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Efficient and enantioselective total syntheses of heliannuols A and K

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ABSTRACT

The second-generation enantioselective synthesis of heliannuol A and the first enantioselective total synthesis of heliannuol K (via two routes) have both been accomplished efficiently; (heliannuol A, nine steps and 25% yield; heliannuol K, seven steps and 47% yield). Highlights of our synthetic strategy include a substrate-controlled chirality transfer in the Lewis acid mediated Claisen rearrangement of the allyl aryl ether for the key construction of a tertiary stereogenic center at the benzylic position followed by, for heliannuol A, ring-closing metathesis, diastereoselective epoxidation, and regioselective cleavage of the epoxide; and for heliannuol K, ring-closing metathesis and conjugate reduction of the eight-membered enone.

1. Introduction

Heliannuol A (**1**),[1] the first member of a class of bioactive sesquiterpenes, and heliannuol K (**2**)[2] were isolated from the moderately polar bioactive fractions of the fresh leaf aqueous extracts of the cultivar *Helianthus annuus* L. var. SH-222 in 1993 and in 1999, respectively, by Macías et al. These natural products have been reported to exhibit significant allelopathic activity against several dicotyledon (*Lactuca sativa* and *Lepidium sativum*) and monocotyledon species (*Hordeum vulgare* and *Triticum aestivum*) at concentrations of 10^{-4}–10^{-9} M.[3] The structure of **1**, including the relative stereochemistry, was determined by single crystal X-ray diffraction analysis. This intriguing compound contains an aryl ring fused to the eight-membered oxygen heterocycle with two tertiary stereogenic centers at the C7 and C10 positions. Its absolute structure was established to be (7*R*,10*S*) by our enantioselective total synthesis of the unnatural enantiomer of (+)-heliannuol A,[4a] while the structure of heliannuol K (**2**) was elucidated mainly by ^{1}H NMR and found to have the same carbon framework as heliannuol A except for the presence of a C10 carbonyl function. Although the absolute stereochemistry at C7 has never been established, it can be deduced to be *R* based on the biogenetic parallelism with heliannuol A. Because of the interesting structural features and phytotoxic properties of these compounds, several reports on the total synthesis of the heliannuols A (**1**) and K (**2**) have been published.[5] During the course of our studies directed toward the enantioselective synthesis of helianane-type terpenoids with allelopathic activity,[6] we reported the first enantioselective total synthesis of the natural enantiomer (−)-heliannuol A (**1**),[4b] which was completed in seventeen steps from 2,5-dimethoxy-4-methyliodobenzene with an overall yield of 5%. The obvious challenge was to improve both the low yield and the many reaction steps. Herein we describe the efficient and enantioselective total syntheses of heliannuols A (**1**) and K (**2**) (Fig. 1).

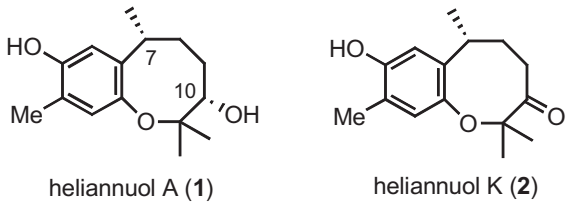

Fig. 1. Structures of heliannuols A and K.

2. Results and discussion

2.1. The second-generation synthesis of (−)-heliannuol A (1) and the first enantioselective synthesis of (−)-heliannuol K (2)

Our retrosynthetic analysis of **1** is shown in Scheme 1. For the synthesis of **1**, we chose the dihydrobenzoxocine **3**[7] with a stereogenic center at C7 as the key compound, because it has been converted efficiently to **1** by sequential diastereoselective epoxidation, regioselective cleavage of the epoxide, and deprotection of the phenolic hydroxyl function in good overall yield.[4b] The MOM protected heliannuol A, the penultimate intermediate of **1**, would be transformed to heliannuol K (**2**) by a simple two-step sequence; oxidation followed by deprotection. The eight-membered heterocycle fused to the aryl ring can be assembled by ring-closing

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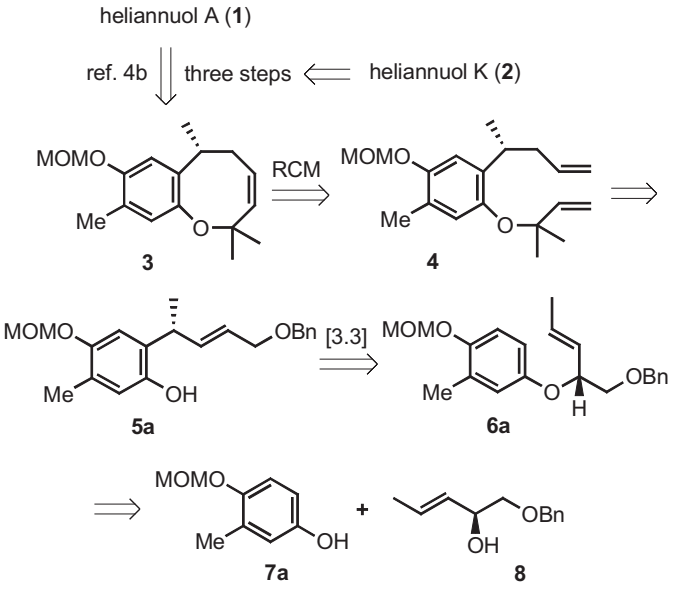
metathesis of the diene **4**, which would be prepared from the phenol **5a** via Pd-catalyzed dimethylallyl etherification.[4b,8] For the key construction of the tertiary stereogenic center at the benzylic position, we planned to use a substrate-controlled chirality transfer in the Claisen rearrangement[9,10] of the allyl aryl ether **6a** prepared from the phenol **7a** and *S*-(*E*)-1-(benzyloxy)pent-3-en-2-ol (**8**)[11] by the Mitsunobu coupling[12] (Scheme 1).



Scheme 1. Retrosynthetic analysis.

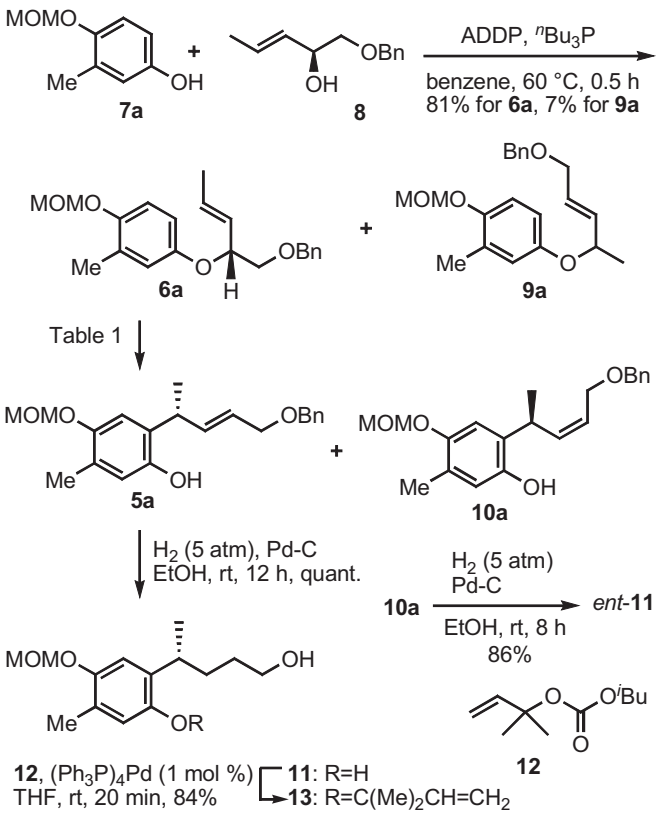
The Mitsunobu reaction between 4-(methoxymethoxy)-3-methylphenol (**7a**), prepared from 3-hydroxy-4-methylacetophenone in two steps, and the allylic alcohol **8**, derived from *S*-(+)-benzyl glycidyl ether in two steps, in the presence of 1,1-(azodicarbonyl)dipiperidine (ADDP)[13] and $^{n}Bu_3P$ provided a chromatographically separable mixture of the requisite ether **6a** (>99% ee; by HPLC analysis using a Chiralcel OD column) and the regioisomer **9a**, which was derived via the S_N2' process, in 81% and 7% yield, respectively. The key Claisen rearrangement of **6a** was examined and the results are shown in Table 1. Treatment of

Table 1
Claisen rearrangement of **6a**

Entry	Conditions	Yield, %	(% ee)[a]
		5a	**10a**
1	$Eu(fod)_3$ (8 mol %) $ClCH_2CH_2Cl$, 90 °C, 24 h	92 (90)	7
2	Et_2AlCl (1.5 equiv), hexane 0 °C, 4 h	27 (>99)	5
3	Me_3Al (3 equiv), hexane rt, 0.5 h	85 (>99)	4

[a] HPLC (Chiralcel AD column).

a solution of **6a** in dichloroethane with 8 mol % of $Eu(fod)_3$[9d] at 90 °C for 24 h gave a separable mixture of *R*-**5a** and the *Z*-isomer **10a** with the *S* configuration in 92% and 7% yield, respectively. However, the enantiomeric excess of **5a** was 90% (determined by HPLC analysis using a Chiralcel AD column) (entry 1). When the reaction was conducted with 1.5 equiv of Et_2AlCl in hexane at 0 °C for 4 h, the enantiomerically pure **5a** was obtained in only 27% yield along with 5% of **10a** (entry 2). The optimized reaction conditions call for 3 equiv of Me_3Al[14] in hexane at room temperature for 0.5 h; the requisite **5a** was obtained in 85% yield (>99% ee), together with **10a** (4%) (entry 3). On exposure of **5a** to hydrogenation conditions, the phenolic alcohol **11** {$[\alpha]_D^{27}$ −17.3 (*c* 2.65, $CHCl_3$)} was obtained quantitatively. As for the absolute configuration of the stereogenic center in **10a**, it was determined to be *S* by hydrogenation providing *ent*-**11** {$[\alpha]_D^{27}$ +18.0 (*c* 1.48, $CHCl_3$)} in 86% yield. Treatment of **11** with the mixed carbonate **12** in the presence of catalytic $(Ph_3P)_4Pd$ (1 mol %)[8] provided the alkenyl alcohol **13** in 84% yield (Scheme 2).



Scheme 2. Preparation of **13**.

The alcohol **13** was exposed to the dehydration protocol of Nishizawa–Grieco[15] to give the diene **4** (R=MOM), which was identical with the authentic material prepared previously, in 76% yield for the two steps. It was then treated with the Grubbs' second-generation catalyst **14** (0.5 mol %)[16] in refluxing methylene chloride to give the dihydrobenzoxocine **3** in 93% yield. Attempts at a substrate-controlled diastereoselective epoxidation of **3** using *m*CPBA provided a lower yield (73%) of the product **15**. However reaction of **3** with methyl(trifluoromethyl)dioxirane[17] generated in situ from methyl trifluoromethyl ketone and Oxone® in the presence of $Na_2{\cdot}EDTA{\cdot}2H_2O$ and sodium hydrogen carbonate in acetonitrile provided only the epoxide **15** in 83% yield. The stereochemistry was confirmed by the observation of a distinct NOE correlation between the Ha (δ 3.11) and Hb (δ 2.55) protons. $LiAlH_4$ reduction of the epoxide occurred at the sterically less congested carbon (C9) regioselectively to give the alcohol **16** in 91% yield as a single product. Finally, acidic hydrolysis of the MOM ether produced heliannuol A (**1**), whose spectroscopic (^1H and ^{13}C NMR) properties as well as optical rotation, {$[\alpha]_D^{26}$ −78.0 (*c* 2.4, MeOH) {lit.[1a] $[\alpha]_D$ −55.4 (*c* 0.3, MeOH)}, were identical with those of the natural product. Thus, the second-generation enantioselective total synthesis of heliannuol A (**1**) has been accomplished in a longest linear sequence of nine steps in 25% yield from the phenol **7a**. For the synthesis of heliannuol K (**2**), the penultimate intermediate **16** was oxidized with Dess–Martin periodinane to give the ketone **17**, which was exposed to the acidic hydrolysis conditions producing **2** in 99% yield for the two steps. The spectroscopic properties (^1H and