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STEREOCHEMICAL STUDIES ON THE NUCLEOPHILIC SUBSTITUTION IN THE REACTION OF ALLYL PHOSPHATES WITH ORGANOALUMINIUM REAGENTS

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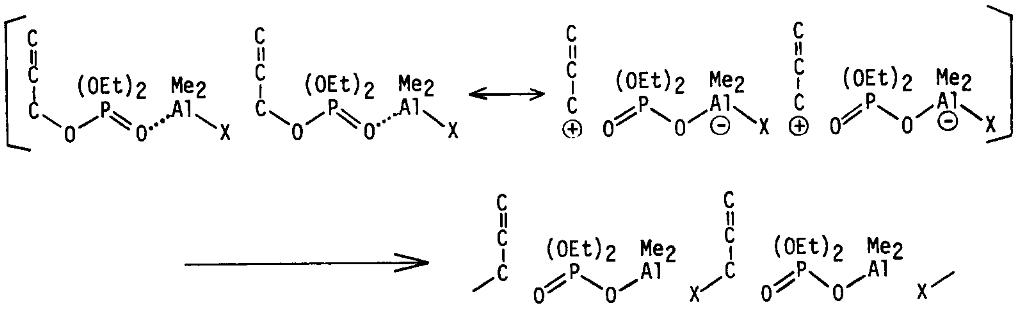
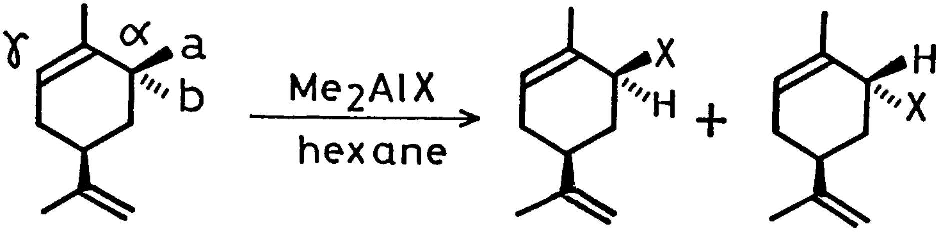
Abstract: The reaction of *cis*- or *trans*-5-isopropenyl-2-methyl-2-cyclohexenyl diethyl phosphate (I) with Me_2AlX (X = OPh, SPh, NHPh) in hexane results in substitution of the $-O-PO(OEt)_2$ group with X under predominant inversion. The solvent effects on the stereochemistry in these reactions have been disclosed.

Much attention has been paid to the conversion of esters to RCOX by means of R_2AlX (X = NR^1R^2,[1] SR,[2] SeR^3). Few examples[4] are known, however, for the nucleophilic substitution of this type on a saturated carbon. We wish to report the stereochemistry of the reaction between allyl phosphate and Me_2AlX in various solvents and to discuss the possible reaction mechanism.

Treatment of *cis*-I[5] or *trans*-I[6] with a heterogeneous white suspension of Me_2AlX (2 equiv) in hexane at 0 °C for 2 h resulted in formation of substitution products II in good yields,[8] as summarized in Table I. Substitution occurred almost exclusively with inversion. Possibly, the high stereoselectivity is explained as follows. The organoaluminium reagent is coordinated first on the P=O oxygen of allyl phosphate and an aggregated complex depicted below is formed. Elastic collisions of hexane molecules can separate both ions to some extent and induce the intermolecular transfer of X under inversion.





cis-I a = $O\text{-}PO(OEt)_2$, b = H(D)
trans-I a = H, b = $O\text{-}PO(OEt)_2$

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

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

Substrate	Reagent X	Yield (%)[b]	Product II *cis* (%)[c]	*trans* (%)[c]
cis-I	OPh	80	2	98 (84/16)
cis-I	SPh	92	3	97 (60/40)
cis-I	NHPh	70	12	88 (76/24)
trans-I	OPh	86	89 (90/10)	11
trans-I	SPh	94	90 (76/24)	10
trans-I	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.[8] The isolated yields refer to the isomeric mixtures.
c. Isomeric composition was determined by glpc. PEG 20M 10% on Celite 545, 2 m, 195 °C (X = OPh), 205 °C (X = SPh), 215 °C (X = NHPh). The data in parentheses indicate α/γ ratio for the predominant isomer which was determined by NMR spectra of deuterium labelled products.

A priori, substitution can occur at either end of the allylic system to give an unrearranged, α attack product (S_N2) or the enantiomeric, rearranged, γ attack product (S_N2'). In order to determine the α/γ ratio, the reactions of α-deuterio-*cis*-I or *trans*-I[9] with Me_2AlX were examined[10] (see Table I and II). Obviously, α attack predominated in every case

Solvent effect on the reaction between α-deuterio-*cis*-I and Me_2AlOPh was studied and the results were shown in Table II. The pronounced stereochemical outcome of the reaction must be related to the nature of an ion pair. As the solvent polarity increases, the ion pair should be more separated. The more the cation becomes free, the more the fraction of S_Ni or S_Ni' reaction should be increased at the expense of that of S_N2. Actually, the retention product was predominant in tetrahydrofuran.

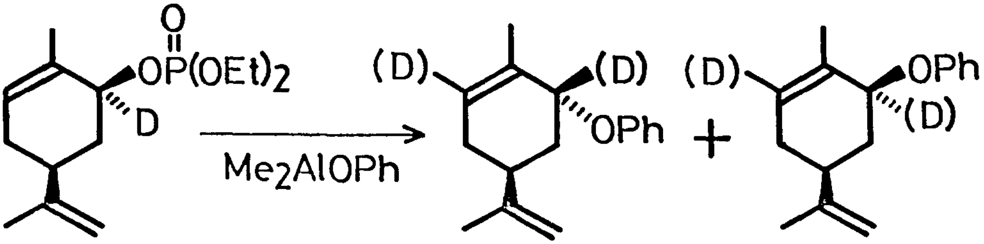


Table II. Solvent effect on the substitution

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.

The S_N2 type reaction with organoaluminium reagents in hexane was observed with a prosaic secondary mesylate as well. Treatment of 2-octyl mesylate ($[\alpha]_D^{20}$ + 9.1° (neat)) derived from (S)-(+)-2-octanol ($[\alpha]_D^{20}$ + 9.9° (neat)) with 2 equiv. of Me_2AlSR[11] in hexane gave corresponding products with inversion of the configuration. The products were reduced ($LiAlH_4$[12] for thiolester, Na in liq. NH_3-DME[13] for S-CH_2Ph) to 2-octanethiol to determine the optical purities (Table III).[14]

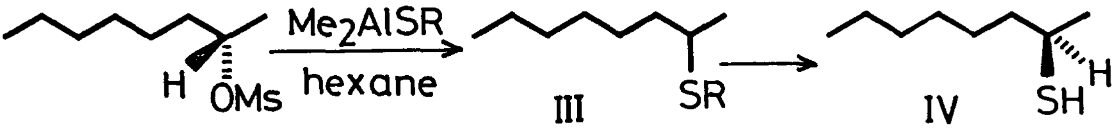


Table III. Reaction of 2-octyl mesylate with Me_2AlSR

R	Reaction Cond.		Yield of III (%)	$[\alpha]_D^{20}$ of III in benzene	$[\alpha]_D^{20}$ of IV^a in abs. EtOH
$COCH_3$	0 °C	2 h	86	+6.0° (c 1.5)	-30.8° (c 1.2)
CH_2Ph	25 °C	25 h	59	-16.5° (c 1.7)	-32.2° (c 1.1)

a. $[\alpha]_D^{23}$ -32.8° (c 1.48, abs. EtOH) has been reported for the optically pure (R)-(-)-2-octanethiol.[12]

References and Notes

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3. A. P. Kozikowski and A. Ames, *ibid.*, 43, 2735 (1978).
4. (a) Y. Kitagawa, S. Hashimoto, S. Iemura, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, 98, 5030 (1976); (b) H. Yamamoto and H. Nozaki, *Angew. Chem. Internat. Ed. Engl.*, 17, 169 (1978).
5. Carvone was reduced with lithium aluminium hydride in tetrahydrofuran at -15 °C to give *cis*-carveol contaminated by 5-8% *trans* isomer. Pure *cis*-carveol was obtained by repeated crystallization of 3,5-dinitrobenzoate.[6] α-Deuterio-*cis*-carveol was prepared by the reduction of carvone with $LiAlD_4$ (Merck >98% d) and successive purification. For phosphorization, see ref. 4a.
6. R. G. Johnston and J. Read, *J. Chem. Soc.*, 233 (1934).
7. All other solvents examined except hexane gave a homogeneous solution.
8. The procedure for the reaction between *cis*-I and Me_2AlOPh is illustrative. A mixture of phenol (0.18 ml, 2.0 mmol), Me_3Al (1.0 M solution in hexane, 2.0 ml, 2.0 mmol) and hexane (10 ml) was placed in 25 ml round-bottomed flask at 0 °C. After stirring for 30 min, the resulting white suspension was treated with a solution of *cis*-I (0.29 g, 1.0 mmol) in hexane (3 ml) at 0 °C and the mixture was held there for 2 h. Work up (ether, 1N HCl), followed by column chromatography on silica gel with ether-hexane (1:50) afforded IIa (0.18 g, 80%, *trans*:*cis* = 98:2) as a colourless oil. Further purification by preparative TLC (hexane, three developments) gave pure *trans*-IIa: IR (neat) 1645, 1600, 1590, 1495, 1235 cm^{-1}; NMR (CCl_4) δ1.70 (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). NMR data in CCl_4 of other products were as follows. *cis*-IIa: δ4.76 (m, 1H), 5.53 (m, 1H). *trans*-IIb: δ1.73 (s, 3H), 1.90 (s, 3H), 1.7-2.6 (m, 5H), 3.56 (m, 1H), 4.67 (s, 2H), 5.53 (m, 1H), 7.1-7.5 (m, 5H). *cis*-IIb: δ3.65 (m, 1H), 5.56 (m, 1H). *trans*-IIc: δ1.70 (s, 3H), 1.78 (s, 3H), 1.85-2.50 (m, 5H), 3.43 (m, 1H), 3.80 (m, 1H), 4.76 (s, 2H), 5.53 (m, 1H), 6.4-7.2 (m, 5H). *cis*-IIc: δ3.95 (m, 1H), 5.50 (m, 1H).
9. Conversion of α-Deuterio-*cis*-I to α-deuterio-*trans*-carveol with KO_2 (E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 3183 (1975)).
10. α-Deuterio-*cis*-I and *trans*-I were recovered unchanged without any scrambling.
11. Prepared *in situ* from Me_3Al and RSH (1.0 equiv), at 0 °C.
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14. Financial support by the Ministry of Education, Science, and Culture, Japanese Government (Grant-in-Aid #303023) is acknowledged.

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