JOC Article

The Rearrangement of 2,3-Epoxysulfonates and Its Application to Natural Products Syntheses: Formal Synthesis of (−)-Aphanorphine and Total Syntheses of (−)-α-Herbertenol and (−)-Herbertenediol

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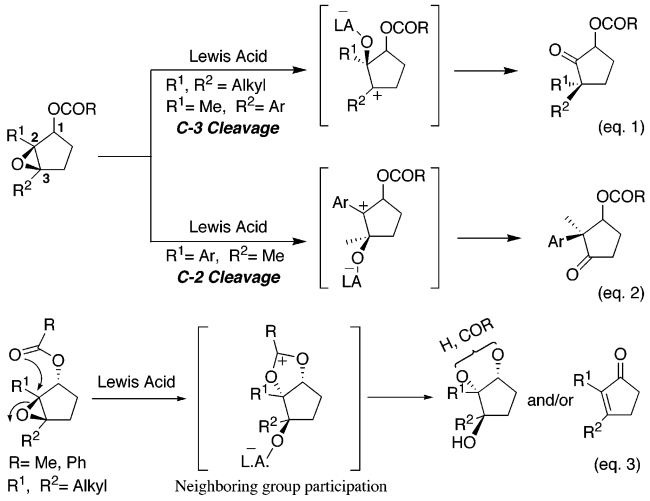
The Lewis acid treatment of 2,3-epoxysulfonates with 2,3-dialkyl substituents or 2-alkyl-3-aryl substituents produced the rearrangement products via C3-cleavage of the oxirane ring in high yields. On the other hand, 2-aryl-3-alkyl-2,3-epoxysulfonates produced the products via C2-cleavage of the oxirane ring. The sulfonyloxy groups of the α-sulfonyloxy ketones, having a chiral benzylic quaternary carbon center obtained by the rearrangement of 2-alkyl-3-aryl-2,3-epoxysulfonates, were reductively eliminated to give the ketones with a chiral benzylic quaternary carbon center. The method was applied to the formal synthesis of (−)-aphanorphine and total syntheses of (−)-α-herbertenol and (−)-herbertenediol.

Introduction

We have studied the rearrangements of epoxides with adjoining electron-withdrawing functional groups such as 2,3-epoxy acylates.[1−3] Epoxides with 2,3-dialkyl substituents react through cleavage of the oxirane ring at the C3-position due to the electron-withdrawing nature of the acyloxyalkyl group. A similar reaction course is observed for epoxides with a C3-aryl substituent (eq 1).[1,2] On the other hand, the reactions of epoxides with a C2-aryl substituent occur through the cleavage of the oxirane ring at the C2-position due to the cation-stabilizing ability of the aromatic ring (eq 2).[3] In these cases, the relationship between the epoxide and the acyloxy group sometimes played an important role. Namely, the *trans*-epoxy acylates with an acetyl or benzoyl group sometimes involved neighboring group participation and led to the formation of diols and enones, rather than rearranged products (eq 3).



To overcome neighboring group participation, a stronger electron-withdrawing group than an acyloxy group was explored. We found that the rearrangements of epoxysulfonates provide a useful method for synthesizing many kinds of compounds. We report on the reactions of 2,3-epoxysulfonates and the application of the rearrangement of 2,3-epoxysulfonates to the formal synthesis of (−)-aphanorphin (**11**) and total syntheses of (−)-α-herbertenol (**19a**) and (−)-herbertenediol (**19b**) (Scheme 1, Figure 1).[4]

(1) (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.

(2) Kita, Y.; Furukawa, A.; Futamura, J.; Ueda, K.; Sawama, Y.; Hamamoto, H.; Fujioka, H. *J. Org. Chem.* **2001**, *66*, 8779−8786.

(3) (a) Kita, K.; Kitagaki, S.; Imai, R.; Okamoto, S.; Mihara, S.; Yoshida, Y.; Akai, S.; Fujioka, H. *Tetrahedron Lett.* **1996**, *37*, 1817−1820. (b) Kita, Y.; Furukawa, A.; Futamura, J.; Higuchi, K.; Ueda, K.; Fujioka, H. *Tetrahedron Lett.* **2000**, *41*, 2133−2136. Quite recently we found that the reaction of acyclic 2-aryl-2,3-epoxy acylates proceeded via the C3-cleavage of the oxirane ring. However, the intermediates are phenonium ions, which are completely different from the intermediates of eqs 1 and 2 due to the flexibility of the substrates. Kita, Y.; Furukawa, A.; Futamura, J.; Higuchi, K.; Ueda, K.; Fujioka, H. *Tetrahedron* **2001**, *57*, 815−825.

(4) We have recently reported the asymmetric synthesis of (−)-herbertenediol through the rearrangement of 3-aryl-2-methyl-2,3-epoxy tosylate. See: Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J. K.; Fujioka, H. *Tetrahedron Lett.* **2003**, *44*, 411−413.

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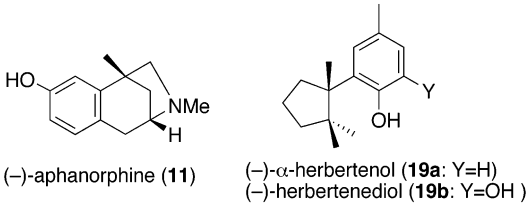
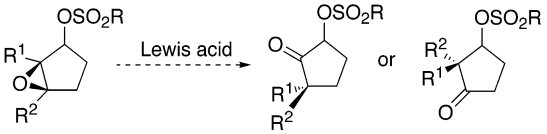


FIGURE 1. Natural products synthesized by the rearrangement of 2,3-epoxysulfonates.

SCHEME 1

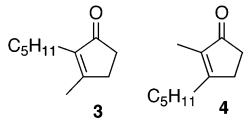


The Nature of Sulfonyloxy Groups (RSO_3^-)
- Strong electron-withdrawing nature
- No neighboring group participation ability
- High elimination ability

Results and Discussion

Rearrangements of 2,3-Epoxysulfonates.[5]

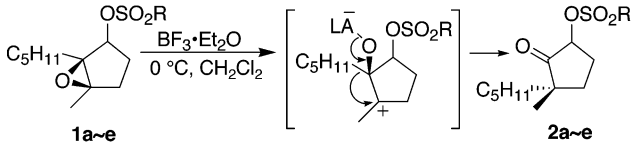
Rearrangements via C3-carbocation: The treatment of *cis*-2,3-epoxysulfonates (**1a**−**e**) with 1 equiv of BF_3·Et_2O afforded the desired products (**2a**−**e**) in moderate yields with enones **3** and **4** as byproducts (Table 1,



entries 1−5).[6] The use of other Lewis acids such as $SnCl_4$, $SnBr_4$, $Al(OC_6F_5)_3$,[7] and $InCl_5$ did not produce better yields of the desired products (**2a**−**e**) than reactions with BF_3·Et_2O. We studied the amount of BF_3·Et_2O using epoxy tosylate *cis*-**1c** (entries 6 and 7) and found that 10 equiv of BF_3·Et_2O resulted in a high yield of the rearranged product *cis*-**2c**, whereas the use of 0.1 equiv of BF_3·Et_2O afforded enones **3** and **4** as the major products. A similar high yield was obtained from *trans*-2,3-epoxysulfonate *trans*-**1c** to give the rearranged product *trans*-**2c** (entry 8). These results showed that the relationship between the epoxide ring and sulfonyloxy group (cis or trans) is not very significant.

The rearrangement via the C3-carbocation was also observed in the reaction of the 2,3-epoxysulfonates with the C3-phenyl group (Table 2). The reaction of *cis*-**5** afforded the rearranged product *cis*-**6** in high yields with 1 equiv of $EtAlCl_2$, whereas the use of 1 equiv of BF_3·Et_2O afforded enone **7**, not the rearranged product (entries 1 and 2). The results from *cis*-**5** and *trans*-**5** were consistent with the prior finding that there was a stereochemical relationship between the oxirane ring and the sulfonyloxy group (entries 2 and 3). This ability of $EtAlCl_2$ to give better results than BF_3·Et_2O may be rationalized as the outcome of the ionic nature of the O−metal bond to aluminum metal, as previously discussed in the reactions of the epoxy acylates with a C3-aryl substituent.[2]

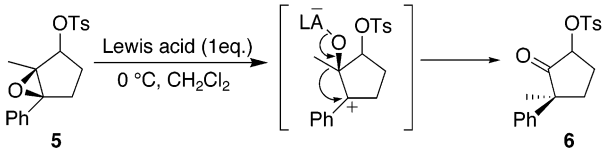
TABLE 1. Rearrangement of 3-Methyl-2-pentyl-2,3-epoxy Sulfonates

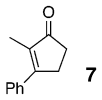
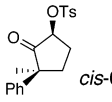
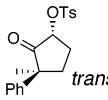


entry	substrate	RSO_2	BF_3·Et_2O (equiv)	yield (%)
1	*cis*-**1a**	Ms	1.0	40[a]
2	*cis*-**1b**	$PhSO_2$	1.0	43[a]
3	*cis*-**1c**	Ts	1.0	48[a]
4	*cis*-**1d**	*p*-F-$C_6H_4SO_2$	1.0	40[a]
5	*cis*-**1e**	*p*-MeO-$C_6H_4SO_2$	1.0	45[a]
6	*cis*-**1c**	Ts	0.1	4[b]
7	*cis*-**1c**	Ts	10	83
8	*trans*-**1c**	Ts	10	87

[a] Other products, enones **3** and **4**, were obtained in 20−40% yield. [b] Other products, enones **3** and **4**, were obtained in 75% combined yield.

TABLE 2. Rearrangement of 2-Methyl-3-phenyl-2,3-epoxy Sulfonates



Entry	Substrate	Lewis acid	Product	Yield (%)
1	*cis*-**5**	BF_3·Et_2O	 **7**	81
2	"	$EtAlCl_2$	 *cis*-**6**	89
3	*trans*-**5**	"	 *trans*-**6**	93

Rearrangements via C2-carbocation: In our study of the rearrangement of 2,3-epoxyacylates with the C2-aromatic substituent, the reaction proceeded as expected through a C2-carbocation.[3] The reaction of the 2,3-epoxysulfonates **8** with the C2-phenyl group proceeded in the same manner, although a sulfonyloxy group has a stronger electron-withdrawing ability than an acyloxy group. The reaction of *cis*-**8** or *trans*-**8** smoothly produced the rearranged products *cis*-**9** or *trans*-**9**, respectively, in almost the same high yields with 1 equiv of BF_3·Et_2O. The relationships between the epoxide and sulfonyloxy group (cis or trans) did not effect the desired rearrangement reaction (Scheme 2).

Natural Products Syntheses.

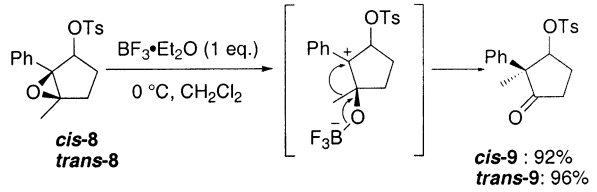
Formal synthesis of (−)-aphanorphine (11): (−)-Aphanorphine **11** was isolated from *Aphanizomenon flas-*

(5) In this section, racemic epoxysulfonates were used to examine their reactivity under Lewis acid treatment.

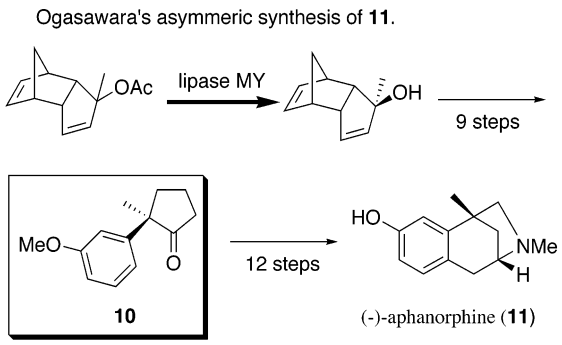
(6) The reaction mechanism for compounds **3** and **4** will be discussed elsewhere.

(7) For synthetic applications of $(C_6F_5O)_3Al$, see: (a) Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 7074−7075. (b) Ishihara, K.; Hanaki, N.; Yamamoto, H. *Synlett* **1993**, 127−129.

SCHEME 2



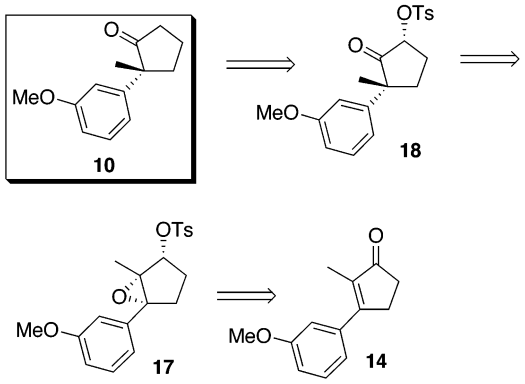
SCHEME 3



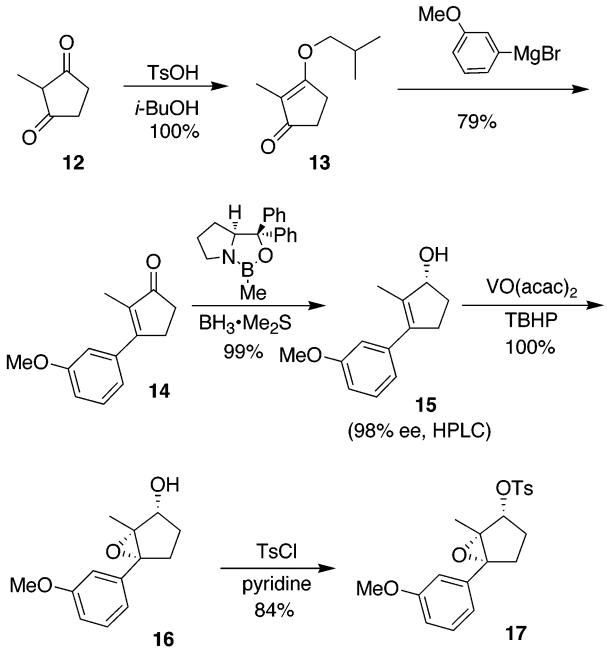
aquae by Gulavita et al. in 1988.[8] Three asymmetric total syntheses and many formal syntheses have been reported.[9−12] Among them, we focused on Ogasawara's intermediate **10** as a target compound with a chiral quaternary carbon center on the cyclopentanone ring.[9] Scheme 3 shows Ogasawara's asymmetric synthesis of **11**. The asymmetric synthesis of **10** would constitute a formal enantioselective synthesis of **11**, and our plan for the synthesis of **10** would take advantage of the stereoselective rearrangement of 2,3-epoxysulfonates followed by reductive elimination of the α-tosyloxyketone as shown in Scheme 4.

Optically active epoxytosylate **17** was synthesized as shown in Scheme 5. 2-Methylcyclopentane-1,3-dione (**12**) was converted to 3-isobutoxy-2-methyl-2-cyclopenten-1-one (**13**) following a literature procedure.[13] The nucleophilic addition of 2-methoxyphenylmagnesium bromide to **13** followed by acidic treatment gave enone **14**. The asymmetric reduction of enone **14** with Corey's reagent[14] gave the optically active allylic alcohol **15** with 98% ee. The stereoselective epoxidation[15] and tosylation gave *cis*-epoxysulfonate **17**.

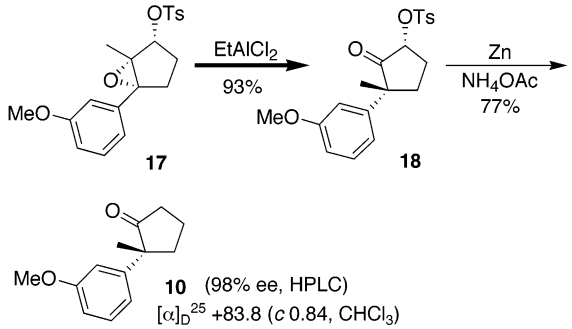
SCHEME 4



SCHEME 5



SCHEME 6



The treatment of **17** with 1 equiv of $EtAlCl_2$ gave the rearranged product **18** in 93% yield. The tosyloxyl group of **18** was removed under reductive condition to give Ogasawara's intermediate **10** in good yield (Scheme 6).

Our asymmetric synthesis of Ogasawara's intermediate **10** from the commercially available starting material **12** in 47% overall yield required a 7-step sequence (5 steps shorter than Ogasawara's procedure for **10**), and completed a formal asymmetric synthesis of (−)-aphanorphine (**11**).

(8) Gulavita, N.; Hori, A.; Shimizu, Y.; Laszlo, P.; Clardy, J. *Tetrahedron Lett.* **1988,** *29*, 4381−4384.

(9) Takano, S.; Inomata, K.; Sato, T.; Takahashi, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1990**, 290−292.

(10) (a) Shiotani, S.; Okada, H.; Nakamura, K.; Yamamoto, T.; Sekino, F. *Heterocycles* **1996**, *43*, 1031−1047. (b) Shimizu, M.; Kamikubo, T.; Ogasawara, K. *Heterocycles* **1997**, *44*, 21−26.

(11) Asymmetric synthesis of unnatural (+)-aphanorphine, see: Takano, S.; Inomata, K.; Sato, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1591−1592.

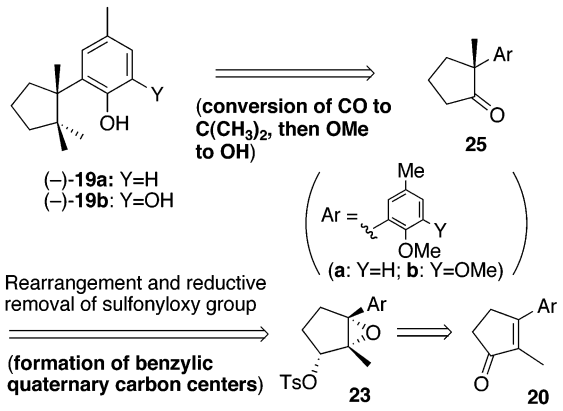
(12) For formal sythesis of (−)-aphanorphine, see: (a) Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 1049−1052. (b) Fadel, A.; Arzel, P. *Tetrahedron*: *Asymmetry* **1997**, *6*, 371−374. (c) Fadel, A.; Arzel, P. *Tetrahedron*: *Asymmetry* **1995**, *6*, 893−900. (d) Hulme, A. N.; Henry, S. S.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 1265−1270. (e) Hallinan, K. O.; Honda, T. *Tetrahedron* **1995**, *45*, 12211−12216. (f) Node, M.; Imazato, H.; Kurosaki, R.; Kawano, Y.; Inoue, T.; Nishide, K.; Fuji, K. *Heterocycles* **1996**, *42*, 811−819.

(13) Crisan, C.; Normant, H. *Bull. Soc. Chim. Fr.* **1957**, 1451−1453.

(14) 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 study (refs 1−3). This deduction was consequently determined by agreement of the synthesized **10** to the authentic one.

(15) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136−6137.

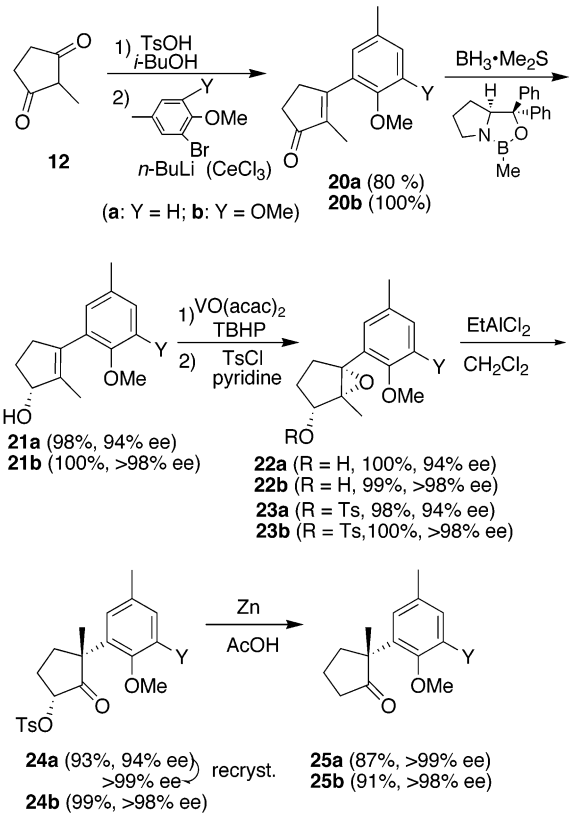
SCHEME 7



Total Syntheses of (−)-α-Herbertenol ((−)-19a) and (−)-Herbertenediol ((−)-19b). The herbertane group of sesquiterpenes are chemical markers for the liverworts belonging to the genus Herbertus.[16] (−)-α-Herbertenol ((−)-**19a**), one of the simplest herbertanes isolated from *liverwort Herberta adunca*, has anti-fungal activity.[16] There are several racemic syntheses and two asymmetric syntheses of **19a**.[17,18] (−)-Herbertenediol ((−)-**19b**)[16] has also been isolated from the same source as (−)-**19a** and it is postulated that the phenolic coupling of two molecules of (−)-**19b** leads to the dimers, mastigophorenes A and B, since both co-occur in the same source as (−)-**19b**.[19,20] The promising antilipid peroxidation activity of (−)-**19b**[21a] and the activities of mastigophorenes that promote neuronral outgrowth and enhance choline acetyltransferase activity[22] make (−)-**19b** an attractive synthetic target. In addition to the racemic syntheses of (±)-**19b**,[21] a few groups, Mayers et al.,[20b] Bringmann et al.,[20c] Fukuyama et al.,[20d] and our own group,[4] have reported the asymmetric syntheses of (−)-**19b**.

Scheme 7 shows our synthetic plan. The benzylic quaternary carbon centers of **19a** and **19b** would be constructed by rearrangement of the optically active 2,3-epoxysulfonates **23** followed by reductive removal of the sulfonyloxy goups as described in aphanorphin synthesis (see above). Conversion of the ketones **25** to *gem*-dimethyl functions and cleavage of the methyl ether would afford (−)-**19a** and (−)-**19b**.

SCHEME 8



(i) Construction of Chiral Benzylic Quaternary Carbon Centers in Optically Active Forms. The chiral benzylic quaternary carbon centers of (−)-**19a** and (−)-**19b** were synthesized by a method similar to that for the intermediate of (−)-aphanorphine described above. The nucleophilic addition of the 2-methoxy-5-methylphenyllithium or cerium reagent of 2,3-dimethoxy-5-methylphenyllithium[23] to the isobutyl ether[13] of 2-methylcyclopentane-1,3-dione (**12**) followed by acidic workup afforded enones **20a** and **20b**. The asymmetric reduction of enones **20a**,**b** with Corey's reagent[14] gave the optically active allyl alcohols **21a**,**b**. The enantiomeric excesses (ee) of **21a**,**b** were determined by HPLC analysis to be 94% ee for **21a** and >98%ee for **21b**. Enantiomeric enhancement to optically pure **21a** was unsuccessful at this stage. The stereoselective epoxidation[15] of **21a**,**b** followed by tosylation gave *cis*-epoxytosylates **23a**,**b**. The treatment of **23a**,**b** with 1 equiv of $EtAlCl_2$ gave the rearranged products **24a**,**b** in high yields. At this stage, compound **24a** (94% ee) was recrystallized to give optically pure **24a** (>99% ee). The removal of the tosyloxy groups of **24a**,**b** afforded ketones **25a**,**b** with chiral benzylic quaternary carbon centers (Scheme 8).

(ii) Conversion of Ketones 25a,b to (−)-α-Herbertenol ((−)-19a) and (−)-Herbertenediol ((−)-19b).

Me_2TiCl_2 treatment: The use of Me_2TiCl_2, a common reagent for the dimethylation of carbonyl compounds,

(16) (a) Matsuo, A.; Nakayama, M.; Maeda, T.; Noda, Y.; Hayashi, S. *Phytochemistry* **1975**, *14*, 1037−1040. (b) Matsuo, A.; Yuki, S.; Nakayama, M.; Hayashi, S. *Chem. Lett.* **1982**, 463−466. (c) Matsuo, A.; Yuki, S.; Nakayama, M. *Chem. Lett.* **1983**, 1041−1042. (d) Matsuo, A.; Yuki, S.; Nakayama, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 701−710. (e) Irita, H.; Hashimoto, T.; Fukuyama, Y.; Asakawa, Y. *Phytochemistry* **2000**, *55*, 247−253.

(17) For racemic synthesis, see ref 21f and references therein.

(18) For asymmetric synthesis, see: Adad, A.; Agulló, C.; Cuñat, A. C.; Perni, R. H. *J. Org. Chem.* **1999**, *64*, 1741−1744 and ref 20d.

(19) Chau, P.; Mo, W.-L. *Proc. Natl. Sci. Counc. ROC(A)* **1987**, *43*, 124−128.

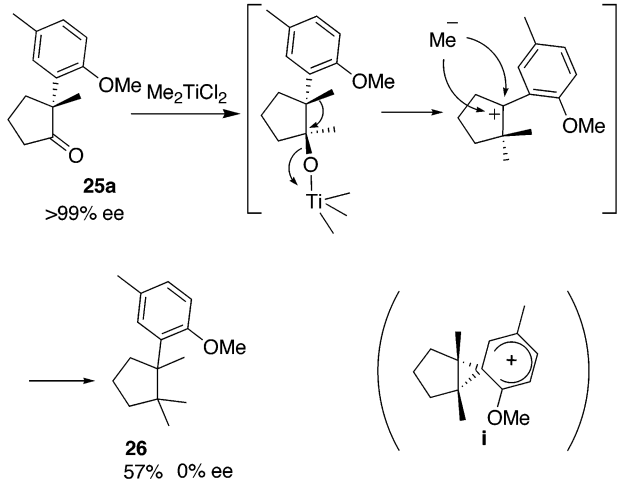
(20) (a) Bringmann, G.; Pabst, T.; Rycroft, D. S.; Connolly, J. D. *Tetrahedron Lett.* **1999**, *40*, 483−486. (b) Degnan, A. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1999**, *121*, 2762−2769. (c) Bringmann, G.; Pabst, T.; Henschel, P.; Kraus, J.; Peters, K.; Peters, E. M.; Rycroft, D. S.; Connolly, 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.

(21) (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.

(22) Fukuyama, Y.; Asakawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2737−2741.

(23) Tomita, M.; Bessho, K. *Yakugaku Zasshi* **1959**, *79*, 1097−1099.

SCHEME 9



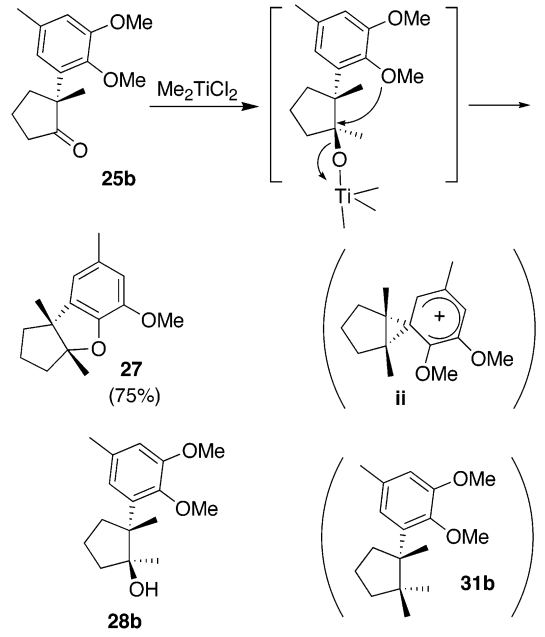
failed.[24] The desired trimethyl compound **26** was obtained from **25a** in moderate yield, but to our surprise, its ee value proved to be zero (Scheme 9). The first monomethylation of ketone **25a** probably occurred from the same side as the aromatic group through chelation-controlled addition. The migration of the benzylic methyl group, driven by the preferable formation of the benzylic carbocation, led to racemization. The possibility of the mechanism via the phenonium ion intermediate **i** was excluded for the following reasons: (1) the formation of a bicyclo[3.1.0] ring system **i** is sterically unfavorable, and (2) in the case of compound **25b**, the oxacyclic compound **27** is the major product, which is very difficult to obtain from the phenonium ion intermediate **ii** and supports the mechanism through the carbocation intermediate (see Scheme 10).[25]

In the case of **25b**, the oxacyclic compound **27** was obtained as the major product through nucleophilic attack of the methoxy group and demethylation. The formation of **31b** (see Scheme 11) was not observed with TLC. In fact, the treatment of **28b** (see Scheme 11), obtained by the MeLi−$CeCl_3$ treatment of **25b**, with Me_2TiCl_2 gave the same oxacyclic compound **27** as the major product and no **31b**. The mechanism via the phenonium ion intermediate **ii** was excluded for the reasons described above (Scheme 10).

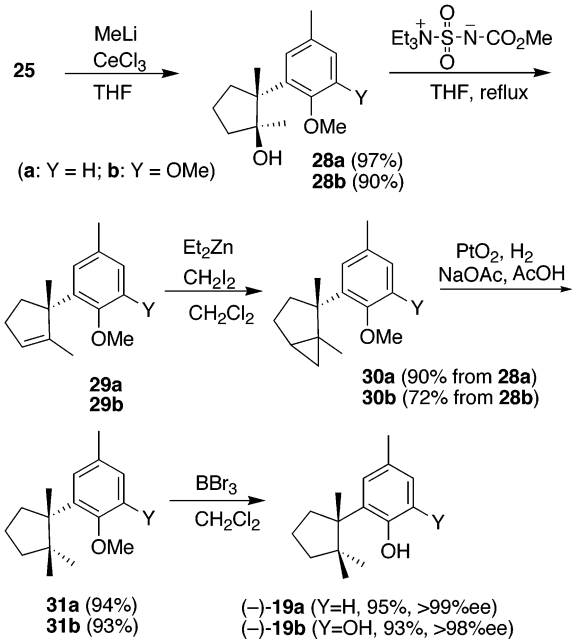
The difference between **25a** and **25b** is the absence or presence of one methoxy group on the aromatic ring. The reasons for the difference in the reactivity between the two are not clear at the present time.

Route via cyclopropane ring: On the basis of the above results, a route involving reductive cyclopropanation was next examined (Scheme 11). The methylation of **25a**,**b** with $MeCeCl_2$ (prepared in situ from MeLi−$CeCl_3$) gave the products **28a**,**b** in high yields, respectively. Their stereochemistries were determined by NOE experiments. Presumably, the attack occurred from the same side as the phenyl group by chelation between the reagent and the methoxy groups. The treatment of **28a**,**b** with Burgess reagent[26] gave olefins **29a**,**b**, which were cyclopropanated in the usual way[27] to afford the products **30a**,**b** as a diastereomeric mixture, respectively. The reductive opening of the cyclopropane ring of **30a**,**b** gave the trimethyl compounds **31a**,**b**, whose ee values were determined by HPLC analysis, respectively. Acidic cleavage of the methyl ether bond of **31a**,**b** with BBr_3 led to

SCHEME 10



SCHEME 11



(24) Reetz, M. T.; Westermann, J.; Steinbach, R. *Angew. Chem., Int. Ed.* **1980**, *19*, 900−901.

(25) The same tendency in the formation of the phenonium ion intermediate, i.e., the difference between the cyclic system not forming the phenonium ion and the acyclic system forming the phenonium ion, was observed in our previous study; see: Kita, Y.; Furukawa, A.; Futamura, J.; Higuchi, K.; Ueda, K.; Fujioka, H. *Tetrahedron* **2001**, *57*, 815−825.

(26) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26−31. For a 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.

(27) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53−58.

(−)-**19a** and (−)-**19b**, respectively, whose physical data were in agreement with reported values.

Asymmetric syntheses of (−)-α-herbertenol ((−)-**19a**) and (−)-herbertenediol ((−)-**19b**) from commercially available **12** were completed in 12 steps with a 48.5% total yield for (−)-**19a** and with a 49.9% total yield for (−)-**19b**. The method described here is short compared with other asymmetric syntheses, and the yield of each step is very high.

Conclusion

We have developed a rearrangement reaction of 2,3-epoxysulfonates and succeeded in applying this reaction to the formal synthesis of (−)-aphanorphine and total syntheses of of (−)-α-herbertenol and (−)-herbertenediol. This method provides a reliable way to construct the optically pure chiral quaternary carbon centers next to a carbonyl function and may find application in the synthesis of many natural products.

Experimental Section

2-Methyl-3-(2-methoxy-5-methyl)phenyl-2-cyclopentenone (20a) and 2-Methyl-3-(2,3-dimethoxy-5-methyl)-phenyl-2-cyclopentenone (20b). n-BuLi (*n*-hexane solution, 29 mL, 45.2 mmol) was added slowly to a solution of 2-bromo-4-methylanisole (8.98 g, 44.7 mmol) in THF (100 mL) at −78 °C under N_2 and the resulting mixture was stirred for 1 h at −40 °C. A solution of isobutyl ether of **12** (3.01 g, 18.1 mmol) in THF (30 mL) was added dropwise to the resulting solution at −78 °C. The mixture was allowed to warm to room temperature and stirred for 20 h. The mixture was quenched by 10% aq HCl and extracted with Et_2O. The organic layer was washed with saturated $NaHCO_3$ aq and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (4/1−3/1) as the eluent to give **20a** (3.13 g, 14.5 mmol, 80%). **20a**: Colorless oil; IR (KBr) 1697, 1499, 1258, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (s, 3H), 2.32 (s, 3H), 2.49−2.53, (m, 2H), 2.86−2.89 (m, 2H), 3.80 (s, 3H), 6.87 (d, 1H, J = 8.4 Hz), 6.96 (d, 1H, J = 2.2 Hz), 7.16 (dd, 1H, J = 2.2, 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 9.5, 20.4, 30.5, 34.3, 55.4, 111.0, 125.5, 129.0, 129.5, 130.3, 138.0, 153.9, 167.4, 209.8. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.91; H, 7.58.

n-BuLi (1.5 M hexane soluution, 2.0 mL, 3.0 mmol) was added slowly to a solution of 2-bromo-4-methyl-6-methoxyanisole (692 mg, 3.0 mmol) in THF (6.0 mL) at −78 °C under N_2 and the resulting mixture was stirred for 1 h. The mixture was added dropwise to a solution of $CeCl_3$, dried from $CeCl_3 \cdot 7H_2O$ (1.12 g, 3.0 mmol) before use, and stirred in THF (6.0 mL) for 1 h, at −78 °C under N_2, and the mixture was stirred for 1 h. A solution of isobutyl ether of **12** (100 mg, 0.60 mmol) in THF (4.0 mL) was added dropwise to the resulting solution at −78 °C and stirred for 3 h. The mixture was quenched by 10% aq HCl and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ aq and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (5/1) as the eluent to give **20b** (148 mg, 0.60 mmol, 100%). **20**b: Colorless crystals; mp 111−112 °C; IR (KBr) 1697, 1466, 1352, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (s, 3H), 2.34 (s, 3H), 2.53 (m, 2H), 2.87 (m, 2H), 3.69 (s, 3H), 3.89 (s, 3H), 6.55 (s, 1H), 6.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.2, 21.2, 30.6, 34.3, 55.6, 61.0, 113.5, 120.2, 130.3, 133.8, 138.2, 143.7, 152.5, 167.5, 209.9. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.10; H, 7.32.

(1*R*)-2-Methyl-3-(2-methoxy-5-methyl)phenyl-2-cyclopropen-1-ol (21a) and (1*R*)-2-Methyl-3-(2,3-dimethoxy-5-methyl)phenyl-2-cyclopropen-1-ol (21b). $BH_3 \cdot Me_2S$ (1 M in THF, 12.5 mL, 12.5 mmol) was added dropwise to a solution of (*S*)-5,5-diphenyl-2-methyl-3,4-propan-1,3,2-oxazaborolidine (3.5 g, 12.5 mmol) in THF (130 mL) at 0 °C under N_2. After being stirred for 30 min, a solution of enone **20a** (2.70 g, 12.5 mmol) in THF (150 mL) was added slowly to the resulting mixture. After being stirred for 5 min, MeOH was added to the mixture. The solvent was removed in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (2/1) as the eluent to give **21a** (2.68 g, 12.3 mmol, 98%, 94% ee by HPLC analysis). **21a**: Colorless oil; IR (KBr) 3287, 1495, 1242, 1034, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (s, 3H), 1.69−1.79 (m, 1H), 2.29 (s, 3H), 2.36−2.43 (m, 1H), 2.54−2.78 (m, 2H), 3.77 (s, 3H), 4.73 (br s, 1H), 6.80 (d, 1H, J = 8.1 Hz), 6.91 (d, 1H, J = 2.1 Hz), 7.04 (dd, 1H, J = 8.1, 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 12.5, 20.5, 33.1, 34.3, 55.5, 81.2, 110.8, 126.8, 128.4, 129.3, 130.5, 136.8, 137.1, 154.6. HPLC analysis: 94% ee (CHIRAL CEL OJ; hexane/^{i}PrOH = 99/1; flow rate 0.5 mL/min); $[\alpha]^{26}_D$ +4.63 (*c* 1.63, $CHCl_3$). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.97; H, 8.34.

In the same procedure as for **21a**, **21b** (1.10 g, 4.5 mmol, 100%) was obtained from $BH_3 \cdot Me_2S$ (1 M in THF, 4.5 mL, 4.5 mmol), (*S*)-5,5-diphenyl-2-methyl-3,4-propan-1,3,2-oxazaborolidine (1.2 g, 4.5 mmol), **20b** (1.1 g, 4.5 mmol), THF (20 mL+25 mL), and SiO_2 column (hexane−AcOEt (1/1)). **21b**: Colorless oil; IR (KBr) 3354, 1481, 1229, 1126, 1012 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (s, 3H), 1.78 (m, 1H), 2.21 (br s, 1H), 2.30 (s, 3H), 2.38 (m, 1H), 2.60 (m, 1H), 2.73 (m, 1H), 3.68 (s, 3H), 3.85 (s, 3H), 4.73 (br s, 1H), 6.52 (s, 1H), 6.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.2, 21.2, 33.1, 34.6, 55.6, 60.7, 80.9, 111.9, 122.0, 132.0, 133.2, 136.5, 137.6, 144.4, 152.3. HPLC analysis: 98% ee (CHIRAL CEL OD; hexane/^{i}PrOH = 99/1; flow rate 1 mL/min); $[\alpha]^{25}_D$ +4.77 (*c* 1.02, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.20; H, 8.15.

(−)-(1*R*,2*R*,5*R*)-1-Methyl-5-(2-methoxy-5-methyl)phenyl-6-oxabicyclo[3.1.0]hexan-2-ol (22a) and (−)-(1*R*,2*R*,5*R*)-1-Methyl-5-(2,3-dimethoxy-5-methyl)phenyl-6-oxabicyclo-[3.1.0]hexan-2-ol (22b). A solution of *t*-BuOOH (dried over molecular sieves 4A before use, 68%, 1.50 g, 11.3 mmol) in benzene (7.0 mL) was added dropwise to a solution of **21a** (770 mg, 3.77 mmol) and 0.1 equiv of $VO(acac)_2$ in benzene (20 mL) at 0 °C under N_2. After being stirred for 1.5 h at room temperature, the mixture was poured into the mixture of saturated $Na_2S_2O_3$ aq and saturated $NaHCO_3$ aq. The resulting solution was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (2/1) as the eluent to give **22a** (830 mg, 3.77 mmol, 100%). **22a**: Colorless oil; IR (KBr) 3385, 1504, 1242, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (s, 3H), 1.26−1.39 (m, 1H), 1.97−2.16 (m, 3H), 2.29 (s, 3H), 3.79 (s, 3H), 4.21 (dd, 1H, J = 17.3, 7.9 Hz), 6.76 (d, 1H, J = 9.0 Hz), 7.07 (br d, 1H, J = 9.0 Hz), 7.13 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 20.5, 29.1, 29.6, 55.4, 70.2, 70.5, 76.4, 110.0, 125.0, 129.0, 129.3, 129.6, 154.3; $[\alpha]^{27}_D$ −35.6 (*c* 1.29, $CHCl_3$). HPLC analysis: 94% ee (CHIRAL CEL AD-H; hexane/^{i}PrOH = 95/5; flow rate 1 mL/min, 15 °C). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.67; H, 7.66.

In the same procedure as for **22a**, **22b** (820 mg, 3.10 mmol, 99%) was obtained from **21b** (776 mg, 3.13 mmol), 0.1 equiv of $VO(acac)_2$, *t*-BuOOH (1.2 g, 9.4 mmol), benzene (15 mL), and SiO_2 column (hexane−AcOEt (4/1)). **22b**: Colorless oil; IR (KBr) 3443, 1589, 1219, 1126, 772 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 3H), 2.03−2.16 (m, 5H), 2.31 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 4.22 (br s, 1H), 6.70 (s, 1H), 6.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.0, 21.1, 28.7, 29.9, 55.6, 60.6, 70.2, 70.6, 76.3, 113.0, 120.7, 129.8, 133.4, 144.4, 151.8; $[\alpha]^{24}_D$ −36.6 (*c* 1.08, $CHCl_3$). HPLC analysis: 98% ee (CHIRAL CEL AD-H; hexane/^{i}PrOH = 99/1; flow rate 1 mL/min, 25 °C). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.91; H, 7.60.

(1*R*,2*R*,5*R*)-1-Methyl-5-(2-methoxy-5-methyl)phenyl-6-oxabicyclo[3.1.0]hex-2-yl 4-Methylbenzenesulfonate (23a) and (1*R*,2*R*,5*R*)-1-Methyl-5-(2,3-dimethoxy-5-methyl)-

phenyl-6-oxabicyclo[3.1.0]hex-2-yl 4-Methylbenzenesulfonate (23b). *p*-Methylbenzenesulfonyl chloride (2.44 g, 12.81 mmol) was added to a solution of **22a** (2.00 g, 8.54 mmol) in pyridine (8.0 mL) at 0 °C, and the resulting solution was stirred for 3 h at room temperature. The excess reagent was quenched by addition of water, and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (5/1−4/1) as the eluent to give **23a** (3.25 g, 8.37 mmol, 98%). **23a**: Colorless oil; IR (KBr) 1504, 1365, 1176, 914, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.51−1.61 (m, 1H), 1.79−1.88 (m, 1H), 1.94−2.17 (m, 2H), 2.26 (s, 3H), 2.45 (s, 3H), 3.77 (s, 3H), 5.01 (t, 1H, J = 8.3 Hz), 6.74 (d, 1H, J = 8.3 Hz), 7.06 (d, 1H, J = 8.3 Hz), 7.09 (s, 1H), 7.34 (d, 1H, J = 8.4 Hz), 7.84 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 12.8, 20.5, 21.7, 25.4, 29.1, 55.4, 67.9, 68.1, 85.1, 109.9, 123.9, 127.7, 129.4, 129.5, 129.6, 129.7, 134.1, 144.5, 154.4. HPLC analysis: 94% ee (CHIRAL CEL OD; hexane/^{i}PrOH = 99/1; flow rate 1 mL/min, 25 °C); HRMS calcd for $C_{21}H_{24}O_5S$ 388.1344, found 388.1358.

In the same procedure as for **23a**, **23b** (1.27 g, 3.03 mmol, 100%) was obtained from **22b** (800 mg, 3.03 mmol), TsCl (870 mg, 4.55 mmol), pyridine (3.0 mL), and SiO_2 column (hexane−AcOEt (4/1)). **23b**: Amorphous; IR (KBr) 1589, 1177, 1339, 957 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 3H), 1.52 (m, 1H), 1.85 (m, 1H), 2.09 (m, 2H), 2.28 (s, 3H), 2.45 (s, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 4.97 (t, 1H, J = 8.1 Hz), 6.69 (s, 2H), 7,32 (d, 2H, J = 8.1 Hz), 7.83 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 13.1, 21.3, 21.7, 25.3, 29.7, 55.7, 60.8, 68.0, 68.3, 84.9, 113.3, 120.6, 127.7, 128.7, 129.6, 133.5, 134.0, 144.3, 144.6, 151.6. HPLC analysis: 98% ee (CHIRAL CEL OD; hexane/^{i}PrOH = 99/1; flow rate 1 mL/min, 25 °C); HRMS calcd for $C_{22}H_{26}O_6S$ 418.1450, found 418.1456**.**

(1*R*,3*R*)-3-Methyl-3-(2-methoxy-5-methyl)phenyl-2-oxocyclopentyl 4-Methylbenzenesulfonate (24a) and (1*R*,3*R*)-3-Methyl-3-(2,3-dimethoxy-5-methyl)phenyl-2-oxo-cyclopentyl 4-Methylbenzenesulfonate (24b). $EtAlCl_2$ (0.9 M *n*-hexane solution, 0.83 mL, 0.75 mmol) was added to a solution of **23a** (282 mg, 0.75 mmol) in CH_2Cl_2 (7.5 mL) at 0 °C under N_2. The mixture was stirred at 0 °C (the reaction was checked by TLC). After having been diluted with CH_2Cl_2, 10% HCl was added to the mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with saturated $NaHCO_3$ aq. and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (4/1) as the eluent to give **24a** (263 mg, 0.70 mmol, 93%), which was recrystalized by hexane−AcOEt to give the optically pure **24a**. **24a**: Colorless crystals; mp 123−125 °C; IR (KBr) 1759, 1499, 1364, 1177, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.79−1.83 (m, 1H), 2.27 (s, 3H), 2.44 (s, 3H), 2.26−2.39 (m, 3H), 3.66 (s, 3H), 4.99 (t, 1H, J = 8.1 Hz), 6.73 (d, 1H, J = 8.0 Hz), 6.99 (s, 1H), 7.00 (d, 1H, J = 8.0 Hz), 7.34 (d, 2H, J = 8.2 Hz), 7.89 (d, 2H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.8, 23.9, 27.0, 35.3, 47.6, 55.4,-79.1, 111.6, 127.5, 128.0, 128.4, 129.7, 129.9, 132.9, 133.4, 144.7, 153.2, 211.9; $[\alpha]^{21}_D$ −15.6 (*c* 0.55, $CHCl_3$). HPLC analysis: >99% ee (CHIRAL CEL AS; hexane/^{i}PrOH = 99/1; flow rate 1.0 mL/min). Anal. Calcd for $C_{21}H_{24}O_5S$: C, 64.93; H, 6.23; S, 8.25. Found: C, 64.85; H, 6.15; S, 8.18.

In the same procedure as for **24a**, **24b** (988 mg, 2.55 mmol, 99%) was obtained from **23b** (1.00 g, 2.58 mmol), $EtAlCl_2$ (0.98 M *n*-hexane solution, 2.6 mL, 2.58 mmol), CH_2Cl_2 (20 mL), and SiO_2 column (hexane−AcOEt (3/1)). **24b**: Colorless oil; IR (KBr) 1751, 1487, 1177, 764 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.77 (m, 1H), 2.18 (m, 3H), 2.32 (s, 3H), 2.43 (s, 3H), 3.55 (s, 3H), 3.80 (s, 3H), 5.03 (t, 1H, J = 9.6 Hz), 6.60 (s, 1H), 6.61 (s, 1H), 7.33 (d, 2H, J = 8.1 Hz), 7.87 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 21.7, 24.8, 26.5, 36.2, 47.2, 55.6, 59.0, 79.5, 112.4, 118.8, 127.9, 129.6, 133.0, 133.7, 138.5, 142.6, 144.6, 151.9, 210.9; $[\alpha]^{26}_D$ +26.5 (*c* 1.04, $CHCl_3$). HPLC analysis: >98% ee (CHIRAL CEL AD-H; hexane/^{i}PrOH = 99/1; flow rate 1 mL/min, 25 °C). Anal. Calcd for $C_{22}H_{26}O_6S$: C, 63.14; H, 6.26; S, 7.66. Found: C, 63.14; H, 6.24; S, 7.58.

(2*R*)-2-Methyl-2-(2-methoxy-5-methyl)phenylcyclopentanone (25a) and (2*R*)-2-Methyl-2-(2,3-dimethoxy-5-methyl)phenylcyclopentanone (25b). Zn powder (951 mg, 14.6 mmol) was added to a solution of **24a** (113 mg, 0.29 mmol) in glacial AcOH (4 mL) under N_2 and the mixture was refluxed for 6 h. After removal of AcOH in vacuo, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (7/1) as the eluent to give **25a** (55 mg, 0.254 mmol, 87%). **25a**: Colorless crystals; mp 95−96 °C; IR (KBr) 1738, 1450, 1238, 1030, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.77−2.10 (m, 3H), 2.29 (s, 3H), 2.33−2.65 (m, 3H), 3.71 (s, 3H), 6.76 (d, 1H, J = 8.1 Hz), 7.02 (d, 1H, J = 8.1 Hz), 7.09 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.9, 20.4, 20.8, 36.8, 38.4, 50.5, 55.1, 111.5, 128.0, 128.1, 129.7, 132.8, 153.6, 222.0; $[\alpha]^{25}_D$ +25.3 (*c* 0.89, $CHCl_3$). HPLC analysis: >99% ee (CHIRAL CEL AD-H; hexane/^{i}PrOH = 99/1; flow rate 1 mL/min, 25 °C). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.02; H, 8.44.

In the same procedure as for **25a**, **25b** (73 mg, 0.29 mmol, 91%) was obtained from **24b** (134 mg, 0.32 mmol), Zn powder (1.01 g, 15.4 mmol), glacial AcOH (4.5 mL), and SiO_2 column (hexane−AcOEt (5/1)). **25b**: Colorless oil; IR (KBr) 1736, 1487, 1329, 1146, 1997 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.92 (m, 2H), 2.02 (m, 1H), 2.30 (s, 3H), 2.42 (m, 2H), 2.56 (m, 1H), 3.67 (s, 3H), 3.81 (s, 3H), 6.65 (s, 1H), 6.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.7, 20.9, 21.5, 36.8, 40.0, 50.7, 55.6, 58.6, 112.4, 119.7, 132.6, 138.3, 143.1, 151.0, 221.6; $[\alpha]^{25}_D$ +86.0 (*c* 1.05, $CHCl_3$). HPLC analysis: >98% ee (CHIRAL CEL AD-H; hexane/^{i}PrOH = 99/1; flow rate 1 mL/min, 25 °C). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.53; H, 8.00.

(1*R*,2*R*)-1,2-Dimethyl-2-(2-methoxy-5-methyl)phenylcyclopentanol (28a) and (1*R*,2*R*)-1,2-Dimethyl-2-(2,3-dimethoxy-5-methyl)phenylcyclopentanol (28b). THF (5 mL) was added to dry $CeCl_3$ {obtained by drying of $CeCl_3 \cdot 7H_2O$ (1.30 g, 3.49 mmol) at 140 °C under 0.3 mmHg} under N_2 and the mixture was stirred for 2 h. MeLi (Et_2O solution, 3.1 mL, 3.53 mmol) was added dropwise slowly to the mixture at −78 °C. After being stirred for 2 h at room temperature, a solution of **25a** (76 mg, 0.348 mmol) in THF (4 mL) was added dropwise slowly to the resulting mixture at −78 °C. The reaction mixture was allowed to warm to 0 °C over 3 h and the excess reagent was quenched by saturated NH_4Cl aq. The mixture was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (8/1) as the eluent to give **28a** (79 mg, 0.338 mmol, 97%). **28a**: Colorless oil; IR (KBr) 3506, 1496, 1232, 1030, 912, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.36 (s, 3H), 1.66−1.90 (m, 5H), 2.30 (s, 3H), 2.65−2.72 (m, 1H), 2.87 (br s, 1H), 3.82 (s, 3H), 6.82 (d, 1H, J = 8.1 Hz), 7.02 (dd, 1H, J = 8.1, 2.1 Hz), 7.23 (d, 1H, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 20.4, 20.9, 24.4, 25.0, 38.6, 40.8, 52.7, 55.2, 83.5, 111.8, 127.7, 129.8, 129.9, 132.7, 155.8; $[\alpha]^{26}_D$ −24.2 (*c* 0.23, $CHCl_3$). HPLC analysis: >99% ee (CHIRAL CEL OD; hexane/^{i}PrOH = 99/1; flow rate 1 mL/min, 25 °C). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.89; H, 9.36.

In the same procedure as for **28a**, **28b** (50 mg, 0.189 mmol, 92%) was obtained from **25b** (51 mg, 0.205 mmol), $CeCl_3 \cdot 7H_2O$ (765 mg, 2.05 mmol), MeLi (1.5 mL, 2.05 mmol), THF (2 mL-2 mL), and SiO_2 column (hexane−AcOEt (5/1)). **28b**: Colorless oil; IR (KBr) 3501, 1462, 1232, 1059 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.36 (s, 3H). 1.83 (m, 5H), 2.30 (s, 3H), 2.59 (m, 1H), 2.74 (br s, 1H), 3.82 (s, 3H), 3.85 (s, 3H), 6.65 (d, 1H, J = 1.8 Hz), 6.85 (d, 1H, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 20.2, 21.7, 24.2, 25.5, 38.6, 40.4, 52.9, 55.7, 60.6, 83.4, 111.9, 121.2, 132.4, 137.3, 146.0, 152.9; $[\alpha]^{27}_D$ −13.8 (*c* 1.05, $CHCl_3$). HPLC analysis: >98% ee (CHIRAL CEL OD; hexane/^{i}PrOH = 99/1;

flow rate 1 mL/min, 25 °C). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.95; H, 9.06.

(3*S*)-2,3-Dimethyl-3-(2-methoxy-5-methyl)phenylcyclopent-1-ene (29a) and (3*S*)-2,3-Dimethyl-3-(2,3-dimethoxy-5-methyl)phenylcyclopent-1-ene (29b). A solution of Burgess reagent (90 mg, 16.8 mmol) and **28a** (500 mg, 2.14 mmol) in THF (21 mL) was refluxed for 0.5 h under N_2. The mixture was poured into water and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography with hexane as the eluent to give **29a** (360 mg, 1.67 mmol, 78%). **29a**: Colorless oil; IR (KBr) 1497, 1242, 912, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3H), 1.59 (dd, 3H, J = 3.7, 2.0 Hz), 1.76−1.84 (m, 1H), 2.18−2.25 (m, 2H), 2.27 (s, 3H), 2.31−2.40 (m, 1H), 3.76 (s, 3H), 5.45 (d, 1H, J = 1.5 Hz), 6.76 (d, 1H, J = 8.3 Hz), 6.92 (d, 1H, J = 2.2 Hz), 6.98 (dd, 1H, J = 8.3, 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.7, 20.8, 25.1, 29.9, 40.0, 52.6, 55.3, 111.5, 124.5, 127.2, 128.7, 128.9, 135.3, 146.4, 156.3. HPLC analysis: >99% ee (CHIRAL CEL ODH; hexane only; flow rate 0.5 mL/min); HRMS calcd for $C_{15}H_{20}O$ 216.1514, found 216.1518 (**29a** is volatile).

In the same procedure as for **29a**, **29b** (47 mg, 0.19 mmol, 100%) was obtained from **28b** (50 mg, 0.19 mmol), Burgess reagent (8.0 mg, 1.51 mmol), THF (2 mL), and SiO_2 column (hexanes−Et_2O (1/3)). **29b**: Colorless oil; IR (KBr) 1464, 1313, 1059 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.50 (m, 3H), 1.82 (m, 1H), 2.24 (s, 3H), 2.25 (s, 3H), 3.68 (s, 3H), 3.76 (s, 3H), 5.37 (br s, 1H), 6.52 (br s, 1H), 6.56 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.5, 21.5, 26.1, 30.2, 41.2, 53.6, 55.6, 60.1, 111.4, 120.5, 124.5, 124.7, 132.0, 140.8, 146.9, 153.0. HPLC analysis: >98% ee (CHIRAL CEL OD-H; hexane only; flow rate 0.5 mL/min, 10 °C); HRMS calcd for $C_{16}H_{22}O_2$ 246.1620, found 246.1618 (**29b** is volatile).

2-(2-Methoxy-5-methyl)phenyl-1,2-dimethylbicyclo[3.1.0]hexane (30a) and 2-(2,3-Dimethoxy-5-methyl)phenyl-1,2-dimethylbicyclo[3.1.0]hexane (30b). CH_2I_2 (2.6 mL, 32.0 mmol) was added dropwise to a solution of Et_2Zn (1 M *n*-hexane solution, 32 mL, 32 mmol) in CH_2Cl_2 (10 mL) at 0 °C under N_2, and the mixture was stirred for 0.5 h at the same temperature. A solution of **29a** (360 mg, 1.67 mmol) in CH_2Cl_2 (11 mL) was added dropwise to the resulting solution, and the mixture was stirred for 30 h at room temperature. Excess reagent was quenched by saturated NH_4Cl aq at 0 °C. The mixture was extracted with Et_2O. The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by SiO_2 column chromatography with hexane as the eluent to give **30a** (345 mg, 1.50 mmol, 90%, ca. 2:1 mixture of two isomers). **30a**: Colorless oil; IR (KBr) 1497, 1242, 1036, 804 cm^{-1}; ^1H NMR ($CDCl_3$) (major product) δ 0.14−0.18 (m, 1H), 0.46−0.47 (m, 1H), 1.07 (s, 3H), 1.26−1.70 (m, 4H), 1.70 (s, 3H), 1.81−1.98 (m, 1H), 2.29 (s, 3H), 3.77 (s, 3H), 6.77 (d, 1H, J = 8.1 Hz), 6.97 (dd, 1H, J = 8.1, 2.1 Hz), 7.19 (d, 1H, J = 2.1 Hz), (minor product) δ 0.46−0.52 (m, 2H), 1.07 (s, 3H), 1.26−1.70 (m, 4H), 1.70 (s, 3H), 2.17−2.31 (m, 1H), 2.31 (s, 3H), 3.76 (s, 3H), 6.77 (d, 1H, J = 8.1 Hz), 6.97 (dd, 1H, J = 8.1, 2.1 Hz), 7.38 (d, 1H, J = 2.1 Hz). HRMS calcd for $C_{16}H_{22}O$ 230.1671, found 230.1669.

In the same procedure as for **30a**, **30b** (23 mg, 0.089 mmol, 72%, ca. 5:2 mixture of two isomers) was obtained from **29b** (30 mg, 0.12 mmol), CH_2I_2 (30 μL, 0.365 mmol × 4), Et_2Zn (1 M *n*-hexane solution, 0.37 mL, 0.365 mmol × 4) in CH_2Cl_2 (0.8 mL), and SiO_2 column (hexane−AcOEt (20/1)). Cyclopropanation of **29b** was very slow and the reagents were added to the reaction mixture 4 times. **30b**: IR (KBr) 1462, 1317, 1061, 743 cm^{-1}; ^1H NMR ($CDCl_3$) (major product) δ 0.14−0.19 (m, 1H), 0.47−0.48 (m, 1H), 1.10 (s, 3H), 1.15−1.61 (m, 4H), 1.61 (s, 3H), 1.85−1.87 (m, 1H), 2.32 (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 6.61 (br s, 1H), 6.83 (br s, 1H), (minor product) δ 0.50−0.52 (m, 2H), 1.10 (s, 3H), 1.15−1.61 (m, 4H), 1.61 (s, 3H), 2.10−2.12 (m, 1H), 2.30 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 6.62 (br s, 1H), 7.26 (br s, 1H). HRMS calcd for $C_{17}H_{24}O_2$ 260.1802, found 260.1776.

(1*S*)-1,2,2-Trimethy-1-(2-methoxy-5-methyl)phenylcyclopentane (31a) and (1*S*)-1,2,2-Trimethy-1-(2,3-dimethoxy-5-methyl)phenylcyclopentane (31b). Compound **30a** (50 mg, 0.22 mmol), AcONa (142 mg, 1.74 mmol), and PtO_2 (195 mg, 0.87 mmol) in AcOH (1.0 mL) were hydrogenated with H_2 under 3 atm. After completion of the reaction (TLC check), the reaction mixture was filtered through Celite pad with CH_2Cl_2. The filtrate was washed with water and brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography with hexane as the eluent to give **31a** (47 mg, 0.20 mmol, 94%). **31a**: Colorless oil; IR (KBr) 1497, 1242, 1034, 804 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (s, 3H), 1.14 (s, 3H), 1.33 (s, 3H), 1.50−1.73 (m, 5H), 2.28 (s, 3H), 2.50−2.54 (m, 1H), 3.74 (s, 3H), 6.75 (d, 1H, J = 8.1 Hz), 6.96 (br d, 1H, J = 8.1 Hz), 7.11 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.5, 20.9, 23.1, 26.0, 27.6, 39.8, 42.0, 44.1, 51.1, 54.8, 111.4, 127.0, 128.7, 129.6, 135.9, 156.7; $[\alpha]^{25}_D$ −50.2 (*c* 1.37, $CHCl_3$). HPLC analysis: >99% ee (CHIRAL CEL OD-H; hexane only; flow rate 0.5 mL/min); HRMS calcd for $C_{16}H_{24}$: 232.1827, found 232.1813 (**31a** is slight volatile).

In the same procedure as for **31a**, **31b** (37 mg, 0.14 mmol, 93%) was obtained from **30b** (40 mg, 0.15 mmol), AcONa (101 mg, 1.23 mmol), PtO_2 (136 mg, 0.61 mmol) in AcOH (1.5 mL), and SiO_2 column (hexane−benzene (1/1)). **31b**: Colorless oil; IR (KBr) 1479, 1234, 1058, 1011, 831 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (s, 3H), 1.13 (s, 3H), 1.36 (s, 3H), 1.47−1.82 (m, 5H), 2.30 (s, 3H), 2.62 (m, 1H), 3.78 (s, 3H), 3.83 (s, 3H), 6.62 (s, 1H), 6.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.3, 21.7, 24.2, 25.2, 26.8, 38.9, 40.8, 45.9, 51.5, 55.6, 60.4, 111.0, 121.6, 131.6, 140.1, 146.6, 153.0; $[\alpha]^{24}_D$ −32.3 (*c* 0.54, $CHCl_3$). HPLC analysis: 98% ee (CHIRAL CEL OD-H; hexane/^{i}PrOH = 99/1; flow rate 1 mL/min, 10 °C). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 72.80; H, 9.94.

(−)-α-Herbertenol ((−)-19a) and (−)-Herbertenediol ((−)-19b). BBr_3 (1 M CH_2Cl_2 solution, 0.44 mL, 0.44 mmol) was added dropwise to a solution of **31a** (41 mg, 0.178 mmol) in CH_2Cl_2 (1.8 mL) under N_2. After being stirred for 0.5 h at room temperature, saturated $NaHCO_3$ aq was added to the mixture, which was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (20/1) as the eluent to give (−)-**19a** (37 mg, 0.17 mmol, 95%). **(−)-19a:** Colorless oil; IR (KBr) 3535, 1506, 1165, 808 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (s, 3H), 1.18 (s, 3H), 1.41 (s, 3H), 1.46−1.79 (m, 5H), 2.26 (s, 3H), 2.31−2.66 (m, 1H), 4.58 (s, 1H), 6.57 (d, 1H, J = 7.9 Hz), 6.86 (dd, 1H, J = 7.9, 2.1 Hz), 7.69 (d, 1H, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 20.3, 20.9, 22.9, 25.6, 26.9, 39.4, 41.2, 44.6, 50.9, 116.7, 127.2, 129.0, 130.0, 133.0, 152.2; $[\alpha]^{25}_D$ −56.3 (*c* 1.28, $CHCl_3$) (lit.[1c] $[\alpha]_D$ −55.0). HPLC analysis: >99% ee (CHIRAL CEL OD-H; hexane/^{i}PrOH = 98/2; flow rate 0.5 mL/min); HRMS calcd for $C_{15}H_{22}O$ 218.1671, found 218.1704.

In the same procedure as for **19a**, **19b** (29 mg, 0.125 mmol, 93%) was obtained from **31b** (35 mg, 0.134 mmol), BBr_3 (1 M CH_2Cl_2 solution, 0.40 mL, 0.40 mmol), CH_2Cl_2 (1.3 mL), and SiO_2 column (hexane−AcOEt (5/1)). **19b**: Colorless crystal; mp 89−90 °C; IR (KBr) 3508, 2959, 1302 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (s, 3H), 1.18 (s, 3H), 1.41 (s, 3H), 1.52−1.76 (m, 5H), 2.22 (s, 3H), 2.60−2.61 (m, 1H), 5.34 (s, 1H), 5.40 (s, 1H), 6.55 (s, 1H), 6.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.3, 21.1, 22.8, 25.4, 26.8, 39.2, 40.9, 44.8, 51.1, 113.4, 121.8, 128.2, 133.4, 141.0, 143.3; $[\alpha]^{28}_D$ −57.0 (*c* 0.78, $CHCl_3$) {lit.[7b] $[\alpha]^{25}_D$ −53.8 (*c* 1.0, $CHCl_3$)}. HPLC analysis: >98% ee (CHIRAL CEL OD-H; hexane/^{i}PrOH = 99/1; flow rate 1 mL/min, 25 °C).

Supporting Information Available: Experimental procedures and spectral data for *cis*- and *trans*-2,3-epoxysulfonates **1a**−**e**, **5**, and **8**, the rearranged products **2a**−**e**, **6**, and **9**, and the compounds in the formal synthesis of (−)-aphanorphine **14**, **15**, **16**, **17**, **18**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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