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Enantiocontrolled access to the ionone type bisnorsesquiterpenes. Total syntheses of 3-oxo-α-ionol and related natural products

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ABSTRACT

The enantiocontrolled total syntheses of three ionone type bisnorsesquiterpenes have been accomplished employing a highly diastereoselective intramolecular Heck reaction as the key step.

(+)-3-Oxo-α-ionol (**1**)[1] and (−)-3-hydroxy-β-ionone (**2**)[1d,2] were isolated from various tobacco leaves as neutral aroma constituents and from Kudzu oil (*Pueravia lobata* Ohwi). In 2010, these representatives of ionone type bisnorsesquiterpenes were isolated by Fujii and co-workers from aqueous methanol extracts of rattail fescue (*Vulpia myuros*) and identified as growth inhibitors against lettuce, alfalfa, timothy, *Digitaria sanguinalis*, and *Lolium multiflorum*, that is, allelochemicals.[3] However, in 1998, it had already been reported that 3-oxo-α-ionol (**1**), isolated from *Helianthus annus* (sunflower) var. SH-222® and VYP®, was shown to be a potential allelochemical.[4] Although several synthetic reports on these ionone type natural products have been published,[5] very few strategies toward their efficient and enantiocontrolled total synthesis have been reported. During the course of our synthetic studies on natural products having allelopathic activity, we wanted to develop an efficient and enantioselective synthetic method focused on the ionone type bisnorsesquiterpenes with a stereogenic center at the C6 position. In our previous paper, we reported a highly diastereoselective construction of the chiral building blocks with an allylic quaternary carbon stereogenic center by employing a 1,4-chirality transfer *via* an intramolecular Heck reaction.[6] It was thought that this methodology could be applied to construct the tertiary C6 stereogenic center[7] of the natural products. We report here the enantiocontrolled total syntheses of three natural products, 3-oxo-α-ionol (**1**),[8] 3,9-dihydroxy-4,7-megastigmadiene (**3**),[9] and 3-hydroxy-α-ionone (**4**),[10] from a common precursor **5**, which was efficiently prepared using a highly diastereoselective intramolecular Heck cyclization of the acyclic precursor **6** as the key reaction step (Fig. 1).

Our retrosynthetic analysis is shown in Scheme 1. We envisaged the target natural products being synthesized from the cyclohexenol derivative **5**, with three stereogenic centers (at C3, C6 and C9) and the skipped diene functionality, as a common intermediate. The key compound **5** would be constructed by employing an intramolecular Heck reaction of **6**. The newly generated stereogenic center at C6 would be created diastereoselectively by a 1,4-chirality transfer of the C3 stereogenic center. The substrate **6** would in turn be prepared from the aldehyde **7**, which could be derived from the readily available PMB-protected (*R*)-3-hydroxybutanal **8**[11] (Scheme 1).

Treatment of **8** with (2-methylprop-1-enyl)magnesium bromide provided the alcohol **9**, as a mixture of diastereoisomers, which was converted into the vinyl ether **10**. The methylaluminum bis(4-bromo-2,6-di-*tert*-butyl-4-methylphenoxide) (MABR)-mediated Claisen rearrangement[12] proceeded at −78 °C for 15 min to afford the aldehyde **7** in a 72% yield. Addition of prop-1-ynyllithium, prepared in situ from 1-bromoprop-1-ene and *n*-BuLi,[13] to **7** provided compound **11**, as a 1:1 mixture of diastereoisomers, which was then oxidized with Dess–Martin periodinane to give the ynone **12** in good yield (Scheme 2).

To obtain the optically pure acetylenic alcohol **15**, we initially tried to separate a mixture of diastereoisomers of **11**. After numerous attempts, the method using (*R*)-5-allyl-2-oxabicyclo[3.3.0]oct-8-ene (ALBO) (**13**)[14] proved to be the best. Treatment of **11** with **13** in the presence of a catalytic amount of PPTS provided a

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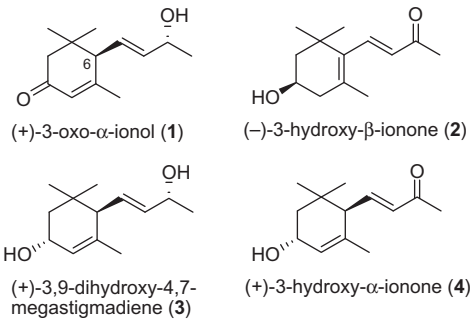
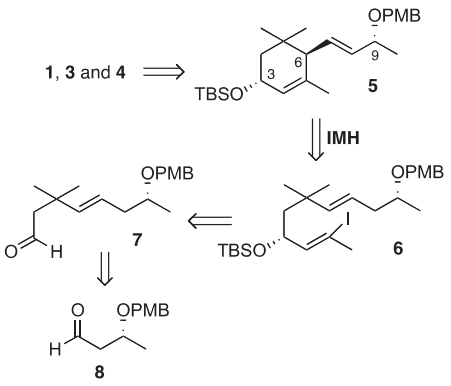
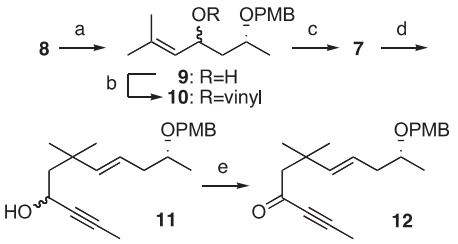


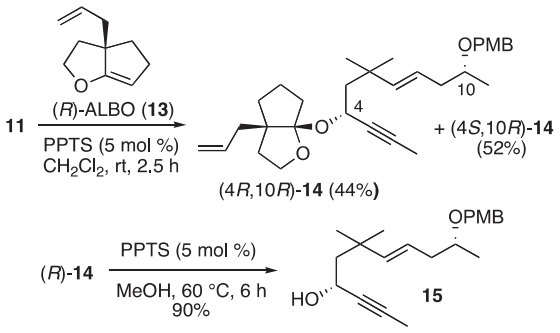
Figure 1. Ionone type bisnorsesquiterpenes.



Scheme 1. Retrosynthetic analysis.

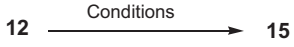


Scheme 2. Synthesis of **11** and **12**. Reagents and conditions: (a) $(Me)_2C{=}CHMgBr$, THF, 0 °C, 0.5 h, 86%; (b) $Hg(OAc)_2$ (5 mol %), n-butyl vinyl ether, reflux, 36 h, 98%; (c) MABR, CH_2Cl_2, −78 °C, 15 min, 72%; (d) 1-bromoprop-1-ene, ^{n}BuLi, THF, −78 °C, 2 h, 89%; (e) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 1 h, 98%.



Scheme 3. Separation of diastereoisomers by (*R*)-ALBO.

Table 1
Asymmetric reduction of **12**



Entry	Conditions	Yield (%)	*dr*
1	(*R*)-Me-CBS (20 mol %), BH_3·THF (2 equiv), THF −20 °C, 3 h	93	7:1
2	(*R*)-Me-CBS (100 mol %), BH_3·THF (2 equiv), THF −40 °C, 6 h	68	33:1[a]

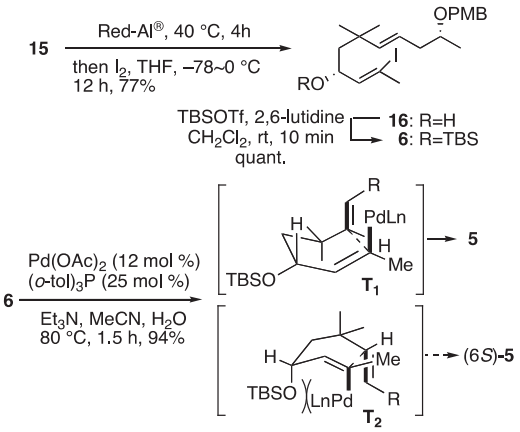
[a] Determined by HPLC.

chromatographically separable mixture of (4*R*,10*R*)-**14** and (4*S*,10*R*)-**14** in 44% and 52% yields, respectively. On exposure of (4*R*,10*R*)-**14** to PPTS and methanol, the requisite alcohol **15** was obtained in a 90% yield in optically pure form. The absolute configuration at the future C3 was confirmed by the modified Mosher method[15] (Scheme 3).

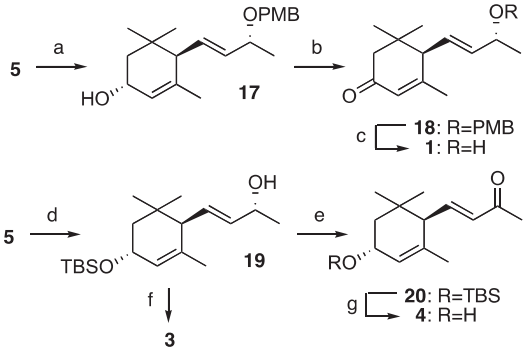
Alternatively, to obtain a more efficient synthesis of **14**, asymmetric reduction of the acetylenic ketone **12** was attempted using various reducing agents (e.g., (*R*)-Binal-H,[16] (*R*)-Alpine-Borane®,[17] (−)-DIP-Chloride™,[18] etc.). However, none of the desired product was obtained, only the recovered ketone **12**. In the end, it was found that reduction, using Me-CBS/BH_3·THF,[19] was the best choice. The results are shown in Table 1. Treatment of a solution of **12** in THF with (*R*)-Me-CBS (20 mol %) and BH_3·THF (2 equiv) at −20 °C for 3 h provided **15** in a 93% yield as a 7:1 mixture of diastereoisomers. When the reaction was performed at a lower temperature (−40 °C), a longer reaction time (6 h) was required to give **15** very diastereoselectively, albeit in a 68% yield (Table 1).

The acetylenic alcohol thus prepared was sequentially treated with Red-Al® and iodine in one pot to provide the *Z*-vinyl iodide **16**, the secondary alcohol moiety of which was protected as the TBS ether to provide **6** in a 77% yield for the two steps. With the requisite substrate **6** in hand, we then examined the key intramolecular Heck reaction. On exposure of **6** to $Pd(OAc)_2$ (12 mol %), (*o*-tol)$_3$P (25 mol %) and triethylamine in aqueous acetonitrile at 80 °C, the desired cyclized product **5** was obtained in a 94% yield as a single product.[20] The diastereoselection attained in the cyclization step from either the boat-like transition state T_1 or T_2, which would collapse to form the undesired (6*S*)-**5**, can be rationalized as a consequence of the allylic strain between the two transition states ($T_1 > T_2$). The structure of **5** was deduced from the proposed mechanism and the confirmation was made by its eventual conversion into the natural products (vide infra, Schemes 4 and 5).

Desilylation of **5** using HF·pyridine provided the allyl alcohol **17**, which was oxidized with TPAP/NMO to give enone **18**. Finally, the



Scheme 4. Intramolecular Heck reaction of **6**.



Scheme 5. Synthesis of **1**, **3** and **4**. Reagents and conditions: (a) HF-pyridine, THF/pyridine = 4/1, 40 °C, 3 h, 87%; (b) TPAP, NMO, CH_2Cl_2, 0 °C, 1 h, 85%; (c) TFA, CH_2Cl_2, rt, 1 h, 74%; (d) DDQ, CH_2Cl_2/phosphate buffer (pH 7.0) = 10/1, 0 °C, 1.5 h, quant.; (e) MnO_2, CH_2Cl_2, 40 °C, 24 h, 87%; (f) HF·pyridine, THF/pyridine = 4/1, 40 °C, 4 h, 77%; (g)HF pyridine, THF/pyridine=4/1, 40 °C, 5 h, quant.

PMB ether was cleaved with trifluoroacetic acid producing 3-oxo-α-ionol (**1**), {$[\alpha]_D^{29}$ +280 (*c* 0.70, $CHCl_3$); lit.[1e] $[\alpha]_D$ +269 (*c* 1.29, $CHCl_3$)}, whose spectroscopic properties matched those reported for the natural product. On the other hand, selective deprotection of the PMB ether of **5** with DDQ provided the allyl alcohol **19**, which was desilylated to give 3,9-dihydroxy-4,7-megastigmadiene (**3**), {$[\alpha]_D^{31}$ +182 (*c* 0.62, $CHCl_3$); lit.[1e] $[\alpha]_D$ +197 (*c* 1.54, $CHCl_3$)}. Sequential oxidation and desilylation of **19** produced 3-hydroxy-α-ionone (**4**), {$[\alpha]_D^{31}$ +243 (*c* 0.44, dioxane); lit.[10] $[\alpha]_D^{25}$ +302 (*c* 1.00, dioxane)}. The spectral properties of the synthetic **3** and **4** were identical with those for the natural products[21] (Scheme 5).

In summary, we have completed the first enantiocontrolled total synthesis of the ionone type bisnorsesquiterpene (+)-3-oxo-α-ionol (**1**) with a longest linear sequence of 12 steps and an overall yield of 8.5%. In addition, the first total synthesis of (+)-3,9-dihydroxy-4,7-megastigmadiene (**3**) and the synthesis of (+)-3-hydroxy-α-ionone (**4**) have been accomplished from an optically pure common precursor **5**, which was synthesized by employing an intramolecular Heck reaction as the key step in a highly diastereoselective fashion. Since the synthetic route developed here is efficient and adaptable, our synthetic studies may contribute not only to the synthesis of other inone type natural products but also to the assembly of a library of ionone type compounds for the development of new types of environmentally benign agricultural chemicals.

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20. Attempted Heck reaction of the substrate **16** possessing the unprotected secondary alcohol moiety resulted in the formation of the cyclized product in 55% yield as a 1:1 mixture of diastereoisomers.
21. The homogeneity of **3** and **4** was firmly established through spectroscopic analyses, particularly by the ^{13}C NMR.