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Syntheses of the Carotane-type Terpenoids (+)-Schisanwilsonene A and (+)-Tormesol via a Two-Stage Approach

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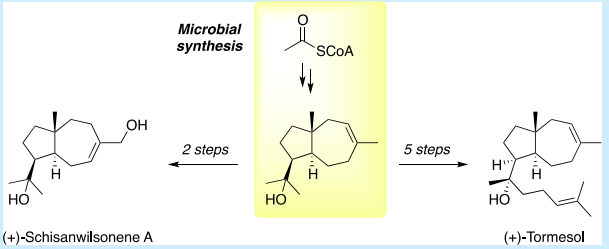
ABSTRACT: Stereoselective syntheses of terpenoids in a more efficient manner have been a long-term pursuit for synthetic chemists. Herein we describe the two-step, enantiospecific and protecting-group-free synthesis of (+)-schisanwilsonene A from a carotane compound, which was produced in *E. coli*. We also completed the first enantiomeric synthesis of (+)-tormesol in five steps. The two-stage strategy offers a step- and redox-economical approach to prepare terpene natural products and their analogues.



Terpenoids have a variety of important biological functions in plants, including essential roles in growth, development, defense, communication, and environmental sensing.[1] They are also the sources of many commercially valuable chemicals, such as pharmaceuticals, fragrances, flavors, and insecticides.[2] Traditionally, plant terpenoids can be obtained by extraction from their natural sources or by total synthesis and semisynthesis.[2,3] In the past two decades, the heterologous production of high-value terpenoids or their precursors in genetically engineered microorganisms has attracted much attention.[4] For example, Keasling and coworkers have developed strains of *Saccharomyces cerevisiae* for the high-yielding production of artemisinic acid and converted them into artemisinin through chemical transformations.[5] However, the applications of this strategy to produce medicinal plant terpenoids are limited thus far owing to a few reasons. First, only a small percentage of plant terpenoids has been biosynthetically characterized, largely due to the difficulties in the identification of the biosynthetic pathways for plant natural products. Unlike bacteria and fungi, the genes for the secondary metabolites in plant are scattered throughout the entire genome, which makes the identification of a complete biosynthetic pathway tedious and time-consuming.[6] Second, the functional characterization of the plant terpene synthases in an engineered host can be problematic due to low activity, incorrect localization, or limited solubility.[5c,7] Third, orchestrating a series of enzymatic reactions to maximize the production in a microbe without influencing the primary metabolism is a formidable task.[4c] Recently, genome sequencing of bacteria and fungi has revealed many terpene synthases, and biochemical studies demonstrated that their products share the same or similar scaffolds as many known plant terpenoids.[8] Although some terpenes from bacteria have the opposite absolute configurations of plant terpenoids,[9] these findings have enriched the toolbox for synthetic biologists to reconstruct the biosynthetic pathways of terpenoids in microorganisms. For example, two groups reported the heterologous production of guaian-6,10(14)-diene in *E. coli* and *S. cerevisiae* and the synthesis of (−)-englerin A, a potent and selective inhibitor toward renal cancer cell lines.[10] Additionally, Smanski and coworkers reported the production of *ent*-atiserenoic acid in an engineered *Streptomyces* strain and the synthesis of serofendic acid, a natural neuroprotective compound found in fetal calf serum.[11] Herein we describe the concise syntheses of plant terpenoids (+)-schisanwilsonene A (**1**) and (+)-tormesol (**2**) (Figure 1A) from a carotane-type precursor produced in *E. coli* (Figure 1C).

(+)-Schisanwilsonene A (Figure 1A) is a carotane-type sesquiterpenoid that is isolated from the fruits of *Schisandra wilsoniana* and exhibits antiviral activity.[12] Studies show that it inhibits HBsAg and HBeAg secretion by 76.5 and 28.9% at 50 μg/mL. (+)-Schisanwilsonene A features a trans-fused bicyclo[5.3.0]carotane scaffold and a syn relationship between the angular methyl group and the side chain, which makes it a challenging synthetic target. In 2013, Echavarren and coworkers reported the only total synthesis of (+)-schisanwilsonene A in 13 steps (ca. 4% overall yields from a known synthetic intermediate **4**, Figure 1B).[13] The synthesis comprises the gold-catalyzed tandem cyclization, 1,5-migration, and cyclopropanation as key steps to construct the carotane skeleton. To develop an efficient synthetic approach of (+)-schisanwilsonene A, we searched for a sesquiterpene synthase, which could convert farnesyl pyrophosphate (FPP)

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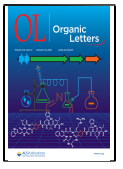

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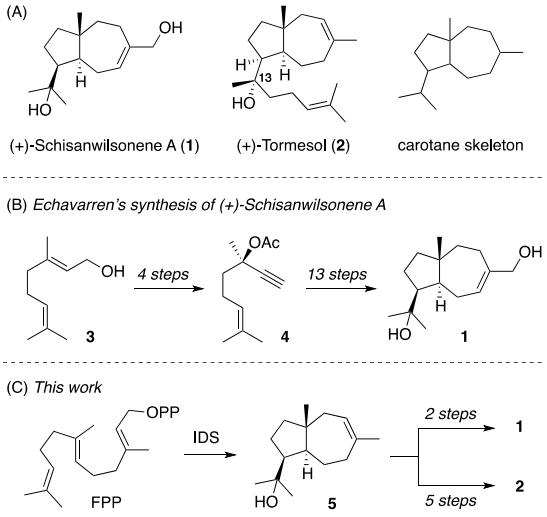

Figure 1. (A) Structures of (+)-schisanwilsonene A and (+)-tormesol. (B) Echavarren's synthesis of (+)-schisanwilsonene A. (C) General approach toward the syntheses of (+)-schisanwilsonene A and (+)-tormesol.

into a carotane scaffold. In 2016, Dickschat and coworkers reported that a sesquiterpene synthase from *Streptomyces venezuelae* ATCC 10712 (CCA53839) could transform FPP to (+)-isodauc-8-en-11-ol (**5**), which has the same scaffold and absolute configuration as our target molecule.[14] On the basis of this result, we designed a two-step conversion by using the olefin isomerization reaction and the allylic oxidation reaction to synthesize (+)-schisanwilsonene A.

We first set out to reconstruct a biosynthetic pathway in *E. coli* to produce compound **5** for the following chemical transformations. In our previous studies, we used a two-plasmid system to produce guaian-6,10(14)-diene for the syntheses of epoxy-guaiane sesquiterpenoids.[10b] The mevalonate (MVA) pathway was divided into two parts and was overexpressed from the vector pACYCDuet-T1-B1; the FPP synthase ERG20 and the sesquiterpene synthase STC5 were overexpressed from the vector pETDuet-ERG20-STC5. Herein we first attempted to replace the *STC5* gene with the codon-optimized *IDS* gene (Figure S1). Strain XW1 (Table S1) containing pACYCDuet-T1-B1 and pETDuet-ERG20-IDS was tested for the synthesis of compound **5** under two-phase flask conditions. A peak was observed from the organic phase after 72 h of induction and its mass spectrum was identical to the spectrum reported by Dickschat and coworkers[14] (Figure 2A). The compound was purified, and the structure was confirmed by ^{1}H NMR and ^{13}C NMR. To improve the titer of compound **5**, we first replaced the FPP synthase gene from *S. cerevisiae* (*erg20*) with the FPP synthase gene from *E. coli* (*ispA*). However, the titer of compound **5** produced by the strain XW2 decreased to 57.94 ± 6.91 mg/L/OD_{600} (Figure 2B, Table S1). We also cloned *erg20* and *ispA* into the pACYCDuet-T1-B1 vector separately and cotransformed them with pET28a-IDS, respectively. To our delight, the titers of compound **5** produced by strain XW3 and strain XW4 increased by 64.83 and 59.12% compared with strain XW1, respectively. Previously, Brodelius and coworkers reported that the fusion of the FPP synthase with the *epi*-aristolochene synthase showed a more efficient conversion of isopentenyl diphosphate to *epi*-aristolochene than the single enzymes.[15a] A similar strategy was also used in miltiradiene production in *S. cerevisiae*

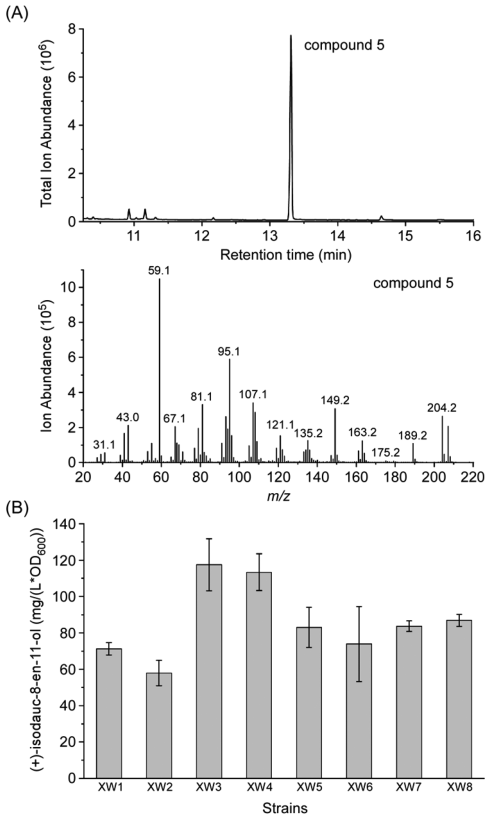

Figure 2. (A) GC-MS analysis of compound **5** produced by *E. coli*. (B) Production of compound **5** by *E. coli* strains harboring modules overproducing various enzymes.

by Zhao and coworkers.[15b] Inspired by these studies, we constructed two fusions, ERG20/IDS (strain XW5) and IDS/ERG20 (strain XW6), with a GGGS linker. Strains XW5 and XW6 showed a slight increase in the titer compared with strain XW1, but it was lower than that of strain XW3. We then attempted to increase the expression level of FPP synthase to increase the yield of compound **5**. Both strain XW7 and strain XW8 gave a higher titer than strain XW1. Among the strains examined above, strain XW3 provided the highest titer, and 1.16 ± 0.11 g/L of compound **5** was obtained after purification.

With grams of (+)-isodauc-8-en-11-ol in hand, we tested the olefin isomerization with different conditions (Table 1). Transition-metal-catalyzed olefin isomerization is a powerful method in natural product synthesis and has attracted much attention recently.[16] Several methodologies using cobalt,[17] palladium,[18] iron,[19] and ruthenium[20] catalysts have been reported. However, to the best of our knowledge, most of these methodologies were developed using terminal mono- or disubstituted olefins as substrates. Only a few examples of the isomerization of an internal carbon−carbon double bond have been reported.[20e,f] Moreover, the isomerization of a trisubstituted carbon−carbon double bond remains challenging, possibly due to the lack of a thermodynamic driving force. We first tested the reaction using (*S*,*S*)-Co(Sal) as the catalyst and found that it gave the isomerization product at room temperature. The ratio of the isomerization product versus the substrate was 1:5 based on the ^{1}H NMR analysis (entry 1). The ratio increased when the reaction temperature was elevated (entries 2−4). Extending the reaction time lead to a slight decrease in the ratio (entry 5). When (*R*,*R*)-Co(Sal) was

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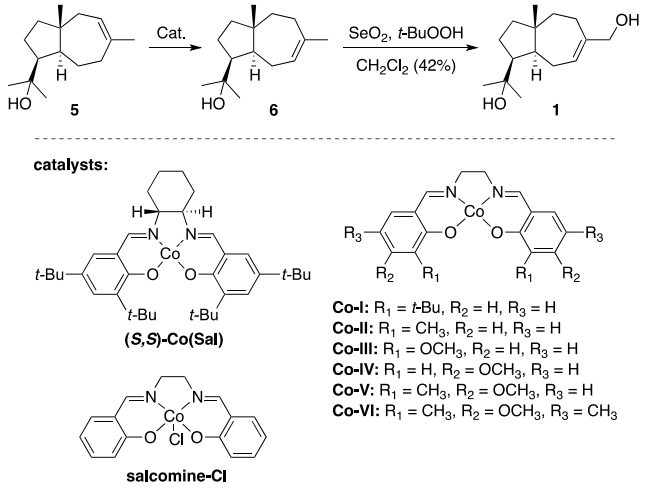
Table 1. Synthesis of (+)-Schisanwilsonene A from Compound 5 via the Olefin Isomerization Reaction and the Allylic Oxidation Reaction



entry	catalyst[a]	solvent	temperature (°C)	time (h)	6/5[b]
1	(*S*,*S*)-Co(Sal)	acetone	25	20	1:5
2	(*S*,*S*)-Co(Sal)	acetone	56	20	1:3
3	(*S*,*S*)-Co(Sal)	benzene	80	20	1:2.3
4	(*S*,*S*)-Co(Sal)	toluene	110	20	1:1.7
5	(*S*,*S*)-Co(Sal)	toluene	110	48	1:2
6	(*R*,*R*)-Co(Sal)	toluene	110	24	1:1.7
7	salcomine-Cl	toluene	110	24	1:7.5
8	Co-I	toluene	110	24	1:2
9	Co-II	toluene	110	24	1:1.8
10	Co-III	toluene	110	24	1:25
11	Co-IV	toluene	110	24	1:3.5
12	Co-V	toluene	110	24	1:1.4
13	Co-VI	toluene	110	24	1:2
14	Co-VII	toluene	110	24	1:3

[a]Reaction conditions: catalyst (20%), $PhSiH_3$ (80%). [b]Determined by ^1H NMR analysis of the crude product.

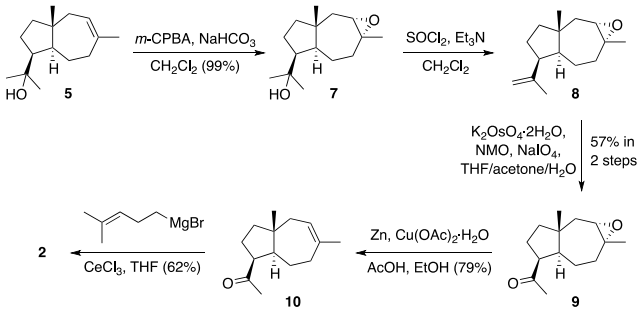
used, the ratio was about the same (entry 6), suggesting that the configuration of the catalyst had no effect on the substrate. We also tested salcomine-Cl and found that it gave the isomerization product with a lower ratio (1:7.5) compared with (*S*,*S*)-Co(Sal) (entry 7). Other transition-metal catalysts and potassium *tert*-butyloxide have also been examined, but none of these conditions afforded a higher isomerization ratio (Table S2).

On the basis of the above results, we considered that the Co(salen)-catalyzed hydrogen-atom-transfer process was superior to other methodologies and the electronic effect of the salen ligands had an enormous effect on the catalytic activity. Therefore, we designed and synthesized seven Co(II) catalysts and investigated the isomerization reaction (entries 8−14). We first tested the different groups at the R_1 position and found that the *tert*-butyl and methyl groups gave a similar isomerization ratio (entries 8 and 9) as the (*S*,*S*)-Co(Sal) catalyst (entry 4), whereas the methoxy group significantly reduced the isomerization ratio (entry 10). When the R_2 position was substituted by the methoxy group, the ratio increased to 1:3.5 (entry 11) compared with salcomine-Cl (entry 7), suggesting that the electron-donating conjugative effect at this position would promote the reaction. We therefore synthesized Co−V and found that it provided the highest isomerization ratio 1:1.4 (entry 12). We also synthesized Co−VI and Co−VII but could not further improve the isomerization reaction with these two catalysts (entries 13 and 14). Using the condition described in entry 12, compound **6** was synthesized in 23% yield. The allylic oxidation of compound **6** using selenium(IV) oxide and *tert*-butylperoxide[21] afforded (+)-schisanwilsonene A (**1**) in 42% yield.

Encouraged by the concise synthesis of (+)-schisanwilsonene A, we decided to synthesize (+)-tormesol using compound **5** as the precursor. (+)-Tormesol is a diterpenoid isolated from *Halimium viscosum*[22] with similar structural features as (+)-schisanwilsonene A. Synthetic efforts toward tormesol have been described. Urones and coworkers reported the racemic synthesis of 10-*epi*-tormesol.[23a] In 2006, Tori and coworkers reported the synthesis of (−)-tormesol through a ring-closing metathesis strategy and confirmed the absolute configuration of (+)-tormesol.[23b] In 2011, Lee and coworkers reported the racemic synthesis of tormesol in 18 steps in 4.1% overall yield.[23c] However, no enantiomeric synthesis of (+)-tormesol has been reported to date.

We began our synthesis of (+)-tormesol by protecting the carbon−carbon double bond of (+)-isodauc-8-en-11-ol by epoxidation (Scheme 1). In the presence of *m*-CPBA, compound **7** was obtained as a single diasteromer in 99% yield.[14b] Compound **7** was then treated with thionyl chloride and triethylamine to afford compound **8**. Compound **8** was subjected to the one-pot dihydroxylation/oxidative cleavage and provided compound **9** in 57% yield over two steps. We tested different conditions for the deoxygenation of compound **9** and found that in the presence of zinc and copper(II) acetate, compound **10** was obtained in 79% yield. The final transformation of compound **10** was achieved using the method reported by Lee and coworkers[23c] to give (+)-tormesol in 62% yield and its separable C_{13}-epimer (dr = 4.6:1). The synthesis takes five steps with 28% overall yield.

Scheme 1. Synthesis of (+)-Tormesol from Compound 5



In summary, we have developed a two-stage approach toward the syntheses of the carotane-type terpenoids (+)-schisanwilsonene A and (+)-tormesol by combining the microbial production of (+)-isodauc-8-en-11-ol and concise chemical transformations. Both syntheses are step- and redox-economical,[24] and the synthesis of (+)-schisanwilsonene A is protective-group-free.[25] We also demonstrated that the cobalt-catalyzed olefin isomerization can be used with internal trisubstituted alkenes as substrates. This work, together with the syntheses of (−)-englerin A and serofendic acid, demonstrated that a two-stage strategy combining synthetic biology and synthetic chemistry can be used to prepare bioactive terpenoids in a more efficient manner. The discovery of new terpene synthases in bacteria and fungi will facilitate

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this strategy, even though the functions of their products in their host organisms remain unclear.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03894.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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