Claisen Rearrangement Strategy in Alkenyl Dihydropyran Leading to Total Synthesis of (+)-α-Vetispirene and (−)-Agarospirol

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Total synthesis of (+)-α-vetispirene and (−)-agarospirol based on a Claisen rearrangement has been achieved. This is the first example of a Claisen rearrangement in an enantio-enriched alkenyl bicyclic dihydropyran system with perfect asymmetric transmission.

Spiro[4.5]decane scaffolds are embedded in many naturally occurring terpenes, including candidates for medicines, perfumes, and agricultural chemicals (Figure 1).[1] Recently, we have reported an efficient approach to spiro[4.5]decanes based on a Claisen rearrangement.[2–5] Thus, alkenyl bicyclic dihydropyran can be converted to a multi-functionalized spiro[4.5]decane in a highly stereoselective manner. This protocol is applicable to the synthesis of racemic vetivane sesquiterpenes, as we reported.[3b] In this publication, we describe the total synthesis of (+)-α-vetispirene (**1**)[6] and (−)-agarospirol (**2**)[7] based on a Claisen rearrangement strategy.

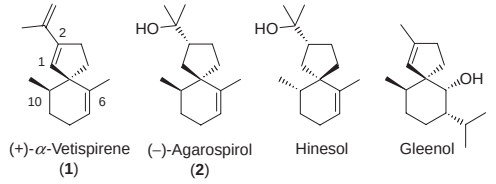
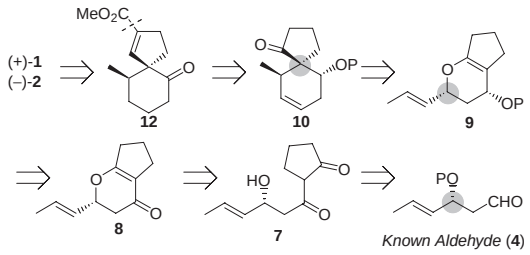
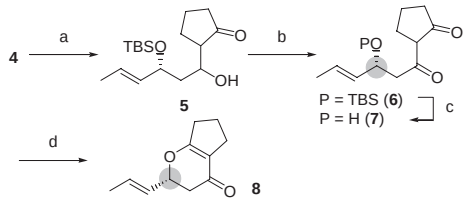


Figure 1. Spiro[4.5]decane frameworks in terpenes.

Retrosynthetic analysis of (+)-α-vetispirene (**1**) and (−)-agarospirol (**2**) is depicted in Scheme 1. (+)-α-Vetispirene (**1**) and (−)-agarospirol (**2**) would be synthesized from a common key intermediate **12**, which in turn would have been derived from spiro[4.5]decane **10** according to our racemic synthesis of vetivane sesquiterpenes including (±)-**1**.[3b] Spiro[4.5]decane **10** could be synthesized from alkenyl bicyclic dihydropyran **9** by a Claisen rearrangement, while dihydropyrone **8**, the precursor of **9**, would be prepared from a corresponding 5-hydroxy-1,3-diketone **7** by means of acid-catalyzed cyclization. The chirality of the allylic alcohol of **7** would be introduced via the enantio-enriched known aldehyde **4**.



Scheme 1. Retrosynthetic analysis of (+)-α-vetispirene (**1**) and (−)-agarospirol (**2**). P = TBS.

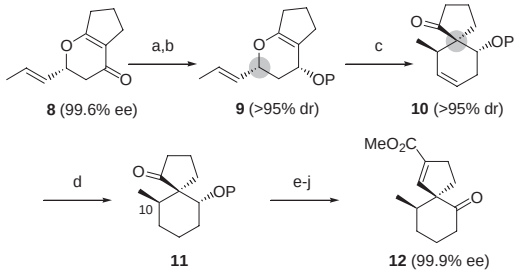


Scheme 2. Reagents and conditions: (a) LDA, cyclopentanone, 95%; (b) TFAA, DMSO, Et_3N, 93%; (c) TBAF, 84%; (d) $TsOH \cdot H_2O$, CH_2Cl_2, rt, 76%, 99.5% ee.

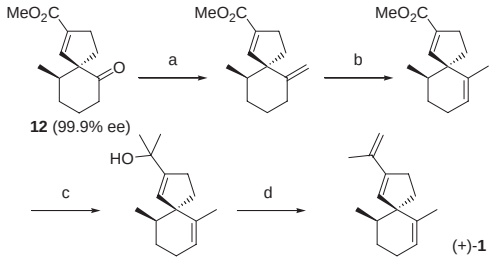
At the outset, for acid-catalyzed cyclization, we synthesized the precursors **6** and **7** as enantio-enriched forms (Scheme 2). Enantio-enriched aldehyde **4** [95% ee, determined by ^1H and ^{19}F NMR analyses of the MTPA ester of (*R*)-**3**] was prepared from a racemate of 1,5-heptadien-4-ol **3** via a four-step sequence involving Sharpless asymmetric epoxidation, according to Paterson's report.[8] Transformation of aldehyde **4** to **6** or **7** was then performed in two or three steps, respectively.

With the cyclization precursors, **6** and **7**, now in hand, acid-catalyzed cyclization was attempted. In the case of the attempted cyclization of **6** with an excess of trifluoroacetic acid (TFA), using the same conditions as previously used in the racemic synthesis, the desired dihydropyrone **8** was obtained in 84% yield. However, its enantiomeric excess was 88.4%. In contrast, hydroxy diketone **7** was treated with a catalytic amount of TsOH to provide **8** in respectably high yield with 99.5% ee, which was determined by chiral HPLC Analysis (Chiralcel OD-H, rt, 254 nm, Hex/*i*PrOH = 99/1, flow rate: 0.4 mL/min).

Synthesis of a key intermediate **12** was performed in the same manner as described in our previous publication,[3b] except for the hydrogenation step (Scheme 3). A Claisen rearrangement of enantio-enriched dihydropyran **9**, derived from **8** in two steps, was conducted in a sealed tube at 250 °C to afford the desired spiro[4.5]decane **10** ($[\alpha]_D^{24}$ −179.5) in 73% yield as a single di-



Scheme 3. Reagents and conditions: (a) $LiAlH_4$; (b) TBSCl, imidazole, 82% (2 steps); (c) sealed tube, toluene, 250 °C, 73%; (d) H_2 (1 atm), $[Ir(cod)(Pcy_3)py]PF_6$, CH_2Cl_2, 96%; (e) $(MeO)_2CO$, KH, 80%; (f) $NaBH_4$, 78%; (g) MsCl, pyridine; (h) DBU, 98% (2 steps); (i) HF, 98%; (j) Dess–Martin periodinane, 95%. P = TBS.



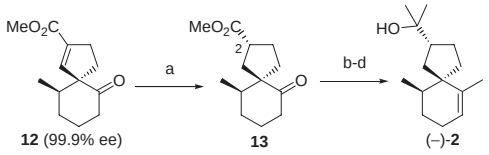
Scheme 4. Reagents and conditions: (a) CH_2I_2, $TiCl_4$, Zn, 49% (88%: based on the recovered starting material); (b) $TsOH \cdot H_2O$, benzene, Δ; (c) MeLi, Et_2O; (d) CSA, benzene, Δ, 75% (3 steps).

astereomer. While our interest was focused on the enantiomeric excess of **10**, we were unable to determine it by chiral HPLC assay and so we decided to convert **10** to **12**. Hydrogenation of the double bond in **10** with 5% palladium on charcoal was unsatisfactory due to a slight epimerization at the C10 position,[3b] however no epimerization was observed with Crabtree's catalyst.[9] Transformation of ketone **11** to the key intermediate **12** was conducted in a six-step sequence according to the method used for racemic synthesis of vetivanes. Then, the enantiomeric excess of **12** was finally determined as 99.9% ee, which means that the Claisen rearrangement of **9** proceeds with perfect asymmetric transmission. This is the first example of a Claisen rearrangement in enantio-enriched alkenyl bicyclic dihydropyran system.

Next, our attention was turned to the total synthesis of (+)-α-vetispirene (**1**) (Scheme 4). Following the methods for our synthesis of (±)-**1**, the total synthesis of (+)-**1** was achieved in four steps. The ^1H and ^{13}C NMR spectra and the optical rotation of our synthetic (+)-**1** are consistent with the natural ones[6b] {$[\alpha]_D^{23}$ +226 ($c \approx 0.367$, MeOH); Ref. 6a: $[\alpha]_D$ +220 ($c \approx$ 0.04, MeOH)}. This is the first asymmetric total synthesis of (+)-α-vetispirene.

The final task was to synthesize (−)-agarospirol (**2**) (Scheme 5). In order to construct the C2 stereogenic center in **2**, we envisaged that stereoselective hydrogenation of **12** would be controlled by iridium-based catalyst because of its oxophilic nature. Thus, the double bond in **12** was saturated by Crabtree's catalyst[9] to afford the desired ester **13** in 87% yield with >95% diastereomeric ratio. When Pd on charcoal was used as a catalyst, the undesired C2-epimer of **13**, which is a synthetic intermediate of hinesol, was mainly obtained.[10] After final three-step sequence, total synthesis of (−)-agarospirol (**2**) was accomplished. The ^1H NMR spectrum and the optical rotation of our synthetic (−)-**2** are consistent with the natural ones[7b] {$[\alpha]_D^{20}$ −4.69 (*c* 0.20, $CHCl_3$); Ref. 7a: $[\alpha]_D^{25}$ −5.7 (*c* 28.7, $CHCl_3$)}.

In conclusion, we described the total synthesis of (+)-α-vetispirene and (−)-agarospirol based on a Claisen rearrangement strategy. This is the first example of a Claisen rearrangement in enantio-enriched alkenyl bicyclic dihydropyran system and demonstrating perfect asymmetric transmission. This strategy could be applicable to the asymmetric synthesis of a variety of terpenes based on the spiro[4.5]decane scaffold.



Scheme 5. Reagents and conditions: (a) H_2 (1 atm), [Ir(cod)-(PCy_3)py]PF_6, CH_2Cl_2; (b) CH_2I_2, $TiCl_4$, Zn; (b) $TsOH \cdot H_2O$, benzene, Δ; (c) MeLi, Et_2O 42% (3 steps).

We thank Shin-Etsu Chemical Co., Ltd., for the gift of silicone oil.

The paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

References and Notes

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