Stereochemical Studies on the Nucleophilic Substitution in the Reaction of Allylic Phosphates with Organoaluminum Reagents

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The reaction of *cis*- or *trans*-5-isopropenyl-2-methyl-2-cyclohexenyl diethyl phosphate (**1**) with Me_2AlX (X= OPh, SPh, NHPh) in hexane results in substitution of the $-O-PO(OEt)_2$ group with X under predominant inversion. In contrast, treatment of *cis*- or *trans*-**1** with trialkylaluminum produces predominantly the allyl-nonallyl couplingproducts of the same (thermodynamically more stable) configuration. Similar alkylation of *endo*- and *exo*-2-acetoxynorcarane gave *endo*-2-methylnorcarane, exclusively.

The reaction of geranyl and neryl phosphates with R_2AlX type organoaluminum reagents[1] or trialkylaluminum compounds[2] results in nucleophilic substitution. The interest in stereoselectivity of these unique "ionic" reactions proceeding in nonpolar or less polar solvents has motivated the present studies on (1) the reaction of *cis*- or *trans*-5-isopropenyl-2-methyl-2-cyclohexenyl diethyl phosphate (**1**) with R_2AlX and (2) the reaction of *cis*- or *trans*-**1** with R_3Al.[3]

(1) Reaction of cis- *or* trans-*1 with R_2AlX.* Much attention has been paid to the conversion of esters to RCOX by means of R_2AlX (X=NR^1R^2,[4] SR,[5] SeR[6]). However, few examples are known for the nucleophilic substitution on a saturated carbon. The reaction of geranyl and neryl diethyl phosphates with R_2AlX (X=SPh, S^{t}Bu, OPh, NHPh) reagents results in the replacement of the $OPO(OEt)_2$ group by X group without affecting both olefinic bonds in any sense of the words. No allylic migration, no *E,Z*-isomerization, and no cyclization occur. Notably, this ionic reaction proceeds in *hexane*, which is a poor solvent of the reaction system and the whole forms a white suspension.

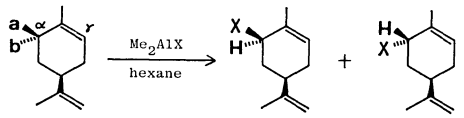
Further investigation of this kind of substitution with *cis*- and *trans*-**1** has clarified the steric course of the reaction. Treatment of *cis*- or *trans*-**1** with a heterogeneous white suspension of Me_2AlX (2 equiv) in hexane at 0 °C for 2 h gave substitution products **2** in good yields, as summarized in Table 1.

Invariably, substitution occurs under extensive configurational inversion and accompanies considerable allylic migration in contrast to the open chain geranyl and neryl diethyl phosphates. In order to determine the α/γ ratios, or S_N2/S_N2' ratios, products in the reaction of α-deuterio-*cis*-**1** or *trans*-**1** have been analyzed by NMR method.[7]

Solvent effect on the reaction between α-deuterio-*cis*-**1** and Me_2AlOPh is shown in Table 2. All the solvents except hexane gave clear solutions, in which ions should be much more free than in hexane. In the extreme tetrahydrofuran solvent, the retention product was predominant and the α/γ ratio was almost close to unity. Possibly an intimate ion-pair in a solvent cage could explain the findings. The similar solvent effect was observed in the reaction of *cis*-**1** with Me_2AlSPh or $Me_2AlNHPh$ (Table 3).

Assignments of the products were based on the examination of those NMR spectra. All the *trans* isomers, **2a**, **2b**, and **2c**, exhibited the narrow signals for the protons attached to carbon bearing X group at higher field than those for protons in *cis* isomers. The spectra are consistent with the postulated configuration

Table 1. Reaction of *cis*-**1** or *trans*-**1** with Me_2AlX in hexane[a]



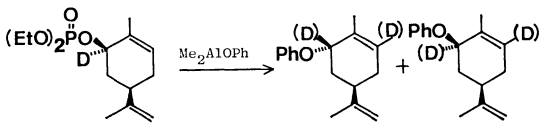
cis-**1**: **a**=O-PO(OEt)$_2$, **b**=H(D)
trans-**1**: **a**=H(D), **b**=O-PO(OEt)$_2$

cis-**2a,b,c** *trans*-**2a,b,c**
a: X=OPh, **b**: X=SPh, **c**: X=NHPh

Substrate	Reagent X	Ptoduct **2** Yield (%)[b]	*cis* (%)[c]	*trans* (%)[c]
cis-**1**	OPh	80	2	98 (84/16)
cis-**1**	SPh	92	3	97 (60/40)
cis-**1**	NHPh	70	12	88 (76/24)
trans-**1**	OPh	86	89 (90/10)	11
trans-**1**	SPh	94	90 (76/24)	10
trans-**1**	NHPh	87	99 (82/18)	1

a) These data are averages of at least three independent experiments. b) Isolated by chromatography on silica gel and adequately characterized by analytical and spectral data. The isolated yields refer to the isomeric mixtures. c) Isomeric compositions were determined by GLPC. The data in parentheses indicate α/γ ratios for the predominant isomer which were determined by NMR spectra of deuterium labelled products.

Table 2. Solvent effect on the substitution



Solvent	Yield (%)[a]	*trans* (α/γ)	*cis* (α/γ)
Hexane	80	98 (84/16)	2
CH_2Cl_2	70	76 (74/26)	24 (71/29)
Et_2O	79	87 (75/25)	13 (77/23)
DME	82	57 (63/37)	43 (63/37)
THF	91	25 (60/40)	75 (63/37)

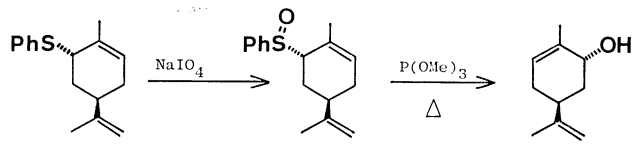
a) Isolated as mixtures of *trans* and *cis* isomers.

Table 3. Solvent effect on the substitution reaction of *cis*-**1** with Me_2AlSPh or $Me_2AlNHPh$

Solvent	Me_2AlSPh Yield (%)[a]	*trans*/*cis*	Solvent	$Me_2AlNHPh$ Yield (%)[a]	*trans*/*cis*
Hexane	92	97/ 3	Hexane	70	88/12
CH_2Cl_2	82	80/20	CH_2Cl_2	63	71/29
THF	79	58/42	THF	76	20/80

a) Isolated as mixtures of *trans* and *cis* isomers.

assuming those chair conformations in which the isopropenyl group is equatorial and the H–C–X protons therefore pseudo-equatorial. On the other hand, the much broader, lower field proton signals of *cis* isomers are ascribed to pseudo-axial ones.[8] Further support for the assignment has been given by the following transformation of *trans*-**2b** to *trans*-carveol (Scheme 1).

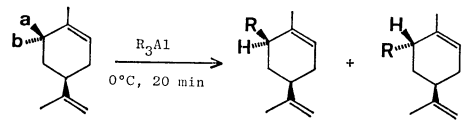


Scheme 1.

(*2*) *Reaction of* cis- *or* trans-*1 with* R_3Al. An investigation of the reaction of allylic phosphates with organoaluminum reagents has provided an exceptionally mild procedure to effect allyl-nonallyl coupling.[2] This C–C bond formation is now found to be characterized by carbocationic intermediates being produced from allylic phosphates in hexane.

Treatment of *cis*- or *trans*-**1** with trialkylaluminum (3 equiv) in hexane at 0 °C for 20 min gave a mixture of **4** and **5**. The results are summarized in Table 4, which indicates that the alkylation occurs predominantly from the side opposite to the isopropenyl group.

Table 4. Alkylation of *cis*-**1** or *trans*-**1** with R_3Al



cis-**1**: **a**=OPO(OEt)$_2$, **b**=H
trans-**1**: **a**=H, **b**=OPO(OEt)$_2$
cis-**3**: **a**=OCOCH$_3$, **b**=H (D)
trans-**3**: **a**=H (D), **b**=OCOCH$_3$

4a,b,c: **a**: R=Me, **b**: R=Et, **c**: R=^{i}Bu

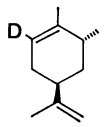
5a,b,c

Run	Substrate	Reagent R	Solvent	Product Yield (%)[a]	**4**:**5**[b]
1	*trans*-**1**	Me	Hexane	85	4:96
2	*cis*-**1**	Me	Hexane	87	16:84
3	*trans*-**3**	Me	Hexane	78	4:96
4	*cis*-**3**	Me	Hexane	85	18:82
5	*trans*-**1**	Et	Hexane	89	6:94
6	*cis*-**1**	Et	Hexane	82	51:49
7	*trans*-**1**	^{i}Bu	Hexane	93	9:91
8	*cis*-**1**	^{i}Bu	Hexane	88	37:63
9	*cis*-**1**	Me	CH_2Cl_2	89	22:78
10	*cis*-**1**	Me	THF	63	8:92

a) Isolated yields refer to the epimeric mixtures. b) Isomeric ratios were determined by GLPC.

It is worth noting that this alkylation takes place also with carboxylic esters (runs 3 and 4) instead of the phosphate as a leaving group. A synthetically useful transformation of alcoholic substrates R^1OH into the coupling products R^1–R^2 [9] is thus based on the reaction of the corresponding esters R^1–OCOR with organometallic reagents R^2Mtl. No carbonyl attack[10] is observed with trialkylaluminum reagents.

The α-deuterio-*cis*-**3** and *trans*-**3** gave mainly *trans*-methylated products, **5** and its regioisomer **6** being produced in a ratio of 45: 55 and 40: 60 respectively. The product distribution of the alkylation was also independent of the solvent (runs 1, 9, and 10). The reaction of allylic phosphates with trialkylaluminum is in sharp contrast to the substitution reaction of those with Me_2AlX reagents described in section 1, where S_N2 type introduction of the X group predominates with inversion of the configuration.[11]



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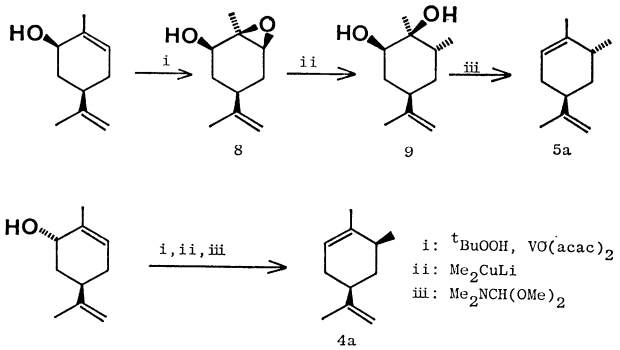
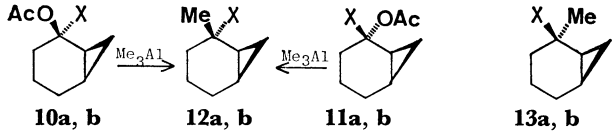
The structures of the products were unambiguously confirmed by the alternative synthesis of **4a** and **5a** according to Scheme 2.[12]



Scheme 2.

Similar stereochemistry was observed in the transformation of *endo*-2-acetoxynorcarane **10a** and its epimer **11a**. Subjection of the acetate **10a** to the action of trimethylaluminum in dichloromethane for 2 h at room temperature gave **12a** (contaminated with less than 7% of its epimer **13a**) in 80% yield. The exclusive product from **11a** was again **12a** (80%). As the deuterated acetates (**10b** and **11b**, a 22 : 78 mixture) gave



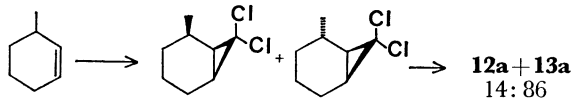
10a, b **12a, b** **11a, b** **13a, b**

a: X=H; **b**: X=D

Scheme 3.

12b (>93%), a mechanism involving rearrangement with ring opening can be rejected.[14]

Authentic samples of the products were prepared from 3-methylcyclohexene (Scheme 4). The stereochemical identities were established by hydrogenating this mixture (H_2, 1 atm, PtO_2, AcOH) to 1:5 mixture of *cis*- and *trans*-1,2-dimethylcyclohexane, each of which was separated by GLPC and compared spectrometrically with the corresponding authentic sample.[15]



Scheme 4.

Experimental

The optical rotations were measured using a Yanaco-OR-50 polarimeter. The infrared spectra were determined on a Shimadzu IR-27-G spectrometer; the mass spectra on a Hitachi RMU-6L machine; the GLPC analyses on a Yanagimoto GCG-550F; and the NMR spectra on a JEOL-C-60H or Varian EM-390H spectrometer. The chemical shifts are given in δ in ppm with TMS as the internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The microanalyses were carried out by the staffs at the Elemental Analyses Center of Kyoto University. All experiments were carried out under an atmosphere of dry argon. Tetrahydrofuran was dried by distillation from sodium–benzophenone. Thin layer or thick layer plates were made of E. Merck PF-254, and preparative column chromatography on silica gel E. Merck Art. 7734.

Preparation of cis-*Carveol.* (−)-Carvone (21.0 g, 140 mmol) was reduced by lithium aluminum hydride (2.66 g, 70 mmol) in THF (300 ml) at −15 °C.[16] The crude carveol (*cis*: *trans*=92:8, determined by GLPC, 10% PEG 20M on Celite 545, 2 m, 140 °C) was then treated with 3,5-dinitrobenzoyl chloride (37.8 g, 164 mmol) in pyridine (120 ml) at 25 °C. The mixture was stirred at the same temperature for 12 h, poured into precooled 1 M (1 mol dm^{-3}) HCl, and extracted with ethyl acetate twice. The organic phase was washed with 1 M HCl, and brine, dried, and concentrated. The crude product was passed through a short column of silica gel and the *cis*-benzoate was recrystallized from ethanol–ethyl acetate (3 : 1) twice (mp 92.5 °C). Hydrolysis (5% KOH in methanol, 100 ml, 20 min at reflux) followed by purification by column chromatography on silica gel (hexane: ethyl acetate=3 : 1) afforded *cis*-carveol (6.84 g, 32%) contaminated by <0.5% *trans* isomer.

Preparation of trans-*Carveol.* According to the reported procedure,[17] the title compound (>99.5% pure) was prepared from (−)-carvone by reduction with aluminum triisopropoxide in isopropyl alcohol and purification by recrystallization of 3,5-dinitrobenzoate (mp 111.5 °C) followed by hydrolysis.

*Preparation of α-Deuterio-*cis-*carveol.* (−)-Carvone (3.0 g, 20 mmol) was reduced by lithium aluminum deuteride (0.42 g, 10 mmol, Merck 98% d) in THF (25 ml) at −15 °C and the product was further purified by the method described above.

*Preparation of α-Deuterio-*trans-*carveol.* A solution of diethyl phosphate of α-deuterio-*cis*-carveol (1.15 g, 4.0 mmol) in 1,2-dimethoxyethane (3.0 ml) was added to a mixture of potassium superoxide (0.98 g, 13.8 mmol), 18-crown-6 (2.43 g, 9.2 mmol), dimethyl sulfoxide (10.0 ml), and 1,2-dimethoxyethane (10.0 ml) at 25 °C. After 16 h, the reaction mixture was poured into water and the organic phase was extracted with ethyl acetate three times. The combined extracts were washed with brine, dried, and freed of the solvent. Purification by column chromatography on silica gel afforded α-deuterio-*trans*-carveol (0.19 g, 1.3 mmol, contaminated by <5% *cis* isomer) in 32% yield. Absence of γ-deuterio-carveol was confirmed by the examination of its NMR spectrum.

cis-*5-Isopropenyl-2-methyl-2-cyclohexenyl Diethyl Phosphate* (cis-*1*). Butyllithium in hexane (1.5 M, 31.4 ml, 47.2 mmol) was added to a solution of *cis*-carveol (6.82 g, 44.9 mmol) in ether (40 ml) at −23 °C. After 20 min, a solution of diethyl phosphorochloridate (13.0 ml, 89.8 mmol) and triethylamine (12.5 ml, 89.8 mmol) in ether (30 ml) was added. The mixture was stirred for 2 h at the same temp, poured into ice–water, and extracted with ethyl acetate three times. The organic phase was washed with brine, dried, and freed of the solvent. Purification by column chromatography on silica gel (hexane: ethyl acetate=3:1) afforded *cis*-**1** (9.54 g, 33.1 mmol) in 74% yield as a colorless oil: NMR (CCl_4) δ 1.33 (t, J=7.2 Hz, 6H), 1.74 (s, 6H), 1.6—2.3 (m, 5H), 4.03 (m, 4H), 4.69 (s, 2H), 4.85 (m, 1H), 5.49 (m, 1H).

trans-*5-Isopropenyl-2-methyl-2-cyclohexenyl Diethyl Phosphate* (trans-*1*): NMR (CCl_4) δ 1.33 (t, J=7.2 Hz, 6H), 1.74 (s, 6H), 1.6—2.3 (m, 5H), 4.03 (m, 4H), 4.57 (m, 1H), 4.69 (s, 2H), 5.60 (m, 1H).

General Procedure for the Reaction between Me_2AlX (*X*=*OPh*,[18] *SPh*,[19] *NHPh*,[20]) *and* **1** *in Hexane.* The substitution of *cis*-**1** with Me_2AlOPh is representative. Phenol (0.18 ml, 2.0 mmol) was added dropwise to a solution of trimethylaluminum (1.0 M solution in hexane, 2.0 ml, 2.0 mmol) in hexane (10 ml) at 0 °C. After stirring for 30 min, a solution of *cis*-**1** (0.29 g, 1.0 mmol) in hexane (3.0 ml) was added to the resulting white suspension at 0 °C and the mixture was held there for 2 h. Workup (1 M HCl and ether) followed by column chromatography on silica gel with ether–hexane (1:50) afforded a mixture of *trans*-**2a** and *cis*-**2a** (0.18 g, 80% yield) in a ratio of 98 : 2 as determined by GLPC (PEG 20 M 10% on Celite 545, 2 m, 195 °C). Further purification by preparative TLC (hexane, three developments) gave pure *trans*-**2a**: bp 152 °C (bath temp, 2 Torr); IR (neat) 1645, 1600, 1590, 1495, 1235 cm^{-1}; NMR (CCl_4) δ 1.70 (s, 3H), 1.76 (s, 3H), 1.83—2.50 (m, 5H), 4.48 (m, 1H), 4.66 (s, 2H), 5.63 (m, 1H), 6.75—7.33 (m, 5H); MS *m/e* (%) 228 (M^+, 3), 185 (2), 135 (18), 134 (71), 119 (50), 107 (62), 93 (100).

Found: C, 83.94; H, 8.93%. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83%.

cis-*5-Isopropenyl-2-methyl-3-phenoxycyclohexene* (cis-*2a*): Bp 160 °C (bath temp, 2 Torr); IR (neat) 1645, 1595, 1585, 1492, 1238, 1030, 888 cm^{-1}; NMR (CCl_4) δ 1.71 (s, 3H), 1.76 (s, 3H), 1.9—2.4 (m, 5H), 4.67 (s, 2H), 4.76 (m, 1H), 5.53 (m, 1H), 6.72—7.23 (m, 5H); MS *m/e* (%) 228 (M^+, 3), 185 (3), 135 (17), 134 (51), 119 (47), 107 (78), 93 (100).

Found: C, 84.38; H, 8.96%. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83%.

trans-*5-Isopropenyl-2-methyl-3-(phenylthio)cyclohexene* (trans-*2b*): Bp 155 °C (bath temp, 2 Torr); IR (neat) 1645, 1583, 1479, 889 cm^{-1}; NMR (CCl_4) δ 1.7—2.6 (m, 5H), 1.73 (s, 3H), 1.90 (s, 3H), 3.56 (m, 1H), 4.67 (s, 2H), 5.53 (m, 1H), 7.1—7.5 (m, 5H); MS *m/e* (%) 245 (1), 244 (M^+, 4), 134 (62), 119 (28), 107 (64), 93 (100).

Found: C, 78.90; H, 8.51%. Calcd for $C_{16}H_{20}S$: C, 78.63; H, 8.25%.

cis-*5-Isopropenyl-2-methyl-3-(phenylthio)cyclohexene* (cis-*2b*):

Bp 155 °C (bath temp, 2 Torr); IR (neat) 1645, 1585, 1483, 889 cm^{-1}; NMR (CCl_4) δ 1.8—2.7 (m, 5H), 1.70 (s, 3H), 1.89 (s, 3H), 3.65 (m, 1H), 4.61 (s, 2H), 5.56 (m, 1H), 7.1—7.5 (m, 5H); MS *m/e* (%) 245 (5), 244 (M^+, 10), 134 (59), 119 (45), 107 (78), 93 (100).

Found: C, 78.54; H, 8.46%. Calcd for $C_{16}H_{20}S$: C, 78.63; H, 8.25%.

trans-*3-(Phenylamino)-5-isopropenyl-2-methylcyclohexene (*trans-**2c**)*: Bp 175 °C (bath temp, 2 Torr); IR (neat) 3420, 1645, 1600, 1506, 1313, 1250, 888 cm^{-1}; NMR (CCl_4) δ 1.70 (s, 3H), 1.78 (s, 3H), 1.6—2.4 (m, 5H), 3.43 (m, 1H), 3.80 (m, 1H), 4.76 (s, 2H), 5.53 (m, 1H), 6.4—7.2 (m, 5H); MS *m/e* (%) 228 (6), 227 (M^+, 29), 159 (29), 158 (13), 119 (26), 93 (100).

Found: C, 84.63; H, 9.55%. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31%.

cis-*3-(Phenylamino)-5-isopropenyl-2-methylcyclohexene (*cis-**2c**)*: Bp 175 °C (bath temp, 2 Torr); IR (neat) 3400, 1645, 1601, 1506, 1315, 1248, 890 cm^{-1}; NMR (CCl_4) δ 1.70 (s, 6H), 1.6—2.3 (m, 5H), 3.27 (m, 1H), 3.95 (s, 1H), 4.66 (s, 2H), 5.50 (m, 1H), 6.4—7.1 (m, 5H); MS *m/e* (%) 228 (7), 227 (M^+, 29), 159 (37), 158 (14), 119 (26), 93 (100).

Found: C, 84.56; H, 9.38%. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31%.

General Procedure for the Reaction between Me_2AlX *and* **1** *in Various Solvents.* Me_2AlX (2.0 mmol) was prepared in hexane and the solvent was removed *in vacuo* to leave a white solid. Dichloromethane (ether, DME, THF) (10 ml) was added and the mixture was stirred for 5 min at 25 °C. A solution of *cis*-**1** (0.29 g, 1.0 mmol) in the same solvent (3.0 ml) was added at 0 °C. After 2 h, the mixture was worked up as previously described.

Transformation of trans-**2b** *into* trans-*Carveol.* A solution of **2b** (*trans*: *cis*=97: 3, 1.54 g) in methanol (20 ml) was treated with sodium periodate (2.8 g, 13.1 mmol) at 25 °C for 2 d. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane: ethyl acetate=5: 1) to give a diastereomeric mixture of the sulfoxide (0.91 g, 3.5 mmol) in 66% yield. A mixture of trimethyl phosphite (2.1 ml, 17.8 mmol, freshly distilled from sodium), the sulfoxide (0.91 g, 3.5 mmol), and methanol (3.3 ml) was heated to reflux for 1 h. The mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate three times. The combined extracts were washed with brine, dried, and concentrated. Purification by column chromatography on silica gel (hexane: ethyl acetate=10 : 1) afforded *trans*-carveol (0.28 g, 1.9 mmol, contaminated by $<2\%$ *cis*-carveol) in 53% yield.

General Procedure for the Alkylation of **1** *or* **3** *with Trialkylaluminum.* Trialkylaluminum (1.0 M solution in hexane, 3.0 ml, 3.0 mmol) was added dropwise to a solution of **1** or **3** (1.0 mmol) in hexane, dichloromethane or tetrahydrofuran (7.0 ml) at 0 °C. After 20 min, ethanol (1.0 ml) was added to decompose the excess trialkylaluminum. The mixture was poured into 1 M HCl and extracted twice with pentane. The combined extracts were washed with brine, dried, and freed of the solvent. Purification by preparative TLC (hexane) afforded a mixture of **4** and **5** whose ratio was determined by GLPC (PEG 20 M 10% on Celite 545, 2 m, 72 °C (R=Me), 88 °C (R=Et), 114 °C (R=^{t}Bu)). Pure samples of **4** and **5** were obtained by preparative GLPC (PEG 20 M 30% on Celite 545, 3 m, 98 °C (R=Me), 110 °C (R=Et), 120 °C (R=^{t}Bu)).

cis-*2,3-Dimethyl-5-isopropenylcyclohexene (**4a**)*: Bp 130 °C (bath temp, 20 Torr); IR (neat) 3185, 1645, 888, 800 cm^{-1}; NMR (CCl_4) δ 0.94 (d, J=6.9 Hz, 3H), 1.57 (s, 3H), 1.65 (s, 3H), 1.8—2.3 (m, 6H), 4.57 (s, 2H), 5.28 (m, 1H); MS *m/e* (%) 151 (3), 150 (M^+, 16), 135 (19), 121 (26), 108 (100), 107 (73), 93 (89), 82 (24), 67 (99).

Found: C, 88.17; H, 11.84%. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07%.

trans-*2,3-Dimethyl-5-isopropenylcyclohexene (**5a**)*: Bp 130 °C (bath temp, 20 Torr); IR (neat) 3185, 1645, 888, 800 cm^{-1}; NMR (CCl_4) δ 1.07 (d, J=6.9 Hz, 3H), 1.64 (s, 3H), 1.72 (s, 3H), 1.6—2.3 (m, 6H), 4.64 (s, 2H), 5.29 (m, 1H); MS *m/e* (%) 151 (4), 150 (M^+, 20), 135 (11), 121 (10), 107 (100), 93 (39), 82 (54), 67 (92).

Found: C, 87.72; H, 11.97%. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07%.

cis-*3-Ethyl-5-isopropenyl-2-methylcyclohexene (**4b**)*: Bp 188 °C (bath temp, 760 Torr); IR (neat) 3080, 1643, 887, 802 cm^{-1}; NMR (CCl_4) δ 0.94 (t, J=7.5 Hz, 3H), 1.67 (s, 3H), 1.74 (s, 3H), 1.2—2.3 (m, 8H), 4.64 (s, 2H), 5.30 (m, 1H); MS *m/e* (%) 165 (4), 164 (M^+, 22), 149 (8), 135 (14), 121 (65), 107 (32), 96 (28), 93 (99), 91 (28), 81 (100).

Found: C, 87.73; H, 11.99%. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27%.

trans-*3-Ethyl-5-isopropenyl-2-methylcyclohexene (**5b**)*: Bp 188 °C (bath temp, 760 Torr); IR (neat) 3080, 1645, 881, 800 cm^{-1}; NMR (CCl_4) δ 0.85 (t, J=7.5 Hz, 3H), 1.63 (s, 3H), 1.73 (s, 3H), 1.1—2.2 (m, 8H), 4.63 (s, 2H), 5.38 (m, 1H); MS *m/e* (%) 165 (2), 164 (M^+, 8), 135 (11), 122 (28), 121 (18), 107 (23), 96 (36), 93 (55), 81 (100), 80 (47).

Found: C, 88.00; H, 12.52%. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27%.

cis-*3-Isobutyl-5-isopropenyl-2-methylcyclohexene (**4c**)*: Bp 220 °C (bath temp, 760 Torr); IR (neat) 3100, 1646, 1381, 1377, 886, 800 cm^{-1}; NMR (CCl_4) δ 0.87 (d, J=4.5 Hz, 3H), 0.93 (d, J=4.5 Hz, 3H), 1.62 (s, 3H), 1.72 (s, 3H), 1.1—2.3 (m, 9H), 4.64 (s, 2H), 5.34 (m, 1H); MS *m/e* (%) 193 (5), 192 (M^+, 27), 149 (44), 107 (51), 93 (100), 81 (48), 80 (45), 68 (43), 57 (66).

Found: C, 86.70; H, 12.57%. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58%.

trans-*3-Isobutyl-5-isopropenyl-2-methylcyclohexene (**5c**)*: Bp 220 °C (bath temp, 760 Torr); IR (neat) 3060, 1643, 1376, 1364, 888, 800 cm^{-1}; NMR (CCl_4) δ 0.87 (d, J=3.0 Hz, 3H), 0.96 (d, J=3.0 Hz, 3H), 1.64 (s, 3H), 1.73 (s, 3H), 1.2—2.3 (m, 9H), 4.66 (s, 2H), 5.30 (m, 1H); MS *m/e* (%) 193 (5), 192 (M^+, 23), 150 (21), 149 (23), 109 (40), 107 (50), 93 (97), 81 (69), 80 (100), 68 (67), 57 (36).

Found: C, 87.65; H, 12.77%. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58%.

Alternative Synthesis of **4a** *and* **5a**. Epoxidation of (−)-*cis*-carveol (0.61 g, 4.0 mmol) by the method of Sharpless afforded epoxy alcohol **8**[21] (0.42 g, 64% yield). A solution of **8** (0.10 g, 0.61 mmol) in ether (2.0 ml) was treated with lithium dimethylcuprate(I) (3.7 mmol) in ether (6.0 ml) at 0 °C.[22] After 1.3 h at 0 °C and 1 h at 25 °C, the mixture was poured into ice–water and filtered. The filtrate was washed with 1 M HCl, saturated sodium hydrogencarbonate, and brine, dried, and concentrated. The residue was submitted to column chromatography on silica gel to afford the diol **9** (0.11 g, 97% yield) as a colorless solid: mp 68 °C; IR (Nujol) 3340, 3080, 1645, 1130, 1077, 1043, 887 cm^{-1}; NMR (CCl_4) δ 0.95 (d, J=7.5 Hz, 3H), 1.22 (s, 3H), 1.70 (s, 3H), 1.3—2.2 (m, 6H), 2.88 (bs, 2H, −O<u>H</u>), 3.52 (dd, J=5.7 and 10.4 Hz, 1H), 4.65 (s, 2H); MS *m/e* (%) 184 (M^+, 6), 166 (26), 151 (22), 140 (29), 122 (58), 97 (65), 69 (100), 57 (65), 55 (67). A mixture of the diol **9** (70 mg, 0.38 mmol), *N,N*-dimethylformamide (1.0 ml), and *N,N*-dimethylformamide dimethyl acetal (0.5 ml) was heated at 150 °C for 1 h. Acetic anhydride (1.0 ml) was added and the

resulting mixture was heated for another 3.5 h.[23] Purification of the product by column chromatography on silica gel (pentane) afforded **5a** (20 mg, $[\alpha]_{25}^{D}$ +125° (*c* 0.84, MeOH)) in 36% yield.

In similar fashion, the authentic sample of **4a** ($[\alpha]_{25}^{D}$ +28° (*c* 0.78, MeOH)) was obtained from (−)-*trans*-carveol *via* a corresponding diol: mp 104 °C; IR (CCl_4) 3410, 3090, 1645, 1139, 1102, 1041, 886 cm^{-1}; NMR (CCl_4) δ 0.90 (d, J=7.1 Hz, 3H), 1.05 (s, 3H), 1.71 (s, 3H), 1.1—2.5 (m, 6H), 3.60 (m, 1H), 3.93 (bs, 2H, -OH), 4.62 (s, 2H); MS *m/e* (%) 184 (M^+, 3), 166 (30), 151 (11), 140 (13), 125 (15), 124 (20), 123 (21), 122 (23), 97 (26), 85 (100), 72 (79).

exo- *and* endo-*2-Norcaranol.* The title compounds were prepared from 2-cyclohexenol following the method reported by Dauben and Berezin.[24] Acetylation (acetic anhydride and pyridine) of these alcohols gave **10a** and **11a**.

2-Norcaranol-2-d. Lithium aluminum deuteride reduction of 2-norcaranone gave a mixture of *endo*-alcohol-2-*d* and *exo*-isomer (*endo* : *exo*=22 : 78).

Alkylation of ***10a*** *or* ***11a*** *with Trimethylaluminum.* A solution of trimethylaluminum in hexane (1.0 M, 3.0 ml, 3.0 mmol) was added to a solution of **10a** or **11a** (1.0 mmol) in dichloromethane (3.5 ml) at 0 °C. After 2 h at 25 °C, the mixture was worked up in a usual way. A ratio of **12a**: **13a** was determined by GLPC (Apiezone 10% on Celite 545, 3 m, 100 °C). Purification by preparative GLPC (PEG 20 M 20% on Celite 545, 2 m, 50 °C) gave pure samples of **12a** and **13a**: IR (neat) 3100, 3025, 2950, 2880, 1468, 1015 cm^{-1}; NMR (CCl_4) δ 0.33—0.59 (m, 2H), 0.60—2.13 (m, 9H), 0.94 (d, J=4.4 Hz, for **12a**) and 1.08 (d, J=4.4 Hz, for **13a**).

endo-*2-Methylnorcarane-2*-d *(**12b**)*: NMR (CCl_4) δ 0.26—0.66 (m, 2H), 0.71—2.12 (m, 8H), 0.95 (d, J=0.6 Hz, 3H); MS *m/e* (%) 111 (M^+, 10), 110 (3), 96 (76), 82 (100), 69 (59), 68 (94), 67 (58), 54 (76), 41 (53).

Alternative Synthesis of a Mixture of ***12a*** *and* ***13a***.[25] A solution of 3-bromocyclohexene (8.1 g, 50 mmol) in ether (20 ml) was treated with lithium dimethylcuprate (I) (50 mmol) in ether (200 ml) at −20 °C for 1.5 h. A mixture of the resulting crude 3-methylcyclohexene, hexadecyltrimethylammonium bromide (0.5 g), and chloroform (30 ml) was treated with aqueous NaOH (50%, 30 g) at 50 °C. After stirring for additional 40 min, the mixture was diluted with ice-water and 10% HCl and extracted with dichloromethane. Distillation under reduced pressure (bp 95 °C, 20 Torr) afforded a mixture of 7,7-dichloro-*endo*-2-methylnorcarane and its 2-epimer (4.3 g, 48% yield). The mixture was reduced with sodium (0.91 g, 39 mg-atoms) in liquid ammonia(25 ml)-ethanol (0.24 g) to give *endo*-2-methylnorcarane **12a** and *exo*-epimer **13a** in 14: 86 ratio (0.22 g, 35% yield).

Stereochemical Assingnment of ***12a*** *and* ***13a***. A mixture of **12a** and **13a** (96 mg, 0.87 mmol, **12a**: **13a**=14: 86), platinum(IV) oxide (20 mg), and acetic acid (2.0 ml) was stirred at 25 °C for 12 h under hydrogen atmosphere to yield a mixture of *cis*- and *trans*-1,2-dimethylcyclohexane (*cis*: *trans*=17: 83). Both isomers were separated by preparative GLPC (Apiezone 5% on Celite 545, 3 m, 100 °C) and their IR spectra were compared with published data.

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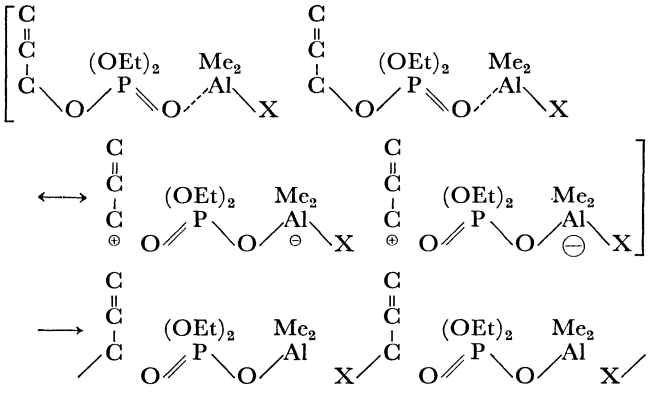
7) We are tempted to explain the observed results by assuming an aggregated complex in Scheme 5. Elastic collisions of hexane molecules can separate the ions to some extent and induce the intermolecular transfer of X under inversion.



Scheme 5.

8) S. H. Schroeter and E. L. Eliel, *J. Org. Chem.*, **30**, 1 (1965).

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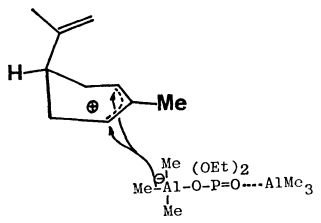
10) Another example is a cuprate reaction with allylic, propargylic acetates. See G. H. Posner, *Org. React.*, **22**, 253 (1975).

11) The present alkylation is explained by assuming a symmetrical cationic intermediate of type **7**, the cyclohexenyl cation moiety of which is attacked by the methyl group from the side opposite to the isopropenyl group.



12) Treatment of *cis*-**3** and *trans*-**3** with lithium dimethylcuprate(I) according to the method of Goering (Ref. 13) afforded a mixture of **4a** and **5a** in low yields (20—30%) predominantly with inversion. A mixture of **4a** and **5a** (30: 70) was produced from *cis*-**3** and a 93: 7 mixture of the same products was produced from *trans*-**3**.

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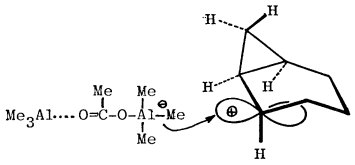
Soc., **98**, 7854 (1976). See also C. Gallina and P. G. Ciattini, *ibid.*, **101**, 1035 (1979).

14) The data are all consistent with a common cationic intermediate **14**, to which methyl anion is delivered from the less hindered *cis* direction as indicated below.



14

15) The Simmons-Smith reaction of 3-methylcyclohexene yields **13a** preferentially: P. A. Tardella and L. Pellacani, *Gazz. Chim. Ital.*, **107**, 107 (1977).

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