Asymmetric Induction via an Intramolecular Haloetherification Reaction of Chiral Ene Acetals: A Novel Approach to Optically Active 1,4- and 1,5-Diols

Hiromichi Fujioka,* Hidetoshi Kitagawa, Yasushi Nagatomi, and Yasuyuki Kita*

Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565, Japan

Received April 18, 1996[⊗]

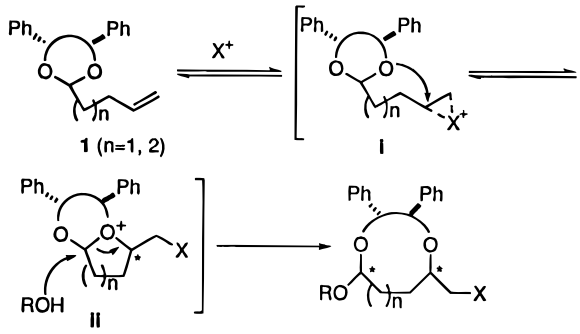
An asymmetric synthesis of chiral 1,4- and 1,5-diols has been developed from the ene acetals **1a** and **1c**, prepared from the corresponding aldehydes and chiral C_2-symmetric diols, involving remote asymmetric induction as a key step. In the first step, treatment of **1** with $I(coll)_2ClO_4$ in the presence of an alcohol afforded the macrocyclic acetals (**3**−**5** and **7**) in a highly stereoselective manner. Subsequent nucleophilic substitution of iodide followed by a Grignard reaction with complete retention of stereochemistry and a final deprotection of the diphenylethylene or diphenylpropylene unit successfully gave optically active 1,4- and 1,5-diols in good yields.

Introduction

Nucleophilic addition to a carbocation or oxonium ion, formed by C−O bond fission of an acetal, has been recognized as a useful synthetic tool in organic chemistry, and many variants have been developed so far. In these reactions, a Lewis acid is usually used as an initiator to accelerate the cleavage of an acetal.[1] Cationic species, formed by electrophilic addition of halonium ion to a double bond, have also been developed as initiators to cleave an acetal, since Fraser-Reid *et al.* had recently reported that a remote double bond can cleave an acetal under neutral, oxidative conditions through an intramolecular haloetherification reaction.[2] On the other hand, asymmetric synthesis using chiral acetals from C_2-symmetric diols has been vigorously studied as an important approach to optical active compounds.[3] This transformation involves two types of reactions: (1) an asymmetric reaction involving cleavage of the C−O bond of the acetal, which functions as the chiral synthetic equivalent of a carbonyl group, and (2) asymmetric induction on a neighboring prochiral center. However, no report that involves these two types of reactions has been published. Also, in the type-1 reactions, only a Lewis acid was used to cleave an acetal, not a carbocation.

It occurred to us that the intramolecular haloetherification reaction of the ene acetal **1** prepared from a C_2-symmetric diol in the presence of an alcohol could proceed by the cascade of cationic intermediates **i** ⇒ **ii** to give a cyclic acetal with two newly formed asymmetric centers. This reaction is unprecedented as it involves two types of reactions using C_2-symmetric acetals (Scheme 1).[4]

Scheme 1



To develop this chemistry, we studied the transformation of several ene acetals and found that the ene acetal **1a** (cf. Table 1) derived from chiral hydrobenzoin in the case of $n = 1$ and the ene acetal **1c** (cf. Table 2) derived from chiral 1,3-diphenyl-1,3-propanediol in the case of $n = 2$ were found to be best substrates for affording cyclic mixed acetals with high diastereoselectvity (Scheme 2, first step). After substitution of the iodide by the nucleophile, the alkoxy group of the mixed acetal was then converted to an alkyl group by Grignard substitution (Scheme 2, second step). Finally, deprotection of the diphenylethylene or diphenylpropylene unit gave chiral 1,4- or 1,5-diols, respectively (Scheme 2, third step). We present here the full details of our results[5] and the formal synthesis of Solenopsin A,[6] which is isolated from the venom secreted by the fire ant *Solenopsis invicta*, and the synthesis of a civet constituent.[7]

[⊗] Abstract published in *Advance ACS Abstracts,* September 15, 1996.

(1) For examples, see: (a) Kotsuki, H. *Synlett* **1992**, 97. (b) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043. (c) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

(2) For studies of halonium ion mediated neighboring group activation of acetal cleavage, see: (a) Robert, M.; Udodong, U. E.; Roberts, C.; Mootoo, D. R.; Konradsson, P.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 1554. (b) Roberts, C.; Madsen, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1995**, *117*, 1546. (c) Madsen, R.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 772. (d) Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, J.; Merritt, J. R.; Rao, C. S.; Roberts, C. *Synlett* **1992**, 927. (e) Zhang, H.; Wilson, P.; Shan, W.; Ruan, Z.; Mootoo, D. R. *Tetrahedron Lett.* **1995**, *36*, 649. (f) Wilson, P.; Shan, W. F.; Mootoo, D. R. *J. Carbohydr. Chem.* **1994**, *13*, 133. (g) Elvey, S. P.; Mootoo, D. R. *J. Am. Chem. Soc.* **1992**, *60*, 9685. (h) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1987**, 1462. References e−h include the reactions of remote stereocontrol.

(3) For reviews on the asymmetric synthesis using the chiral C_2-symmetric acetals, see: (a) Alexakis, A.; Mangeny, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477. (b) Fujioka, H.; Kita, Y. *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Elsevier, Ed.; Amsterdam: 1994; Vol. 14, p 469.

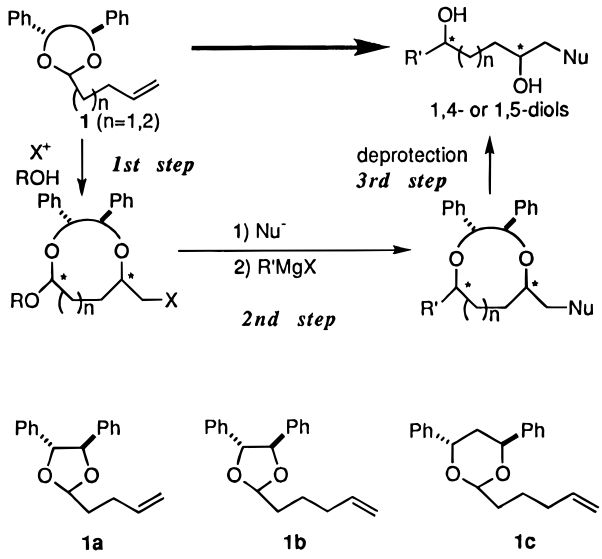
(4) For our representative studies using the chiral C_2-symmetric acetals, see: (a) Fujioka, H.; Kitagawa, H.; Yamanaka, T.; Kita, Y. *Chem. Pharm. Bull.* **1992**, *40*, 3118. (b) Fujioka, H.; Annoura, H.; Murano, K.; Kita, Y.; Tamura, Y. *Chem. Pharm. Bull.* **1989**, *37*, 2047. (c) Tamura, Y. Annoura, H.; Yamamoto, H.; Kondo, H.; Kita, Y. Fujioka, H. *Tetrahedron Lett.* **1987**, *28*, 5709. (d) Tamura, Y. Annoura, Fujioka, H. *Tetrahedron Lett.* **1987**, *28*, 5681. (e) Tamura, Y.; Ko, T.; Kondo, H.; Annoura, H.; Fuji, M.; Takeuchi, R.; Fujioka, H. *Tetrahedron Lett.* **1986**, *27*, 2117. (f) Tamura, Y.; Kondo, H.; Annoura, H.; Takeuchi, R.; Fujioka, H. *Tetrahedron Lett.* **1986**, *27*, 81.

(5) The preliminary stereoselective synthesis of optically active 1,4-diols has been recently communicated: Fujioka, H.; Kitagawa, H.; Matsunaga, N.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **1996**, *37*, 2245.

(6) Solladié, G.; Huser, N. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 153 and references therein.

S0022-3263(96)00714-1 CCC: $12.00

Scheme 2



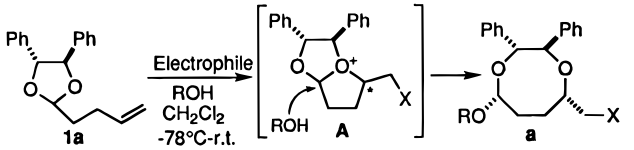
Results and Discussion

First Step: Haloetherification Reaction. Initially, the haloetherification reaction of **1a** which has a chiral hydrobenzoin[8] as an auxiliary was studied. Electrophiles such as NBS and $I(coll)_2ClO_4$[9] gave the cyclic mixed acetals (**2**−**5**) in the presence of ROH. The reaction using I_2 gave the product of addition of I_2 to the double bond. As shown in Table 1, $I(coll)_2ClO_4$ proved to be a better choice than NBS in terms of diastereoselectivity (entry 1 vs 2). Several alcohols were examined in this reaction, and the stereoselectivities are similar (entries 2−4). The structures of the major products (**a**) were determined by ^{1}H NMR study and conversion to a known compound[10] and shown in Table 1 (for the structures of **b**, **c**, and **d**, see Scheme 5).[11]

Furthermore, the reaction of **1b** prepared from chiral hydrobenzoin and 5-hexenal was studied. In this case, only normal haloetherification reaction products **6** were obtained with no diastereoselectivity (Scheme 3).

The different reactivity between **1a** and **1b** might be rationalized as follows: (1) the longer distance between the acetal oxygen atom and the cation formed on the double bond in **1b** prevents the formation of a bicyclic cationic intermediate like **A** in **1a**[12] and (2) the 5,6-membered bicyclic cationic intermediate **B′** is more unstable than the 5,5-membered one **A**. We then prepared the ene acetal **1c** derived from chiral 1,3-diphenyl-1,3-propanediol,[13] hoping that the 6,6-membered bicyclic intermediate **C** is more stable and more easily formed (Scheme 4).[14]

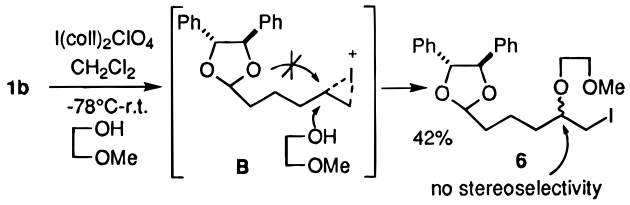
Table 1. Reaction of 1a with Electrophile in the Presence of an Alcohol



entry	electrophile	R	product	yield, %	selectivity[a] (**a**:**b**:**c**:**d**)[b]
1	NBS	Me	**2** (X = Br)	95	74:8:18:0
2	$I(Coll)_2ClO_4$	Me	**3** (X = I)	86	85:3:12:0
3	$I(Coll)_2ClO_4$	Bn	**4** (X = I)	74	90:10[c]
4	$I(Coll)_2ClO_4$	$MeOCH_2CH_2$	**5** (X = I)	90	86:2:11:1

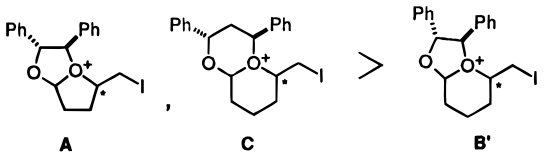
[a] Determined by ^{1}H NMR studies and HPLC analysis. [b] For **a**, **b**, **c**, and **d**, see Scheme 5. [c] The ratio is **a** + **b**:**c** + **d**. Determined by converting the product to the corresponding aldehyde by acid hydrolysis.

Scheme 3



As expected, although a higher temperature (−20 °C) was necessary compared to **1a** (−78 °C) and the selectivity was slightly reduced, the reaction of **1c** proceeded successfully to give cyclic acetal **7** in good yields (Table 2). In this case, CH_3CN is the solvent of choice (entry 1 vs 2), and bis(*sym*-collidine)iodine hexafluorophosphate $[I(coll)_2PF_6]$[15] showed the best stereoselectivity and reactivity (entry 4). The structure of the major product **7** was determined by conversion to the known compounds

Scheme 4

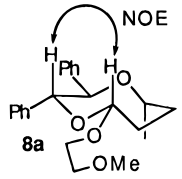


(7) For previous synthesis of the optically active natural product, see: (a) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474. (b) Seebach, D.; Pohmakotr, M. *Helv. Chim. Acta* **1979**, *62*, 1096. (c) Lichtenthaler, F. W.; Klingler, F. D.; Jarglis, P. *Carbohydr. Res.* **1984**, *132*, C1.

(8) Chiral hydrobenzoin is readily available in both enantiomeric forms by asymmetric synthesis or resolution; for asymmetric synthesis, see, Wang *et al*. (Wang, Z. -M.; Sharpless, K. B. *J. Org. Chem*. **1994**, *59*, 8302) and for resolution of *dl*-hydrobenzoin, see *Optical Resolution Procedures for Chemical Compounds*; Mewman, P., Optical Information Center: Manhattan College, Riverdale, NY 1984; Vol. 3, p 353.

(9) Preparation: Lemieux, R. U.; Morgan, A. R. *Can. J. Chem*. **1965**, *43*, 2190.

(10) The stereochemistries of the major products **a** were determined from the NOE experiment on **8a** (Table 3) derived from **5a**. The stereochemistries of the halomethyl substituent were determined by converting **5** to the (*R*)-enriched-pentane-1,4-diol {$[\alpha]^{23}_D$ −10° (*c* 0.46, MeOH) lit. $[\alpha]^{21}_D$ −13.4° (*c* 1.05, MeOH); Kitahara, T.; Mori, K.; Matsui, M. *Tetrahedron Lett.* **1979**, *32*, 3021} in a three-step sequence: (1) acid hydrolysis, (2) $LiAlH_4$ reduction, and (3) hydrogenolysis.



(11) The structures of **b**, **c**, and **d** were postulated from consideration of the reaction mechanism and the assignment is tentative.

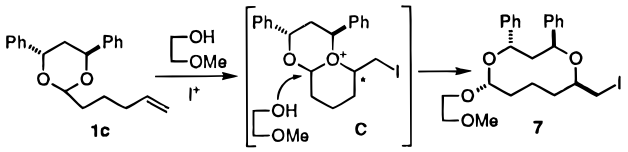
(12) A similar result was reported by B. Fraser-Reid *et al.* They suggested that the formation of the 6-membered oxonium ion was slower than that of the 5-membered one (see ref 2d).

(13) Optically active 1,3-diphenyl-1,3-propanediol is available in both enantiomeric forms by asymmetric synthesis or microbial resolution; for asymmetric synthesis, see, Wang *et al*. (Wang, Z. -M.; Ito, K.; Harada, T.; Tai, A. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 3367) and for microbial resolution, see: Yamamoto, K.; Ando, H.; Chikamatsu, H. *J. Chem. Soc., Chem. Commun*. **1994**, 334.

(14) There is another possible 6,5-membered bicyclic intermediate from reaction of the acetal derived from 4-pentenal and 1,3-diphenyl-1,3-propanediol. We did not feel it necessary to examine its reaction in order to develop the asymmetric synthesis of 1,4-diols.

(15) Bis(*sym*-collidine)iodine(I) hexafluorophosphate ($I(coll)_2PF_6$) is also used during halolactonization, see: Simonot, B.; Rousseau, G. *J. Org. Chem*. **1994**, *59*, 5912.

Table 2. Reaction of 1c with Electrophile in the Presence of $MeOCH_2CH_2OH$



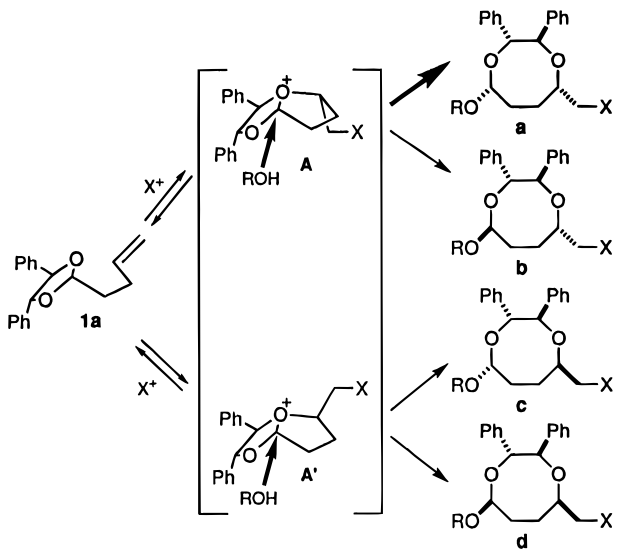
entry	I^+	solvent	temp, °C	yield, %	selectivity[a]
1	$I(coll)_2ClO_4$	CH_2Cl_2	−78 °C−rt	57	76:4:18:2
2	$I(coll)_2ClO_4$	CH_3CN	−20 °C−rt	66	78:9:14:1
3	$I(coll)_2ClO_4$	CH_3CN	0 °C−rt	74	78:11:10:1
4	$I(coll)_2PF_6$	CH_3CN	−20 °C−rt	85	80:6:12:2
5	NIS	CH_3CN	−20 °C−rt	41	72:12:15:1

[a] Determined by chiral HPLC (Celamospher chiral Ru-1) analysis of the reductive derivative **8d**.

(**11** and **15**) and by postulating that the reaction proceeded through an S_N2-type attack of an alcohol to the bicyclic oxonium ion **C** as observed in the reaction of **1a** (see the section Reaction Mechanism).

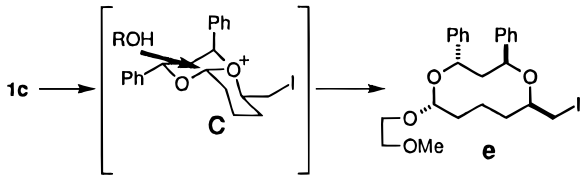
Reaction Mechanism. The plausible reaction mechanism in the case of **1a** is shown in Scheme 5. First,

Scheme 5



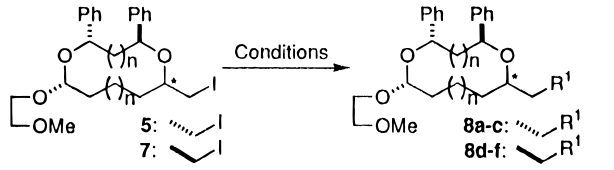
addition of the halonium ion to the double bond followed by attack of one of the acetal oxygen atoms forms the bicyclic oxonium ion intermediate **A** or **A′**. Subsequent S_N2-type attack of an alcohol to **A** or **A′** occurs to give the 8-membered acetal (**a** > **b**, **c** > **d**). In view of the fact that this reaction gives rise exclusively to 8-membered acetal **a** as the major product, we think that intermediate **A** should be more favorable than **A′** (Scheme 5, **a** + **b** > **c** + **d**). In the case of **1c**, the reaction might proceed in a similar way through the most stable intermediate **C** among the possible bicyclic intermediates (Scheme 6).[16]

Scheme 6



Second Step: Substitution of Iodide and Alkoxy Group. Substitution of the iodide in compounds **5** and **7**, involving four stereoisomers respectively, with several nucleophiles proceeded without any problem by known procedures. The results are summarized in Table 3. At this stage, **8a**−**f** were obtained in a pure state and the yields shown in Table 3 are the yields of pure **8a**−**f**.

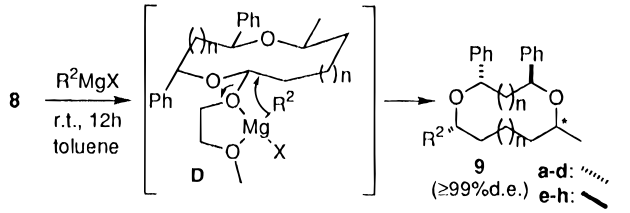
Table 3. Nucleophilic Substitution of Iodide

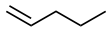


entry	substr	conditions	product	yield, %
1	**5** (n = 0)	$LiAlH_4$, THF	R^1 = H (**8a**)	72
2	**5** (n = 0)	NaCN, DMSO	R^1 = CN (**8b**)	70
3	**5** (n = 0)	NaH, $CH_2(CO_2Me)_2$	R^1 = $CH(CO_2Me)_2$ (**8c**)	65
4	**7** (n = 1)	$LiAlH_4$, THF	R^1 = H (**8d**)	79
5	**7** (n = 1)	NaCN, DMSO	R^1 = CN (**8e**)	82
6	**7** (n = 1)	NaH, $CH_2(CO_2Me)_2$	R^1 = $CH(CO_2Me)_2$ (**8f**)	79

We next studied the nucleophilic replacement of the alkoxy group of **8a** and **8d** with carbon nucleophiles. Grignard reagents[17] reacted at the acetal carbon and substitution occurred in good yields with complete retention of stereochemistry to give **9** (Table 4).[18] A long chain

Table 4. Grignard Reaction of 8



entry	substr	R^2	product	yield, %
1	**8a** (n = 0)	Me	**9a**	96
2	**8a** (n = 0)	Et	**9b**	87
3	**8a** (n = 0)	allyl	**9c**	92
4	**8a** (n = 0)		**9d**	86
5	**8d** (n = 1)	Me	**9e**	90
6	**8d** (n = 1)	Et	**9f**	90
7	**8d** (n = 1)	allyl	**9g**	98
8	**8d** (n = 1)	$C_{11}H_{23}$	**9h**	97

carbon nucleophile can be introduced without any problem (entry 8). In these reactions, the methoxyethoxy group is essential since the derivatives with a methoxy group or benzyloxy group derived from **3** or **4** by $LiAlH_4$ reduction showed disappointing results (with MeMgI;

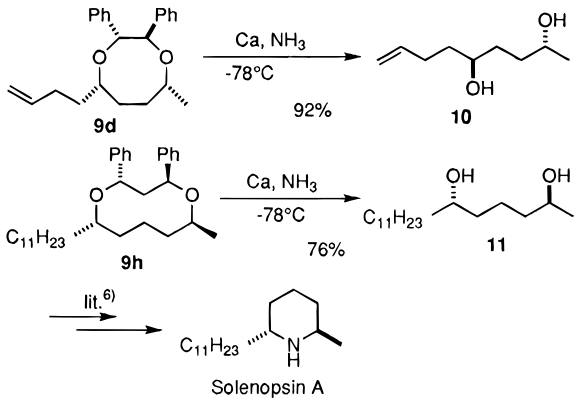
(16) We performed MO calculations for all of possible 6,6-membered bicyclic oxonium ions by SPARTAN (version 3.1.2) using the AM1 Hamiltonian. The results showed that the *cis*-decalin form intermediate **C** is the most stable among the others involving *trans*-decalin form intermediates. (The heat of formation of **C** was 145.71 kcal/mol. The others were 146.80 kcal/mol for another *cis*-decalin form intermediate and 148.79, 151.16 kcal/mol for *trans* ones.) These calculational results were consistent with our experimental results. We think that the stability of bicyclic intermediates has a large influence on the reaction of **1c**. We also performed MO calculations on 5,5-membered bicyclic intermediates. In these cases, the intermediate **A′** was more stable than **A**. (The heat of formation of **A** was 159.30 kcal/mol, and of **A′** was 157.18 kcal/mol.) This calculational result did not fit with our experimental results. It is probable that the repulsion between the halomethyl substituent and anion species, which should exist on the convex side of the cation, has a large influence on the reaction of **1a** and makes the formation of **A′** undesirable.

(17) For the reaction of a Grignard reagent and an acetal, see: Yuan, T.-M.; Yeh, S.-M.; Hsieh, Y.-T.; Luh, T.-Y. *J. Org. Chem.* **1994**, *59*, 8192 and references therein.

43% for the methoxy derivative and 0% for the benzyloxy derivative). The reason for the good yields and complete retention of stereochemistry can be attributed to the formation of complex **D**. With Lewis acidic conditions ($TiCl_4$/allyltrimethylsilane/CH_2Cl_2/−78 °C) the reaction gave complex mixtures.

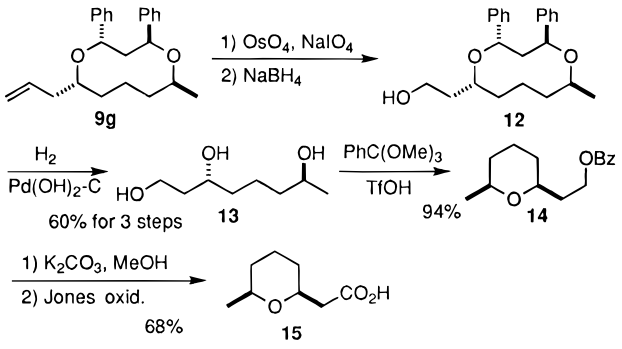
Third Step: Deprotection. As highly stereoselective construction of compounds **9a**−**h** had been achieved, we next examined the removal of the chiral auxiliary unit using catalytic hydrogenolysis or Birch reduction. Both processes proceeded smoothly and afforded the corresponding optically active 1,4- and 1,5-diols (**10**, **11**) in good yields, respectively. Since the 1,5-diol (**11**) had already been converted to solenopsin A, a constituent of the venom of the fire ant *S. invicta*, by G. Solladié *et al.*,[6] a formal synthesis of solenopsin A was achieved (Scheme 7).

Scheme 7



Synthesis of a Civet Constituent. We next synthesized (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**15**), a civet constituent that was isolated from the perfume material civet,[19] a glandular secretion of the civet cat *Viverra civetta* (Scheme 8). Oxidative cleavage of the olefin of **9g** followed by $NaBH_4$ reduction gave the alcohol **12**. Catalytic hydrogenolysis of **12** afforded the triol **13**, which was combined with $PhC(OMe)_3$ to give the cyclic ether **14**.[20] Alkaline hydrolysis of **14** followed by Jones oxidation gave a civet constituent, the cyclic ether **15**.

Scheme 8



(18) The stereochemistry of compounds **9a**−**h** were determined by X-ray crystallography of the *p*-nitrobenzoate derivative **16** derived from **9d** by hydroboration−oxidation followed by *p*-nitrobenzoylation. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Conclusions

A new asymmetric synthesis of chiral 1,4- and 1,5-diols has been developed on the basis of remote asymmetric induction as a key step. In the first step, the acetal acts initially as a nucleophile and then as an electrophile in a one-pot operation and the two remote stereogenic centers are built up simultaneously. It is noteworthy that the formation of a bicyclic cationic intermediate makes the reaction stereoselective. In the second step, the conversion of an alkoxy group to alkyl groups has been achieved in high yields with complete retention of stereochemistry. The use of a methoxyethoxy functionality is noteworthy. In the third step, the usual deprotection procedure worked well to give optically active 1,4- and 1,5-diols. These results suggest that the diphenylethlene or diphenylpropylene unit is a useful protecting group for diols.

Experimental Section

All melting points are uncorrected. NMR spectra were measured on 270 MHz and 500 MHz spectrometers with $CDCl_3$ as a solvent and with $SiMe_4$ as an internal standard. Infrared (IR) absorption spectra were recorded as a KBr pellet. All solvents were dried and distilled according to standard procedure.

Preparation of Ene Acetals 1a−c. To a solution of ene aldehyde (1.0 mmol) and optical active diol (1.0 mmol) in C_6H_6 (10 mL) was added *p*-toluenesulfonic acid (0.05 mmol). The reaction mixture was refluxed for 1 h with azeotropic removal of water. K_2CO_3 was added to the mixture at rt. After being stirred for 15 min, the solution was filtered through Celite and concentrated in vacuo. The residue was purified by SiO_2 column chromatography using hexane−AcOEt (20/1) as an eluent to give the ene acetal quantitatively.

(4*R*,5*R*)-2-(3-Butenyl)-4,5-diphenyl-1,3-dioxolane (1a): colorless oil; bp 140−150 °C (bath temperature)/0.2 mmHg; $[\alpha]^{25}_D$ +53° (*c* 2.4, $CHCl_3$); IR (KBr) 1496, 1452 cm^{-1}; ^1H NMR δ 1.9−2.1 (m, 2H), 2.3−2.5 (m, 2H), 4.7−4.8 (m, 2H), 5.0−5.2 (m, 2H), 5.55 (t, J = 4.5 Hz, 1H), 5.8−6.0 (m, 2H), 7.2−7.4 (m, 10H). Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.16; H, 7.27.

(4*S*,6*S*)-2-(4-Pentenyl)-4,6-diphenyl-1,3-dioxane (1c): colorless oil; bp 180−190 °C (bath temperature)/0.2 mmHg; $[\alpha]^{21}_D$ +69° (*c* 1.8, $CHCl_3$); IR (KBr) 1495, 1448 cm^{-1}; ^1H NMR δ 1.5−1.8 (m, 4H), 2.0−2.1 (m, 2H), 2.4−2.5 (m, 2H), 4.75 (dd, J = 9.2, 5.0 Hz, 1H), 4.88 (dd, J = 10.2, 5.3 Hz, 1H), 4.9−5.1 (m, 2H), 5.33 (t, J = 3.3 Hz, 1H), 5.7−5.9 (m, 1H), 7.2−7.5 (m, 10H). Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.86; H, 7.82.

General Procedure for the Reactions in Table 1. To a solution of the ene acetal (**1a**, 1.0 mmol) and an alcohol (5.0 mmol) in CH_2Cl_2 (10.0 mL) was added an electrophile (1.5 mmol) at −78 °C under a nitrogen atmosphere. The reaction mixture was stirred overnight at rt, then quenched with saturated aqueous $Na_2S_2O_3$, and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography to give the products in yields shown in Table 1. The products involving four stereoisomers were used for the next nucleophilic substitution of iodide (Table 3).

The following data for **3a**−**5a** were collected from the products (**3**−**5**) involving four stereoisomers. ^1H NMR data show the signals of the major ones (**3a**−**5a**).

(2*R*,3*R*,5*S*,8*R*)-5-(Iodomethyl)-8-methoxy-2,3-diphenyl-1,4-dioxocane (3a). The ratio of four stereoisomers (**3a**:**3b**:

(19) (a) van Dorp, D. A.; Word, J. P. *Experientia* **1981**, *37*, 917. (b) Maurer, B.; Tohmmen, W. *Ibid.* **1979**, *62*, 1096. (c) Maurer, B.; Grieder, A.; Tohmmen, W. *Helv. Chim. Acta* **1979**, *62*, 44.

(20) (a) Fujioka, H.; Kitagawa, H.; Kondo, M.; Kita, Y. *Heterocycles* **1994**, *37*, 743. (b) Fujioka, H.; Kitagawa, H.; Kondo, M.; Matsunaga, N.; Kitagaki, S.; Kita, Y. *Heterocycles* **1993**, *35*, 665.

3c:**3d** = 85:3:12:0) was determined by ^{1}H NMR spectra: IR (KBr) 1493, 1454 cm^{-1}; ^{1}H NMR δ 1.9−2.4 (m, 4H), 3.1−3.2 (m, 2H), 3.30 (s, 3H), 4.1−4.3 (m, 1H), 4.42 (d, J = 8.6 Hz, 1H), 4.56 (d, J = 8.6 Hz, 1H), 5.4−5.5 (dd, J = 9.5, 4.0 Hz, 1H), 6.9−7.4 (m, 10H); MS (m/z) 407 (M^+ − OMe); HRMS calcd for $C_{19}H_{20}O_2I$ (M^+ − OMe) 407.0507, found 407.0514.

(2*R*,3*R*,5*S*,8*R*)-8-(Benzyloxy)-5-(iodomethyl)-2,3-diphenyl-1,4-dioxocane (4a). The ratio of four stereoisomers (**4a** + **4b**:**4c** + **4d** = 90:10) was determined by ^{1}H NMR spectra of the hydrolyzed derivatives of **4**: IR (KBr) 1495, 1454 cm^{-1}; ^{1}H NMR δ 1.9−2.4 (m, 4H), 3.11 (d, J = 7.0 Hz, 2H), 4.0−4.8 (m, 5H), 5.57 (t, J = 6.7 Hz, 1H), 6.8−7.2 (m, 15H). Anal. Calcd for $C_{26}H_{27}O_3I$: C, 60.71; H, 5.29; I, 24.67. Found: C, 60.45; H, 5.29; I, 24.43.

(2*R*,3*R*,5*S*,8*R*)-5-(Iodomethyl)-8-(methoxyethoxy)-2,3-diphenyl-1,4-dioxocane (5a). The ratio of four stereoisomers (**5a**:**5b**:**5c**:**5d** = 86:2:11:1) was determined by ^{1}H NMR spectra and HPLC analysis (5SL packed column, 4.6 mm i.d. × 250 mm, CH_2Cl_2/AcOEt = 9/1, 1.0 mL/min flow rate): IR (KBr) 1493, 1454, 1200 cm^{-1}; ^{1}H NMR δ 1.9−2.3 (m, 4H), 3.0−3.2 (m, 2H), 3.29 (s, 3H), 3.4−3.7 (m, 4H), 4.1−4.2 (m, 1H), 4.41 (d, J = 8.6 Hz, 1H), 4.53 (d, J = 8.6 Hz, 1H), 5.55 (dd, J = 8.6, 4.3 Hz, 1H), 6.9−7.3 (m, 10H); MS (m/z) 407 (M^+ − OCH_2CH_2OMe); HRMS calcd for $C_{19}H_{20}O_2I$ (M^+ − OCH_2CH_2-OMe) 407.0507, found 407.0507.

(2*S*,4*S*,6*R*,10*R*)-6-(Iodomethyl)-10-(methoxyethoxy)-2,4-diphenyl-1,5-dioxecane (7, Table 2, Entry 4). To a solution of the ene acetal (**1c**, 1.0 mmol) and $MeOCH_2CH_2OH$ (3.0 mmol) in CH_3CN (20.0 mL) was added $I(coll)_2PF_6$ (3.0 mmol) under a nitrogen atmosphere at −20 °C. The resulting solution was stirred for 2 h at the same temperature and then warmed to 0 °C. After being stirred for 2 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (4/1) as an eluent to give **7** (382 mg) in 75% yield. The ratio of the diastereoisomers (**7a**:**7b**:**7c**:**7d** = 80:6:12:0) was determined by HPLC analysis (Ceramospher chiral Ru-1, MeOH, 0.5 mL/min flow rate). The product involving four stereoisomers were used for the next nucleophilic substitution of iodide (Table 3): colorless oil; IR (KBr) 1493, 1450 cm^{-1}; ^{1}H NMR δ 1.5−2.3 (m, 8H), 3.01 (dd, J = 9.4, 7.7 Hz, 1H), 3.09 (dd, J = 9.4, 4.7 Hz, 1H), 3.27 (s, 3H), 3.1−3.2 (m, 1H), 3.2−3.4 (m, 2H), 3.5−3.6 (m, 2H), 4.63 (dd, J = 6.0, 2.6 Hz, 1H), 4.80 (dd, J = 9.4, 5.1 Hz, 1H), 4.87 (dd, J = 9.8, 4.7 Hz, 1H), 7.2−7.4 (m, 10H). Anal. Calcd for $C_{24}H_{31}IO_4$: C, 56.48; H, 6.12; I, 24.86. Found: C, 56.23; H, 6.06; I, 24.56.

(2*R*,3*R*,5*R*,8*R*)-8-(Methoxyethoxy)-5-methyl-2,3-diphenyl-1,4-dioxocane (8a). To a solution of 1,4-dioxocane (**5**, 810 mg, 1.68 mmol) in THF (16.8 mL) was added $LiAlH_4$ (127 mg, 3.36 mmol) in THF (2.0 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 1 h, then warmed to rt, and stirred for an additional 1 h. To the mixture were added AcOEt (0.5 mL) and saturated aqueous NH_4Cl successively. The reaction mixture was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with CH_2Cl_2−AcOEt (30/1) as an eluent to give **8a** (430 mg, 72%) in a pure state: colorless oil; $[\alpha]^{25}_D$ +16° (c 1.1, $CHCl_3$); R_f 0.30;IR (KBr) 1452 cm^{-1}; ^{1}H NMR δ 1.10 (d, J = 6.4 Hz, 3H), 1.5−1.6 (m, 1H), 1.9−2.1 (m, 2H), 2.2−2.4 (m, 1H), 3.31 (s, 3H), 3.4−3.8 (m, 4H), 4.0−4.2 (m, 1H), 4.41 (d, J = 8.7 Hz, 1H), 4.56 (d, J = 8.7 Hz, 1H), 5.60 (dd, J = 9.0, 4.7 Hz, 1H), 6.9−7.2 (m, 10H). Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.86; H, 7.91.

(2*R*,3*R*,5*S*,8*R*)-5-(Cyanomethyl)-8-(methoxyethoxy)-2,3-diphenyl-1,4-dioxocane (8b). To a solution of **5** (74.1 mg, 0.15 mmol) in DMSO (1.5 mL) was added NaCN (11.3 mg, 0.23 mmol) at rt under a nitrogen atmosphere. The mixture was stirred at 80 °C for 3 h. Saturated aqueous $NaHCO_3$ was added to the reaction mixture. The mixture was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with CH_2Cl_2−AcOEt (30/1) as an eluent to give **8b** (40.5 mg, 70%) in a pure state: colorless oil; $[\alpha]^{28}_D$ +23° (c 1.0, $CHCl_3$); R_f 0.11; IR (KBr) 2249, 1495, 1454 cm^{-1}; ^{1}H NMR δ 1.7−1.9 (m, 1H), 2.0−2.2 (m, 2H), 2.4−2.6 (m, 3H), 3.31 (s, 3H), 3.4−3.8 (m, 4H), 4.25−4.35 (m, 1H), 5.29 (dd, J = 8.1, 5.6 Hz, 1H), 6.9−7.2 (m, 10H). Anal. Calcd for $C_{23}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.46; H, 7.14; N, 3.65.

(2*R*,3*R*,5*S*,8*R*)-5-(2′,2′-Bis(methoxycarbonyl)ethyl)-8-(methoxyethoxy)-2,3-diphenyl-1,4-dioxocane (8c). To a solution of NaH (60% in oil, 8.0 mg, 0.20 mmol, washed with dry Et_2O) in DMF (0.55 mL) was added dimethyl malonate (0.025 mL, 0.22 mmol) at rt under a nitrogen atmosphere. After being stirred at rt for 30 min, **5** (26.6 mg, 0.055 mmol) in THF (0.10 mL) was added to the reaction mixture, and the mixture was stirred at 100 °C for 3 h. A few drops of MeOH and saturated aqueous NH_4Cl were added to the reaction mixture successively, and the resulting solution was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−Et_2O (1/1) as eluent to give **8c** (17.4 mg, 65%) in a pure state: colorless oil; $[\alpha]^{26}_D$ +51° (c 3.2, $CHCl_3$); R_f 0.09; IR (KBr) 1751, 1736 cm^{-1}; ^{1}H NMR δ 1.5−1.7 (m, 1H), 1.9−2.2 (m, 4H), 2.2−2.4 (m, 1H), 3.06 (dd, J = 11.0, 2.8 Hz, 1H), 3.30 (s, 3H), 3.42 (s, 3H), 3.69 (s, 3H), 3.4−3.8 (m, 4H), 3.8−4.0 (m, 1H), 4.42 (d, J = 8.6 Hz, 1H), 4.50 (d, J = 8.6 Hz, 1H), 5.57 (dd, J = 8.7, 5.1 Hz, 1H), 6.8−7.2 (m, 10H). Anal. Calcd for $C_{27}H_{34}O_8$: C, 66.65; H, 7.04. Found: C, 66.88; H, 7.15.

(2*S*,4*S*,6*S*,10*R*)-10-(Methoxyethoxy)-6-methyl-2,4-diphenyl-1,5-dioxecane (8d). To a solution of 1,4-dioxocane (**7**, 610 mg, 1.20 mmol) in THF (10.0 mL) was added $LiAlH_4$ (90.8 mg, 2.40 mmol) in THF (2.0 mL) at 0 °C under a nitrogen atmosphere. After being stirred for 1 h at the same temperature, the reaction mixture was allowed to warm to rt and stirred for an additional 1 h. AcOEt (0.5 mL), MeOH, and aqueous NH_4Cl were added to the reaction mixture successively. The resulting solution was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (10/1) as eluent to give **8d** (362 mg, 79%) in a pure state: colorless oil; $[\alpha]^{22}_D$ −95° (c 2.4, $CHCl_3$); R_f 0.18; IR (KBr) 1493, 1450 cm^{-1}; ^{1}H NMR δ 1.10 (d, J = 6.3 Hz, 3H), 1.3−1.5 (m, 1H), 1.6−1.8 (m, 3H), 2.0−2.3 (m, 4H), 3.12 (ddd, J = 10.6, 6.8, 3.8 Hz, 1H), 3.27 (s, 3H), 3.2−3.4 (m, 2H), 3.5−3.7 (m, 2H), 4.59 (dd, J = 5.6, 3.6 Hz, 1H), 4.79 (dd, J = 10.2, 5.0 Hz, 1H), 4.93 (dd, J = 10.2, 4.6 Hz, 1H), 7.2−7.4 (m, 10H). Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.84; H, 8.40.

(2*S*,4*S*,6*R*,10*R*)-6-(Cyanomethyl)-10-(methoxyethoxy)-2,4-diphenyl-1,5-dioxecane (8e). To a solution of **7** (74.0 mg, 0.14 mmol) in DMSO (1.4 mL) was added NaCN (14.0 mg, 0.28 mmol) at rt under a nitrogen atmosphere. After being stirred at 80 °C for 3 h, the mixture was quenched with saturated aqueous $NaHCO_3$. The resulting solution was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (4/1) as eluent to give **8e** (48.8 mg, 82%) in a pure state: colorless oil; $[\alpha]^{25}_D$ −69° (c 1.0, $CHCl_3$); R_f 0.11; IR (KBr) 2249, 1493, 1452 cm^{-1}; ^{1}H NMR δ 1.6−1.8 (m, 2H), 1.8−1.9 (m, 2H), 2.0−2.2 (m, 4H), 2.31 (dd, J = 16.7, 6.4 Hz, 1H), 2.38 (dd, J = 16.7, 5.5 Hz, 1H), 3.17 (ddd, J = 10.3, 6.4, 3.9 Hz, 1H), 3.28 (s, 3H), 3.2−3.4 (m, 1H), 3.38 (ddd, J = 10.3, 6.4, 3.4, Hz 1H), 3.63 (ddd, J = 11.1, 6.0, 3.4, Hz 1H), 3.6−3.7 (m, 1H), 4.60 (dd, J = 5.6, 2.1 Hz, 1H), 4.78 (dd, J = 9.8, 4.7 Hz, 1H), 4.87 (dd, J = 10.3, 4.3 Hz, 1H), 7.2−7.4 (m, 10H). Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42. Found: C, 73.06; H, 7.72; N, 3.31.

(2*S*,4*S*,6*R*,10*R*)-6-(2′,2′-Bis(methoxycarbonyl)ethyl)-10-(methoxyethoxy)-2,4-diphenyl-1,5-dioxecane (8f). To a solution of NaH (60% in oil, 48.0 mg, 1.20 mmol, washed with dry Et_2O) in DMF (6.0 mL) was added dimethyl malonate (0.14 mL, 0.22 mmol) at rt under a nitrogen atmosphere. After being stirred for 30 min at rt, to the reaction mixture was added **7** (343 mg, 0.67 mmol) in THF (1.0 mL). The resulting solution was stirred at 100 °C for 3 h. The reaction mixture

was quenched with a few drops of MeOH and aqueous NH_4Cl and then extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (4/1) as eluent to give **8f** (273 mg, 79%) in a pure state: colorless oil; $[\alpha]^{22}_D$ −74° (*c* 1.7, $CHCl_3$); R_f 0.15; IR (KBr) 1753, 1736, 1493, 1452 cm^{-1}; ^1H NMR δ 1.4−1.5 (m, 1H), 1.6−1.7 (m, 2H), 1.7−1.9 (m, 1H), 1.9−2.2 (m, 5H), 2.3−2.5 (m, 1H), 3.03 (ddd, *J* = 10.6, 6.9, 3.8 Hz, 1H), 3.27 (s, 3H), 3.40 (s, 3H), 3.73 (s, 3H), 3.2−3.4 (m, 2H), 3.5−3.6 (m, 2H), 4.52 (dd, *J* = 5.6, 3.6 Hz, 1H), 4.75 (d, *J* = 9.7, 5.4 Hz, 1H), 4.82 (dd, *J* = 9.9, 5.6 Hz, 1H), 7.2−7.4 (m, 10H); MS (*m*/*z*) 514 (M^+).

General Procedure for the Grignard Reaction in Table 4. To a solution of the acetal (**8a** or **8d**, 1.0 mmol) in toluene (50.0 mL) was added RMgX (5.0 mmol) at rt under a nitrogen atmosphere. The reaction mixture was stirred for 12 h and then quenched with aqueous NH_4Cl. The resulting solution was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography using hexane−AcOEt as eluent to give **9**.

(2*R*,3*R*,5*S*,8*R*)-5,8-Dimethyl-2,3-diphenyl-1,4-dioxocane (9a): colorless crystal; mp 106−7 °C (hexane); $[\alpha]^{25}_D$ +61° (*c* 0.56, $CHCl_3$); IR (KBr) 1493, 1452 cm^{-1}; ^1H NMR δ 1.11 (d, *J* = 6.0 Hz, 3H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.4−1.5 (m, 1H), 1.6−1.8 (m, 2H), 2.3−2.4 (m, 1H), 4.1−4.2 (m, 1H), 4.35 (d, *J* = 9.0 Hz, 1H), 4.64 (d, *J* = 9.0 Hz, 1H), 4.6−4.8 (m, 1H), 6.9−7.2 (m, 10H). Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.74; H, 8.13.

(2*R*,3*R*,5*S*,8*R*)-5-Ethyl-8-methyl-2,3-diphenyl-1,4-dioxocane (9b): colorless oil; $[\alpha]^{25}_D$ +45° (*c* 1.0, $CHCl_3$); IR (KBr) 1493, 1452 cm^{-1}; ^1H NMR δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.12 (d, *J* = 6.0 Hz, 3H), 1.3−1.8 (m, 5H), 2.3−2.4 (m, 1H), 4.1−4.2 (m, 1H), 4.30 (d, *J* = 9.0 Hz, 1H), 4.4−4.5 (m, 1H), 4.68 (d, *J* = 9.0 Hz, 1H), 6.9−7.2 (m, 10H). Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.16; H, 8.43.

(2*R*,3*R*,5*R*,8*R*)-5-Allyl-8-methyl-2,3-diphenyl-1,4-dioxocane (9c): colorless oil; $[\alpha]^{25}_D$ +23° (*c* 1.5, $CHCl_3$); IR (KBr) 1637, 1493, 1452 cm^{-1}; ^1H NMR δ 1.11 (d, *J* = 6.8 Hz, 3H), 1.4−1.5 (m, 1H), 1.6−1.8 (m, 2H), 2.1−2.2 (m, 2H), 2.3−2.4 (m, 1H), 4.1−4.2 (m, 1H), 4.30 (d, *J* = 8.6 Hz, 1H), 4.5−4.6 (m, 1H), 4.66 (d, *J* = 8.6 Hz, 1H), 4.9−5.1 (m, 2H), 5.8−5.9 (m, 1H), 6.9−7.2 (m, 10H). Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.85; H, 8.15.

(2*R*,3*R*,5*R*,8*R*)-5-Butenyl-8-methyl-2,3-diphenyl-1,4-dioxocane (9d): colorless oil; $[\alpha]^{27}_D$ +32° (*c* 2.9, $CHCl_3$); IR 1639, 1493, 1454 cm^{-1}; ^1H NMR δ 1.16 (d, *J* = 6.8 Hz, 3H), 1.4−2.4 (m, 8H), 4.1−4.2 (m, 1H), 4.29 (d, *J* = 9.0 Hz, 1H), 4.4−4.6 (m, 1H), 4.65 (d, *J* = 9.0 Hz, 1H), 4.9−5.0 (m, 2H), 5.7−5.9 (m, 1H), 6.9−7.2 (m, 10H). Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 82.04; H, 8.48.

(2*S*,4*S*,6*S*,10*S*)-6,10-Dimethyl-2,4-diphenyl-1,5-dioxecane (9e): colorless crystal; mp 108−9 °C (hexane); $[\alpha]^{21}_D$ −142° (*c* 1.0, $CHCl_3$); IR (KBr) 1491, 1450 cm^{-1}; ^1H NMR δ 1.15 (d, *J* = 6.8 Hz, 3H), 1.3−1.4 (m, 2H), 1.6−1.8 (m, 2H), 1.9−2.0 (m, 2H), 2.2−2.3 (m, 2H), 3.5−3.7 (m, 1H), 4.88 (t, *J* = 9.0 Hz, 2H), 7.2−7.5 (m, 10H). Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.12; H, 8.56. Found: C, 81.41; H, 8.62.

(2*S*,4*S*,6*S*,10*S*)-6-Ethyl-10-methyl-2,4-diphenyl-1,5-dioxecane (9f): colorless crystal; mp 66−67 °C (hexane); $[\alpha]^{21}_D$ −147° (*c* 1.1, $CHCl_3$); IR (KBr) 1491, 1450 cm^{-1}; ^1H NMR δ 0.81 (t, *J* = 7.3 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H), 1.2−1.7 (m, 6H), 1.9−2.0 (m, 2H), 2.2−2.4 (m, 2H), 3.3−3.4 (m, 1H), 3.5−3.7 (m, 1H), 4.8−4.9 (m, 2H), 7.2−7.4 (m, 10H). Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.61; H, 8.93. Found: C, 81.71; H, 8.94.

(2*S*,4*S*,6*R*,10*S*)-6-Allyl-10-methyl-2,4-diphenyl-1,5-dioxecane (9g): colorless crystal; mp 73.5−74.5 °C (hexane); $[\alpha]^{23}_D$ −124° (*c* 1.3, $CHCl_3$); IR (KBr) 1641, 1491, 1450 cm^{-1}; ^1H NMR δ 1.13 (d, *J* = 6.3 Hz, 3H), 1.3−1.5 (m, 2H), 1.6−1.8 (m, 2H), 1.9−2.0 (m, 2H), 2.2−2.4 (m, 4H), 3.4−3.7 (m, 2H), 4.8−5.0 (m, 4H), 5.6−5.8 (m, 1H), 7.2−7.4 (m, 10H). Anal. Calcd for $C_{24}H_{32}O_2$: C, 82.24; H, 8.63. Found: C, 82.29; H, 8.68.

(2*S*,4*S*,6*S*,10*S*)-10-Methyl-2,4-diphenyl-6-undecyl-1,5-dioxecane (9h): colorless oil; $[\alpha]^{20}_D$ −87° (*c* 1.2, $CHCl_3$); IR (KBr) 1493, 1450 cm^{-1}; ^1H NMR δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H), 1.2−1.8 (m, 24H), 1.9−2.0 (m, 2H), 2.0−2.4 (m, 2H), 3.3−3.5 (m, 1H), 3.5−3.7 (m, 1H), 4.8−5.0 (m, 2H), 7.2−7.5 (m, 10H). Anal. Calcd for $C_{32}H_{48}O_2$: C, 82.70; H, 10.41. Found: C, 82.64; H, 10.33.

(2*R*,5*S*)-8-Nonene-2,5-diol (10). To a solution of Ca (134.5 mg, 3.35 mmol) in liquid NH_3 (100 mL) was added a solution of **9d** (281 mg, 0.84 mmol) and EtOH (0.20 mL, 3.35 mmol) in ether (5.0 mL) at −78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at the same temperature and then quenched with saturated aqueous NH_4Cl. After removal of NH_3 at rt, the resulting solution was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (1/1) as eluent to give **10** (122 mg, 92%): colorless oil; $[\alpha]^{25}_D$ −11° (*c* 0.47, $CHCl_3$); IR (KBr) 3300, 1641 cm^{-1}; ^1H NMR δ 1.21 (d, *J* = 5.9 Hz, 3H), 1.5−1.7 (m, 6H), 2.1−2.3 (m, 4H), 3.6−3.7(m, 1H), 3.8−3.9 (m, 1H), 4.9−5.1 (m, 2H), 5.8−5.9 (m, 1H). Anal. Calcd for $C_9H_{18}O_2$: C, 67.91; H, 11.49. Found: C, 67.79; H, 11.38.

(2*S*,6*S*)-2,6-Heptadecanediol (11). To a solution of Ca (114 mg, 2.85 mmol) in liquid NH_3 (100 mL) was added a solution of **9h** (264 mg, 0.57 mmol) and EtOH (0.17 mL, 2.85 mmol) in ether (5.7 mL) at −78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at the same temperature and then quenched with saturated aqueous NH_4Cl. After removal of NH_3 at rt, the resulting solution was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (1/1) as eluent to give **11** (118 mg, 76%): colorless crystal; mp 55−56 °C (hexane/AcOEt); $[\alpha]^{18}_D$ +11° (*c* 1.1, $CHCl_3$) {lit.[6] mp 55−56 °C; $[\alpha]_D$ +11° (*c* 1, $CHCl_3$)}. ^1H NMR spectral data of **11** were good agreement with the reported values[6] of (2*S*,6*S*)-2,6-heptadecanediol.

(3*R*,7*S*)-1,3,7-Octanetriol (13). To a solution of **9g** (73.2 mg, 0.21 mmol) in dioxane−H_2O (v/v = 3/1, 4.0 mL) were added $NaIO_4$ (89.3 mg, 0.42 mmol) and a catalytic amount of OsO_4 at rt. After being stirred for 3 h, the reaction mixture was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. To a solution of the residue in MeOH (2.0 mL) was added $NaBH_4$ (16.0 mg, 0.42 mmol). After being stirred for 1 h at rt, the reaction mixture was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. To a solution of the obtained crude alcohol (**12**) in EtOH (4.2 mL) was added a catalytic amount of $Pd(OH)_2$−C at rt under a medium pressure of H_2 (4 kgf/cm^2). After the completion of the reaction, the product was purified by SiO_2 column chromatography with CH_2Cl_2−MeOH (20/1) as eluent to give **13** (20.1 mg, 60%): colorless oil; $[\alpha]^{18}_D$ +2.3° (*c* 1.0, MeOH); IR (KBr) 3325 cm^{-1}; ^1H NMR δ 1.20 (d, *J* = 6.3 Hz, 3H), 1.4−1.8 (m, 8H), 2.5−3.4 (brs, 2H), 3.7−4.0 (m, 4H); MS (*m*/*z*) 163 (M^+ + H); HRMS calcd for $C_8H_{18}O_3$ (M^+) 162.1257, found 162.1267.

(2*S*,6*S*)-2-(2-(Benzyloxy)ethyl)-6-methyltetrahydropyran (14). To a solution of **13** (18.0 mg, 0.12 mmol) in CH_2Cl_2−MeOH (v/v = 3/1, 1.2 mL) were added $PhC(OMe)_3$ (0.03 mL, 0.18 mmol) and a catalytic amount of trifluoromethansulfonic acid at 0 °C. After being stirred for 12 h, the reaction mixture was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with hexane−AcOEt (20/1) to give **14** (26.0 mg, 94%): colorless oil; $[\alpha]^{25}_D$ +39° (*c* 0.85, $CHCl_3$); IR (KBr) 1720 cm^{-1}; ^1H NMR δ 1.16 (d, *J* = 6.3 Hz, 3H), 1.1−1.3 (m, 2H), 1.5−1.7 (m, 3H), 1.8−2.0 (m, 3H), 3.4−3.6 (m, 2H), 4.44 (t, *J* = 6.6 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 8.05 (d, *J* = 7.3 Hz, 2H). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.49; H, 8.22.

(2*S*,6*S*)-2-(6-Methyltetrahydropyran-2-yl)acetic Acid (15). To a solution of **14** (8.8 mg, 0.035 mmol) in MeOH (1.0 mL) was added 10% aqueous NaOH (1.0 mL). After being stirred for 15 min, the reaction mixture was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. To the resulting crude

alcohol in acetone (1.5 mL) was added Jones reagent (5 equiv). After being stirred for 30 min, $NaHSO_3$ (excess) was added to the reaction mixture. The resulting mixture was extracted with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography with $CH_2Cl_2-Et_2O$ (3/1) to give **15** (3.8 mg, 68%). ^1H NMR spectral data of **15** were good agreement with the reported values[7a] of (2*S*,6*S*)-2-(6-methyltetrahydropyran-2-yl)acetic acid: $[\alpha]^{25}_D$ +26° (*c* 0.18, $CHCl_3$); $[\alpha]^{23}_D$ +36° (*c* 0.14, C_6H_6) {lit.[7a] $[\alpha]^{22}_D$ +18.6° (*c* 2.77, $CHCl_3$); $[\alpha]^{22}_D$ +43.85° (*c* 2.52, C_6H_6), lit.[7b] $[\alpha]^{22}_D$ +32.86° (*c* 1.05, C_6H_6), lit.[7c] $[\alpha]^{22}_D$ +35° (*c* 0.5, $CHCl_3$)}.[21]

(21) The discrepancies of the values are clear although the acid **15** in each citation is optically pure. We think the variation in the optical rotations is due to concentration differences.

Acknowledgment. We are grateful to Takasago International Co. for the generous gift of (1*S*,3*S*)-1,3-diphenyl-1,3-propanediol. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

Supporting Information Available: ^1H NMR spectra of **5**, **7**, **8a**, **8d**, **9a**, **9d**, **9g**, and **9h** and DIFNOE spectra of **8a**. X-ray experimental data of **16**. Cartesian coordinates of optimized geometries of the intermediate **C** and the others (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960714L