Stereocontrolled Total Synthesis of (−)-Gleenol Using Claisen Rearrangement of Sterically Congested Dihydropyran

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A stereocontrolled total synthesis of enantiomerically pure (−)-gleenol using an improved substrate to construct the spiro[4.5]decane through Claisen rearrangement has been achieved. The most striking feature of this synthesis is that the rearrangement of sterically congested dihydropyran, bearing all requisite substituents with proper stereochemistry, afforded the fully functionalized spiro[4.5]decane in a single step.

(−)-Gleenol (**1**) is an axane sesquiterpene which is isolated from *Picea glehni*,[1a] *Picea koraiensis*,[1b] *Criptomeria japonica*,[1c] *Juniperus oxycedrus*,[1d] and the brown alga *Taonia atomaria*[1e] (Figure 1). Its enantiomer (+)-**1** was also found in marine sponge,[1f] and exhibits several biological activities such as termiticidal, antihelmintic, and growth regulation effects on plant seeds.[2] The structure and relative stereochemistry of (−)-**1** were determined by X-ray analysis of the corresponding epoxide,[1a] and Ohira and co-workers established its absolute stereochemistry by total synthesis.[3a]

Because of its structural features as well as its biological importance, the total synthesis of **1** has been reported by several groups.[3] Recently, we reported the stereoselective synthesis of spiro[4.5]decanes based on the Claisen rearrangement of the bicyclic 2-(alkenyl)dihydropyran system,[4,5] and have achieved the total synthesis of (±)-**1**.[3d] In this synthesis, the introduction of the isopropyl group at C7 required several extra steps after the Claisen rearrangement.

In this communication, we wish to report a stereocontrolled total synthesis of enantiomerically pure (−)-**1** using an improved Claisen precursor with the C7 isopropyl group. The most striking feature of this synthesis is that the rearrangement of sterically congested dihydropyran, bearing all requisite substituents with proper stereochemistry, afforded the fully functionalized spiro[4.5]decane in a single step. The results of our research demonstrate the utility of the Claisen rearrangement approach to the synthesis of this structural type.

Retrosynthetic analysis of (−)-**1** is depicted in Scheme 1. (−)-Gleenol (**1**) could be simplified to ketone **A** with four contiguous stereogenic centers. Ketone **A** would be accessible through our Claisen rearrangement methodology. The C5 and C10 stereogenic centers would be stereoselectively established utilizing the Claisen rearrangement of bicyclic 2-(alkenyl)dihydropyran **B**. The stereogenic center C6 could be constructed during the synthesis of **B**, while the two stereogenic centers of C7 and the allylic position (gray carbons in **B**) would be introduced from the (2*R*,3*S*)-aldol **C**. The success of this strategy depends on whether the Claisen rearrangement does proceed in such a sterically congested dihydropyran as **B** through a boat-like transition state **D**.[6]

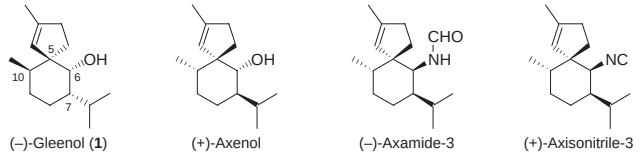
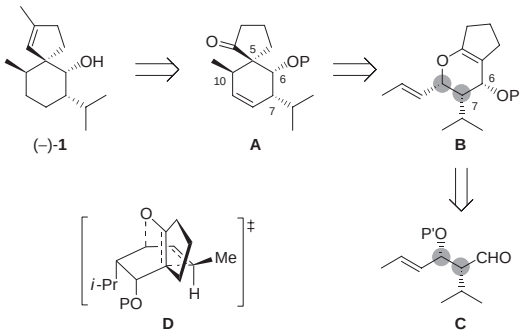


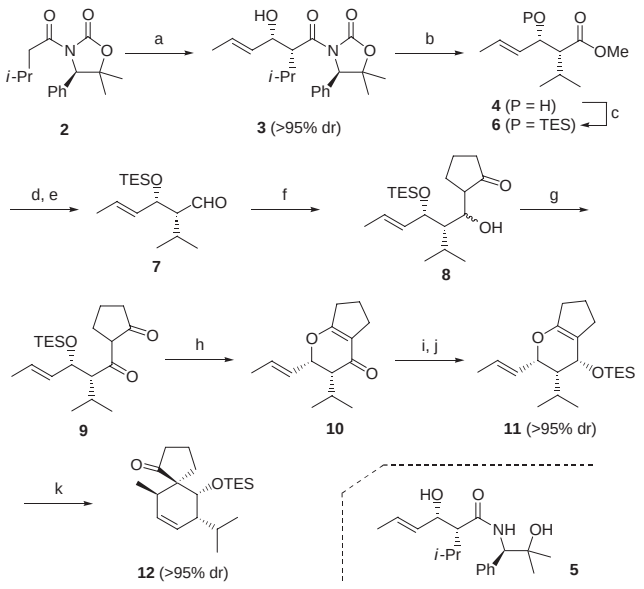
Figure 1. Structures of axane sesquiterpenes.



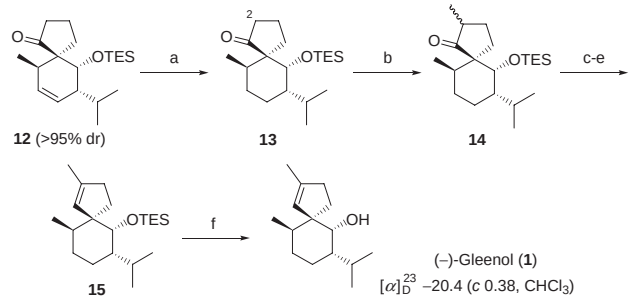
Scheme 1. Retrosynthetic analysis (P and P′: protective group).

The synthesis of alkenyl dihydropyran **11**, a substrate for the key rearrangement, commenced with the isovaleric acid derivative **2** bearing SuperQuat chiral auxiliary,[7] which was derived from D-phenylglycine (Scheme 2). According to Evans' protocol,[8] treatment of a boron enolate, generated from **2**, with crotonaldehyde afforded the desired (2*R*,3*S*)-aldol adduct **3** in 56% yield (80% yield based on recovered **2**) with excellent syn selectivity (>95% dr).[9] Removal of the chiral auxiliary from **3** was achieved by using NaOMe in methanol to provide the corresponding methyl ester **4** in 71% yield, along with 17% of the ring-opened product **5**. Protection of the hydroxy group on **4** as a TES ether, DIBAL reduction of the resulting **6**, followed by oxidation utilizing the Dess–Martin periodinane[10] provided the aldehyde **7**. We performed the remaining steps in the synthesis of **11** according to our previously developed procedure[4] with a slight modification. Treatment of aldehyde **7** with the lithium enolate derived from cyclopentanone afforded the corresponding aldol **8**. After the Swern oxidation of **8** using TFAA/DMSO,[11] exposure of the resulting 1,3-diketone **9** to 0.01 M HCl in ethanol led to dihydropyrone **10** in 90% yield without epimerization at the stereogenic centers. Diastereoselective 1,2-reduction of **10** with $LiAlH_4$ in Et_2O, followed by protection by TES group, furnished the desired alkenyl dihydropyran **11** as a single diastereomer (>95% dr). The relative stereochemistry was determined by NOE enhancement. We were delighted to observe that the key Claisen rearrangement of **11** in triglyme afforded the desired spiro[4.5]decane **12** in 75% yield as a single diastereomer.[12] To the best of our knowledge, this is the first example of the Claisen rearrangement of such a sterically congested dihydropyran to spiro[4.5]decane.

Completion of the total synthesis of (−)-**1** was accomplish-



Scheme 2. Stereocontrolled synthesis of spiro[4.5]decane **12**. Reagents and conditions: a) crotonaldehyde, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, $-78 \rightarrow 0\,^{\circ}C$, 56% (brsm 80%); b) NaOMe, MeOH, rt, 71% of **4**, 17% of **5**, c) TESCl, imidazole, DMAP, DMF, rt; d) DIBAL, CH_2Cl_2, $-78\,^{\circ}C$, 75% (two steps); e) Dess–Martin periodinane, CH_2Cl_2, rt; f) LDA, cyclopentanone, THF, $-78\,^{\circ}C$, 82% (two steps); g) TFAA, DMSO, Et_3N, CH_2Cl_2, $-78\,^{\circ}C$, 67% (brsm 79%); h) 0.01 M HCl, EtOH, rt, 90%; i) $LiAlH_4$, Et_2O, $0\,^{\circ}C$; j) TESCl, imidazole, DMAP, DMF, rt, 42% (two steps); k) triglyme, $250\,^{\circ}C$, 75%.



Scheme 3. Completion of the total synthesis of (−)-**1**. Reagents and conditions: a) H_2 (1 atm), $[Ir(cod)(PCy_3)py]PF_6$, CH_2Cl_2, rt; b) LDA, MeI, THF, $-78\,^{\circ}C$, 88% (two steps); c) $LiAlH_4$, Et_2O, $-78\,^{\circ}C$; d) MsCl, pyridine, $0\,^{\circ}C$; e) DBU, toluene, $150\,^{\circ}C$; f) TBAF, THF, rt, 78% (four steps).

ed from the fully functionalized key intermediate **12** through conventional transformations (Scheme 3). Reduction of the double bond in ketone **12** under 1 atm of hydrogen gas in the presence of Crabtree's catalyst,[13] followed by methylation at C2, led to ketone **14** as a mixture of diastereomers in 88% yield for the two steps. After reduction of the carbonyl group in **14** with $LiAlH_4$, the hydroxyl group was mesylated and subjected to elimination with DBU at $150\,^{\circ}C$ to provide the desired alkene **15**. Finally, removal of the TES group of **15** with tetra-*n*-butylammonium fluoride in THF produced gleenol (**1**) in 78% yield from **14**.

Chiral HPLC analysis revealed that synthetic **1** is in enantiomerically pure form (99.8% ee; CHIRALCEL OD-H column, hexane/2-propanol = 100:1, flow rate = 0.50 mL/min, detection 210-nm light, $30\,^{\circ}C$). The ^1H and ^{13}C NMR spectra and a specific rotation of our synthetic **1** are consistent with those of the natural ones[1d] {$[\alpha]_D^{23}$ −20.4 (*c* 0.38, $CHCl_3$); Ref. 1d: $[\alpha]_D^{20}$ −15.02 (*c* 0.5, $CHCl_3$); Ref. 3a: $[\alpha]_D^{22}$ −17 (*c* 0.50, $CHCl_3$)}.

In conclusion, we have achieved a stereocontrolled total synthesis of (−)-gleenol (**1**), demonstrating the Claisen rearrangement of an alkenyl dihydropyran in constructing the functionalized spiro[4.5]decane scaffold. We believe that the chemistry described herein would be useful for the preparation of a variety of axane sesquiterpenes.

References and Notes

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