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Transforming terpene feedstock into polyketide architecture†‡

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The Cu-catalyzed synthesis of skipped 1,4-dienes from allylic acetates and vinyl-Grignard reagents is key to bidirectional modifications of acyclic terpene acetates. As a result, trisubstituted double bond containing subunits can be readily transferred into complex polyketides from inexpensive bulk terpenes.

The focus on target-oriented synthesis of biologically active molecules is shifting toward more economic[1] and sustainable chemical processes.[2] Among many approaches[3] to quantify synthetic efficiency, it has been recently suggested[4] along the lines of Hendrickson's (1975) definition[5] to use the quotient (construction reactions + strategic redox reactions)/total number of reaction steps as a yardstick for the "ideality" of a given synthesis. We feel that this definition undervalues the importance of minimizing construction steps, *i.e.* the overall number of C–C-bond forming reactions. Our group's research is dedicated to making larger substructures within natural products[6] available from terpene feedstock,[7] fermentation or catalytic build-up reactions,[8] *e.g.* telomerizations.[9]

As a step toward this goal, we have embarked on the use of oxidized monoterpenes in conjunction with the development of efficient C–C bond forming reactions. Following this loose strategic blueprint, we recently completed the synthesis of englerin A[10] from the epoxide of the readily available monoterpene nepetalactone (Fig. 1).

In this communication, we would like to disclose a strategy for the conversion of epoxygeranyl acetate (**1a**) and related molecules into 1,4-dienes and representative subsequent conversions into polyketide building blocks using organo-catalytic and transition metal catalyzed reactions.

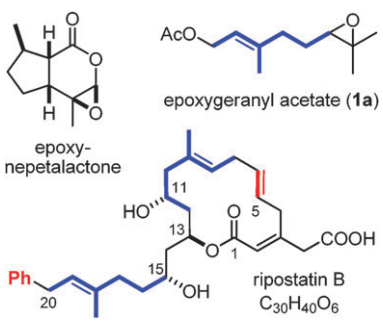


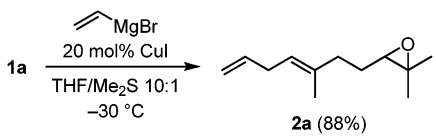
Fig. 1 Terpene epoxides and substructure analysis within ripostatin B.

In contrast to terpene biosynthesis which has a sudden increase in complexity through cationic cyclization events, polyketide complexity grows in a rather sequential fashion by two- and three-carbon building blocks. Instead of mimicking the intricate biosynthetic machinery of polyketide synthases, a potential shortcut lies in the possibility to disconnect polyketides into larger fragments. When pondering over the retrosynthesis of ripostatin B,[11] a potent RNA polymerase inhibitor,[12] we realized that 22 out of its 30 carbon atoms could—in principle—be derived from two molecules of epoxygeranyl acetate (blue), phenyl- and vinylmagnesium bromide (red) as starting materials. The key transformation in such an approach would be the coupling of the Grignard reagents with the allylic acetates.

While the substitution of allylic acetates with phenyl- and alkylmagnesium halides using Li_2CuCl_4 was precedented by Gansäuer *et al.*,[13] surprisingly, apart from particular examples of Pd-catalyzed couplings with vinylstannanes,[14] no general and scalable method for the synthesis of 1,4-dienes[15,16] (skipped dienes) from allylic acetates has been reported to our knowledge.

The use of those previously established catalytic conditions (Li_2CuCl_4 in THF) with vinylmagnesium bromide as the nucleophile met limited success as only 23% of the desired substitution product **2a** was detected. After extensive optimization,[17] we found that using copper(I)-bromide dimethylsulfide complex (20 mol% in THF) afforded 70% of the desired substitution product. The yield could be further improved by using 1.5 equivalents of vinylmagnesium bromide with copper(I)-iodide (20 mol%) as catalyst in a solvent mixture of tetrahydrofuran/dimethylsulfide (10 : 1) giving rise to 88% of the skipped 1,4-diene **2a** (Scheme 1).

In order to probe the generality (functional group tolerance, integrity of the trisubstituted double bond configuration) of this reaction, we applied our best conditions to the vinyl substitution of a variety of allylic acetates (Table 1). Both epoxygeranyl and epoxyneryl acetate afforded the expected 1,4-dienes with complete retention of the configuration of the allylic double bond (entries 1 and 2) in good to excellent yields. In this instance, the epoxide serves as a handle in subsequent transformations, readily converted to an aldehyde moiety upon treatment with sodium periodate. In addition, their parent derivatives (entries 3 and 4) reacted smoothly to give the desired trienes. In the presence of non-allylic acetates, only



Scheme 1 Optimized conditions for the synthesis of 1,4-dienes.

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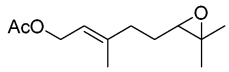
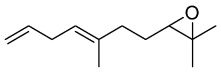
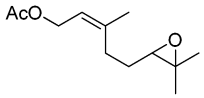
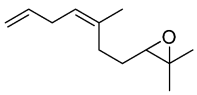
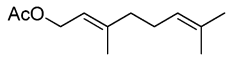
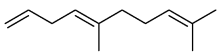
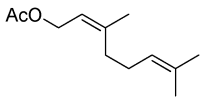
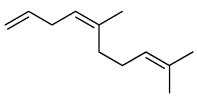
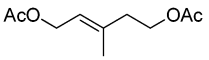
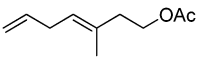
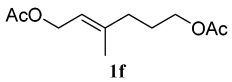
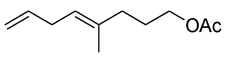
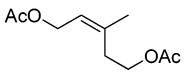
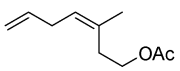
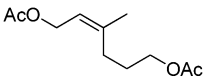
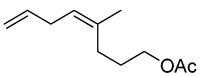
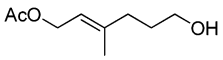
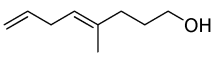
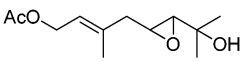
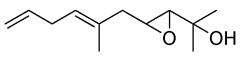
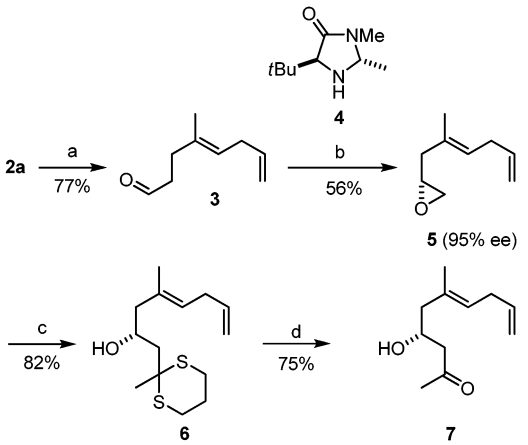
Table 1 Investigation of the substrate scope

Entry	Substrate	Product	Yield[a] (%)
1	 **1a**	 **2a**	88
2	 **1b**	 **2b**	69
3	 **1c**	 **2c**	76
4	 **1d**	 **2d**	90
5	 **1e**	 **2e**	54
6	 **1f**	 **2f**	52
7	 **1g**	 **2g**	66
8	 **1h**	 **2h**	47
9	 **1i**	 **2i**	58
10	 **1j**	 **2j**	78

[a] Isolated yields.

those in the allylic position are substituted in good to moderate yield while the others remain unaffected (entries 5 to 8). Furthermore, the presence of free alcohols is well tolerated at the expense of one additional equivalent of Grignard reagent (entries 9 and 10).

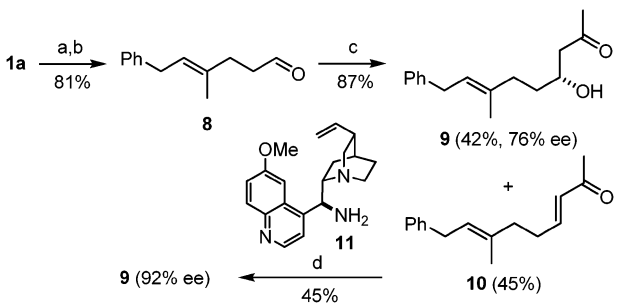
In order to showcase the bidirectional modification of epoxydiene **2a** and its potential use in the synthesis of polyketides, we converted it into the C5–C15 fragment of ripostatin B (Scheme 2). The four-step synthetic sequence commenced with the cleavage of the epoxide moiety to yield dienal **3**. MacMillan *et al.*[18] recently reported the elegant conversion of aldehydes into epoxides using SOMO organocatalysis. Applying this methodology, we were able to isolate the terminal epoxide **5** in an unoptimized 56% yield and with 95% ee. Epoxide opening[19] (**5** → **6**) followed by the oxidative removal of the dithiane[20] afforded hydroxyketone **7** in good yield.



Scheme 2 *Reagents and conditions*: (a) $NaIO_4$, THF/H_2O (2 : 1), 20 °C; (b) (1) **4**·TFA, $K_2S_2O_8$, LiCl, $Cu(TFA)_2{\cdot}xH_2O$, acetonitrile, water, 4 °C, (2) $NaBH_4$, 0 °C, (3) NaOH, EtOH, H_2O, 20 °C; (c) 2-methyl-1,3-dithiane, *n*-BuLi, THF, 20 °C; (d) $PhI(TFA)_2$, $CaCO_3$, MeOH/acetonitrile (9 : 4), 20 °C.

Interestingly, the ripostatin C12–24 subunit **9** bearing a skipped arene-ene moiety can be prepared in a similar approach from epoxygeranyl acetate **1a** (Scheme 3). Substitution with phenylmagnesium chloride is followed by periodate cleavage of the epoxide. In order to show the general potential of combining the allylic substitution with an organocatalytic aldol reaction with acetone,[21] we obtained the quite advanced fragment **9** in just three synthetic steps from **1a**. The major byproduct **10** can be converted to **9** with significantly higher enantioselectivity than for the direct aldol reaction using an oxa-Michael addition developed by List *et al.*[22]

Finally, we want to provide an example for the further functionalization of the terminal alkene moiety in **2a**. Apart from possible hydroborations, oxidative cleavage and cross-metathesis reactions, we want to use the hydroformylation reaction for the introduction of a free aldehyde functionality on one end of the aliphatic chain while the epoxide on the other terminus remains a masked aldehyde (Scheme 4). Using 2 mol% of $Rh(acac)(CO)_2$ and Xantphos[23] as the ligand, we obtained the unbranched aldehyde **12** in virtually quantitative yield. We think that this model compound represents a useful and orthogonally functionalized fragment for the natural product dolabelide D.[24]



Scheme 3 *Reagents and conditions*: (a) Li_2CuCl_4, PhMgCl, THF, 0 °C; (b) $NaIO_4$, THF/H_2O (2 : 1), 20 °C; (c) D-proline, *i*-PrOH, acetone, 20 °C; (d) **11**, Cl_3CCO_2H, H_2O_2, dioxane, 32 °C, then $P(OEt)_3$.

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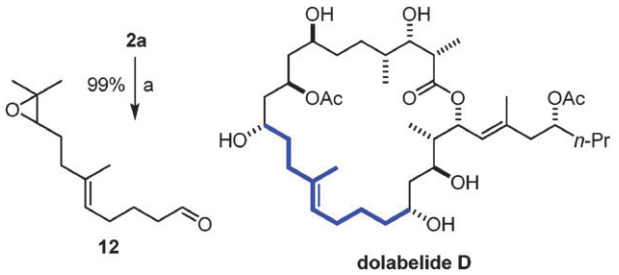

Scheme 4 *Reagents and conditions*: (a) Rh(acac)$(CO)_2$, Xantphos, toluene, H_2/CO (20 bar), 60 °C.

In conclusion, we have developed a simple protocol for the Cu-catalyzed substitution of allylic acetates with vinyl Grignard reagents that is tolerant towards a variety of functional groups. A possible ramification of this method is the reduction of construction steps in the total synthesis of polyketides. In particular, the efficient conversion of terpene acetate derivatives into polyketide building blocks is a harbinger of their increasing importance as cheap and renewable resource in complex molecule synthesis.

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