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Concise asymmetric synthesis of (−)-herbertenediol

Yasuyuki Kita,* Junko Futamura, Yusuke Ohba, Yoshinari Sawama, Jnaneshuwara K. Ganesh and Hiromichi Fujioka

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan

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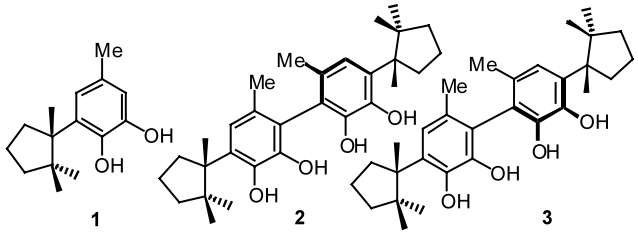
Abstract—The rearrangement of the optically active 3-aryl-2-methyl-2,3-epoxy tosylate (>98% ee) afforded the α-keto tosylate with a chiral quaternary carbon center and without loss of chirality. Reductive removal of the tosyloxy group gave the keto compound with a chiral quaternary carbon center, which was converted to (−)-herbertenediol (>98% ee).

(−)-Herbertenediol ((−)-**1**),[1] isolated from *liverwort Herberta adunca*, is a herbertane-type sesquiterpene. Phenolic coupling of two (−)-**1** is supposed to presumably biosynthesize the dimer, mastigophorenes A (**2**) and B (**3**), since both co-occur in the same source as (−)-**1**.[2] Indeed, compounds **2** and **3** were synthesized by phenolic coupling of the two (−)-**1**.[3] Promising biological activity of (−)-**1** itself, anti-lipid peroxidation activity,[4a] and the activities of its dimer **2** and **3**, intriguing neurotrophic properties, i.e. promote neuronal outgrowth and enhance choline acetyltransferase activity,[5] make (−)-**1** an attractive synthetic target. In addition to the racemic syntheses of (±)-**1**,[4] a few groups, Meyers et al.,[3b] Bringmann et al.,[3c] and Fukuyama et al.,[3d] have reported the asymmetric syntheses of (−)-**1**. Compound (−)-**1** is composed of a cyclopentane ring with three methyl groups and the methylated dihydroxyphenyl group. The benzylic quaternary carbon center of (−)-**1** becomes chiral, and only its center makes the (−)-**1** chiral, non-racemic one. The most important point in an asymmetric synthesis of (−)-**1** is then how to construct the chiral benzylic quaternary carbon center in the optically active form. We present here our synthetic study leading to the concise asymmetric synthesis of (−)-**1**.

For the asymmetric synthesis of (−)-**1**, we planned the rearrangement of an epoxy sulfonate as the key reaction for the asymmetric construction of the chiral quaternary carbon center for the following reasons. First, the fact that the success of our recently developed



rearrangements of epoxy acylates depends on the electron-withdrawing nature of the acyloxy groups[6] suggested that the epoxy derivatives with a similar electron-withdrawing group would proceed with the same type of rearrangement. For the epoxy sulfonates, α-keto sulfonates would be obtained. Second, the sulfonyloxy groups are widely recognized not only as strong electron-withdrawing groups, but also as good leaving groups. The reductive removal of the sulfonyloxy group of the α-keto sulfonates would then proceed without any problem. Third, since the rearrangement of the epoxy sulfonates with a Lewis acid is unknown, the study of their reactivity will provide new information.

Scheme 1 shows the retrosynthetic analysis of (−)-**1**. Optically active epoxy tosylate **7** would be prepared from the corresponding enone **5** by a method similar to our previously reported synthesis of the optically active epoxy acylates.[6g] If the rearrangement reaction of **7** would proceed in a manner similar to that of the epoxy acylates, β-cleavage of the oxirane ring, the α-keto tosylate **8** would be obtained, which would be converted to the optically active **9** by reductive removal of the tosyloxy group. Further transformation and dimethylation of the ketone of **9** followed by cleavage of the methyl ether, would give **1**.

* Corresponding author. E-mail: kita@phs.osaka-u.ac.jp

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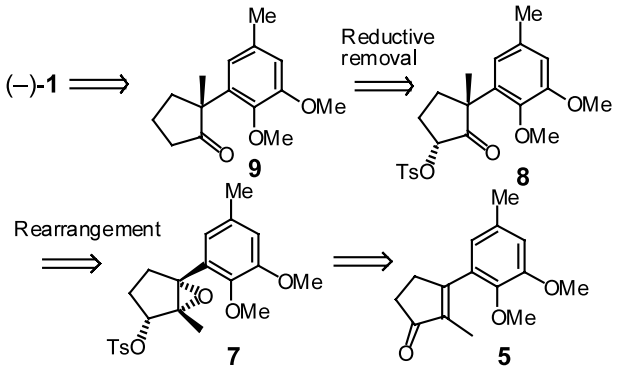
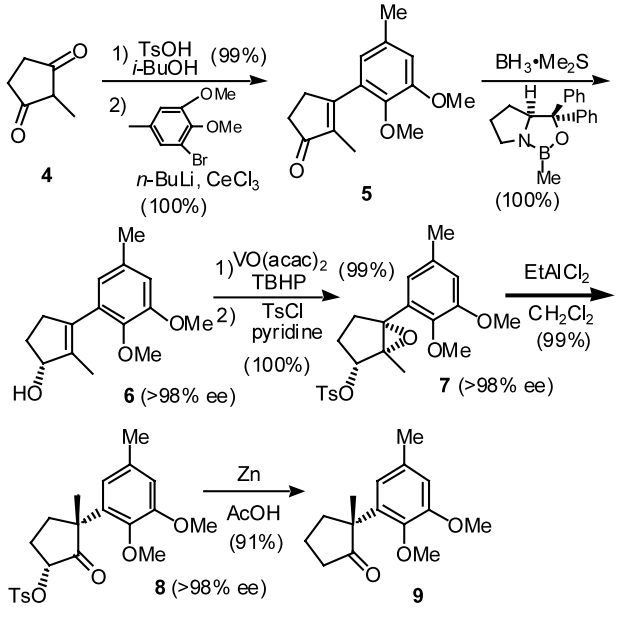


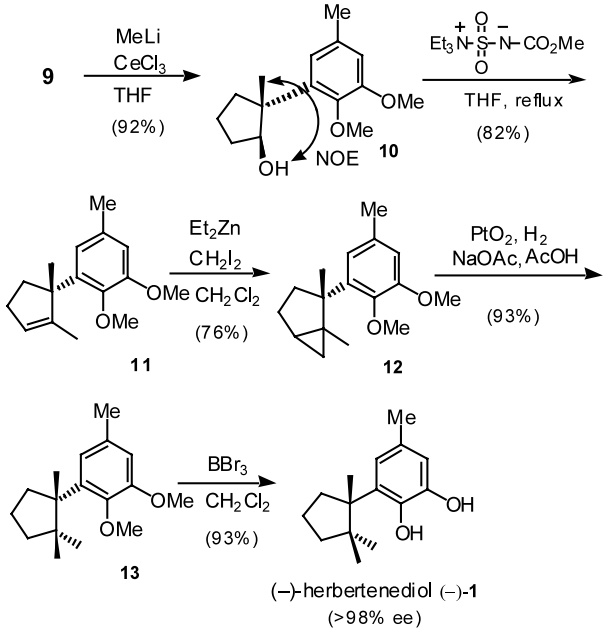
Scheme 1.

The nucleophilic 1,2-addition of 2,3-dimethoxy-5-methylphenyl lithium[7] to the *iso*-butyl ether[8] of 2-methylcyclopentane-1,3-dione **4** followed by acidic work-up afforded the enone **5**. Asymmetric reduction of the enone **5** with Corey's reagent[9] gave the highly enantiomeric allyl alcohol **6**, whose enantiomeric excess (ee) was determined to be >98% ee by HPLC analysis.[10] The stereoselective epoxidation[11] of **6** followed by tosylation gave the *cis*-epoxy tosylate **7**. As our expectation, the treatment of **7** with aluminum reagent ($EtAlCl_2$) proceeded in the same manner as that of epoxy acylates to give the desired rearranged product **8** in a high yield. The treatment of **8** with Zn powder in AcOH removed the tosyloxyl group without any problem to give the ketone **9** in a one-step operation (Scheme 2).



Scheme 2.

Although Me_2TiCl_2-treatment, the usual condition for the dimethylation of carbonyl compounds, of **9** did not give the dimethylated compound,[12] it was transformed to (–)-**1** through a cyclopropane compound as shown in Scheme 3. The methylation of **9** with $MeCeCl_2$ gave the single product **10** in a high yield. Its stereochemistry was determined by an NOE experiment. Maybe the attack of the reagent was controlled by chelation between the reagent and the oxygen atom of the methoxy group. The treatment of **10** with Burgess' reagent[13] gave the dehydrated product **11** in a high yield. The cyclopropanation of **11** under the usual Simmons–Smith condition afforded the cyclopropanated product **12** as a diastereomeric mixture (ca. 3 to 1). The reductive opening of the cyclopropane ring of **12** gave the trimethyl compound **13**, whose ee value was determined to be >98% by HPLC analysis.[10] The acidic cleavage of the methyl ether bond of **13** with BBr_3 furnished the formation of (–)-**1** (>98% ee by HPLC analysis),[10] whose physical data were in good agreement with the reported ones: $[\alpha]_D^{28}$ −57 (*c* 0.78, $CHCl_3$) {lit. $[\alpha]_D$ −47;[1] $[\alpha]_D$ −53.8 (*c* 1.0, $CHCl_3$);[3b] $[\alpha]_D^{28}$ −47.1 (*c* 1.0, $CHCl_3$)[3d]}.



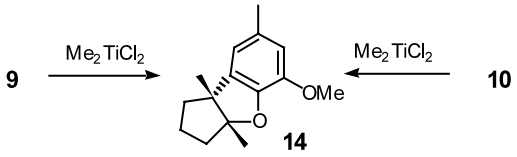
Scheme 3.

In conclusion, we have succeeded in the asymmetric synthesis of (–)-herbertenediol (–)-**1** from the commercially available **4** in 12 steps with 44% total yield. The method described here is short compared to the other asymmetric syntheses, and the yield of the each step is very high. In addition, during the synthesis we have developed a reliable way to construct the optically pure chiral quaternary carbon center in the herbertane sesquiterpenes. The method here would open the way for the asymmetric synthesis of other simple herbertane sesquiterpenes.[14]

References

1. For isolation, see: (a) Matsuo, A.; Yuki, S.; Nakayama, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 701–710; (b) Matsuo, A.; Yuki, S.; Nakayama, M. *Chem. Lett.* **1983**, 1041–1042.
2. Chau, P.; Mo, W.-L. *Proc. Natl. Sci. Counc. ROC(A)* **1987**, *43*, 124–128.

3. (a) Bringmann, G.; Pabst, T.; Rycroft, D. S.; Connolly, J. D. *Tetrahedron Lett*. **1999**, *40*, 483–486; (b) Degnan, A. P.; Meyers, A. I. *J. Am. Chem. Soc*. **1999**, *121*, 2762–2769; (c) Bringmann, G.; Pabst, T.; Henschel, P.; Kraus, J.; Peters, K.; Peters, E. M.; Rycroft, D. S.; Connolly, J. D. *J. Am. Chem. Soc*. **2000**, *122*, 9127–9133; (d) Fukuyama, Y.; Matsumoto, K.; Tonoi, Y.; Yokoyama, R.; Takahashi, H.; Minami, H.; Okazaki, H.; Mitsumoto, Y. *Tetrahedron* **2001**, *57*, 7127–7135.
4. (a) Fukuyama, Y.; Kiriyama, Y.; Kodama, M. *Tetrahedron Lett*. **1996**, *37*, 1261–1264; (b) Harrawven, D. C.; Hannam, J. C. *Tetrahedron Lett*. **1998**, *39*, 9573–9574; (c) Gupta, P. D.; Pal, A.; Roy, A.; Mukherjee, D. *Tetrahedron Lett*. **2000**, *41*, 7563–7566; (d) Srikrishna, A.; Rao, M. S. *Tetrahedron Lett*. **2001**, *42*, 5781–5782; (e) Abad, A.; Agulló, C.; Cuñat, A. C.; Jiménez, D.; Perni, R. H. *Tetrahedron* **2001**, *57*, 9727–9735; (f) Srikrishna, A.; Rao, M. S. *Synlett* **2002**, 340–342.
5. Fukuyama, Y.; Asakawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2737–2741.
6. For the novel rearrangement reactions of 2,3-epoxy acylates due to the electron-withdrawing nature of the acyloxy group, see: (a) Fujioka, H.; Kitagaki, S.; Imai, R.; Kondo, M.; Okamoto, S.; Yoshida, Y.; Akai, S.; Kita, Y. *Tetrahedron Lett*. **1995**, *36*, 3219–3222; (b) Kita, Y.; Kitagaki, S.; Yoshida, Y.; Mihara, S.; Fang, D.-F.; Fujioka, H. *Tetrahedron Lett*. **1997**, *38*, 1061–1064; (c) Kita, Y.; Kitagaki, S.; Yoshida, Y.; Mihara, S.; Fang, D.-F.; Kondo, M.; Okamoto, S.; Imai, R.; Akai, S.; Fujioka, H. *J. Org. Chem*. **1997**, *62*, 4991–4997; (d) Kita, Y.; Yoshida, Y.; Kitagaki, S.; Mihara, S.; Fang, D.-F.; Furukawa, A.; Higuchi, K.; Fujioka, H. *Tetrahedron* **1999**, *55*, 4979–4998; (e) Kita, Y.; Furukawa, A.; Futamura, J.; Higuchi, K.; Ueda, K.; Fujioka, H. *Tetrahedron Lett*. **2000**, *41*, 2133–2136; (f) Kita, Y.; Furukawa, A.; Futamura, J.; Higuchi, K.; Ueda, K.; Fujioka, H. *Tetrahedron* **2001**, *57*, 815–825; (g) Kita, Y.; Furukawa, A.; Futamura, J.; Ueda, K.; Sawama. Y.; Hamamoto, H.; Fujioka, H. *J. Org. Chem*. **2001**, *66*, 8779–4786.
7. Tomita, M.; Bessho, K. *Yakugaku Zasshi* **1959**, *79*, 1097–1099.
8. Crisan, C.; Normant, H. *Bull. Soc. Chim. Fr*. **1957**, 1451–1453.
9. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc*. **1987**, *109*, 7925–7926. The absolute configuration of the secondary alcohol was deduced by referring to the literature and our previous work (Ref. 6). This deduction was finally determined by agreement of the synthesized herbertenediol to the natural (−)-**1**.
10. The ee values for **6**, **7**, **8**, and (−)-**1** were determined by HPLC using a chiral column (UV detector: at 259 nm, *i*-PrOH/hexane = 1/99, 1 ml/min) at 25°C: Daicel Chiralpak OD for **6** and **7**, Daicel Chiralpak AD-H for **8**, and Daicel Chiralpak OD-H for (−)-**1**.
11. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc*. **1973**, *95*, 6136–6137.
12. The oxacyclic compound **14** was obtained as the major product, maybe by nucleophilic attack of the oxygen atom of the aromatic methoxy group to the one methyl introduced compound, and the formation of **13** was not observed on TLC. In fact, the treatment of **10** with Me_2TiCl_2 gave the same oxacyclic compound **14** as the major product and no **13** on TLC.



13. Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem*. **1973**, *38*, 26–31. Successful result, see: Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Ueda, K.; Akai, S.; Fujioka, H. *J. Am. Chem. Soc*. **2001**, *123*, 3214–3222.
14. For the synthetic study of (−)-α-herbertenol, the reaction of **15**, with only one methoxy group was missing from **9**, was examined. Although treatment of the optically pure compound **15** with Me_2TiCl_2 afforded the trimethyl compound **16** in moderate yield, the ee value of **16** proved to be zero and racemization occurred under this reaction condition. The optically active one was also synthesized in the similar manner as shown in Scheme 3. These details will be reported elsewhere.