Synthesis of Optically Active *cis*- and *trans*-1,2-Disubstituted Cyclopropane Derivatives by the Simmons-Smith Reaction of Allyl Alcohol Derivatives Derived from (*R*)-2,3-*O*-Isopropylideneglyceraldehyde

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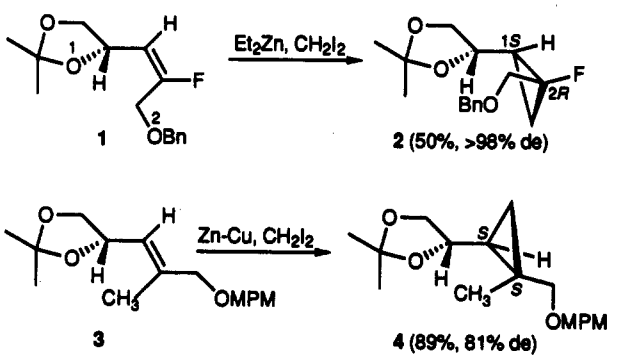
Received July 26, 1993•

The Simmons-Smith reactions of *Z*- and *E*-allyl alcohol derivatives **6** derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**5**) were used for the synthesis of optically active *cis*- and *trans*-1,2-disubstituted cyclopropane derivatives. Reaction of **6** with diethyl zinc and diiodomethane gave cyclopropane derivatives **7** in 84% to quantitative yields with 35 to ≈100% des. Identical facial selectivities toward the double bonds, 1*re*-2*si* for *Z*-**6** and 1*re*-2*re* for *E*-**6**, were observed in the cyclopropanations. The diastereoselectivity was dependent on the protecting group on the terminal allylic oxygen (R of **6**, TBDPS > MOM > Bn) and on the stereochemistry of the double bond (*Z* > *E*). For TBDPS ethers *Z*- and *E*-**6c**, *cis*- and *trans*-**7c** were obtained as single diastereomers, respectively. It was clearly demonstrated that the stereoselectivity of the cyclopropanation is controlled by the directing effect of the allylic oxygen (O-1) of the dioxolane ring, which coordinates to the reagent. The terminal allylic oxygen (O-2) lowered the diastereoselectivity. This reaction was applied to the synthesis of optically active cyclopropane analogs of γ-aminobutyric acid (GABA) **18**, **22**, and *ent*-**22**.

Introduction

The cyclopropane subunit can be found in a number of natural and unnatural substances of biological interest.[1] The importance of optically active cyclopropanes in biological and biochemical investigations has led to intensive efforts to develop an effective method for their construction.[2] The Simmons-Smith reaction is the most widely used method for the stereoselective cyclopropanation of olefins,[3] and its application to asymmetric reactions has been studied.[4] We recently reported that optically active fluorocyclopropane derivative **2** (1*S*,2*R*) could be prepared by the Simmons-Smith reaction of fluoroallyl alcohol derivative **1** with high diastereoselectivity (>98% de).[5] Cyclopropanation occurred from the 1*si*-2*si* face of the double bond (the bottom face of **1**) because of the chiral center of the dioxolane ring derived from 2,3-*O*-isopropylideneglyceraldehyde (**5**).[6] Kodama *et al.* independently reported a related reaction in the total synthesis of (+)-bicyclohumulenone, in which the cyclopropanation of allyl alcohol derivative **3** proceeded with facial selectivity opposite that of **1**; that is, the cyclopropanation occurred from the 1*si*-2*si* face (the top face) of **3** to give cyclopropane **4** (1*S*,2*S*).[7] The directing



effect of proximal oxygen functions with regard to the diastereoselectivity of Simmons-Smith reaction is well documented.[3a,8] In **1** and **3**, the stereochemical relationships of the allylic oxygens (O-1 and O-2) are quite different (*syn* in **1**, *anti* in **3**), although both have the same configuration of the chiral center of the dioxolane ring. It has not been possible to explain the completely opposite diastereoselectivity in the cyclopropanations of **1** and **3** because of the lack of information on the contribution of

• Abstract published in *Advance ACS Abstracts*, December 15, 1993.

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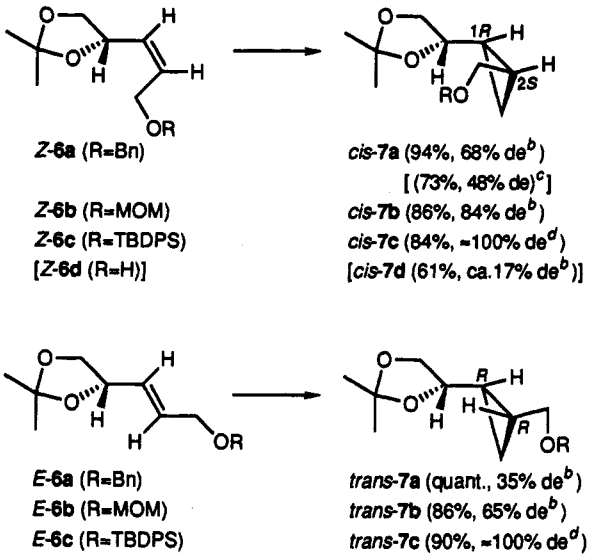
Scheme 1[a]



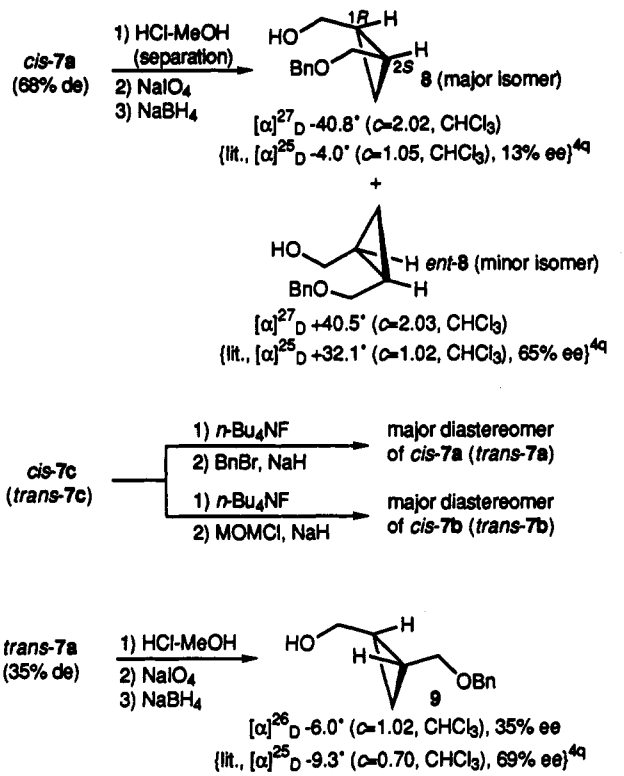
[a] Reaction conditions: Et_2Zn (5 equiv), CH_2I_2 (10 equiv), CH_2Cl_2, −23 to 0 °C, 12 h. [b] Determined by capillary GLC. [c] Reaction conditions: Zn–Cu (10 equiv), CH_2I_2 (3 equiv), cat. I_2, ether, reflux, 4 h. [d] ^1H and ^{13}C NMR showed a single diastereomer.

the terminal allylic oxygen (O-2) to the selectivity.[9] As an extension of our investigation, the reactions of allyl alcohol derivatives **6** containing *E*- and *Z*-disubstituted double bonds were conducted to determine the effects of the terminal allylic oxygen (O-2) on the diastereoselectivity of cyclopropanation. The protective group (R) was shown to have remarkable effects. This paper describes the synthesis of optically active *cis*- and *trans*-1,2-disubstituted cyclopropane derivatives by the Simmons–Smith reaction of allyl alcohol derivatives derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde and application of the reaction to the synthesis of optically active cyclopropane analogs of γ-aminobutyric acid (GABA).

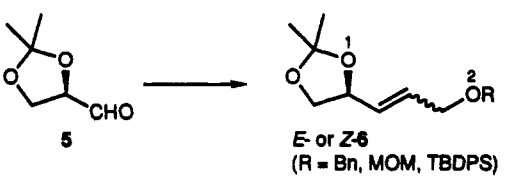
Results and Discussion

Z- and *E*-allyl alcohol derivatives **6** were prepared from **5**[10] by a sequence involving a stereoselective Wittig-type reaction, reduction of the ester group to a hydroxyl group with DIBALH, and protection of the hydroxyl group with a Bn, MOM, or *tert*-butyldiphenylsilyl (TBDPS) group.[11] Reactions of **6** with Et_2Zn (5 equiv) and CH_2I_2 (10 equiv) in methylene chloride at −23 to 0 °C for 12 h gave cyclopropane derivatives **7** in 84% to quantitative yields (Scheme 1). The stereochemistry of cyclopropanes **7** was determined as indicated in Scheme 2. The acidic hydrolysis of *cis*-**7a** gave chromatographically separable diastereomeric diols, which were then converted to the corresponding alcohols **8** and *ent*-**8** by oxidative cleavage followed by reduction. The absolute stereochemistry of the major isomer **8** was assigned as 1*R*,2*S* on the basis of a comparison of its specific rotation value with that in the literature.[4q] The absolute stereochemistries of *cis*-**7b** and *cis*-**7c** were determined by chemical correlation. The

Scheme 2



transformation of the TBDPS group of *cis*-**7c** (≈100% de) into Bn and MOM groups gave the major diastereomers of *cis*-**7a** or *cis*-**7b**, respectively. Similarly, the absolute stereochemistry of *trans*-**7a–c** was assigned by comparison with known compound **9**.[4q] *Z*- and *E*-**6** showed identical facial selectivity toward the double bond in cyclopropanation (cyclopropanation occurred from the bottom face of the double bond of *Z*- and *E*-**6**). The direction of asymmetric induction was correlated with that of **1** containing a trisubstituted double bond (not with that of **3**). The diastereomeric excess (% de) of the cyclopropanated products varied from 35 to ≈100%, depending on the nature of the protective group (R) on the terminal allylic oxygen and on the stereochemistry of the double bond. The diastereoselectivity for the protecting groups increased in the order Bn < MOM < TBDPS for both *Z*- and *E*-**6**, and *Z*-isomers showed higher diastereoselectivity than *E*-isomers. The cyclopropanation of *Z*-**6a** promoted by a zinc–copper couple in ether at reflux temperature showed decreased diastereoselectivity (48% de). When the TBDPS group was used to protect the hydroxyl group, *cis*-**7c** or *trans*-**7c** was obtained as a single diastereomer.



Chelation-controlled positioning of the reagent (the complexation induced proximity effect) has been proposed to account for the diastereoselectivity of the Simmons–Smith reaction of allyl alcohols and ethers.[8] The high diastereoselectivities observed with TBDPS ethers (*Z*- and *E*-**6c**) rule out coordination of the reagent to O-2 in preferential attacks from the 1*re*-2*si* and 1*re*-2*re* faces, respectively, since the bulky TBDPS group hinders the

(9) In ref 7, cyclopropanation of the diol derivative obtained by acidic hydrolysis of **3** gave a cyclopropane with the same configuration (1*S*,2*S*) with a selectivity of more than 98%.

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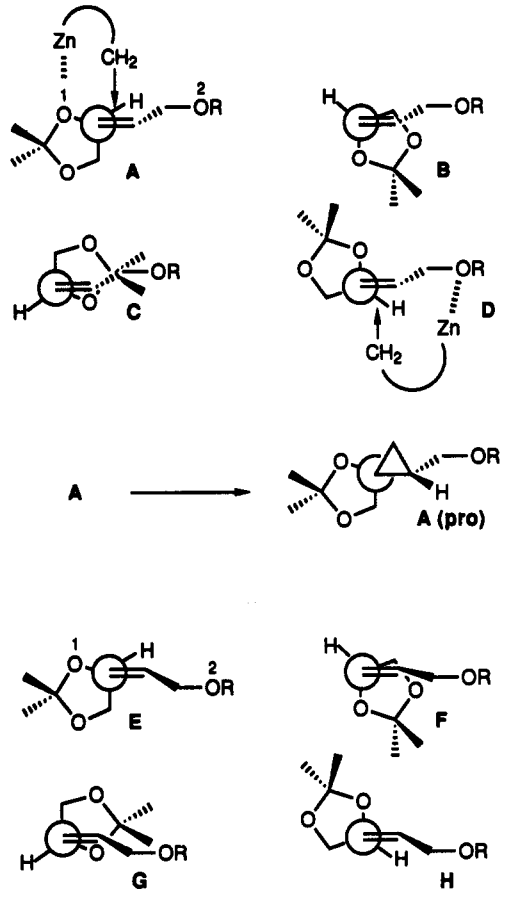
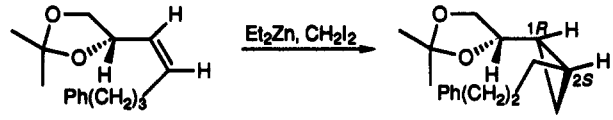


Figure 1.

coordination of the reagent to O-2. As expected, the cyclopropanation of alkyl-substituted **10** proceeded with high diastereoselectivity to give **11** (>98% de),[12] and the



10 **11** (91%, >98% de)

free hydroxyl group in *Z*-**6d** lessened the diastereoselectivity to 17% de,[13] thus showing specific coordination of the reagent to O-1 to be needed for the stereocontrol. Four conformers, **A**–**D**, are considered as possible transition state models for *Z*-**6** (Figure 1).[14] Conformers **A** and **D** are considered to be more favorable than conformers **B** and **C** because of steric repulsion between the dioxolane ring and CH_2OR group. In conformer **A**, coordination of the reagent to the allylic oxygen (O-1) of the dioxolane ring and methylene transfer from the less-hindered face (top face, 1*re*-2*si*) of the double bond would provide the major cyclopropanes. The stereochemical relationship of the dioxolane and cyclopropane rings in **A** (**pro**) obtained from **A** was in good agreement with that of the *p*-nitrobenzoate derivative of **2** (in which the benzyl group of **2** was replaced by a *p*-nitrobenzoyl group) as determined by X-ray crystallographic analysis.[5] The reduction in the % de in the case of *Z*-**6a,b** may be ascribed to reaction through conformer **D** *via* coordination of the reagent to O-2. The similar diastereoselectivity obtained with *E*-**6a–c** may possibly be explained by conformer **E**, which corresponds to conformer **A** for *Z*-**6**. (Conformer **F** does not participate when O-2 is protected by the TBDPS group.) Energy differences between the four conformers of *E*-**6** (**E**–**H**) may be less than those of *Z*-**6** (**A**–**D**) because of the *trans* dioxolane ring. The amounts of conformers **G** and/or **H**, leading to the minor isomer, would thus increase beyond those of **C** and **D**, with consequent reduction in diastereoselectivity of *E*-**6b,c**. The present explanation for the diastereoselectivity of *E*-**6** would not be applicable to the reaction of trisubstituted compound **3**, which gave reversed selectivity.[15] Optically active *cis*- and *trans*-disubstituted cyclopropane derivatives **7**, **8**, and **9** are synthetically useful intermediates since unsymmetrically protected functional groups permit a wide variety of transformations.

γ-Aminobutyric acid (GABA, **12**) functions as an important inhibitory neurotransmitter in the mammalian central nervous system.[16] GABA analogs containing a cyclopropane ring (a 2,3-methano bridge) are a novel class of compounds that possess conformationally restricted frameworks with extended or folded structures. Thus, *trans*-**13** (extended) and *cis*-**13** (folded) were synthesized in racemic form to investigate the active conformers of GABA and the structural features of GABA receptors.[17] The optically active form of **13** is of interest from the standpoint of its conformational structure–activity relationship with enzyme receptors. In an application of the present asymmetric Simmons–Smith reaction, optically active cyclopropane analogs of GABA were synthesized (Scheme 3). Cyclopropane **14**, obtained from *trans*-**7c**, was converted to azide **15** *via* the mesylate. Reduction of the azide group of **15** with tin(II) chloride followed by protection of the amine with a Boc group[18] gave **16**. Deprotection of the TBDPS ether of **16** and Jones oxidation[19] gave **17**. The Boc group was removed by HCl (gas) in ether to give **18** (1*R*,2*R*). Optically active **22** and

(12) By a procedure similar to that used to prepare *cis*-**7a**, **11** was converted to (1*R*,2*S*)-1-(hydroxymethyl)-2-(3-phenyl-1-propyl)-cyclopropane: $[\alpha]^{28}_D$ +25.8° (*c* 1.13, EtOH) {lit.[4p] $[\alpha]^{23}_D$ +19.0° (*c* 0.7, EtOH), 81% ee}.

(13) When 2 equiv of Et_2Zn and 3 equiv of CH_2I_2 were used for the reaction of *Z*-**6d**, ca. 51% de was observed (49% yield).

(14) Diastereoselectivities of addition reactions to the double bond connected to a 2,2-dimethyl-1,3-dioxolan-4-yl group (α,β-unsaturated ester derivatives and allyl alcohol derivatives) have been rationalized on the basis of conformational preferences. (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247–2255. (b) Krief, A.; Dumont, W.; Pasau, P.; Lecomte, Ph. *Tetrahedron* **1989**, *45*, 3039–3052, and references cited therein. (c) Casas, R.; Parella, T.; Branchadell, V.; Oliva, A.; Ortuno, R. M.; Guingant, A. *Tetrahedron* **1992**, *48*, 2659–2680. (d) Smadja, W.; Zahouily, M.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 5511–5514. (e) Morikawa, T. Washio, Y.; Shiro, M.; Taguchi, T. *Chem. Lett.* **1993**, 249–250.

(15) The effect of the *Z*-methyl substituent in **3** on the diastereoselectivity has yet to be determined. A remarkable change in diastereoselectivity was observed in the asymmetric Simmons–Smith reaction of C_2-symmetric acetal derivatives when a *Z*-methyl group was introduced on the double bond (see ref 4c).

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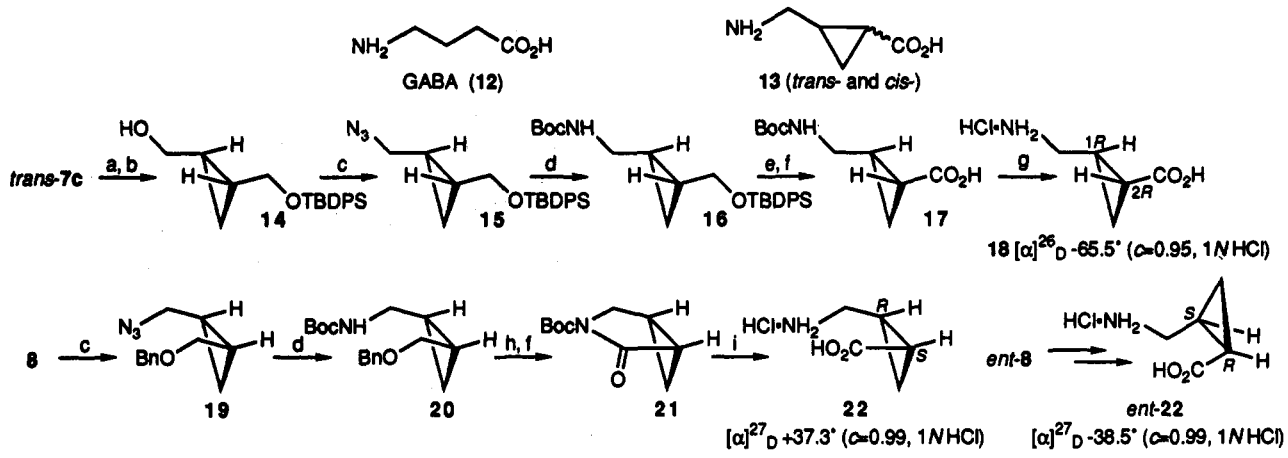
Scheme 3[a]



[a] Reagents: (a) PPTS, MeOH; (b) (i) $NaIO_4$, (ii) $NaBH_4$; (c) (i) MsCl, Et_3N, (ii) NaN_3; (d) (i) $SnCl_2$, (ii) $(Boc)_2O$, $NaHCO_3$; (e) TBAF; (f) CrO_3, H_2SO_4; (g) HCl (gas); (h) H_2, Pd–C; (i) (i) TFA, (ii) 1 N HCl.

ent-**22** were prepared by the same procedure. Cyclopropane **19** (100% ee), obtained from **8** *via* diastereomer separation, was converted to **20**. Removal of the benzyl group and subsequent Jones oxidation[19] gave a product that spontaneously cyclized to lactam derivatives **21** owing to the *cis*-structure of the cyclopropane ring. Treatment of **21** with trifluoroacetic acid followed by 1 N HCl gave optically active *cis*-cyclopropane analog **22** (1*R*,2*S*). *ent*-**22** (1*S*,2*R*), prepared from *ent*-**8**, showed an optical rotation value identical to that of **22** but opposite in sign. No racemization occurred during conversion, and the yield of each step was generally high. Analogs **18**, **22**, and *ent*-**22** are chiral substrates that can be used for clarification of the conformational requirement of GABA for activating enzyme receptors.

Conclusion

An assessment was made of the diastereoselectivity of the Simmons–Smith reaction of *Z*- and *E*-allyl alcohol derivatives **6** derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**5**). *E*- and *Z*-**6** expressed identical facial selectivity in the cyclopropanation on the double bond. When the TBDPS group was used to protect the terminal allylic oxygen (O-2), optically active *cis*- and *trans*-1,2-disubstituted cyclopropane derivatives **7c** were obtained with high diastereoselectivity (≈100% de). For Bn and MOM ethers, *Z*-isomers showed higher diastereoselectivities than did the *E*-isomers. In transition-state models, coordination of the reagent to the allylic oxygen (O-1) of the dioxolane ring and delivery of methylene from the less-hindered side of the double bond may account for the diastereoselectivity. The present reaction was applied to the synthesis of optically active cyclopropane analogs of GABA. The use of readily available 2,3-*O*-isopropylideneglyceraldehyde for asymmetric induction provids a practically useful method for the synthesis of optically active acyclic cyclopropane derivatives.

Experimental Section

^1H- and ^{13}C-NMR spectra were recorded on a Brucker AM400 or on a Varian Gemini-300 spectrometer in $CDCl_3$ unless otherwise indicated. IR spectra were recorded with a Perkin-Elmer FTIR-1710 infrared spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80 or on a VG Auto Spec. GLC analyses were carried out on Hitachi G-3000 gas chromatograph. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. Numbering system in which the number 1 indicated the position of the 2,2-dimethyl-1,3-dioxolan-4-yl group was used for the cyclopropane carbons, and the numbers were used without change for cyclopropane derivatives obtained from the parent cyclopropane.

Preparation of Substrates. By means of the reported procedure,[11] a Wittig-type reaction of **5** followed by reduction with DIBALH gave (1*Z*,4′*S*)- or (1*E*,4′*S*)-1-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-3-hydroxy-1-propene, which was converted to Bn, MOM, and TBDPS ether derivatives **6** by the standard method (BnBr, NaH/THF; MOMCl, *i*-Pr_2NEt/CH_2Cl_2; TBDPSCl, imidazole/DMF).

(1*Z*,4′*S*)-3-(Benzyloxy)-1-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-propene (*Z*-6a): colorless oil; $[\alpha]^{24}_D$ −6.2° (*c* 2.42, $CHCl_3$); ^1H NMR δ 1.38 (3H, s), 1.42 (3H, s), 3.54 (1H, dd, *J* = 8.1, 8.0 Hz), 4.04 (1H, dd, *J* = 8.1, 6.2 Hz), 4.12 (2H, dd, *J* = 6.4, 1.5 Hz), 4.49 (1H, d, *J* = 11.8 Hz), 4.54 (1H, d, *J* = 11.8 Hz), 4.80 (1H, dddd, *J* = 8.3, 8.0, 6.2, 1.1 Hz), 5.63 (1H, ddt, *J* = 11.2, 8.3, 1.5 Hz), 5.82 (1H, dtd, *J* = 11.2, 6.4, 1.1 Hz), 7.27–7.36 (5H, m).

(1*Z*,4′*S*)-1-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-3-(methoxymethoxy)-1-propene (*Z*-6b): colorless oil; $[\alpha]^{28}_D$ +7.0° (*c* 1.26, $CHCl_3$); ^1H NMR δ 1.37 (3H, s), 1.41 (3H, s), 3.35 (3H, s), 3.54 (1H, dd, *J* = 8.1, 8.0 Hz), 4.07 (1H, dd, *J* = 8.1, 6.2 Hz), 4.15 (2H, ddd, *J* = 6.5, 1.4, 1.3 Hz), 4.60 (2H, s), 4.79–4.87 (1H, m), 5.60 (1H, ddt, *J* = 11.6, 8.0, 1.4 Hz), 5.75 (1H, dtd, *J* = 11.6, 6.5, 1.1 Hz).

(1*Z*,4′*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-propene (*Z*-6c): colorless oil; $[\alpha]^{24}_D$ +3.9° (*c* 1.12, $CHCl_3$); ^1H NMR δ 1.05 (9H, s), 1.31 (3H, s), 1.39 (3H, s), 3.44 (1H, dd, *J* = 8.0, 7.7 Hz), 3.90 (1H, dd, *J* = 8.0, 6.1 Hz), 4.25 (1H, ddd, *J* = 13.4, 6.0, 1.5 Hz), 4.32 (1H, ddd, *J* = 13.4, 6.0, 1.5 Hz), 4.64 (1H, ddd, *J* = 8.5, 7.7, 6.1 Hz), 5.46 (1H, ddt, *J* = 11.1, 8.5, 1.5 Hz), 5.82 (1H, dt, *J* = 11.1, 6.0 Hz), 7.37–7.47 and 7.66–7.69 (10H, m).

(1*Z*,4′*S*)-1-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-3-hydroxy-1-propene (*Z*-6d): colorless oil; $[\alpha]^{27}_D$ +9.7° (*c* 1.03, $CHCl_3$); ^1H NMR δ 1.39 (3H, s), 1.42 (3H, s), 1.86 (1H, br), 3.57 (1H, dd, *J* = 8.0, 7.9 Hz), 4.09 (1H, dd, *J* = 8.0, 6.2 Hz), 4.15–4.33 (2H, m), 4.82–4.89 (1H, m), 5.56 (1H, ddt, *J* = 11.2, 8.1, 1.4 Hz), 5.83 (1H, dddd, *J* = 11.2, 7.1, 6.0, 1.1 Hz).

(1*E*,4′*S*)-3-(Benzyloxy)-1-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-propene (*E*-6a): colorless oil; $[\alpha]^{24}_D$ +30.1° (*c* 1.04, $CHCl_3$); ^1H NMR δ 1.39 (3H, s), 1.43 (3H, s), 3.60 (1H, dd, *J* = 8.2, 7.9 Hz), 4.04 (2H, dd, *J* = 5.4, 1.4 Hz), 4.09 (1H, dd, *J* = 8.2, 6.1 Hz), 4.52 (2H, s), 4.50–4.57 (1H, m), 5.75 (1H, ddt, *J* = 15.5, 7.3, 1.4 Hz), 5.92 (1H, dtd, *J* = 15.5, 5.4, 0.7 Hz), 7.25–7.36 (5H, m).

(1*E*,4′*S*)-1-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-3-(methoxymethoxy)-1-propene (*E*-6b): colorless oil; $[\alpha]^{23}_D$ +29.7° (*c* 1.13, $CHCl_3$); ^1H NMR δ 1.38 (3H, s), 1.42 (3H, s), 3.36 (3H, s), 3.60 (1H, dd, *J* = 8.2, 7.7 Hz), 4.07 (2H, dd, *J* = 5.4, 1.3 Hz), 4.09 (1H, dd, *J* = 8.2, 6.3 Hz), 4.52 (1H, ddd, *J* = 7.7, 7.2, 6.3 Hz), 4.63

(2H, s), 5.73 (1H, ddt, J = 15.5, 7.2, 1.3 Hz), 5.89 (1H, dt, J = 15.5, 5.4 Hz).

(1*E*,4′*S*)-3-[(*tert*-Butyldiphenylsilyl)oxy]-1-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-propene (*E*-6c): colorless oil; $[\alpha]^{27}_D$ +23.0° (*c* 1.11, $CHCl_3$); ^1H NMR δ 1.06 (9H, s), 1.40 (3H, s), 1.43 (3H, s), 3.57 (1H, dd, J = 8.1, 7.9 Hz), 4.08 (1H, dd, J = 8.1, 6.2 Hz), 4.21 (2H, dd, J = 4.3, 1.8 Hz), 4.53 (1H, dddd, J = 7.9, 7.2, 6.2, 0.5 Hz), 5.75 (1H, ddt, J = 15.3, 7.2, 1.8 Hz), 5.87 (1H, dtd, J = 15.3, 4.3, 0.5 Hz), 7.35–7.45 and 7.65–7.68 (10H, m).

Typical Procedure for the Cyclopropanation Reaction. Under an argon atmosphere, a solution of *Z*-6a (150 mg, 0.6 mmol) in methylene chloride (6 mL) was cooled to −23 °C, and diethyl zinc (1.0 M solution in hexane, 3 mL, 3 mmol) and diiodomethane (0.48 mL, 6 mmol) were added. After being stirred vigorously for 12 h at −23 to 0 °C, the reaction mixture was treated with aqueous NH_4Cl and extracted with ether. The ether phase was washed with saturated aqueous $NaHCO_3$ and NaCl and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel to give *cis*-7a (148 mg, 94% yield) as a mixture of diastereomers (5.3:1 as determined by GLC, 68% de).

(1*R*,2*S*,4′*S*)-2-[(Benzyloxy)methyl]-1-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)cyclopropane (*cis*-7a): colorless oil; IR (neat) 3066, 2986, 2935, 2864, 1497, 1455 cm^{-1}; ^1H NMR δ 0.22 (1H for minor isomer, ddd, J = 5.5, 5.5, 5.1 Hz), 0.46 (1H for major isomer, ddd, J = 5.4, 5.4, 5.0 Hz), 0.82 (1H for minor isomer, ddd, J = 8.4, 8.4, 5.1 Hz), 0.93 (1H for major isomer, ddd, J = 8.2, 8.2, 5.0 Hz), 0.98–1.12 (1H, m), 1.23–1.37 (1H, m), 1.34 (3H, s), 1.44 (3H, s), 3.20 (1H for major isomer, dd, J = 10.2, 9.4 Hz), 3.44 (1H for minor isomer, dd, J = 10.4, 7.7 Hz), 3.60–3.75 (3H, m), 4.06 (1H for minor isomer, dd, J = 7.2, 5.5 Hz), 4.12 (1H for major isomer, ddd, J = 6.0, 5.3, 1.7 Hz), 4.44 (1H for major isomer, d, J = 11.8 Hz), 4.53 (1H for major isomer, d, J = 11.8 Hz), 4.53 (1H for minor isomer, d, J = 12.1 Hz), 4.59 (1H for minor isomer, d, J = 12.1 Hz), 7.25–7.38 (5H, m); ^{13}C NMR δ 8.68, 14.86, 18.08, 25.67, 26.75, 69.90, 70.34, 72.70, 77.29, 108.43, 127.57, 127.64, 128.29, 137.93 for major diastereomer, 7.13, 15.23, 17.84, 25.80, 26.83, 69.54, 69.65, 72.57, 76.49, 108.93, 127.34, 127.50, 128.18, 138.45 for minor diastereomer; MS m/z 262 [M^+]. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.17; H, 8.50. Reaction of *cis*-7a (diastereomeric mixture, 4.47 g, 17.1 mmol) with 10% hydrochloric acid (15 mL) in MeOH (20 mL) for 40 min at rt gave 2-[(benzyloxy)methyl]-1-(1,2-dihydroxyethyl)-cyclopropane (3.31 g, 88% yield). The (1*R*,2*S*)- and (1*S*,2*R*)-isomers were separated by column chromatography on silica gel (ratio = 4.4:1). (1*R*,2*S*)-Isomer: $[\alpha]^{28}_D$ −45.6° (*c* 1.48, $CHCl_3$). (1*S*,2*R*)-Isomer: $[\alpha]^{28}_D$ +57.1° (*c* 1.05, $CHCl_3$). The (1*R*,2*S*)- and (1*S*,2*R*)-isomers were converted to 8 and *ent*-8, respectively, for structural correlation (*vide infra*).

(1*R*,2*S*,4′*S*)-1-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-2-[(methoxymethoxy)methyl]cyclopropane (*cis*-7b): 86% yield (mixture of diastereomers, 11.7:1 by GLC, 84% de); colorless oil; IR (neat) 2987, 2935, 2882, 2823, 1456 cm^{-1}; ^1H NMR δ 0.21 (1H for minor isomer, ddd, J = 5.6, 5.5, 5.2 Hz), 0.48 (1H for major isomer, ddd, J = 5.4, 5.2, 4.9 Hz), 0.83 (1H for minor isomer, ddd, J = 8.5, 8.5, 5.2 Hz), 0.94 (1H for major isomer, ddd, J = 8.2, 8.2, 4.9 Hz), 1.04 (1H for major isomer, ddd, J = 8.5, 8.5, 8.2, 5.2 Hz), 1.20–1.39 (1H for major isomer and 2H for minor isomer, each m), 1.35 (3H, s), 1.44 (3H, s), 3.33 (1H for major isomer, dd, J = 10.7, 8.9 Hz), 3.36 (3H for major isomer, s), 3.38 (3H for minor isomer, s), 3.47 (1H for minor isomer, dd, J = 10.9, 7.8 Hz), 3.69–3.79 (3H, m), 4.04–4.18 (1H, m), 4.59 (1H for major isomer, d, J = 6.6 Hz), 4.64 (1H for major isomer, d, J = 6.6 Hz), 4.66 (2H for minor isomer, s); MS m/z 201 [$M^+ - CH_3$]. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.28; H, 9.34. Major diastereomer of *cis*-7b (obtained from *cis*-7c): $[\alpha]^{29}_D$ −16.7° (*c* 1.37, $CHCl_3$); ^{13}C NMR δ 8.58, 14.81, 18.07, 25.72, 26.75, 55.20, 67.98, 69.86, 77.18, 96.20, 108.56.

(1*R*,2*S*,4′*S*)-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)cyclopropane (*cis*-7c): 84% yield; colorless oil; $[\alpha]^{27}_D$ −1.4° (*c* 1.06, $CHCl_3$); IR (neat) 3071, 3050, 2985, 2958, 2933, 1473, 1428 cm^{-1}; ^1H NMR δ 0.37 (1H, ddd, J = 5.7, 5.5, 5.0 Hz), 0.83 (1H, ddd, J = 8.4, 8.3, 5.0 Hz), 0.97–1.08 (1H, m), 1.06 (9H, s), 1.15–1.28 (1H, m), 1.36 (3H, s), 1.46 (3H, s), 3.41 (1H, dd, J = 11.3, 9.4 Hz), 3.73–3.83 (2H, m), 3.91 (1H, dd, J = 11.3, 5.5 Hz), 4.17–4.27 (1H, m), 7.36–7.46 and 7.64–7.69 (10H, m); ^{13}C NMR δ 8.19, 17.54, 18.36, 19.17, 25.78, 26.87, 26.93, 64.18, 70.16, 77.53, 108.58, 127.67, 127.70, 129.68 (two carbons), 133.60, 134.79, 135.49, 135.58; MS m/z 395 [$M^+ - CH_3$]. Anal. Calcd for $C_{25}H_{34}O_3Si$: C, 73.12; H, 8.35. Found: C, 73.28; H, 8.42. *cis*-7c was converted to *cis*-7a and *cis*-7b for structural correlation. Reaction of *cis*-7c with *n*-tetrabutylammonium fluoride (TBAF, 3 equiv, rt, 3 h) gave desilylated alcohol derivative (96% yield), which was treated with BnBr (NaH, rt, 12 h) to give major diastereomer of *cis*-7a (75% yield) and with MOMCl (*i*-Pr_2NEt, rt, 6 h) to give major diastereomer of *cis*-7b (76% yield).

(1*R*,2*S*,4′*S*)-1-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-2-(hydroxymethyl)cyclopropane (*cis*-7d): 61% yield (mixture of diastereomers, ca. 1.4:1 by GLC, ca. 17% de). Major isomer of *cis*-7d: colorless oil; $[\alpha]^{28}_D$ −19.8° (*c* 0.72, $CHCl_3$); ^1H NMR δ 0.46 (1H, ddd, J = 5.5, 5.4, 5.0 Hz), 0.90 (1H, ddd, J = 8.3, 8.3, 5.0 Hz), 1.03 (1H, dddd, J = 8.7, 8.7, 8.3, 5.5 Hz), 1.17–1.30 (1H, m), 1.34 (3H, s), 1.43 (3H, s), 1.75 (1H, br), 3.44 (1H, dd, J = 11.3, 8.5 Hz), 3.70 (1H, dd, J = 8.0, 7.8 Hz), 3.79–3.86 (2H, m), 4.14 (1H, dd, J = 8.0, 5.8 Hz); ^{13}C NMR δ 8.30, 17.59, 18.00, 25.77, 26.75, 62.77, 69.88, 76.95, 108.72. Minor isomer of *cis*-7d: colorless oil; $[\alpha]^{29}_D$ −1.1° (*c* 1.13, $CHCl_3$); ^1H NMR δ 0.26 (1H, ddd, J = 5.5, 5.3, 5.2 Hz), 0.81 (1H, ddd, J = 8.2, 8.2, 5.2 Hz), 1.00–1.10 (1H, m), 1.32–1.45 (1H, m), 1.34 (3H, s), 1.45 (3H, s), 3.00 (1H, d, J = 11.3 Hz), 3.26 (1H, dd, J = 11.5, 11.3 Hz), 3.69–3.80 (2H, m), 3.97 (1H, ddd, J = 11.5, 11.3, 5.2 Hz), 4.10–4.17 (1H, m); ^{13}C NMR δ 8.36, 17.69, 18.06, 25.81, 26.93, 63.41, 69.58, 77.66, 109.08.

(1*R*,2*R*,4′*S*)-2-[(Benzyloxy)methyl]-1-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)cyclopropane (*trans*-7a): quantitative yield (mixture of diastereomers, 2.1:1 by GLC, 35% de); colorless oil; ^1H NMR δ 0.47–0.54 (2H for minor isomer, m), 0.58 (1H for major isomer, ddd, J = 8.3, 5.1, 5.0 Hz), 0.69 (1H for major isomer, ddd, J = 8.5, 5.1, 5.0 Hz), 0.82–0.90 (1H, m), 1.00–1.08 (1H, for major isomer, m), 1.14–1.23 (1H for minor isomer, m), 1.34 (3H, s), 1.43 (3H, s), 3.24 (1H for minor isomer, dd, J = 10.3, 7.3 Hz), 3.30 (1H for major isomer, dd, J = 10.2, 6.9 Hz), 3.38 (1H for major isomer, dd, J = 10.2, 6.7 Hz), 3.52–3.62 (1H for major isomer and 2H for minor isomer, m), 3.67 (1H for minor isomer, dd, J = 7.8, 7.3 Hz), 3.71 (1H for major isomer, dd, J = 8.0, 7.4 Hz), 4.04 (1H for minor isomer, dd, J = 7.8, 5.8 Hz), 4.09 (1H for major isomer, dd, J = 8.0, 6.0 Hz), 4.49 (1H for major isomer, d, J = 12.2 Hz), 4.52 (1H for major isomer, d, J = 12.2 Hz), 4.55 (2H for minor isomer, s), 7.25–7.37 (5H, m); ^{13}C NMR δ 8.36, 15.17, 19.32, 25.67, 26.78, 69.27, 72.52, 73.14, 79.32, 108.88, 127.53 (two carbons), 128.35, 138.37 for major isomer, 7.02, 16.23, 18.98, 25.67, 26.83, 69.11, 72.30, 72.90, 79.21, 108.88, 127.47, 127.65, 128.30, 138.37 for minor isomer; MS m/z 247 [$M^+ - CH_3$]. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 72.92; H, 8.44. Major diastereomer of *trans*-7a (obtained from *trans*-7c): $[\alpha]^{26}_D$ −12.1° (*c* 1.22, $CHCl_3$).

(1*R*,2*R*,4′*S*)-1-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-2-[(methoxymethoxy)methyl]cyclopropane (*trans*-7b): 86% yield (mixture of diastereomers, 4.7:1 by GLC, 65% de); colorless oil; IR (neat) 2987, 2935, 2881, 2824, 1456 cm^{-1}; ^1H NMR δ 0.43–0.49 (1H for minor isomer, m), 0.54 (1H for major isomer, ddd, J = 8.3, 5.1, 5.0 Hz), 0.65 (1H for major isomer, ddd, J = 8.5, 5.1, 5.0 Hz), 0.78–0.88 (1H, m), 0.93–1.03 (1H for major isomer, m), 1.08–1.21 (1H for minor isomer, m), 1.29 (3H, s), 1.38 (3H, s), 3.22–3.41 (2H, m), 3.31 (3H, s), 3.51–3.68 (2H, m), 4.00 (1H for minor isomer, dd, J = 7.6, 5.6 Hz), 4.05 (1H for major isomer, dd, J = 8.0, 6.0 Hz), 4.57 (2H for major isomer, s), 4.58 (1H for minor isomer, d, J = 6.5 Hz), 4.62 (1H for minor isomer, d, J = 6.5 Hz); MS m/z 201 [$M^+ - CH_3$]. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.68; H, 9.67. Major diastereomer of *trans*-7b (obtained from *trans*-7c): $[\alpha]^{27}_D$ −15.8° (*c* 1.47, $CHCl_3$); ^{13}C NMR δ 8.07, 14.99, 19.27, 25.57, 26.67, 55.01, 69.18, 70.54, 79.08, 95.91, 108.79.

(1*R*,2*R*,4′*S*)-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)cyclopropane (*trans*-7c): 90% yield; colorless oil; $[\alpha]^{27}_D$ −7.9° (*c* 1.15, $CHCl_3$); IR (neat) 3071, 3050, 2985, 2958, 2933, 1590, 1473, 1428 cm^{-1}; ^1H NMR δ 0.52 (1H, ddd, J = 8.2, 5.2, 5.1 Hz), 0.58 (1H, ddd, J = 8.4, 5.1, 5.0 Hz), 0.77–0.85 (1H, m), 0.89–1.00 (1H, m), 1.05 (9H, s), 1.34 (3H, s), 1.44 (3H, s), 3.39 (1H, dd, J = 10.7, 6.9 Hz), 3.48 (1H, ddd, J = 8.1, 7.4, 6.0 Hz), 3.69 (1H, dd, J = 8.1, 7.4 Hz), 3.72 (1H, dd, J = 10.7, 5.5 Hz), 4.06 (1H, dd, J = 8.1, 6.0 Hz), 7.35–7.46 and 7.64–7.67 (10H, m); ^{13}C NMR δ 7.88, 17.60, 18.87, 19.19, 25.76, 26.83 (two carbons), 66.26, 69.34, 79.90, 108.87, 127.62,

129.61, 133.76, 135.54; MS *m/z* 395 ($M^+ - CH_3$). Anal. Calcd for $C_{25}H_{34}O_3Si$: C, 73.12; H, 8.35. Found: C, 72.94; H, 8.35. By a procedure similar to *cis*-**7c**, *trans*-**7c** was converted to major diastereomer of *trans*-**7a** (71% yield, two steps) and major diastereomer of *trans*-**7b** (62% yield, two steps) for structural correlation.

(1*R*,2*S*)-2-[(Benzyloxy)methyl]-1-(hydroxymethyl)cyclopropane (8). A solution of the major diastereomer of 2-[(benzyloxy)methyl]-1-(1,2-dihydroxyethyl)cyclopropane (453 mg, 2.0 mmol) obtained from *cis*-**7a** (*vide supra*) in THF (11 mL) and H_2O (4 mL) was cooled to 0 °C, and $NaIO_4$ (568 mg, 2.7 mmol) was added. After being stirred for 2 h at 0 °C, the reaction mixture was treated with H_2O and extracted with ether. The ether phase was washed with saturated aqueous NaCl and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel to give the aldehyde derivative (382.3 mg, 99% yield). A solution of the aldehyde derivative (380 mg, 2.0 mmol) in MeOH (3 mL) was cooled to 0 °C, and an excess of $NaBH_4$ was added portionwise. After being stirred for 30 min at 0 °C, the reaction mixture was treated with saturated aqueous NH_4Cl and extracted with ether. The ether phase was washed with saturated aqueous NaCl and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel to give **8** (356.5 mg, 93% yield): colorless oil; $[\alpha]^{24}_D$ −40.8° (*c* 2.02, $CHCl_3$);[4q] ^1H NMR δ 0.21 (1H, ddd, *J* = 5.3, 5.3, 5.1 Hz), 0.81 (1H, ddd, *J* = 8.2, 8.2, 5.1 Hz), 1.25–1.44 (2H, m), 2.65 (1H, br), 3.16 (1H, dd, *J* = 10.4, 10.4 Hz), 3.19 (1H, dd, *J* = 12.0, 10.4 Hz), 3.89–3.97 (2H, m), 4.51 (1H, d, *J* = 11.7 Hz), 4.58 (1H, d, *J* = 11.7 Hz), 7.27–7.38 (5H, m); ^{13}C NMR δ 8.64, 14.72, 18.40, 63.02, 70.74, 73.09, 127.89, 127.93, 128.53, 137.46.

(1*S*,2*R*)-2-[(Benzyloxy)methyl]-1-(hydroxymethyl)cyclopropane (*ent*-8). By a procedure similar to that used to prepare **8**, the minor diastereomer of 2-[(benzyloxy)methyl]-1-(1,2-dihydroxyethyl)cyclopropane (340 mg, 1.53 mmol) obtained from *cis*-**7a** (*vide supra*) was converted to *ent*-**8** (289.8 mg, 99% yield): colorless oil; $[\alpha]^{27}_D$ +40.5° (*c* 2.03, $CHCl_3$).

(1*R*,2*R*)-2-[(Benzyloxy)methyl]-1-(hydroxymethyl)cyclopropane (9). By a procedure similar to that used to prepare **8**, *trans*-**7a** (89.1 mg, 0.34 mmol, 35% de) was converted to **9** (50.8 mg, 78% yield): colorless oil; $[\alpha]^{26}_D$ −6.0° (*c* 1.02, $CHCl_3$) {lit.[4q] $[\alpha]^{25}_D$ −9.3° (*c* 0.70, $CHCl_3$), 69% ee}; ^1H NMR δ 0.46–0.52 (2H, m), 0.98–1.06 (2H, m), 1.82 (1H, br), 3.28 (1H, dd, *J* = 12.4, 7.0 Hz), 3.39–3.44 (2H, m), 3.50 (1H, dd, *J* = 11.3, 6.2 Hz), 4.53 (2H, s), 7.25–7.36 (5H, m).

(1*Z*,4′*S*)-1-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-5-phenyl-1-pentene (10): colorless oil; $[\alpha]^{28}_D$ −1.7° (*c* 2.06, $CHCl_3$); ^1H NMR δ 1.40 (3H, s), 1.44 (3H, s), 1.65–1.80 (2H, m), 2.08–2.23 (2H, m), 2.63 (2H, t, *J* = 7.5 Hz), 3.52 (1H, dd, *J* = 8.0, 7.8 Hz), 4.04 (1H, dd, *J* = 8.0, 6.0 Hz), 4.80 (1H, ddd, *J* = 8.8, 7.8, 6.0 Hz), 5.45 (1H, dd, *J* = 10.8, 8.8 Hz), 5.67 (1H, dt, *J* = 10.8, 7.5 Hz), 7.17–7.35 (5H, m).

(1*R*,2*S*,4′*S*)-1-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-2-(3-phenyl-1-propyl)cyclopropane (11):[12] 91% yield; colorless oil; $[\alpha]^{32}_D$ +24.6° (*c* 1.04, $CHCl_3$); ^1H NMR δ 0.25–0.27 (1H, m), 0.83–0.95 (3H, m), 1.15–1.29 (1H, m), 1.36 (3H, s), 1.46 (3H, s), 1.41–1.52 (1H, m), 1.61–1.85 (2H, m), 2.57–2.73 (2H, m), 3.61–3.69 (2H, m), 4.02–4.09 (1H, m), 7.17–7.32 (5H, m); ^{13}C NMR δ 10.55, 15.22, 18.07, 25.79, 26.86, 28.79, 31.79, 35.67, 69.68, 77.90, 108.40, 125.71, 128.30 (two carbons), 142.32; MS *m/z* 260 [M^+], 245. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.20; H, 9.45.

(1*R*,2*R*)-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1-(hydroxymethyl)cyclopropane (14). A solution of *trans*-**7c** (3.51 g, 8.56 mmol) and an excess of PPTS in MeOH (20 mL) was stirred for 5 h at rt. The reaction mixture was treated with saturated aqueous $NaHCO_3$ and extracted with ether. The ether phase was washed with saturated aqueous NaCl and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel to give the diol derivative (2.30 g, 73% yield). By a procedure similar to that used to prepare **8**, the diol derivative (2.18 g, 5.89 mmol) was converted to **14** (1.89 g, 95% yield): colorless oil; $[\alpha]^{26}_D$ −11.2° (*c* 1.05, $CHCl_3$); IR (neat) 3351, 3071, 3050, 3000, 2957, 2931, 2893, 2858, 1590, 1472 cm^{-1}; ^1H NMR δ 0.38–0.48 (2H, m), 0.91–1.02 (2H, m), 1.05 (9H, s), 1.54 (1H, br), 3.38–3.49 (3H, m), 3.70 (1H, dd, *J* = 10.7, 5.2 Hz), 7.36–7.46 and 7.66–7.70 (10H, m); ^{13}C NMR δ 7.70, 19.14, 19.20, 19.33, 26.86, 66.48 (two carbons), 127.62, 129.60, 133.82, 135.57; MS *m/z* 283 ($M^+ - t$-C_4H_9).

(1*R*,2*R*)-1-(Azidomethyl)-2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]cyclopropane (15). A solution of **14** (1.82 g, 5.34 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C, and triethylamine (2.23 mL, 16.0 mmol) and methanesulfonyl chloride (0.83 mL, 10.7 mmol) were added. After being stirred for 2 h at 0 °C, the reaction mixture was treated with saturated aqueous NH_4Cl and extracted with ether. The ether phase was washed with saturated aqueous $NaHCO_3$ and NaCl and dried over $MgSO_4$. After removal of the solvent, the residue was dissolved in DMF (25 mL), and NaN_3 (1.04 g, 16.0 mmol) was added. After being stirred for 2 h at 60 °C, the reaction mixture was treated with H_2O and extracted with ether. The ether phase was washed with saturated aqueous NaCl and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel to give **15** (1.75 g, 90% yield): colorless oil; $[\alpha]^{26}_D$ −13.1° (*c* 1.28, $CHCl_3$); IR (neat) 3071, 3050, 3001, 2959, 2932, 2895, 2859, 2093, 1590, 1472 cm^{-1}; ^1H NMR δ 0.46 (1H, ddd, *J* = 8.5, 5.5, 5.1 Hz), 0.55 (1H, ddd, *J* = 8.3, 5.5, 5.1 Hz), 0.94–1.06 (2H, m), 1.06 (9H, s), 3.06 (1H, dd, *J* = 12.9, 6.6 Hz), 3.12 (1H, dd, *J* = 12.9, 6.6 Hz), 3.56 (1H, dd, *J* = 10.7, 5.6 Hz), 3.66 (1H, dd, *J* = 10.7, 5.2 Hz), 7.36–7.47 and 7.65–7.70 (10H, m); ^{13}C NMR δ 8.21, 15.22, 19.19, 19.35, 26.82, 54.80, 65.80, 127.61, 129.60, 133.73, 135.54; MS *m/z* 308 ($M^+ - t$-C_4H_9). Anal. Calcd for $C_{21}H_{27}N_3OSi$: C, 69.00; H, 7.45; N, 11.50. Found: C, 68.90; H, 7.45; N, 11.45.

(1*R*,2*R*)-1-[[*N*-(*tert*-Butyloxycarbonyl)amino]methyl]-2-carboxycyclopropane (17). A solution of **15** (813.7 mg, 2.23 mmol) in dioxane (20 mL) and H_2O (10 mL) was cooled to 0 °C, and tin(II) chloride (2.11 g, 11.1 mmol) was added. After the reaction mixture was stirred for 12 h at rt, $(Boc)_2O$ (3.41 g, 15.62 mmol) and aqueous $NaHCO_3$ [2.62 g in H_2O (10 mL)] were added, and the whole was stirred for 3 h at rt.[18] The reaction mixture was treated with H_2O and extracted with ether. The ether phase was washed with saturated aqueous NaCl and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel to give **16** (734 mg, 75% yield): colorless oil; $[\alpha]^{25}_D$ −6.8° (*c* 2.30, $CHCl_3$). A solution of **16** (679.4 mg, 1.55 mmol) in THF (15 mL) was cooled to 0 °C, and TBAF (1.0 M solution in THF, 4.7 mL, 4.7 mmol) was added. After being stirred for 3 h at rt, the reaction mixture was treated with H_2O and extracted with ether. The ether phase was washed with saturated aqueous NaCl and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel to give the alcohol derivative (211.7 mg, 68% yield). By means of the Jones oxidation method,[19] the alcohol derivative (176.1 mg, 0.88 mmol) was oxidized with CrO_3–H_2SO_4 at 0 °C. The reaction mixture was treated with *i*-PrOH to consume the excess reagent, extracted with ether, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel to give **17** (154.7 mg, 82% yield): colorless oil; $[\alpha]^{25}_D$ −53.3° (*c* 1.87, $CHCl_3$); IR (neat) 3344, 2979, 2934, 1696, 1524 cm^{-1}; ^1H NMR δ 0.85–0.91 (1H, m), 1.23 (1H, ddd, *J* = 8.8, 4.7, 4.4 Hz), 1.43 (9H, s), 1.51 (1H, ddd, *J* = 8.8, 4.5, 4.3 Hz), 1.58–1.69 (1H, m), 2.89–3.25 (2H, m), 4.76 and 6.04 (1H, each br); MS *m/z* 200 [$M^+ - CH_3$].

(1*R*,2*R*)-1-(Aminomethyl)-2-carboxycyclopropane Hydrochloride (18). HCl (gas) was introduced to a solution of **17** (63.4 mg, 0.3 mmol) in ether (2.5 mL) for 2 h at rt. After removal of the solvent, the residue was washed with ether to give crude **18** (40 mg, 90% yield): white crystals; mp 131–135 °C (recrystallized from EtOH–ether); $[\alpha]^{26}_D$ −65.5° (*c* 0.95, 1 N HCl); IR (KBr) 3406, 3025, 1718 cm^{-1}; ^1H NMR (D_2O) δ 1.08 (1H, ddd, *J* = 8.3, 6.6, 4.9 Hz), 1.31 (1H, ddd, *J* = 8.8, 5.1, 4.9 Hz), 1.67–1.77 (2H, m), 2.94 (1H, dd, *J* = 13.4, 7.6 Hz), 3.05 (1H, dd, *J* = 13.4, 6.9 Hz). Anal. Calcd for $C_5H_{10}ClNO_2$: C, 39.61; H, 6.65; N, 9.24. Found: C, 39.47; H, 6.54; N, 9.38.

(1*R*,2*S*)-1-(Azidomethyl)-2-[(benzyloxy)methyl]cyclopropane (19). By a procedure similar to that used to prepare **15**, **8** was converted to **19**: 90% yield; colorless oil: $[\alpha]^{28}_D$ −7.2° (*c* 2.00, $CHCl_3$); IR (neat) 3066, 3028, 2861, 2092, 1496, 1454 cm^{-1}; ^1H NMR δ 0.31 (1H, ddd, *J* = 5.5, 5.5, 5.1 Hz), 0.92 (1H, ddd, *J* = 8.4, 8.4, 5.1 Hz), 1.26 (1H, ddddd, *J* = 8.4, 8.3, 7.7, 7.3, 5.5 Hz), 1.34 (1H, ddddd, *J* = 8.4, 8.3, 8.0, 6.3, 5.5 Hz), 3.22 (1H, dd, *J* = 13.2, 7.7 Hz), 3.32 (1H, dd, *J* = 13.2, 7.3 Hz), 3.37 (1H, dd, *J* = 10.4, 8.0 Hz), 3.61 (1H, dd, *J* = 10.4, 6.3 Hz), 4.49 (1H, d, *J* = 12.0 Hz), 4.56 (1H, d, *J* = 12.0 Hz), 7.29–7.36 (5H, m); ^{13}C NMR

δ 8.91, 14.59, 15.26, 51.18, 69.64, 72.86, 127.66, 127.76, 128.39, 138.14; MS *m/z* 189 ($M^+ - N_2$).

(1*R*,2*S*)-2-[(Benzyloxy)methyl]-1-[[*N*-(*tert*-butyloxycarbonyl)amino]methyl]cyclopropane (20). By a procedure similar to that used to prepare **16**, **19** was converted to **20**: 94% yield; colorless oil; $[\alpha]^{28}_D$ +27.8° (*c* 2.00, $CHCl_3$); IR (neat) 3387, 3004, 2977, 2867, 1714, 1511, 1454 cm^{-1}; ^1H NMR δ 0.14 (1H, ddd, *J* = 5.3, 5.3, 5.1 Hz), 0.76 (1H, ddd, *J* = 8.3, 8.3, 5.1 Hz), 1.15 (1H, ddddd, *J* = 10.0, 8.4, 8.3, 5.6, 5.3 Hz), 1.25 (1H, ddddd, *J* = 10.3, 8.4, 8.3, 5.3, 5.3 Hz), 1.43 (9H, s), 2.59 (1H, dd, *J* = 13.9, 10.0 Hz), 3.15 (1H, dd, *J* = 10.4, 10.3 Hz), 3.72 (1H, ddd, *J* = 13.9, 6.8, 5.6 Hz), 3.82 (1H, dd, *J* = 10.4, 5.3 Hz), 4.48 (1H, d, *J* = 11.6 Hz), 4.55 (1H, d, *J* = 11.6 Hz), 5.26 (1H, br), 7.27–7.37 (5H, m); ^{13}C NMR δ 8.10, 14.73, 15.73, 28.39, 40.48, 70.33, 73.06, 78.66, 127.66, 127.83, 128.37, 137.77, 155.75; MS *m/z* 292 ($M^+ + 1$).

(3*S*,4*R*)-*N*-(*tert*-Butyloxycarbonyl)-3,4-methano-2-pyrrolidone (21). Under a hydrogen atmosphere, a solution of **20** (1.62 g, 5.57 mmol) in MeOH (5 mL) containing a catalytic amount of 5% Pd–C was stirred for 3 h at rt. The reaction mixture was passed through short-pad column (silica gel) to give the alcohol derivative (1.13 g, quantitative yield). By a procedure similar to that used to prepare **17**, the alcohol derivative (256 mg, 1.27 mmol) was oxidized to **21** (199.3 mg, 79% yield): white crystals; mp 68.5–70.0 °C; $[\alpha]^{28}_D$ −57.7° (*c* 1.30, $CHCl_3$); IR (KBr) 2999, 2979, 2937, 1765, 1692 cm^{-1}; ^1H NMR δ 0.77 (1H, ddd, *J* = 4.9, 3.2, 3.2 Hz), 1.18 (1H, ddd, *J* = 8.6, 7.7, 4.9 Hz), 1.49 (9H, s), 1.84–1.91 (1H, m), 1.99 (1H, dddd, *J* = 8.6, 6.1, 3.2, 1.4 Hz), 3.70 (1H, d, *J* = 11.2 Hz), 3.79 (1H, dd, *J* = 11.2, 5.5 Hz); ^{13}C NMR δ 10.80, 11.45, 20.61, 27.09, 47.21, 81.39, 149.39, 172.92; MS *m/z* 182 ($M^+ - CH_3$). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.74; H, 7.57; N, 7.07.

(1*R*,2*S*)-1-(Aminomethyl)-2-carboxycyclopropane Hydrochloride (22). A solution of **21** (577 mg, 2.93 mmol) and TFA (1.13 mL, 14.6 mmol) in CH_2Cl_2 (5 mL) was stirred for 30 min at rt. The reaction mixture was concentrated *in vacuo*, and the residue was chromatographed on silica gel to give 3,4-methano-2-pyrrolidone. A solution of the 3,4-methano-2-pyrrolidone in 1 N HCl (10 mL) was stirred for 6 h at 70 °C. The reaction mixture was concentrated *in vacuo*, and the residue was recrystallized from EtOH–ether to give **22** (393.3 mg, 89% yield): white crystals; mp 242–243 °C; $[\alpha]^{26}_D$ +37.3° (*c* 0.99, 1 N HCl); IR (KBr) 2621, 2485, 1710, 1588, 1508 cm^{-1}; ^1H NMR (D_2O) δ 1.11 (1H, ddd, *J* = 7.0, 5.7, 5.0 Hz), 1.37 (1H, ddd, *J* = 8.4, 8.4, 5.0 Hz), 1.70 (1H, ddddd, *J* = 8.4, 8.3, 7.7, 7.5, 7.0 Hz), 1.98 (1H, ddd, *J* = 8.4, 8.3, 5.7 Hz), 3.29 (1H, dd, *J* = 13.4, 7.5 Hz), 3.34 (1H, *J* = 13.4, 7.7 Hz). Anal. Calcd for $C_5H_{10}ClNO_2$: C, 39.62; H, 6.65; N, 9.24. Found: C, 39.53; H, 6.59; N, 9.20.

(1*S*,2*R*)-1-(Aminomethyl)-2-carboxycyclopropane Hydrochloride (*ent*-22). By a procedure similar to that used to prepare **22**, *ent*-**8** was converted to *ent*-**22**: white crystals; mp 239–241 °C; $[\alpha]^{30}_D$ −38.5° (*c* 0.99, 1 N HCl). Anal. Calcd for $C_5H_{10}ClNO_2$: C, 39.62; H, 6.65; N, 9.24. Found: C, 39.52; H, 6.58; N, 9.18.

Supplementary Material Available: Copies of both ^1H and ^{13}C NMR spectra of *cis*-**7a**, *cis*-**7b**, *cis*-**7c**, *cis*-**7d**, *trans*-**7a**, *trans*-**7b**, *trans*-**7c**, *trans*-**7d**, **14**, **15**, **19**, **20**, and **21** and ^1H NMR spectra of **17**, **18**, and **22** (32 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.