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Concise Asymmetric Synthesis of (5*R*)-6-Hydroxy-3,8-dioxabicyclo[3.2.1]octane Derivatives

Chong-Feng Pan, Zu-Hui Zhang, Gao-Jun Sun, and Zhi-Yong Wang*

Department of Chemistry, University of Science and Technology of China, Hefei, Anhui, 230026, P. R. China

zwang3@ustc.edu.cn

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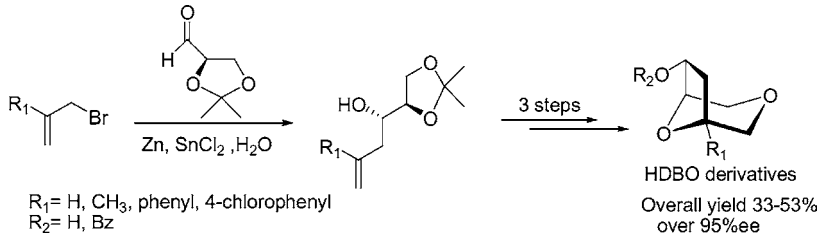
ABSTRACT



A concise method to asymmetrically synthesize 6-hydroxy-3,8-dioxabicyclo[3.2.1]octane (HDBO) derivatives was devised.

3,8-Dioxabicyclo[3.2.1]octane (DBO) exists in natural products and their analogues, notably, in the bicyclic analogues of zoapatanol. Zoapatanol, isolated from the leaves of the zoapatle plant (*Montanoa tomentosa*), has attracted much attention for its antifertility activity and structure features (Figure 1, **a**).[1] Several of its bicyclic analogues have been synthesized, and they possess an even higher antifertility activity (one example is shown in Figure 1, **b**).[2] 6-Hydroxy-3,8-dioxabicyclo[3.2.1]octane (HDBO) also exists in bioactive compounds such as some conformationally restricted nucleoside analogues.[3]

Traditional synthetic methods took at least seven steps to construct DBO or HDBO,[3,4] which usually had a low yield. In this paper, we propose a new, concise method to asymmetrically synthesize HDBO derivatives in only four steps, starting from (*R*)-2,3-*O*-isopropylideneglyceraldehydes (IPG). The corresponding product was obtained with a relatively high total yield and a high enatiomeric excess (ee).

The retrosynthetic analysis is shown in Scheme 1. The C(2)−O(3) bond in the target molecule **i** is disconnected to give the intermediate **ii**. **ii** is a typical product of iodocyclization reaction[5] and can be accessed from **iii**. Retrosynthetic ketal formation of **iii** leads to **iv**. The C(1)−C(2) bond in **iv** is disconnected, which gives allylic substrate **v** and IPG **vi**. The retrosynthetic analysis makes it clear that, in the actual synthetic procedure, iodocyclization of **iii** not only

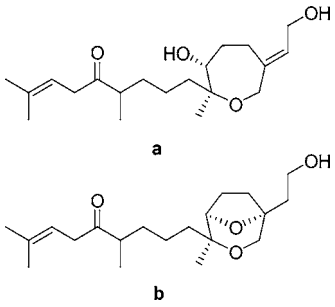


Figure 1. Zoapatanol (**a**) and one of its bicyclic analogues (**b**).

(1) Levine, S. D.; Adams, R. E.; Chen, R.; Cotter, M. L.; Hirsch, A. F.; Kane, V. V.; Kanojia, R. M.; Shaw, C.; Wachter, M. P.; Chin, E.; Huettemann, R.; Ostrowski, P.; Mateos, J. L.; Noriega, L.; Guzman, A.; Mijarez, A.; Tovar, L. *J. Am. Chem. Soc.* **1979**, *101*, 3404.

(2) (a) Kanojia, R. M.; Chin, E.; Smith, C.; Chen, R.; Rowand, D.; Levine, S. D.; Wachter, M. P.; Adams, R. E.; Hahn, D. *J. Med. Chem.* **1985**, *28*, 796. (b) Walba, D. M.; Stoudt, G. S. *J. Org. Chem.* **1983**, *48*, 5404. (c) Takayanagi, H.; Shirasaka, T.; Morita, Y. *Synthesis* **1991**, 722.

(3) Kaemo, L.; Wengel, J. *J. Org. Chem.* **2001**, *66*, 5498.

(4) (a) Chen, R.; Hajos, Z. G. *J. Org. Chem.* **1984**, *49*, 4743. (b) Wachter, M. P.: Hajos, Z. G.; Adams, R. E.; Werblood, H. M. *J. Org. Chem.* **1985**, *50*, 2216.

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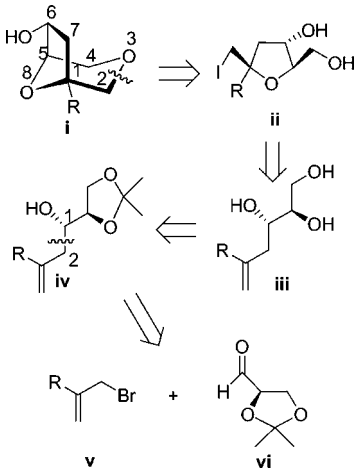
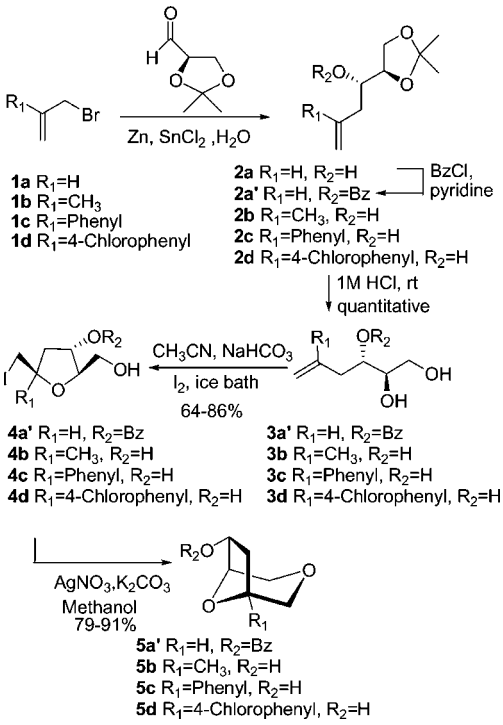
Scheme 1. Retrosynthetic Analysis



forms the tetrahydrofuran ring, but also prepares it for the subsequent intramolecular etherification. The synthetic route is shown in Scheme 2.

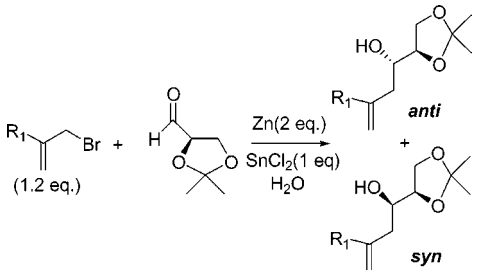
Scheme 2. Synthesis of 6-Hydroxy-3,8-dioxabicyclo[3.2.1]octane Derivatives



The synthesis began with the allylation of IPG (Table 1). Stereoselective synthesis of syn or anti isomers by using appropriate chiral allylborane reagents and titanium reagent is known.[6] Pursuing an economical and more convenient method, we decided to carry out the first step by employing

(5) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.

Table 1.



entry	allylic substrate	isolated yield(%)	anti:syn[a]
1	**1a**	87	75:25
2	**1b**	84	83:17
3	**1c**	78	93:7
4	**1d**	81	90:10

[a] Ratio was estimated by ^{1}H NMR experiment.

the allylation of IPG in water, from which we hoped to obtain the desired anti isomer. It was reported that an anti isomer dominated in the In−THF−H_2O system.[7] However, for our purpose the use of relatively expensive indium made the system undesirable. Therefore, we tried different systems. In our experiments, it was found that freshly prepared chiral IPG favored high ee of products because the enolization of carbonyl group of IPG resulted in slow racemization. The reaction was thus required to be completed as quickly as possible. After many trials, the Zn−$SnCl_2$−H_2O system was identified. Here the use of the water solvent avoided the tedious purification of the starting materials, such as desiccation and removal of air, and this allowed us to immediately use the freshly prepared IPG for the allylation. The allylation reaction can be completed within 30 min, giving us the anti isomer of **2** in a moderate yield, as shown in Table 1. The enhancement of the steric hindrance of R_1 led to the increase of the diastereoselectivity, with a slight decrease of the yield. The existence of the electron-withdrawing group slightly increased the yield (entries 3 and 4, Table 1).

Hydrolysis of the ketal **2** in 1 M HCl proceeded smoothly at room temperature to give rise to **3**.

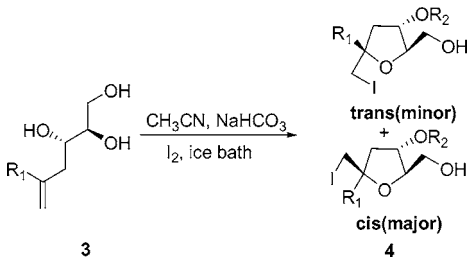
Two isomers were generated from the iodocyclization reaction (Scheme 3), and the cis isomer was the predominant product. Following the procedure described in the literature,[5] initially, we got the desired product in a high diastereoselectivity but with a low yield. Higher temperature enhanced the total yield of these two isomers but decreased the diastereoselectivity. Therefore, we had to resolve the conflict between yield and diastereoselectivity. Many attempts proved that low temperature favored the diastereoselectivity. After optimization, we prolonged the reaction time to 24 h and gradually increased the amount of iodine to a large excess at 0 °C, resulting in a complete disappearance of the starting material without any sacrifice of the selectivity.

The intramolecular etherification of **4** was first performed by using NaH in HMPA−THF.[4b] The low yield (<28%)

(6) (a) Roush, W. R.; Grover, P. T. *J. Org. Chem.* **1995**, *60*, 3806. (b) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117. (c) Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S. *J. Org. Chem.* **2002**, *67*, 1982.

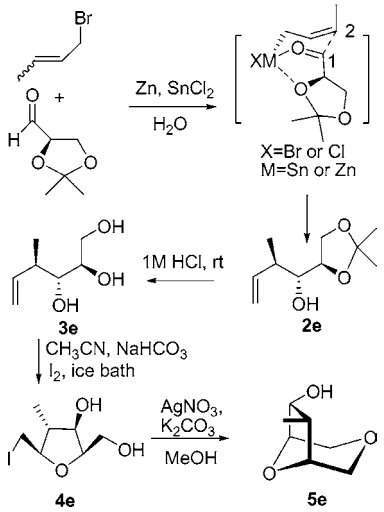
(7) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931.

Scheme 3. Iodocyclization



called for further improvement. Sodium hydride, which is a strong base, failed to improve the etherification, which suggested that the C−I bond needed to be activated. To validate this idea, **4c** and saturated $AgNO_3$ solution were mixed together. A black precipitate was observed, and **5c** was isolated in 55% yield, accompanying some unidentified byproducts. After optimizing the reaction conditions, the $AgNO_3$−K_2CO_3−methanol system was identified for the etherification and **4c** was converted to **5c** with a 91% yield. Afterward, **5a′**, **5b**, and **5d** were prepared smoothly by using this concise method. The structure of **5** was definitively characterized by ^{1}H NMR, ^{13}C NMR, HRMS, H−H NOESY, and H−H COSY, which unambiguously assigned an anti configuration to **2**.[8]

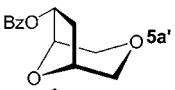
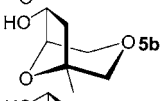
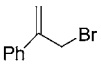
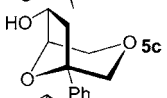
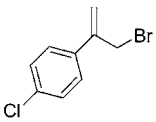
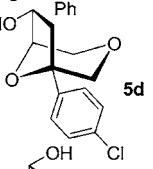
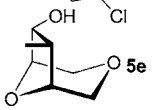
Scheme 4



To extend the scope of the reaction substrate, crotyl bromide also was used to construct this bicycle (Scheme 4). In the crotylation reaction, we attempted to obtain six isomers, two from α-addition and four from γ-addition. In our experiment, at least four spots were observed in TLC, of which **2e** was the main product obtained in 36% yield. A six-membered ring transition state may have been involved in the formation of **2e**, as shown in Scheme 4.[7] First of all, crotyltin or crotylzinc chelates to the two oxygen atoms from the carbonyl group and the neighboring dioxolane group, respectively. Following Cram's rule, the crotyl group transfers to the carbonyl carbon from the less hindered π-surface through the six-membered ring transition state, which results in the (*R*)-configuration of C(1). On the other hand, the methyl group from crotyl bromide and the bulky dioxolane group adopt a trans arrangement in this six-membered ring transition state to further reduce the steric hindrance, which results in the (*R*)-configuration of C(2). As a result, the γ-adduct **2e** is formed as the main product. Afterward, **2e** was smoothly converted to **5e** by the same procedure as described above.[8]

The overall yield of **5a**−**e** and the corresponding ee are summarized in Table 2. It was found that aromatic substi-

Table 2.

entry	allylic substrate	final product	overall yield%(ee)
1		 **5a'**	33(95%)
2		 **5b**	37(97%)
3		 **5c**	57(95%)
4		 **5d**	53(>99%)
5		 **5e**	23(98%)

tutents in allylic substrates favored both the iodocyclization and the intramolecular etherification (entries 3 and 4, Table 2).

In summary, we devised a short and efficient synthetic route for HDBO derivatives by use of chiral aldehyde synthons, (*R*)-2,3-*O*-isopropylideneglyceraldehydes. High diastereoselectivity of the allylation reaction was reached when the allyl bromide was substituted with an aryl group. Further improvement and application of this method to the total synthesis of natural products is underway in our lab.

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Supporting Information Available: Experimental procedures and product characterization data for compounds **2a**−**e**, **3a′**−**e**, **4a′**−**e**, **5a′**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) It was difficult to distinguish the two isomers of **2** only from their ^{1}H NMR spectra. Both isomers gave overlapped multiplets between δ 3.5−4.3. Here we solved this problem by determining the configuration of **5** first. It is easy to ascertain the configuration of **5** by NOESY. Then, the configuration of **2** was determined easily according to the configuration of **5**.