tralization. Upon workup, the resulting solid was recrystallized (EtOH), affording the desired **2b**, 1.9 g (42%), mp 217–219 °C.

Cyclization of 2a and 2b with Sulfuric Acid. In a typical reaction, 1.0 g (2.22 mmol) of **2a** was dissolved by manipulation and stirring with a glass rod in 15 mL of cold (0–5 °C) concentrated sulfuric acid. Upon standing 1 h **3a** was precipitated from the resulting solution by pouring onto 100 g of ice. Melting allowed for collection of the precipitate, and gave 0.73 g (92%) of **3a**, mp 210–213 °C. One recrystallization (EtOH) gave the analytical sample, mp 220–222 °C: mass spectrum, *m/e* (relative intensity) 357 (15), 175 (100), 147 (34), 146 (30), 119 (18), 105 (36), 93 (50), 91 (15); *m*/e* 123.5, 121.8, 98.5, 85.7, 59.2, 56.5. Anal. Calcd for $C_{29}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.06; H, 5.43; N, 3.83. The yield of **3a** from **2b** was 81%.

Cyclization of 2a and 2b by Refluxing Acetic Acid. In a typical reaction, a mixture of 10 mL of acetic acid and 0.75 g (1.66 mmol) of **2b** was refluxed for 1 h. Upon cooling, **3b** was precipitated from the resulting solution by pouring onto 50 g of ice. The precipitate was collected to give 0.51 g (86%) of **3b**, mp 215–218 °C. One recrystallization (EtOH) gave a sample melting at 218–220 °C. The yield of **3a** from **2a** was 89%.

Cyclization of 2a and 2b by Methanolic Hydrogen Chloride. In a typical reaction, $HCl_{(g)}$ was bubbled into a stirred solution of 0.75 g (1.66 mmol) of **2b** in 100 mL of absolute methanol for about 30 min. The solution was evaporated to 25 mL before pouring onto an equal volume of cold (0–5 °C) water. The resulting precipitate was collected and recrystallized (EtOH) affording **3b**, 0.47 g (79%), mp 218–220 °C. The yield of **3a** from **2a** was 91%.

Treatment of 3b with Sulfuric Acid. In 2 mL of cold (0–5 °C) concentrated sulfuric acid, 30 mg (66.6 μmol) of **3b** was dissolved by stirring with a glass rod. After standing 5 min, **16** was precipitated from the solution by adding 20 g of crushed ice. The precipitate was collected and gave 28 mg (93%), mp 120–170 °C. One recrystallization ($EtOH-H_2O$) afforded pure **16**, mp 217–218 °C.

Acknowledgment. We wish to thank Professor Peter W. Jeffs for helpful discussions. This work was supported by Grant No. 2 R01 CA04455 from the United States Public Health Service and by a Traineeship from the National Aeronautic Space Administration (T.C.A.).

Registry No.—**2a**, 23105-20-6; **2b**, 62861-49-8; **3a**, 23105-22-8; **3b**, 62905-90-2; **10**, 5319-67-5; **13**, 62861-50-1; **16**, 62905-91-3; succinanilide, 15510-09-5; benzophenone, 119-61-9; tetramethylethylenediamine, 110-18-9; benzonitrile, 100-47-0.

References and Notes

(1) T. C. Adams, Jr., and C. R. Hauser, *Chem. Ind. (London)*, 697 (1969).
(2) R. F. Raffauf, *J. Am. Chem. Soc.*, **74**, 4460 (1952). P. N. Craig, *ibid.*, **74**, 129 (1952).
(3) G. L. Schmir and B. A. Cunningham, *J. Am. Chem. Soc.*, **87**, 5692 (1965).
(4) T. Yamana, A. Tsuji, and Y. Mizukami, *Chem. Pharm. Bull.*, **20**, 1217 (1972). R. B. Martin, R. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 158 (1964).
(5) The metastable peak for this fragmentation and subsequent fragmentations in this sequence are contained in the Experimental Section.
(6) J. H. Beynon, R. M. Caprioli, R. H. Shapiro, K. B. Tomer, and C. W. J. Chang, *Org. Mass. Spectrom.*, **6**, 863 (1972).
(7) It is of significance that scrambling of the label does not occur during the cyclization reaction and that the hydroxyl oxygen of **2** is specifically located in the ether linkage of **3**.

Stereochemistry of the Cycloaddition Reaction of Methylcarbenoid of Zinc to Cyclic Allylic Alcohols

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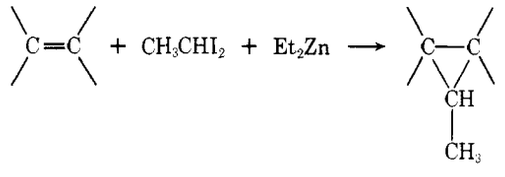
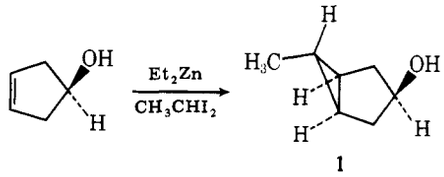
Stereochemistry of the cycloaddition reaction of the methylcarbenoid of zinc to 2-cyclohexen-1-ol, 2-cyclohepten-1-ol, and *cis*-2-cycloocten-1-ol was investigated under two conditions: (A) equimolar amounts of diethylzinc and cyclic allylic alcohol were used; and (B) twice as much diethylzinc as the alcohol by mole was used. Intramolecular ethylidene transfer reaction in an intermediate like **20**, and a quasi-intermolecular ethylidene transfer reaction in an intermediate like **22**, were considered to be predominant under the conditions A and B, respectively. However, with respect to the configuration of the cyclopropane ring with hydroxyl group in the products, highly syn- or anti-selective cycloadditions were observed independently of the two reaction conditions. On the other hand, with respect to the configuration of the methyl group introduced by the organozinc reagent, the stereoselectivity depended upon the two reaction conditions, and the steric restraint caused by the hydroxyl group on the configuration of the methyl group was concluded to be relatively loose under the condition of a quasi-intermolecular ethylidene transfer reaction in an intermediate like **22**.

In a previous paper,[1] we have demonstrated the synthesis of methylcyclopropane derivatives by the reaction of olefins with 1,1-diiodoethane and diethylzinc (eq 1). The reaction



(1)

proceeds stereospecifically, i.e., cis and trans olefins afford cyclopropane derivatives whose configurations with respect to the substituents from original olefins are cis and trans, respectively. With respect to the stereochemistry of the methyl group introduced by the organozinc reagent, the reaction generally yields the endo or cis isomers predominantly over the corresponding exo or trans isomers, respectively. For example, the reaction with cyclohexene gave a 1.5:1 mixture of *endo*- and *exo*-7-methylbicyclo[4.1.0]heptane. On the other hand, the exo or trans isomers were obtained predominantly over the corresponding endo or cis isomers, respectively, from olefins containing hydroxyl group such as allyl alcohol and 2-buten-1-ol. The stereochemistry of the reaction with 3-cyclopenten-1-ol was especially interesting, which gave exclusively *exo*-6-methyl-*cis*-3-hydroxybicyclo[3.1.0]hexane (**1**) among four possible stereoisomers. This work was aimed at



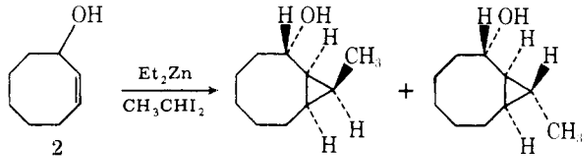
1

an investigation of the stereochemistry of the reaction 1 with olefins containing hydroxyl group to some detail.

In the Simmons–Smith reaction with cyclic allylic and homoallylic alcohols, the hydroxyl group plays an important role in not only the reactivity of the olefin, but also the stereospecificity of the reaction.[2] In most cases, the cyclopropane ring was exclusively cis to the hydroxyl group in the product. However, in the reaction with some larger and relatively complicated cyclic molecules, the cyclopropane ring was exclusively trans to the hydroxyl group in the product. For example, highly anti-selective addition[3] was observed with 2-cycloocten-1-ol and 2-cyclononen-1-ol, whereas syn-selective addition[3] was predominant for 2-cyclohepten-1-ol, 2-cyclohexen-1-ol, and 2-cyclopenten-1-ol.[2n] We studied the steric course of the cycloaddition of the methylcarbenoid of zinc to these cyclic allylic alcohols.

Results

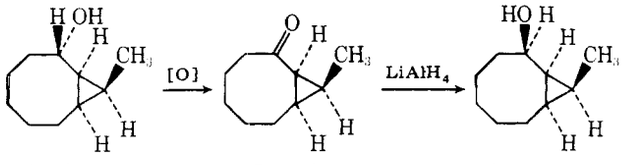
We found that, when equimolar amounts of diethylzinc and *cis*-2-cycloocten-1-ol (**2**) were used, reaction 1 gave *endo*-9-methyl-*trans*-2-hydroxy- (**3**) and *exo*-9-methyl-*trans*-2-hydroxy-*cis*-bicyclo[6.1.0]nonane (**4**) in 29 and 31% yields, respectively, with traces of *endo*-9-methyl-*cis*-2-hydroxy- (**6**) and *exo*-9-methyl-*cis*-2-hydroxy-*cis*-bicyclo[6.1.0]nonane (**8**). The isomer ratio of the endo,trans alcohol **3** to the exo,trans alcohol **4** was thus 0.9. In the case where twice as much diethylzinc as the cyclic allylic alcohol **2** by mole was used, the



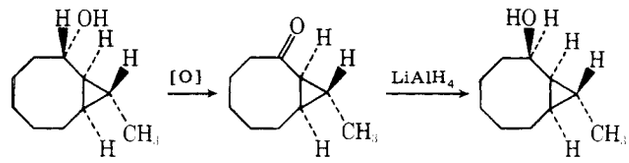
2 3 (endo, trans) 4 (exo, trans)

reaction gave the two trans alcohols **3** and **4** in 54 and 22% yields, respectively, with traces of the two cis alcohols **6** and **8**. The isomer ratio of **3** to **4** was thus 2.5 in this case. In both runs of experiments, the cyclopropane ring was exclusively trans to the hydroxyl group as in the corresponding Simmons–Smith reaction.[2n] The isomer ratio of the cyclopropylcarbinol was independent of the yield and the reaction time under our experimental conditions.

The relative configurations of these alcohols were assigned from the expected direction of hydride reduction of ketones **5** and **7** and by comparison of their ^{1}H NMR spectra.[2n] Jones oxidation[4] of the endo,trans alcohol **3** and the exo,trans alcohol **4** followed by reduction of the corresponding ketones **5** and **7** with lithium aluminum hydride gave the endo,cis alcohol **6** and the exo,cis alcohol **8**, respectively, contaminated with traces of the trans alcohols **3** and **4**, respectively. The protons in the geminal position to the hydroxyl group were observed at higher fields with broader bands in the endo,trans alcohol **3** (τ 6.78 with a width at half-height of 21 Hz) and the exo,trans alcohol **4** (τ 6.61 with a width at half-height of 21 Hz), relative to the endo,cis alcohol **6** (τ 6.49 with a width at half-height of 14 Hz) and the exo,cis alcohol **8** (τ 6.42 with a width at half-height of 14 Hz), in accord with the expected influence of a neighboring cyclopropane ring.[2c,2n] The protons in the geminal position to the hydroxyl group were observed at higher fields in the endo,trans alcohol **3** (τ 6.78) and the endo,cis alcohol **6** (τ 6.49), relative to the corresponding exo alcohols **4** (τ 6.61) and **8** (τ 6.42), respectively, in accord with the expected influence of the C–CH_3 bond.

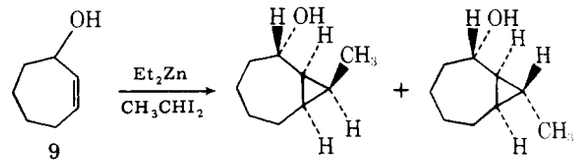


3 (endo, trans) 5 (endo) 6 (endo, cis)



4 (exo, trans) 7 (exo) 8 (exo, cis)

When equimolar amounts of diethylzinc and 2-cyclohepten-1-ol (**9**) were used, *endo*-8-methyl-*trans*-2-hydroxy- (**10**) and *exo*-8-methyl-*trans*-2-hydroxybicyclo[5.1.0]octane (**11**) were obtained in 38 and 36% yields, respectively. In the case where twice as much diethylzinc as the cyclic allylic alcohol **9** by mole was used, the reaction gave the two trans alcohols **10** and **11** in 38 and 41% yields, respectively. In both runs of

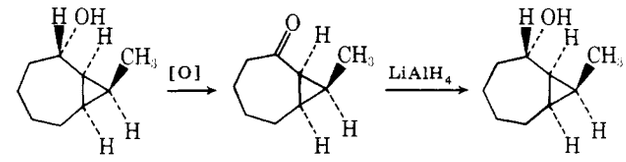


9 10 (endo, trans) 11 (exo, trans)

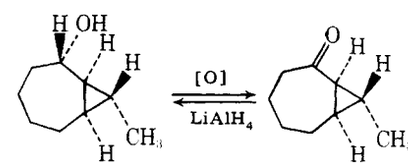
experiments, the cyclopropane ring was exclusively trans to the hydroxyl group, contrary to the corresponding Simmons–Smith reaction.[2n,5]

The relative configurations of these alcohols were assigned based on their ^{1}H NMR spectra. The endo,trans alcohol **10** and the exo,trans alcohol **11** showed the absorptions due to the protons in the geminal position to the hydroxyl group at τ 6.77 (with a width at half-height of 18 Hz) and τ 6.66 (with a width at half-height of 18 Hz), respectively. This result is consistent with the trans configuration of the cyclopropane ring to the hydroxyl group. In the case of 2-hydroxybicyclo[5.1.0]octanes, the peak due to the hydrogen atom in the geminal position to the hydroxyl group of the trans isomer was reported to appear at τ 6.7 with a width at half-height of 15 Hz, whereas the corresponding peak of the cis isomer was reported to appear at τ 5.8 with a width at half-height of 10 Hz.[2c]

Jones oxidation[4] of the endo,trans alcohol **10** and the exo,trans alcohol **11** followed by reduction of the ketones **12** and **13** with lithium aluminum hydride gave predominantly the trans alcohols **10** and **11**, respectively.[6]



10 (endo, trans) 12 (endo) 10 (endo, trans)

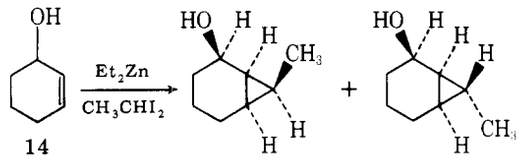


11 (exo, trans) 13 (exo)

Reaction of equimolar amounts of diethylzinc and 2-cyclohexen-1-ol (**14**) with 1,1-diiodoethane gave *endo*-7-methyl-*cis*-2-hydroxy- (**15**) and *exo*-7-methyl-*cis*-2-hydroxybicyclo[4.1.0]heptane (**16**) in 79% yield. The isomer ratio of the exo,cis alcohol **16** to the endo,cis alcohol **15** was 1.6. When twice as much diethylzinc as the cyclic alcohol **14** by mole was used, the reaction gave the two cis alcohols **15** and **16** in 60% yield. The isomer ratio of **16** to **15** was 1.7 in this case.

In both runs of experiments, the cyclopropane ring was cis to the hydroxyl group as in the corresponding Simmons–Smith reaction.[2n]

The relative configurations of these alcohols were also determined based on their ^1H NMR spectra. Since **15** and **16** were thermally unstable, they were not separated. ^1H NMR spectra of mixtures of the endo,cis alcohol **15** and the exo,cis alcohol **16** showed the absorption of the protons in the geminal position to the hydroxyl group at τ 5.74. With the aid of a shift reagent Eu(dpm)$_3$, the absorption was separated into two multiplets, both of which showed the width at half-height of 11 Hz. These chemical shifts and widths at half-height are consistent with the cis configuration of the cyclopropane ring with the hydroxyl group.[2c] ^1H NMR spectra of mixtures of **15** and **16** showed two doublets at τ 8.89 (J = 5.7 Hz) and 8.92 (J = 6.3 Hz), in the intensity ratio of 1.6:1 and 1.7:1, respectively, for the two runs of experiments mentioned above. The former doublet was assigned to the exo,cis alcohol **16**, and the latter to the endo,cis alcohol **15**, respectively, based on the expected



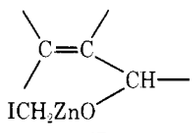
14 15 (endo, cis) 16 (exo, cis)

influence of cyclohexyl ring.[7] The predominant isomer was thus determined to be the exo,cis alcohol **16**. The coupling constants and the intensity ratio of the two doublets were determined with an aid of a shift reagent Eu(dpm)$_3$.

Results were summarized in Table I.

Discussion

Stereoselectivity with Respect to the Configuration of the Hydroxyl Group with the Cyclopropane Ring. Two mechanisms were proposed for the steric course of the Simmons–Smith reaction with cyclic allylic and homoallylic alcohols. One mechanism involves cleavage of the Simmons–Smith reagent by the hydroxyl group of the olefin to give a zinc compound like **17**, and stereospecific intramolecular methylene transfer would then yield the cyclopropylcarbinol after hydrolysis.[2f] Another mechanism includes the formation of a zinc complex like **18**, and the complex would undergo methylene transfer with stereospecificity.[2i] Since the cyclopropane ring was predominantly cis or trans to the hydroxyl group, methylene transfer reaction by a free zinc carbenoid without formation of these intermediates is not probable.



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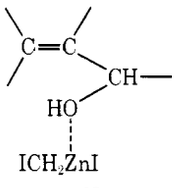
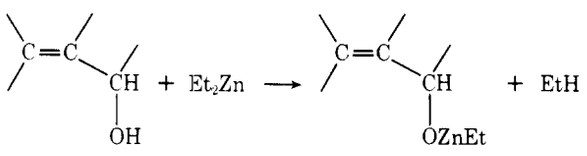


18

In the reaction 1 with cyclic allylic alcohols, the addition of 1,1-diiodoethane was carried out after the unsaturated alcohol was converted to the corresponding ethylzinc alkoxide **19**.



19

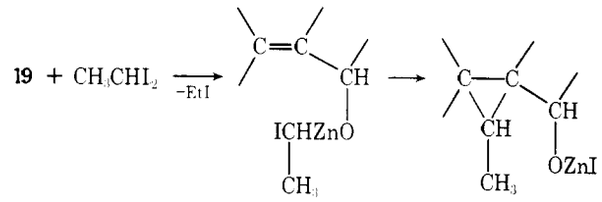
Table I. Product Distribution and Yields of Cyclopropylcarbinols

Cyclic allylic alcohol	Epimer distribution, % Endo, cis	Exo, cis	Endo, trans	Exo, trans	Total yield, %
Under condition A[a]					
2-Cyclohexen-1-ol **14**	38	62			79[c]
2-Cyclohepten-1-ol **9**			51	49	74[d]
cis-2-Cycloocten-1-ol **2**			48	52	60[d]
Under condition B[b]					
2-Cyclohexen-1-ol **14**	37	63			60[c]
2-Cyclohepten-1-ol **9**			48	52	79[d]
cis-2-Cycloocten-1-ol **2**			71	29	76[d]

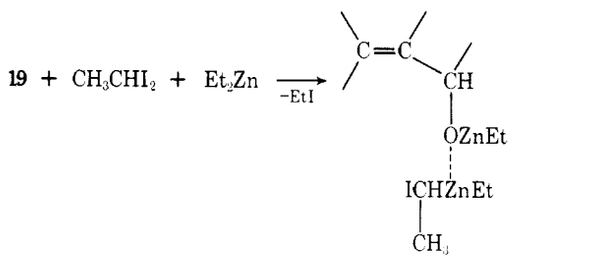
[a] Equimolar amounts of diethylzinc and the cyclic allylic alcohol were used. [b] Twice as much diethylzinc as the cyclic allylic alcohol by mole was used. [c] Isolated yield. [d] Determined by VPC analysis of the reaction mixture.

Thus intermediate **18** is not probable, but the following two types of intermediates **20** and **22** can be conceivable, which correspond to the intermediates **17** and **18**, respectively.

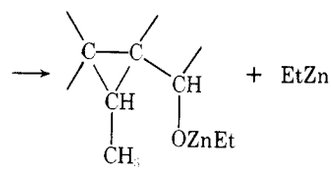
We carried out the reaction 1 with cyclic allylic alcohols under two conditions. (A) Equimolar amounts of diethylzinc and cyclic allylic alcohol were used. In this case, a stereospecific intramolecular ethylidene transfer reaction would occur in an intermediate like **20** and yield the corresponding cyclopropylcarbinol after hydrolysis of **21**. The formation of an



20 21



22



23

intermediate like **22** is very difficult to be conceived. (B) Twice as much diethylzinc as cyclic allylic alcohol by mole was used. In this case, ethylidene transfer reaction would principally occur in an intermediate like **22**. That is, intermolecular reaction of **19** with the methylcarbenoid of zinc would give a complex **22**, which undergoes a quasi-intermolecular ethylidene transfer reaction with stereospecificity to afford the corresponding cyclopropylcarbinol after hydrolysis of **23**. The formation of an intermediate like **20** is much less probable in this case, because diethylzinc is much more reactive than

ethylzinc alkoxide toward 1,1-diiodoethane.[8]

The exo/endo isomer ratio, i.e., the isomer ratio with respect to the configuration of the introduced methyl group, depended upon the reaction conditions A and B, especially in the reaction with cyclooctenol **2**. This fact also supports that the reaction proceeded via different intermediates under the two reaction conditions. However, the cyclopropane ring was exclusively cis or trans to the hydroxyl group in the products independently of the two reaction conditions. Therefore, both of the intermediates **20** and **22** would lead to the same steric configuration between the cyclopropane ring and hydroxyl group.

The reaction 1 with the cyclohexenol **14** and the cyclooctenol **2** showed exclusive syn- and anti-selective additions,[3] respectively, as in the corresponding Simmons–Smith reaction. On the other hand, the reaction 1 with the cycloheptenol **9** showed an exclusive anti-selective addition[3] contrary to the corresponding Simmons–Smith reaction, which was reported to give a 90:10 mixture of the cis and trans alcohols.[2n] The stereospecific syn- or anti-selective additions in the Simmons–Smith reaction with cyclic allylic alcohols were explained in terms of the attack of organozinc reagent on the nearest face of the neighboring double bond.[2n] Models of the cyclohexenol **14** indicate that the allylic hydroxyl group can only function as a syn director. Models of the cyclooctenol **2** shows that the anti-selective addition is favored. On the other hand, models of the cycloheptenol **9** are less helpful in determining which face of the double bond is more accessible. The energy difference between the transition states of syn- and anti-selective additions for the Simmons–Smith reaction was reported to be only 1.3 kcal/mol.[2n] In the transition states **20** or **22** for the reaction with the cycloheptenol **9**, the steric interference between the methyl group of the organozinc reagent and the cycloheptene ring would lead the carbenoid to the anti-selective addition.

Stereoselectivity with Respect to the Configuration of the Methyl Group Introduced by the Organozinc Reagent. Reaction 1 usually gives the endo or cis isomers predominantly over the corresponding exo or trans isomers, respectively.[1] However, the reversal of the stereoselectivity was observed in reaction 1 with olefins containing hydroxyl group,[1] which can be ascribable to the steric restraint in intermediates like **20** and/or **22**. In reaction 1 with the cyclohexenol **14**, the exo,cis alcohol **16** was obtained predominantly over the endo,cis alcohol **15**. In reaction 1 with cycloheptenol **9**, nearly equal amounts of the two trans alcohols **10** and **11** were obtained. In reaction 1 with cyclooctenol **2**, nearly equal amounts of the two trans alcohols **3** and **4** were obtained when equimolar amounts of diethylzinc and **2** were used. On the other hand, the endo,trans alcohol **3** was obtained predominantly over the exo,trans alcohol **4** when twice as much diethylzinc as **2** by mole was used. Based on these observations, we can conclude that the steric restraint on the configuration of the methyl group decreases with ring size of the cyclic allylic alcohols. The nonbonding interaction between the methyl group and the cycloalkane ring would become more significant than the steric restraint caused by the hydroxyl group as the ring size increases. The endo/exo isomer ratio in reaction 1 with the cyclooctenol **2** was 0.9 when equimolar amounts of diethylzinc and the cyclootenol **2** were used, while the ratio was 2.5 in the case where twice as much diethylzinc as the cyclooctenol **2** by mole was used. The endo/exo isomer ratio in the latter case was close to that observed in reaction 1 with *cis*-cyclooctene (see the Experimental Section for detail). This result indicates that the steric restraint caused by the hydroxyl group on the configuration of the methyl group is relatively loose in the reaction with larger cyclic alcohols especially under the condition of a quasi-intermolecular ethylidene transfer reaction in the intermediate like **22**.

Experimental Section

Microanalyses were performed at the Elementary Analyses Center of Kyoto University. ^{1}H NMR spectra were recorded on a Varian Model T-60-A or a Japan Electron Optics Model HA-100 spectrometer using carbon tetrachloride as solvent and tetramethylsilane as internal standard. Mass spectra were obtained on a Hitachi Model RMU-6 spectrometer. VPC analysis and separation were carried out on a Shimadzu GC-4A or GC-4B gas chromatograph.

Materials. Diethylzinc,[9] 1,1-diiodoethane,[10] 2-cyclohexen-1-ol,[2d] 2-cyclohepten-1-ol,[2d] *cis*-2-cycloocten-1-ol,[11] and chromium(VI) oxide[12] were prepared according to the literature methods. Solvents and nitrogen were purified as in a previous paper.[1] Other chemicals were commercially available and used without further purification.

Procedure. The reaction of cyclic allylic alcohols and other olefins with 1,1-diiodoethane and diethylzinc were carried out as in a previous paper.[1] Except for the reaction with cyclohexen-1-ol **14**, yields were determined by VPC analysis of the reaction mixture, and were based on the olefin. Jones oxidation[4] of alcohols was carried out in dry pyridine with the use of chromium(VI) oxide at room temperature as in a previous paper.[1] Reduction of ketones was carried out with use of lithium aluminum hydride in diethyl ether at room temperature.

Reaction of *cis*-2-Cycloocten-1-ol (2) with Diethylzinc and 1,1-Diiodoethane. *cis*-2-Cycloocten-1-ol (10.0 mmol, 1.36 g) was added dropwise to diethylzinc (10.0 mmol, 1.04 mL; or 20.0 mmol, 2.08 mL) in 10.0 mL of cyclohexane at room temperature. After gas evolution ceased, 1,1-diiodoethane (15.0 mmol, 1.70 mL) was added dropwise to the reaction mixture with stirring, and allowed to react at room temperature. After 15 h, the reaction mixture was poured into aqueous ammonium chloride. The aqueous layer was extracted several times with dry ether, and the combined organic solution was submitted for VPC analysis. In other runs of experiments, the organic solution was washed with methanolic sodium hydroxide. Solvents were removed by distillation. A sample of **3** collected from the residue by VPC was analyzed: ^{1}H NMR (CCl_4) τ 6.78 (m, 1 H, width at half-height = 21 Hz), 7.68 (s, 1 H), 7.8–9.8 [m, 16 H, including 8.92 (d, 3 H, J = 4.8 Hz)]; MS *m/e* (rel intensity) 155 (0.29), 154 (2.44 M^+), 71 (100), 55 (68), 41 (74). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.64; H, 11.48. An isolated sample of **3** was oxidized to **5** with use of chromium(VI) oxide in pyridine. Reduction of **5** with lithium aluminum hydride in diethyl ether gave **6**. A sample of **6** collected by VPC was analyzed: ^{1}H NMR (CCl_4) τ 6.49 (m, 1 H, width at half-height = 13 Hz), 7.41 (s, 1 H), 7.7–9.4 [m, 16 H, including 8.95 (d, 3 H, J = 5.0 Hz)].

An isolated sample of **4** collected from the distillation residue by VPC was analyzed: ^{1}H NMR (CCl_4) τ 6.61 (m, 1 H, width at half-height = 21 Hz), 7.27 (s, 1 H), 7.8–9.8 [m, 16 H, including 8.93 (d, 3 H, J = 4.5 Hz)]; MS *m/e* (rel intensity) 155 (0.24), 154 (2.12, M^+), 71 (100), 55 (71), 41 (72). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.95; H, 11.81. An isolated sample of **4** was oxidized to **7** and reduced to **8** in a similar manner. A sample of **8** collected by VPC was analyzed: ^{1}H NMR (CCl_4) τ 6.42 (m, 1 H, width at half-height = 14 Hz), 7.61 (s, 1 H), 7.7–9.4 [m, 16 H, including 9.10 (d, 3 H, J = 7.2 Hz)].

Reaction of 2-Cyclohepten-1-ol (9) with Diethylzinc and 1,1-Diiodoethane. 2-Cyclohepten-1-ol (5.0 mmol, 0.78 g), diethylzinc (5.0 mmol, 0.52 mL; or 10.0 mmol, 1.04 mL), and 1,1-diiodoethane (7.5 mmol, 0.85 mL) were allowed to react in 3.0 mL of diethyl ether at room temperature in a similar way. After solvents were removed by distillation, a sample of **10** was collected from the residue by VPC and analyzed: ^{1}H NMR (CCl_4) τ 6.77 (m, 1 H, width at half-height = 18 Hz), 7.5–9.7 [m, 15 H, including 7.93 (s, 1 H) and 8.93 (d, 3 H, J = 4.5 Hz)]; MS *m/e* (rel intensity) 141 (0.15), 140 (1.45, M^+), 71 (91), 67 (73), 55 (73), 43 (75), 41 (100). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.03; H, 11.50. An isolated sample of **10** was oxidized with the use of chromium(VI) oxide. Reduction of the product by lithium aluminum hydride gave **10**.

A sample of **11** collected from the distillation residue by VPC was analyzed: ^{1}H NMR (CCl_4) τ 6.66 (m, 1 H, width at half-height = 18 Hz), 7.5–9.7 [m, 15 H, including 7.41 (s, 1 H) and 8.99 (d, 3 H, J = 4.5 Hz)]; MS *m/e* (rel intensity) 141 (0.10), 140 (0.96, M^+), 71 (97), 67 (66), 55 (74), 43 (85), 41 (100). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.79; H, 11.50. An isolated sample of **11** was oxidized by chromium(VI) oxide. Reduction of the product with lithium aluminum hydride gave **11**.

Reaction of 2-Cyclohexen-1-ol (14) with Diethylzinc and 1,1-Diiodoethane. 2-Cyclohexen-1-ol (10.0 mmol, 0.97 g), diethylzinc (10.0 mmol, 1.04 mL), and 1,1-diiodoethane (15.0 mmol, 1.70 mL) were allowed to react in 10.0 mL of diethyl ether in a similar way at room

temperature. After solvents were removed under a reduced pressure, the residue was distilled at 44 °C (5 mmHg) to afford a mixture of **15** and **16** in 79% yield. Since **15** and **16** were thermally unstable, they were not separated, and the mixture was analyzed: ^{1}H NMR (CCl_4) τ 5.74 (m, 1 H), 7.89 (s, 1 H), 7.8–9.5 [m, 12 H, including 8.89 (d, J = 5.7 Hz) and 8.92 (d, J = 6.3 Hz)]. With the aid of a shift reagent Eu(dpm)$_3$, the absorption at τ 5.74 was separated into two multiplets with widths at half-height of 11 Hz, respectively. With the aid of the shift reagent, the two doublets were shown to include three protons, and the intensity ratio of the doublets at τ 8.89 and 8.92 to be 1.6:1. The coupling constants of the doublets were also determined with the aid of the shift reagent. Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.11; H, 11.20. When 20.0 mmol (2.08 mL) of diethylzinc was used, a mixture of **15** and **16** was obtained in 60% yield. ^{1}H NMR spectrum of the mixture showed the ratio of **15** to **16** to be 1:1.7.

Reaction of *cis*-Cyclooctene with Diethylzinc and 1,1-Diiodoethane. Reaction of *cis*-cyclooctene (1.2 mmol, 0.23 g) with diethylzinc (1.5 mmol, 0.15 mL) and 1,1-diiodoethane (2.4 mmol, 0.23 mL) in 3.0 mL of octane at 30 °C for 7 h gave a 1:2.6 mixture of *exo*- and *endo*-9-methyl-*cis*-bicyclo[6.1.0]nonane in 87% yield based on the olefin. The exo isomer: ^{1}H NMR (CCl_4) τ 7.8–10.2 [m, 18 H, including 8.99 (d, 3 H, J = 4.8 Hz)]. Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.60; H, 13.23. The endo isomer: ^{1}H NMR (CCl_4) τ 7.9–9.8 [m, 18 H, including 9.09 (d, 3 H, J = 4.5 Hz)]. Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.94; H, 13.02. In the case where 1.5 mmol of ethylzinc methoxide was used instead of diethylzinc, the yield of 9-methyl-*cis*-bicyclo[6.1.0]nonane was <1% when the reaction time was 7 h.

Registry No.—**2,** 14390-23-9; **3,** 62861-98-7; **4,** 62929-18-4; **5,** 62861-99-8; **6,** 62929-19-5; **7,** 62929-20-8; **8,** 62929-21-9; **9,** 4096-38-2; **10,** 62862-00-4; **11,** 62929-22-0; **12,** 62862-01-5; **13,** 62929-23-1; **14,** 822-67-3; **15,** 62862-02-6; **16,** 62862-03-7; diethylzinc, 557-20-0; 1,1-diiodoethane, 594-02-5; *cis*-cyclooctene, 931-87-3; *exo*-9-methyl-*cis*-bicyclo[6.1.0]nonane, 62862-04-8; *endo*-9-methyl-*cis*-bicyclo[6.1.0]nonane, 62929-24-2; ethylzinc methoxide, 15860-82-9.

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(6) Reduction of bicyclo[4.1.0]heptan-2-one with lithium aluminum hydride was reported to give predominantly the trans isomer of 2-hydroxybicyclo[4.1.0]heptane.[2d]
(7) The ^{1}H NMR spectra of *exo*- and *endo*-7-methylbicyclo[4.1.0]heptane showed the absorptions of the methyl protons at τ 9.03 and 9.06, respectively.[1]
(8) For example, the formation of 9-methyl-*cis*-bicyclo[6.1.0]nonanes was extremely slow when ethylzinc methoxide was used instead of diethylzinc in reaction 1 with *cis*-cyclooctene as is given in the Experimental Section.
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Synthesis of Steroidal [16α,17-*b*][1,4]Dioxanes

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Steroidal [16α,17-*b*][1,4]dioxanes have been prepared for the first time. The key reaction involves the selective functionalization of polyhydroxylated steroids via interaction of 16,17-cycloborates and functionalized diazo compounds to give 16α-alkoxylated 17-hydroxy steroids. Conversion of these intermediates to a variety of substituted dioxanes and dioxins is described. ^{1}H NMR and CD spectra of the products are discussed.

The conversion of certain 16α,17α-dihydroxy steroids, such as triamcinolone[1] (**1**), to the corresponding "acetonides" [2′2′-dimethyl[16α,17-*d*][1,3]dioxolanes (**2**)] is accompanied by a marked increase in topical antiinflammatory activity.[2] A variety of other fused five-membered ring systems incorporating an additional boron, carbon, phosphorus, or sulfur atom[3–6] have been prepared from **1**; however, none of these modifications has led to a therapeutic agent. We decided to incorporate a second carbon atom into the moiety bridging the 16- and 17-oxygen atoms in **2** and prepare compounds of the type **5** in order to explore the effect on antiinflammatory activity.

One attractive approach to such compounds appeared to be the cyclization of intermediates of the type **3** or **4**. Conversion of **1** to the penultimate intermediate **3** requires selective functionalization of one of the two most reactive hydroxyl groups in **1**; for conversion to **4**, one of the two least reactive hydroxyls must be alkylated. A simple approach to 16α-alkoxy derivatives such as **3** is provided by the reaction of the 16,17-cycloborate esters of 11β,16α,17,21-tetrahydroxy steroids with diazoalkanes discovered by Fried and Thomas.[8] We have used the reaction of functionalized diazo compounds with cycloborate esters to prepare derivatives of **3** suitable for transformation to various dioxanes, including the parent ring system **5**. At this time, we wish to describe the synthesis of steroidal [16α,17-*b*][1,4]dioxanes; the biologic activity of these compounds will be reported separately.

Results

Reaction of 9-fluoro-11β,16α,17,21-tetrahydroxypregn-4-ene-3,20-dione with a large excess of boric oxide in methanol gives cycloborate **6** in excellent yield.[3] When powdered **6** is added to a well-stirred solution of diazoalkene **8a**[9] in ether–methanol at 0 °C nitrogen is evolved and the ether **9a** is produced in 78% yield. It is necessary to use a large excess of diazo compound, since the boron species that is liberated reacts