Synthetic Methods

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Synthesis of 3-Oxaterpenoids and Its Application in the Total Synthesis of (±)-Moluccanic Acid Methyl Ester**

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3-Oxaterpenoids represent an important class of plant-based natural products and drugs, are oxidative metabolites of terpenoids,[1] and exhibit interesting biological activities and pharmaceutical potentials (Figure 1).[2–4] For example, salvinorin A (**A**)[2] is a selective κ-opioid-receptor agonist, compound **B**[3] is a mild toxin to brine shrimp, and compound **C**[4] shows significant cytotoxic activity. Captivated by the intricate polycyclic structure and diverse bioactivities of 3-oxaterpenoids, and inspired by Nature's uncanny workmanship in constructing them, we were very interested in the development of efficient methods to complement the biosynthesis. Herein, we report the preparation of 3-oxaterpenoids and its application in the total synthesis of (±)-moluccanic acid methyl ester, through a cascade of Prins reaction and polyene cyclization (Scheme 1).[5]

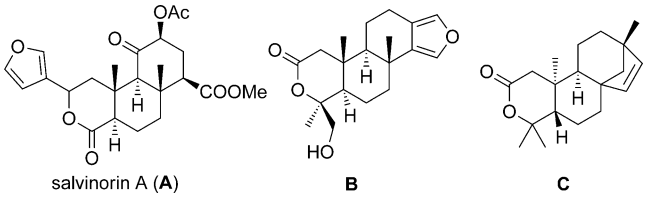
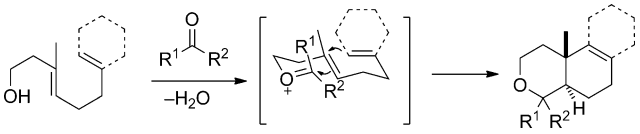


Figure 1. Selected examples of 3-oxaterpenoids.

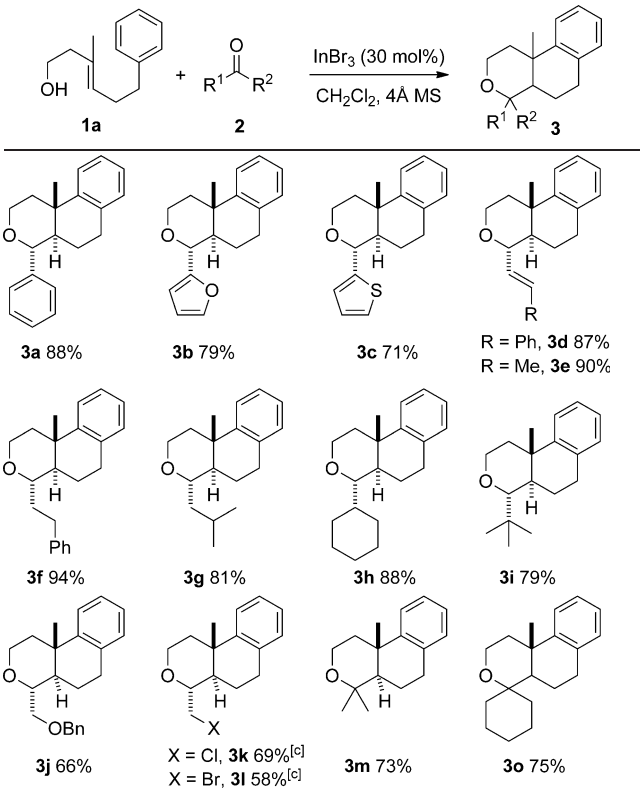
Although methods to construct terpenoid skeletons are well established,[6,7] there is no strategy to access 3-oxaterpenoids directly. As part of our ongoing efforts to develop intermolecular polyene cyclization,[8] we hypothesized that a modified intermolecular polyene cyclization might furnish 3-oxaterpenoids in a straightforward manner (Scheme 1).[9] We envisaged that a Prins reaction, the classic method to form a THP ring,[10] might serve to initiate the cascade cyclization to provide the anticipated 3-oxaterpenoids.



Scheme 1. Proposed mechanism for Prins reaction initiated polyene cyclization.

To test our hypothesis, we focused on an intermolecular reaction between (*E*)-3-methyl-6-arylhex-3-en-1-ol (**1a**) and benzaldehyde, mediated by different Lewis acids (Table 1). Upon extensive investigtion, $InBr_3$ and CH_2Cl_2 were found to be the optimal catalyst and solvent, respectively, for the

Table 1: $InBr_3$-catalyzed Prins–polyene cyclization with different carbonyl substrates.[a,b]



[a] Conditions: $InBr_3$ (0.06 mmol) was added to a solution of **1a** (0.2 mmol), **2** (0.24 mmol), and 4 Å molecular sieves (0.2 g) in anhydrous CH_2Cl_2 (2 mL) at RT. [b] Yields of isolated products. [c] 2-X-1,1-diethoxyethane was used instead of the corresponding aldehyde.

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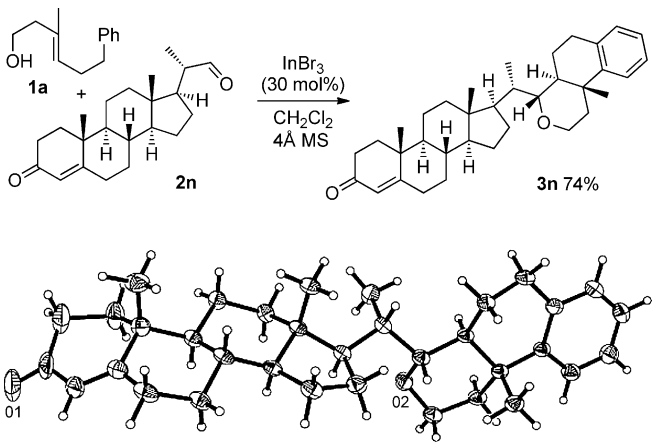
transfomation at room temperature.[11,12] Gratifyingly, the corresponding product **3a** was obtained in 88% yield as a single isomer.

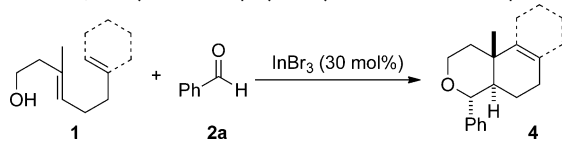
With the optimized conditions in hand, the scope of this Prins reaction initiated polyene cyclization (Prins–polyene cyclization) was subsequently investigated (Table 1). The reaction is compatible with a wide range of carbonyl substrates. Both aryl and heteroaryl aldehydes reacted efficiently and gave the desired products (**3a–c**) in good to high yields (71–88%). Similarly, α,β-unsaturated aldehydes performed well to deliver 3-oxaterpenoids **3d** and **3e** in 87% and 90% yields, respectively. In addition, aliphatic aldehydes also proved to be suitable substrates for the transformation and led to the desired products (**3f** and **3g**) in excellent yields. Sterically demanding aliphatic aldehydes did not suffer from decreased reactivity and the desired products (**3h** and **3i**) were obtained in high yields (88% and 79%, respectively). In the case of benzyloxyacetaldehyde, a functionalized aliphatic aldehyde, the yield of product **3j** was slightly lower (66%). It is notable that 2-chloro-1,1-diethoxyethane and 2-bromo-1,1-diethoxyethane are also reactive substrates, which afforded **3k** and **3l**, respectively, the alkyl halide moiety of which can be readily functionalized. Although ketones are generally considered to be mediocre substrates in Prins reactions,[13] acetone and cyclohexanone are good substrates for this cascade cyclization and provided **3m** and **3o**, respectively, in high yields. When the optically pure aldehyde **2n** was used for this reaction (Scheme 2), a single diastereomer **3n** was obtained in good yield (74%), and its absolute stereochemistry was assigned based on single-crystal X-ray analysis.[17]

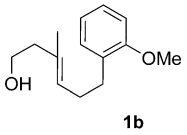
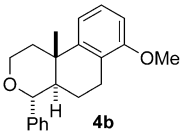
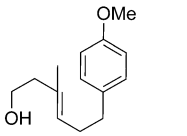
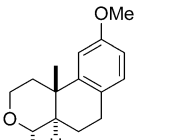
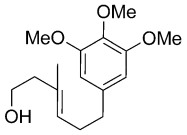
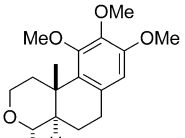
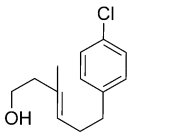
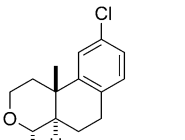
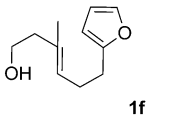
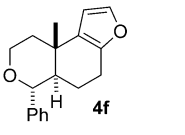
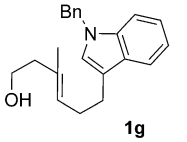
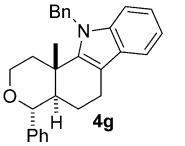
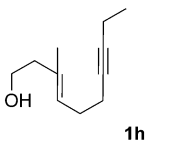
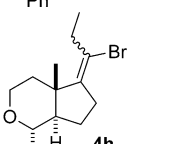
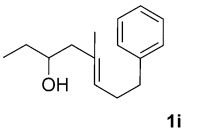
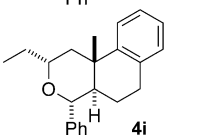
After identification of both aldehydes and ketones as suitable substrates for the Prins–polyene cyclization, we further investigated the reactivity of various homoallylic alcohols toward benzaldehyde (Table 2). Regardless of the presence of electron-donating (Table 2, entries 1–3) or electron-withdrawing (entry 4) groups on the phenyl ring, the reaction provided the desired products in high yield (> 80%). Satisfying results were also obtained when homoallylic alcohols that were tethered to a furan (Table 2, entry 5) and an indole moiety (entry 6) were used. The reaction of



Scheme 2. Prins–polyene cyclization with aldehyde **2n** and single-crystal X-ray structure of cyclization product **3n** (thermal ellipsoids at 50% probability).

Table 2: $InBr_3$-catalyzed Prins–polyene cyclization to 3-oxaterpenoid.[a]



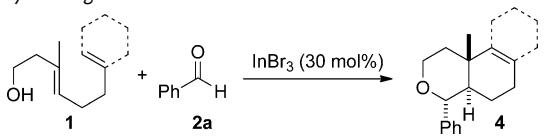
Entry	Reactant **1**	Product (**4**)	Yield [%][b]
1	 **1b**	 **4b**	94
2	 **1c**	 **4c**	82
3	 **1d**	 **4d**	86
4	 **1e**	 **4e**	81
5	 **1f**	 **4f**	63
6	 **1g**	 **4g**	82
7	 **1h**	 **4h**	68[c]
8	 **1i**	 **4i**	75

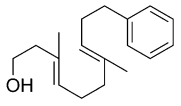
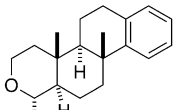
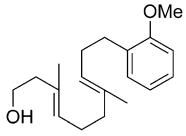
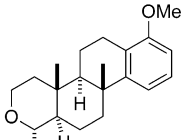
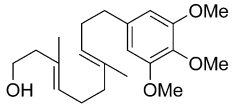
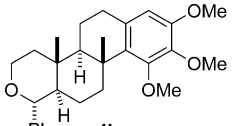
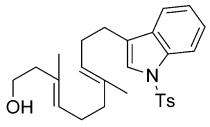
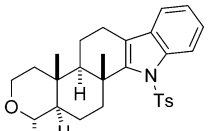
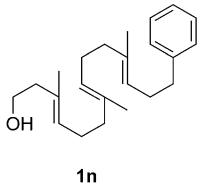
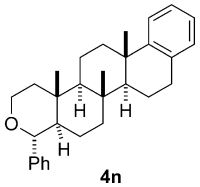
[a] Conditions: see Table 1. [b] All yields are isolated yields. [c] 100 mol% $InBr_3$ was used in this reaction. The stereoselectivity of alkene is 3:1, which is determined by ^1H NMR.

substrate **1h**, the terminating group of which is an internal alkyne (Table 2, entry 7), gave product **4h**, possessing a unique cyclopentane ring fused to a THP ring, in 68% yield.[14] Interestingly, secondary alcohol **1i** (Table 2, entry 8) reacted equally well and gave the desired product in 75% yield as a single isomer.

In view of the cationic character of the Prins–polyene cyclization and our previous studies on bio-inspired polyene cyclization, we envisioned that tetracylic and pentacyclic scaffolds might be accessible (Table 3).[8,15] To our delight, when dienes that were tethered to arenes were used as substrates, the tetracylic products (**4j**–**4k**) were obtained in good yields (>80%) as single isomers (Table 3, entries 1–3).

Table 3: $InBr_3$-catalyzed Prins–polyene cyclization to tetracyclic and pentacyclic rings.[a]



Entry	Reactant **1**	Product (**4**)	Yield [%][b]
1	 **1j**	 **4j**	81
2	 **1k**	 **4k**	87
3	 **1l**	 **4l**	82
4	 **1m**	 **4m**	66
5	 **1n**	 **4n**	59

[a] Conditions: see Table 1. [b] Yields of isolated products.

The relative stereochemistry of **4j** was determined by single-crystal X-ray analysis (Figure 2).[18] When **1m**, a diene tethered to an indole moiety as the terminating group, was employed as the substrate, the reaction proceeded well and a pentacyclic compound **4m** was obtained in 66% yield as a single isomer. It is worth mentionioning that through the impressive cyclization of **1n**, which occurred in a single step, three cyclohexane rings and one THP ring were formed, thus leading to the isolation of the single isomer **4n** in 59% yield (Table 3, entry 5).

Having successfully established an intermolecular polyene cyclization to construct 3-oxaterpenoid skeletons, we

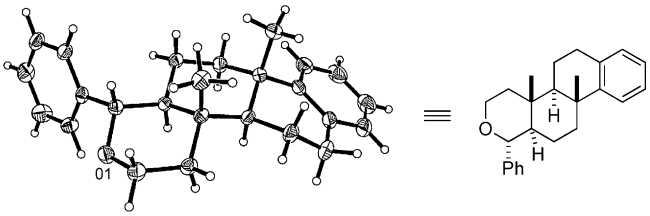
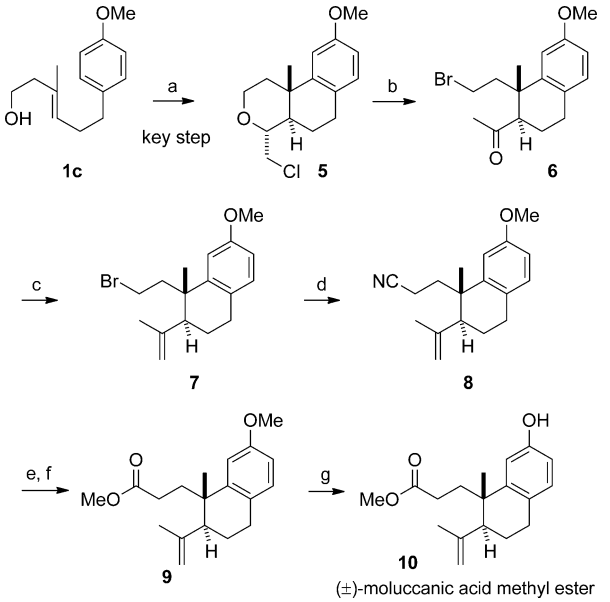


Figure 2. Single-crystal X-ray structure of **4j** (thermal ellipsoids at 50% probability).

progressed to apply the strategy in natural product synthesis. The products of Prins–polyene cyclization share the 1,2-*trans*-tetrahydronaphthalene scaffold, which is commonly found in terpenoids, and have thus considerable value for the synthesis of such compounds. For example, both the cyclization product **5** and (±)-moluccanic acid methyl ester (**10**) consist of a highly functionalized 1,2-*trans*-tetrahydronaphthalene core (Scheme 3). We envisioned that compound **10** can be synthesized from **5** through suitable manipulation of the (chloromethyl)pyran moiety of the latter. Firstly, chloroacetaldehyde dimethyl acetal and **1c** underwent Prins–polyene cyclization to afford key intermediate **5** in 64% yield. The cyclized product **5** was treated with sodium hydride to give the E2 elimination product, which was then subjected to a solution of HBr in acetone to afford bromo-substituted ketone **6** in 55% yield. The installation of a terminal alkene group on **6** was not possible through a Wittig reaction, however, this problem was solved by employing a Tebbe reaction, and olefination product **7** was thus obtained in 71% yield.[16]



Scheme 3. Synthesis of (±)-moluccanic acid methyl ester. a) 30 mol% $InBr_3$, chloroacetaldehyde dimethyl acetal, CH_2Cl_2, 64% yield; b) NaH, DMF, 130°C; then HBr, acetone, 55% yield; c) Tebbe reagent, toluene, 72% yield; d) NaCN, [18]crown-6, CH_3CN, 67% yield; e) KOH, $MeOH/H_2O$ = 4:1, 60°C; f) DCC, MeOH, THF, 58% yield over two steps; g) BCl_3, TBAI, CH_2Cl_2, 71% yield. DMF = *N*,*N*-dimethylformamide, DCC = dicyclohexylcarbodiimide, TBAI = tetra-*n*-butylammonium iodide.

Replacement of the bromine atom in **7** by a nitrile group furnished **8** in 67% yield. Hydrolysis and subsequent esterification of **8** led to **9** in 58% yield. Finally, deprotection of **9** was achieved in 71% yield in the presence of trichloroborane and TBAI,[17] leading to the total synthesis of (±)-moluccanic acid methyl ester in seven steps. The ^{1}H and ^{13}C NMR data of our synthesized compound **10** are consistent with the data reported for the natural product.[5]

In summary, we have developed a novel, efficient synthesis of 3-oxaterpenoids through a cascade of Prins–polyene cyclization, which is compatible with various aldehydes and polyolefinic alcohol substrates. Catalytic amounts of $InBr_3$ (30 mol%) were used and excellent diastereoselectivity was observed with both chiral and achiral substrates. The reaction provides an alternative, concise way to synthesize 3-oxaterpenoidal derivatives, which are also useful building blocks for terpenoid synthesis. The usefulness of this strategy has been demonstrated in the total synthesis of (±)-moluccanic acid methyl ester. Further studies on the enantioselectivity of the reaction and development of more synthetic applications are currently in progress and will be reported in due course.

Please note: Minor changes have been made to this manuscript since its publication in *Angewandte Chemie* Early View. The Editor.

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[18] CCDC 888840 (**3n**) and CCDC 888841 (**4j**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

