CHEMISTRY LETTERS, pp. 791-794, 1990.

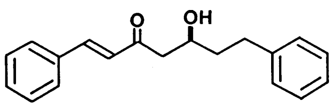
# An Expedient Synthesis of Natural Diarylheptanoids Using the Organoselenium-mediated Reduction of Epoxy Ketone

Masaaki MIYASHITA, Masahide HOSHINO, and Akira YOSHIKOSHI*
Chemical Research Institute of Non-Aqueous Solutions,
Tohoku University, Aoba-ku, Sendai 980

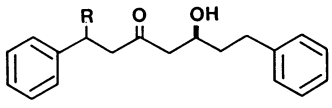
The total synthesis of diarylheptanoids isolated from the male flowers of Alnus sieboldiana, yashabushiketol, yashabushiketodiol A, yashabushiketodiol B, and yashabushitriol, has been achieved in short steps by employing the organoselenium-mediated reduction of epoxy ketone as key steps.

We have recently reported an efficient method for the reduction of α, β-epoxy ketones[1)] and α,β-epoxy esters[2)] to β-hydroxy carbonyl compounds (aldols) using an organoselenium reagent $Na^+[PhSeB(OEt)_3]^-$,[3)] which is readily prepared by reduction of diphenyl diselenide with $NaBH_4$ in ethanol.[3,4)] This method has also been demonstrated to be potentially useful for the synthesis of natural products having polyfunctional groups.[5)]

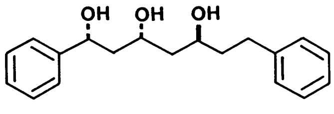
We describe herein the short step synthesis of yashabushiketol (**1**), yashabushiketodiol A (**2**), yashabushiketodiol B (**3**), and yashabushitriol (**4**) using the above organoselenium-mediated reduction as key steps. These diarylheptanoids have been isolated from the male flowers of Alnus sieboldiana, which is used as an erosion-control plant.[6)]



**1** Yashabushiketol

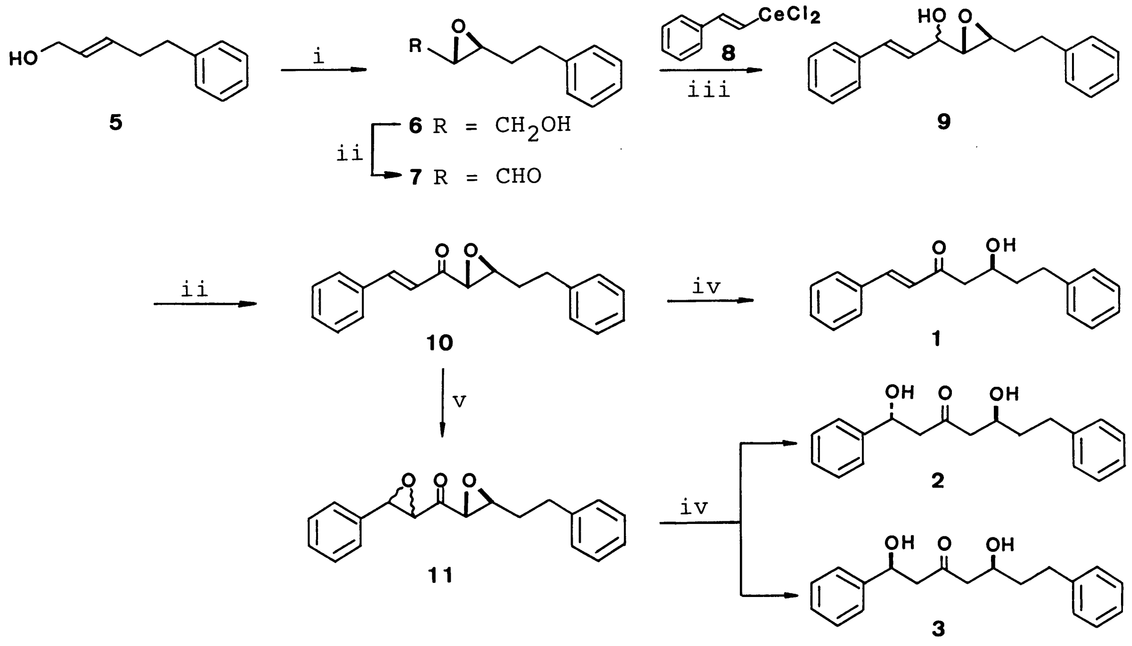


**2** R=α-OH
Yashabushiketodiol A
**3** R=β-OH
Yashabushiketodiol B



**4** Yashabushitriol

5-Phenyl-2-penten-1-ol (**5**),7) starting material of the present synthesis, was converted to (2S,3S)-epoxy alcohol **6** (94% ee)8) in 96% yield via the Katsuki-Sharpless asymmetric epoxidation9) with L(+)-diethyl tartrate. The Swern oxidation10) of **6** afforded epoxy aldehyde **7** in 90% yield. The coupling reaction of the aldehyde **7** and β-styrylcerium reagent **8**, prepared from β-styryllithium11) with anhydrous cerium (III) chloride12) at -120 °C in the Trapp-solvent (THF/$Et_2O$/pentane 4:1:1),13) was carried out at -120 to -70 °C to give an adduct **9** as a diastereomeric mixture (1 : 1) in 58% yield (70% based on the recovered starting material).14) Subsequent Swern oxidation of **9** afforded epoxy enone **10** (mp 80-80.5 °C, $[\alpha]_D^{22}$ -55.4° (c, 1.65, $CHCl_3$)) in 74% yield.



Scheme 1. Reagents and Conditions: i, L(+)-DET, TBHP, $Ti(i\text{-}PrO)_4$, $CH_2Cl_2$, -23 °C; ii, $(COCl)_2$, DMSO, $CH_2Cl_2$, -60 °C, then $NEt_3$; iii, **8**, THF/$Et_2O$/ pentane 4:1:1, -120 to -70 °C; iv, $Na^+[PhSeB(OEt)_3]^-$, EtOH; v, $H_2O_2$, $Bu_4NF$, DMSO.

The key step in this synthesis, the organoselenium-mediated reduction of **10**, was performed with 3 equiv. of the reagent $Na^+[PhSeB(OEt)_3]^-$ in ethanol (room temp, 15 min),1,3) and as expected,15) the chemoselective reduction of the epoxy ketone moiety in **10** was achieved resulting in formation of **1** in 81% yield. The product (mp 81.5-82 °C, $[\alpha]_D^{22}$+56.5° (c, 0.31, $CHCl_3$) was identified as yashabushiketol (**1**) by comparison of its IR, $^1H$ NMR, and MS spectra with those of the authentic compound.16)

On the other hand, epoxidation of the enone **10** with 30% $H_2O_2$ (3 equiv.)/$Bu_4NF$ (1.5 equiv.) in DMSO (room temp, 3 h)17) afforded a 1 : 1 diastereomeric mixture of bis-epoxy ketone **11** in 75% yield, which was then subjected to the organoselenium-mediated reduction without separation. Thus treatment of **11** with 5 equiv. of the selenium reagent $Na^+[PhSeB(OEt)_3]^-$ in ethanol (room temp, 10 min) resulted in formation of **2** (42%) and **3** (41%) as a separable mixture. Both synthetic keto diols **2** (mp 60-60.5 °C (benzene-hexane), $[\alpha]_D^{22}$+63.6° (c, 0.53, $CHCl_3$)) and **3** (mp 59 °C (benzene-hexane), $[\alpha]_D^{22}$-29.3° (c, 0.49, $CHCl_3$)) were proved to be identical with natural yashabushiketodiol A (**2**) (mp 62-63 °C, $[\alpha]_D$ +57.5° ($CHCl_3$)) and yashabushiketodiol B (**3**) (mp 60-61 °C, $[\alpha]_D$ -28.6° ($CHCl_3$)), respectively.

These results clearly demonstrate that the organoselenium-mediated reduction can successfully be applied to bis-epoxy ketones as well as epoxy ketones. Since conversion of **2** into yashabushitriol (**4**) by $NaBH_4$ reduction has been reported,6) the present synthesis also means the synthesis of the latter.18)

Thus the facile synthesis of some diarylheptanoids (**1**, **2**, **3**, and **4**) has been achieved by applying the organoselenium-mediated reduction to the epoxy ketone **10** and the bis-epoxy ketone **11**, and their proposed structures have been unambiguously established.

We thank Professor Y. Asakawa (Tokushima Bunri University) for his helpful discussions and identification of the synthetic compounds.

This work was supported by the CIBA-GEIGY Foundation (Japan) for the Promotion of Science.

## References

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7) This compound was easily prepared from 3-phenylpropionaldehyde by the Horner-Emmons reaction (triethyl phosphonoacetate, NaH, THF, -78 °C) followed by reduction of the resulting unsaturated ester with diisobutylaluminum hydride (toluene, -65 °C) in 94% overall yield.

8) Determined by the NMR spectrum (600 MHz) of the (+)-α-methoxy-α-(trifluoromethyl)phenylacetic ester of the epoxy alcohol **6**. We thank Dr. M. Ueno (Tohoku University, Instrumental Analysis Center For Chemistry) for the measurement of the NMR spectrum.

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14) The coupling reaction of **7** with β-styryllithium was found to give lower yield (30-37%) of the product due to the preferential occurrence of retrograde reactions.

15) M. Miyashita, T. Suzuki, and A. Yoshikoshi, Tetrahedron Lett., 30, 1819 (1989).

16) Mp and $[\alpha]_D$ value of the synthetic compound are not consistent with reported values (mp 59.5-60.5 °C, $[\alpha]_D$ +29.0° (c, 1.0, $CHCl_3$))6) and we are inquiring to the original authors with respect to this point.

17) M. Miyashita, T. Suzuki, and A. Yoshikoshi, Chem. Lett., 1987, 285. Epoxidation of **8** with alkaline hydrogen peroxide resulted in lower yield (55%) of the product.

18) According to our experiments, reduction of **2** with $NaBH_4$ in methanol gave a 2 : 1 mixture of **4** and its $C_3$-epimer, while reduction of **2** with diisobutylaluminum hydride (THF, -78 °C, 20 min) afforded a 1 : 2 mixture of **4** and $C_3$-epimer in 97% yield.

(Received March 8, 1990)