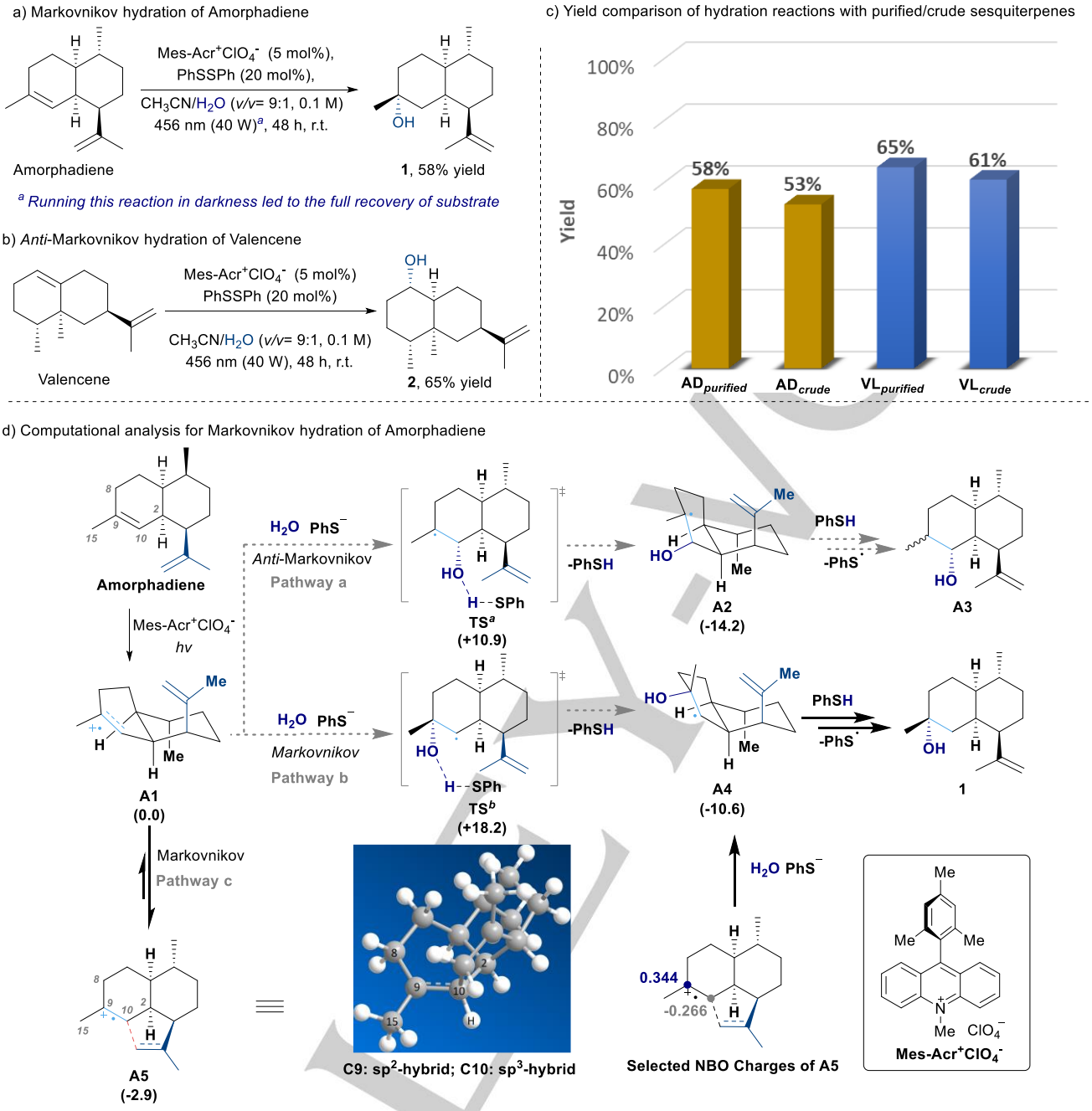


Figure 3. Photocatalytic site-selective hydration of amorphadiene and valencene to deliver two sesquiterpenoids. “ADpurified” and “VLpurified” denote the amorphadiene and valencene from “BIO” process purified by column chromatography and then were used as the reaction starting materials; “ADcrude” and “VLcrude” denote amorphadiene or valencene from “BIO” process without column chromatography purification used as the reaction starting materials. NBO: Natural bond orbital.

that only a minor yield decline was observed with the crude samples without column chromatography purification from the fermentation process employed as the reaction starting materials (Figure 3c).

Notably, the photo-induced hydration over amorphadiene proceeded with Markovnikov selectivity. This regioselectivity was different from the reports from Lei,[14b] Nicewicz,[15] and Shu,[16] where the hydrofunctionalization reactions via acridinium photoredox catalysis were predominantly *anti*-Markovnikov. In fact, the regioselectivity exhibited on valencene was *anti*-Markovnikov (see the calculation rationale in Figure S7). First of all, the results that performing this reaction on amorphadiene in darkness, with either PhSSPh or PhSH as the mediator, led to a full recovery of amorphadiene ruled out the Marovnikov selectivity being resulted by the acidic cation process. Taking the structures of valencene and amorphadiene into comparison enlightened us that the interaction between the *iso*-propenyl group and radical cation unit in **A1** (Figure 3d) may account for this unprecedented selectivity. The density functional theory (DFT) calculation supported our hypothesis: the interaction favoured the

10.1002/chem.202201230

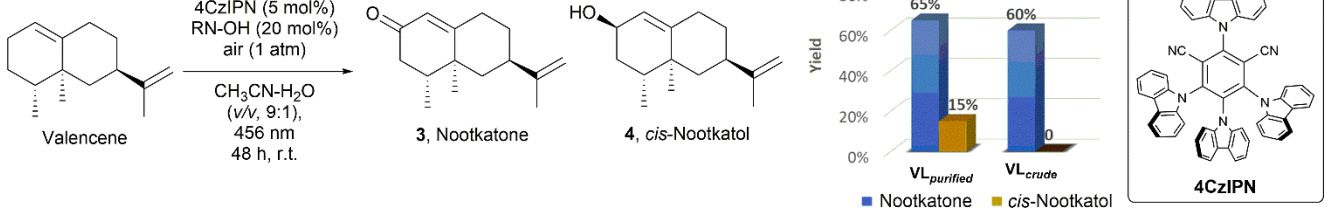
conformational conversion from **A1** to **A5**. In **A5**, as the C10 is pyramidal, i.e. sp3 hybrid (dihedral angle of C9-C10-C2 and C9-C10-H is 138.5°), plus the blocking of *iso*-propenyl group, the C10 is unapproachable from both sides. In contrast, the C9 is planar, i.e., sp2 hybrid (dihedral angle of C8-C9-C10 and C8-C9-C15 is 179.7°), which is easy to be approached by H_2O from downside. Moreover, the substituent effect makes C9 more electropositive than C10 (see NBO analysis in Figure 3d). Therefore, both the stereo-electronic effect and the steric effect incurred by the iso-propenyl group and the substituent effect led to the Markovnikov hydration product.

Visible-light induced allylic C–H oxidation of Valencene via an indirect HAT process

Nootkatone, occurring in grapefruit peel, is widely used in the flavour and fragrance industry. It is commonly included in the ingredients list of grapefruit-flavoured beverages.[17] The allylic oxidation of valencene to yield nootkatone could be an alternative to the traditional extraction-based supply, which is costly.[10b,18] The biotechnology-enabled transformation from valencene to nootkatone has been widely reported, standing out for high site-specificity among multi-allylic sites, but possesses relatively low space-time yields.[17] In contrast, the conventional chemical allylic oxidation of valencene was highlighted by high efficiency, but normally involved the use of toxic metal species, such as chromates,[19] cobalt,[20] bismuth[21] or molybdate.[22] Because of the stringent requirements by the food standards, the downstream processing would be complicated if such metal species were used. Baran and co-workers reported a sustainable electrochemical allylic C–H oxidation for this conversion, involving a hydrogen atom transfer (HAT) process, but employed explosive perchloric salt and peroxide.[23]

We envisioned that visible light induced transformations employing organo-photocatalyst and O_2/air as an oxidant would enable a greener approach for this allylic oxidation (Figure 4a). Our group had applied 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) to develop a variety of photocatalytic reactions.[24] 4CzIPN is attractive because of its metal-free character and flexibility of tuning the redox potential (-1.92 V to +1.79 V vs SCE) via structural modification.[24b] Previous research has shown that singlet-oxygen mediated allylic oxidation encountered the problem of poor selectivity control over multi allylic sites.[22] We envisioned that the indirect HAT process would enable better site selectivity via radical transformations (Figure 4c).[25] We first tested the combination of 4CzIPN/ *N*-hydroxyphthalimide (NHPI)[26] in acetonitrile (CH_3CN) with air (1 atm) as the oxidant. A full conversion was achieved in 48 h, furnishing nootkatone and *cis*-nootkatol in the yield of 60% and 15%, respectively (Figure 4b, entry 1). By employing H_2O as a co-solvent (CH_3CN/H_2O=9:1, *v/v*), the yield of nootkatone was increased slightly to 65% (Figure 4b, entry 2). Replacement of NHPI with *N*-hydroxysuccinimide (NHS) accelerated the reaction to achieve a full conversion within 24 hours, yielding nootkatone and *cis*-nootkatol in the yield of 42% and 33%, respectively (Figure 4b, entry 3). However, extending the reaction time did not improve the yields (Figure 4b, entry 4). *N*-hydroxytetrachlorophthalimide (Cl_4NHPI) slowed down the reaction dramatically (Figure 4b, entry 5). We also revealed that

a) Visible-light induced oxidation of Valencene to Nootkatone and *cis*-Nootkatol



b) Evaluation of reaction conditions[a]

entry	RN-OH	oxidant	solvent	time/h	conversion (%)	**3** (%)	**4** (%)
1	NHPI	air	CH_3CN	48	100	60	15
2	NHPI	air	CH_3CN-H_2O[b]	48	100	65 (62)	15 (13)
3	NHS	air	CH_3CN-H_2O[b]	24	100	42	33
4	NHS	air	CH_3CN-H_2O[b]	48	100	43	19
5	Cl_4NHPI	air	CH_3CN-H_2O[b]	48	79	9	0
6	NHPI	O_2	CH_3CN-H_2O[b]	24	100	n.d.	0
7	NHPI	air	$ClCH_2CH_2Cl$	48	0	0	0
8	NHS	air	H_2O	24	30	12	trace
9[c]	NHPI	air	CH_3CN-H_2O[b]	48	100	60	0

[a]Valencene 0.10 mmol (0.1 M), 4CzIPN (5 mol%), 456 nm Kessil light (40 W), air or O_2 (1 atm), yields determined by ^{1}H NMR analysis using 1,2,3-trimethoxybenzene as an internal standard and yields are referred to isolated yields in parentheses. [b]CH_3CN-H_2O (volume ratio: 9:1). [c]Crude valencene from "BIO" process was used as the substrate without being subjected to silica gel chromatography purification.

c) Propsed reaction mechanisms

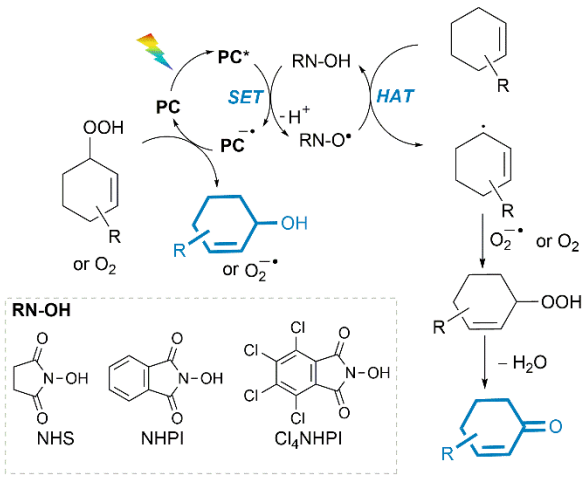


Figure 4. Visible light induced allylic C-H oxidation of valencene delivering nootkatone and cis-nootkatol. "VLpurified" denotes valencene from "BIO" process purified by column chromatography and then was used as the reaction starting material; "VLcrude" denotes valencene directly from "BIO" process without column chromatography purification used as the reaction starting material.

replacement of air with dioxygen resulted in a total decomposition of the substrate through overoxidation (Figure 4b, entry 6). The reaction didn't occur in $ClCH_2CH_2Cl$ (Figure 4b, entry 7). Using water as sole solvent also allowed the reaction to proceed, achieving 12% yield of nootkatone in 24 h (Figure 4b, entry 8). More importantly, the crude valencene obtained from the organic extraction of fermentation liquor without further purification was well compatible with this photocatalytic process, furnishing the nootkatone in 60% yield (Figure 4b, entry 9)

Conclusion

In conclusion, to expand the biologically relevant chemical space in sesquiterpenes and sesquiterpenoids production, fermentation with engineered *E. coli* and metal-free visible-light-promoted photocatalysis were merged in a complementary way, enabling the production of six sesquiterpenoids with high atom-, step- and redox-economy. We demonstrated the first example of combining *Escherichia coli* fermentation processes and visible-light photocatalytic chemical transformations to rapidly access complex chemical scaffolds and diversity by merging the advantages from these two complementary methods. The *E. coli* fermentation process directly accessed the all-carbon skeletons from simple building blocks (prenol and isoprenol) for two sesquiterpenes (amorpahdiene and valencene). A key innovation was to remove the organic overlay and prevent the product evaporation by operating the fermentation under a closed system, which not only increased the product yield but also simplified workup process to enable less material loss. Subsequently, two metal-free photoredox catalytic chemical transformations were developed, enabling structural diversification of these sesquiterpenes. The hydration reaction exclusively occurred at the *tri*-substituted double bonds to deliver two sesquiterpenoids in a selective fashion. The unusual Markovnikov selectivity on amorphadiene was computationally attributed to the stereo-electronic and steric effects. The allylic C–H oxidation involving a mild and sensitive HAT process furnished nootkatone and *cis*-nootkatol. The emerging one-pot photo-enzymatic dual catalysis represents a powerful method to introduce chiral molecules in a single-step process with enhanced greenness.[27] In contrast, our sequential transformations provides an efficient mode for multistep synthesis to access complex molecules with diverse scaffolds and functionalities: the fermentation process constructed ring skeletons with multiple stereocenters, and the subsequent photocatalysis processes introduced additional functionality into the skeletons.

Acknowledgements

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Keywords: Biocatalysis • Photoredox catalysis • Amorphadiene • Valencene • Nootkatone

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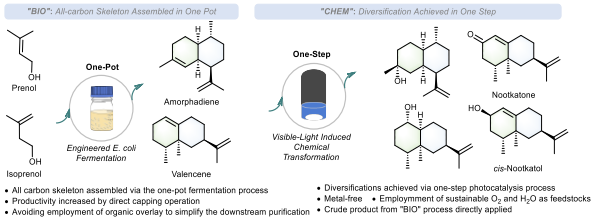
Entry for the Table of Contents



Bio-Chem Collaboration: *Escherichia coli* fermentation and visible-light photocatalysis were combined in a complementary way for the first time, to realize the scaffold assembly in a “one-pot” fashion and the subsequent diversifications in a “one-step” manner respectively, enabling the production of six sesquiterpenoids.