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Synthetic Study of Presilphiperfolan-8-ol: Construction of the Tricyclo[5.3.1.0^{4,11}]undecane Framework Utilizing Intramolecular Aldol Condensation and McMurry Coupling

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The tricyclo[5.3.1.0^{4,11}]undecane framework of presilphiperfolan-8-ol, tricyclic sesquiterpene alcohol was constructed by intramolecular aldol condensation and the McMurry coupling from two types of diketone compounds, which were obtained from (+)-pulegone through a five-step process. This synthetic route does not require the use of any protective groups.

Presilphiperfolan-8-ol (**1**) (Figure 1), a tricyclic sesquiterpene alcohol, was isolated from the California coastal succulent *Eriophyllum staechadifolium* and from *Flourensia heterolepis* by Bohlmann and co-workers in 1981.[1] The relative configuration of the stereogenic centers and the absolute configuration of **1** were determined by Coates and co-workers in 1996.[2] Presilphiperfolan-8-ol (**1**) and other presilphiperfolanols[3] are well known as prebotrydials and considered important biosynthetic precursors to diverse sesquiterpenoids.[1,2,4,5] The main structural feature of presilphiperfolan-8-ol (**1**) is the tricyclo-[5.3.1.0^{4,11}]undecane framework, including a strained *trans*-fused bicyclo[3.3.0]octane moiety. This unprecedented structure and the central biosynthetic role of **1** are of interest to organic chemists. One group has succeeded in the enzymatic formation[5] of presilphiperfolan-8-ol (**1**), but no total synthesis or synthetic study of **1** has been reported. In addition, reports of the asymmetric synthesis of the tricyclo[5.3.1.0^{4,11}]undecane framework are very limited.[6] Therefore, developing a concise route to the tricyclo[5.3.1.0^{4,11}]undecane framework in an optically pure form is needed before the total synthesis of presilphiperfolan-8-ol (**1**) can be accomplished. This report describes the concise synthesis of the tricyclo[5.3.1.0^{4,11}]undecane framework **2** via two paths: intramolecular aldol condensation and the McMurry coupling.

This synthetic strategy for tricyclo[5.3.1.0^{4,11}]undecane framework **2** is outlined in Figure 2. The tricyclic compound **2** could be constructed by intramolecular aldol condensation of diketone **4** followed by reduction of the carbonyl group of resulting enone **3**. Diketone **4** would be obtained from **5** via the regioselective hydroboration–oxidation and oxidation of the resulting alcohol. Bicyclic compound **5** would be synthesized by ring-closing metathesis (RCM) from diene **6**, which could be derived from (+)-pulegone (**7**) using two types of allylation.

The synthesis of diketone **4**, the precursor for intramolecular aldol condensation, is shown in Scheme 1.[7] The 1,4-addition reaction of allylsilane to pulegone (**7**) followed by the isomerization provided the compound **8** in 65% yield with 4:1 diastereoselectivity over two steps.[8] Treatment of **8** with LDA and allyl bromide gave the diene **6** in 75% yield with separable stereoisomers in 5:1 ratio.[9] The RCM[10] of the diene **6** with a second-generation Grubbs catalyst in CH_2Cl_2 under reflux conditions for 2 h gave the bicyclic compound **5** in 83% yield.

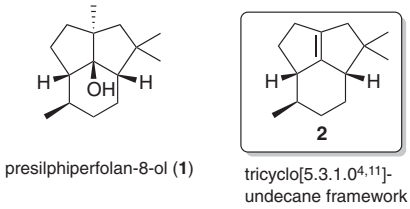


Figure 1. Structure of presilphiperfolan-8-ol (**1**).

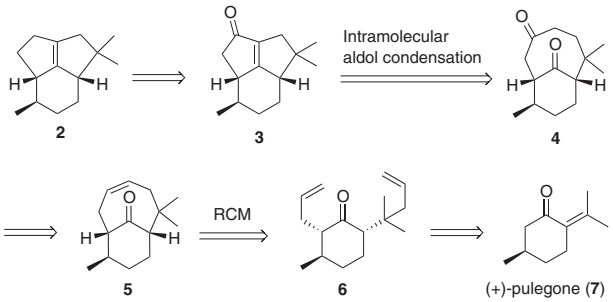
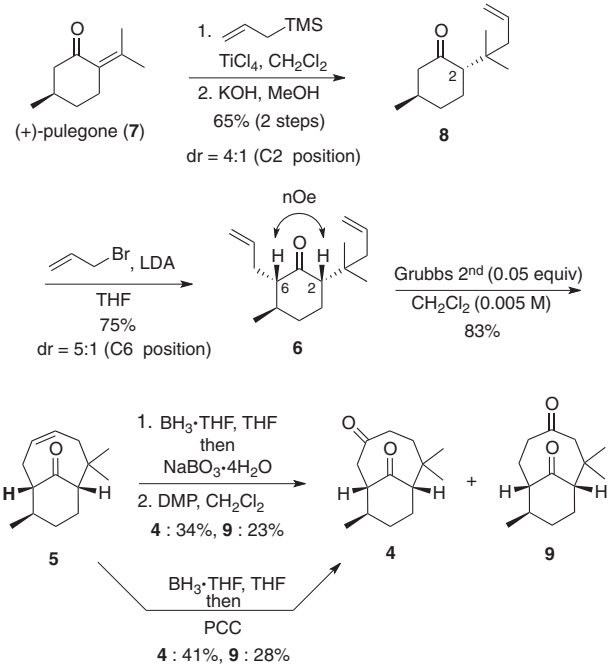


Figure 2. Synthetic strategy toward tricyclo[5.3.1.0^{4,11}]undecane framework **2**.



Scheme 1. Synthesis of diketone **4**.

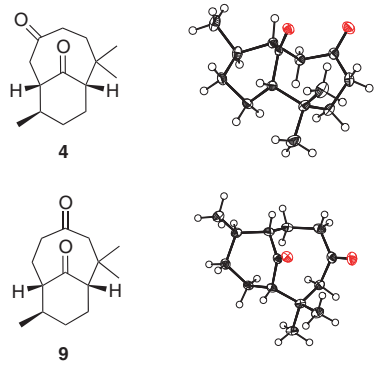
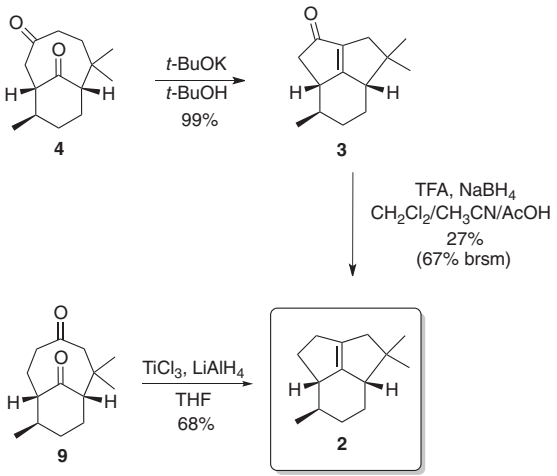


Figure 3. ORTEP drawings of **4** and **9**.



Scheme 2. Synthesis of tricycle[5.3.1.$0^{4,11}$]undecane framework **2**.

Next, the regioselective hydroboration–oxidation of **5** followed by oxidation of the resulting alcohol was attempted. Using BH_3·THF/$NaBO_3$·$4H_2O$ and the Dess–Martin oxidation, the desired diketone **4** was obtained in 34% yield, along with regioisomer **9** in 23% yield. Using PCC as an oxidant[11] after hydroboration of **5** produced diketones **4** and **9** in 41 and 28% yield, respectively. The structures of **4** and **9** were unambiguously confirmed by single-crystal X-ray crystallography[12] (Figure 3). An attempt was made to use bulkier boran reagents (e.g., 9-BBN and catecholborane) to improve the regioselectivity of hydroboration of **5**, but the reactions did not proceed and diketone **4** was not obtained.

Due to the poor regioselectivity of the hydroboration of **5**, diketones **4** and **9** were available. Therefore, the tricyclo-[5.3.1.$0^{4,11}$]undecane framework **2** could be constructed from diketones **4** and **9**: compound **2** could be obtained directly by the intramolecular McMurry coupling of diketone **9**.

The synthesis of tricyclic compound **2** is shown in Scheme 2. The key intramolecular aldol reaction of **4** with *t*-BuOK in *t*-BuOH at room temperature proceeded successfully to provide the tricyclic compound **3** in 99% yield. Conversion of the carbonyl group of **3** to a methylene group in **2** was successful using Gribble's method.[13] Thus, treatment of compound **3** with excess $NaBH_4$ and TFA in CH_2Cl_2, CH_3CN, and AcOH produced the desired tricyclic compound **2** in 27% yield (67% based on recovered starting materials). In addition, the intramolecular McMurry coupling of **9** proceeded successfully using $TiCl_3$/$LiAlH_4$[14] to afford the compound **2** in 68% yield.

In summary, a concise route to the tricyclo[5.3.1.$0^{4,11}$]undecane framework of presilphiperfolan-8-ol (**1**) was developed, utilizing the intramolecular aldol condensation and McMurry coupling as key reactions. This synthetic route does not require the use of any protective groups. Further investigation with the goal of total synthsis of presilphiperfolan-8-ol (**1**) is currently being pursued.

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