

ALKYLATION OF BENZYL, CYCLOPROPYLMETHYL AND ALLYL ACETATES WITH TRIALKYLALUMINUM.
A STEREOCHEMICAL STUDY

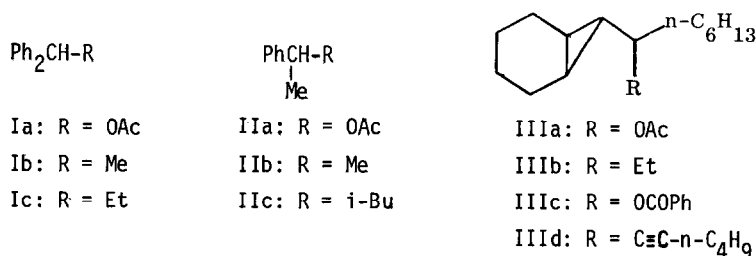
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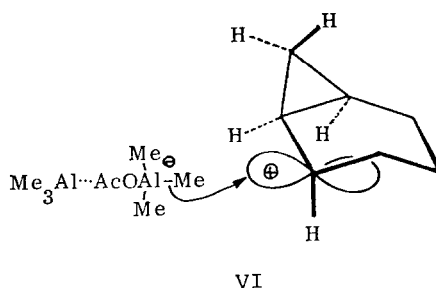
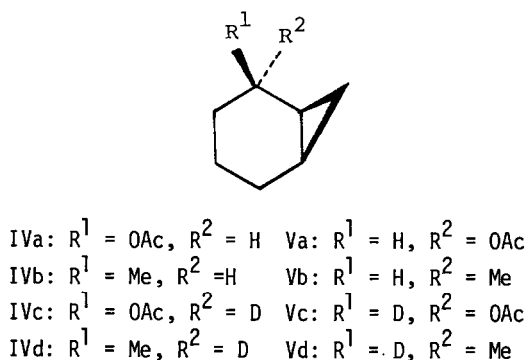
Abstract: The title reaction is found synthetically useful and the stereochemical study has revealed that carbocationic intermediates are involved in the reaction of *endo*-2-acetoxynorcarane, its epimer, and acetates of *cis*- and *trans*-carveol with trimethylaluminum.

Alkylation¹ of alcoholic substrates R^1OH via the esters R^1OCOR with organometallic reagents R^2Mtl to produce R^1-R^2 encounters the problem that the reagents preferentially attack the ester carbonyl², often transforming the substrates to relatively unstable halides prior to alkylation. In contrast, trialkylaluminum compounds³ react with certain allylic acetates to give the corresponding alkylated products as has been reported briefly.⁴ This C-C bond formation⁵ is now extended not only to allyl but benzyl and cyclopropylmethyl acetates and is found to be characterized by *carbocationic intermediates being produced from esters in nonpolar or less polar solvents such as hexane or dichloromethane.*

When the acetates Ia-IIIa were treated in dichloromethane with three mol of trialkylaluminum for several hours at room temperature, alkyl substituted products Ib^{6b} (90%), Ic^{6b} (89%), IIb (94% by GLC), IIc^{6b} (70%), and IIIb^{6a} (91%) were obtained. The reaction proceeded similarly under various conditions as indicated in the IIIa→IIIb transformation (solvent, temperature, yield): dichloromethane, -78 °C, 93%; hexane, r.t., 93%; benzene, r.t., 98%. The benzoate IIIc was converted to IIIb in 68% isolated yield. Treatment of IIIa with $Et_2AlC\equiv C-n-C_4H_9$ gave IIIId^{6b} (56%) without any trace of IIIb. It is worth noting that this alkylation takes place under extremely mild conditions as compared with the reaction of free alcohols^{5a} and hence is useful synthetically. Acetates of saturated primary and secondary alcohols were recovered unchanged. A tertiary acetate, 1-methylcyclododecyl acetate, underwent elimination to afford a mixture of 1-methylcyclododecene and methylenecyclododecane (92:8, 87% yield).

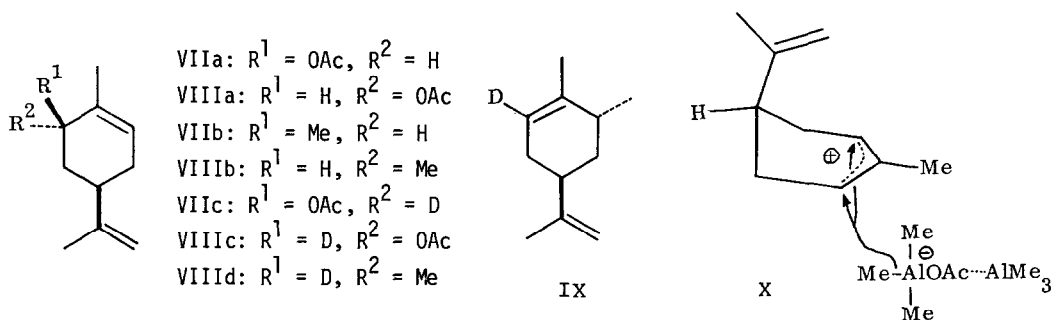


The stereochemical aspect of the reaction was studied in the transformation of *endo*-2-acetoxynorcaradiene (IVa) and its epimer Va. Treatment of IVa with trimethylaluminum (3 mol) in dichloromethane for 2 h at room temperature gave IVb^{6b,7,8} (contaminated with less than 7% of its epimer Vb^{7,8}) in 80% (GLC) yield. Starting with Va, the exclusive product was again IVb in 80% (GLC) yield. As the deuterated acetates⁹ (IVc and Vc, a 22:78 mixture) gave IVd (>93%), a mechanism involving rearrangement with ring opening can be rejected. The above data are all consistent with a common cationic intermediate VI, to which methyl anion is delivered from the less hindered *cis* direction as indicated below.



Similar stereochemistry was observed in the allylic acetate system. Acetates of *cis*- and *trans*-carveol (VIIa and VIIIa, each optical purity >98%) were allowed to react with trimethylaluminum (3 mol) in hexane at 0 °C for 20 min. The results (in order of starting acetate, % yield of the products, and VIIb^{6a,10}:VIIIb^{6a,10} ratio¹¹) are: VIIa, 85%, 18:82; VIIIa, 78%, 4:96; clearly indicating that the alkylation occurs predominantly from the side opposite the isopropenyl group.¹² The deuterated acetates VIIc¹⁴ and VIId¹⁴ gave mainly *trans*-methylated products with VIIIc and its regioisomer IX being produced in a ratio of 45:55 ($[\alpha]_D^{25} +10^\circ$) and 40:60 ($[\alpha]_D^{25} +17^\circ$) respectively. The product distribution of the alkylation also was independent of the solvent (hexane, dichloromethane, ether, tetrahydrofuran) and the leaving group (OAc, OP(O)(OEt)₂).

The reaction of allylic acetates with trialkylaluminum is in sharp contrast to the substitution reaction of allyl phosphates with Me_2AlX ($\text{X} = \text{OPh}, \text{SPh}, \text{NHPh}$) reagent,¹⁴ where $\text{S}_{\text{N}}2$ type introduction of the X group predominates with inversion of the configuration. The most compatible mechanism of the present alkylation should involve a symmetric cationic intermediate of type X, the cyclohexenyl ring of which is attacked by the methyl group from the side opposite the isopropenyl group.^{15,16}

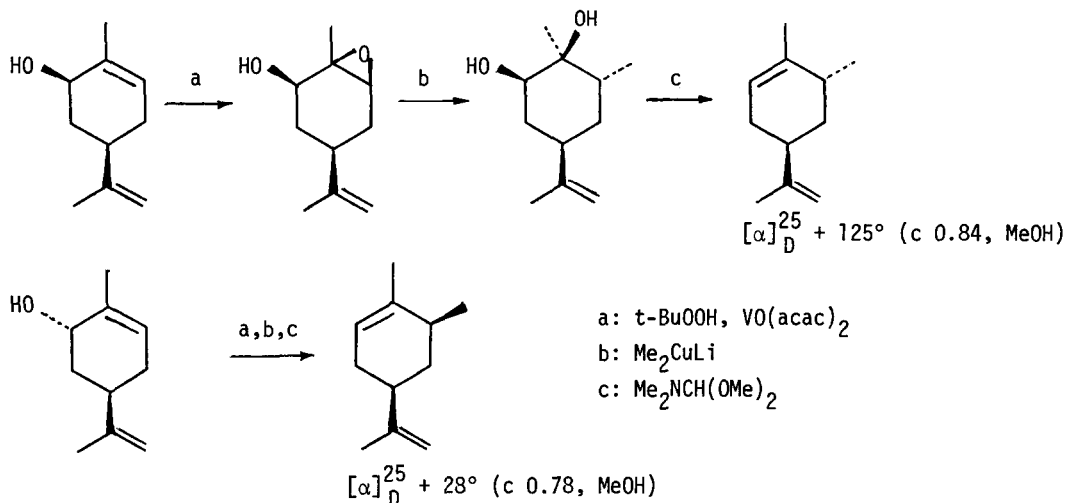


References and Notes

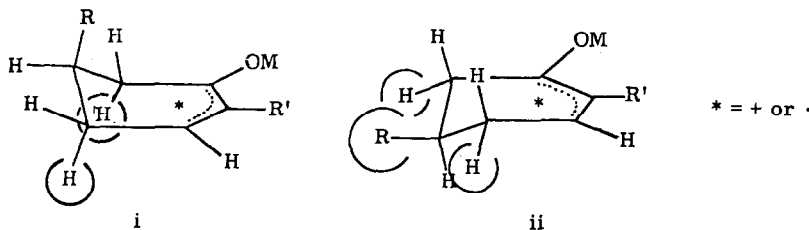
- (a) H. O. House, "Modern Synthetic Reactions," 2nd ed., Benjamin, 1972, p 492. (b) J. F. Normant, *Pure and Appl. Chem.*, **50**, 709 (1978) and references cited therein.
- An exception is cuprate reaction with allylic, propargylic acetates. See G. H. Posner, *Org. Reactions*, **22**, 253 (1975).
- General references to organoaluminum reagents are: (a) T. Mole and E. A. Jeffery, "Organoaluminum Compounds," Elsevier, Amsterdam, 1972. (b) G. Bruno, Ed., "The Use of Aluminum Alkyls in Organic Synthesis," Ethyl Corp., Baton Rouge, La., 1970.
- S. Hashimoto, Y. Kitagawa, S. Iemura, H. Yamamoto, and H. Nozaki, *Tetrahedron Lett.*, 2615 (1976).
- Alkylation of tertiary and benzylic alcohols, phenylketones, and carboxylic acids with trimethylaluminum is recorded by T. Mole et al. under vigorous (150–200 °C) conditions. (a) D. W. Harney, A. Meisters, and T. Mole, *Aust. J. Chem.*, **27**, 1639 (1974). (b) A. Meisters and T. Mole, *ibid.*, **27**, 1655, 1665 (1974); *J. Chem. Soc., Chem. Comm.*, 595 (1972). (c) R. G. Salomon, and J. K. Kochi, *J. Org. Chem.*, **38**, 3715 (1973). (d) A. Basha and S. M. Weinreb, *Tetrahedron Lett.*, 1465 (1977). Alkylation of organic halides: (e) E. Negishi and S. Baba, *J. Am. Chem. Soc.*, **97**, 7385 (1975). (f) G. Giacomelli and L. Lardicci, *Tetrahedron Lett.*, 2831 (1978). Michael addition: (g) L. Bagnell, E. A. Jeffery, A. Meisters, and T. Mole, *Aust. J. Chem.*, **28**, 801 (1975). (h) R. T. Hansen, D. B. Carr, and J. Schwartz, *J. Am. Chem. Soc.*, **100**, 2244 (1978). (i) G. W. Kabalka, and R. F. Daley, *ibid.*, **95**, 4428 (1973).
- (a) The compound was characterized spectrometrically and analytically. (b) The compound was characterized spectrometrically.
- IVb: PMR(CCl_4) δ 0.94 (d, $J = 4.4$ Hz); Vb: PMR(CCl_4) δ 1.08 (d, $J = 4.4$ Hz).
- Authentic samples were prepared as follows: Dichlorocarbene addition to 3-methylcyclohexene gave a mixture of 7,7-dichloro-*exo*-2-methylnorcarane and its 2-epimer. The mixture was reduced with sodium in liquid ammonia-ethanol to give *exo*-2-methylnorcarane (Vb PMR: δ 1.08 (d)) and IVb (PMR: δ 0.94 (d)) in an 86:14 ratio. Stereochemical identities of these were established by hydrogenating this mixture (H_2 , 1 atom, PtO_2 , AcOH) to 5:1 mixture of *trans*- and *cis*-1,2-dimethylcyclohexane, each of which was separated by GLC and compared spectrometrically with the corresponding authentic sample. The Simmons-Smith reaction of 3-methylcyclohexene yields Vb preferentially: P. A. Tardella and L. Pellacani, *Gazz. Chim. Ital.*, **107**, 107 (1977).
- Obtained by the lithium aluminum deuteride reduction of norcaran-2-one and successive acetylation. Deuterium incorporation of >97% was revealed by PMR.

10. VIIb: PMR(CCl_4) δ 0.94 (d, $J = 6.9$ Hz); VIIIb: PMR(CCl_4): δ 1.07 (d, $J = 6.9$ Hz).

11. Isomeric composition was determined by GLC (PEG 20M, 10% on Celite 545, 2 m, 70 °C). Authentic samples of VIIb and VIIIb were obtained as follows:



12. Treatment of VIIa and VIIIa with dimethylcopperlithium according to the method of Goering (ref 13) afforded a mixture of VIIb and VIIIb in low yields (20-30%) predominantly with inversion. From VIIa a mixture of VIIb and VIIIb (30:70) and from VIIIa a 93:7 mixture of the same products were produced.
13. H. L. Goering and V. D. Singleton, Jr., *J. Am. Chem. Soc.*, **98**, 7854 (1976). See also C. Gallina, and P. G. Ciattini, *ibid.*, **101**, 1035 (1979).
14. S. Ozawa, A. Itoh, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, 2909 (1979).
15. This type of selective addition is observed in the Michael addition of nucleophiles to 5-substituted 2-cyclohexenones. (a) Me_2CuLi : H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968). (b) Hydrocyanation: C. Djerassi, R. A. Schneider, H. Vorbrueggen, and N. L. Allinger, *ibid.*, **28**, 1632 (1963). The selectivity in these cases also can be explained by an intermediate *i* which forms the C-C bond by attack from the less hindered site. The conformer *i* is seemingly preferred to its isomer *ii* because in *ii* duplicated interaction between R and H^{\oplus} exists while in *i* no such interaction nor 1,3-diaxial interaction is expected. The same preference is applied to the present alkylation.



16. Financial support by the Ministry of Education, Science and Culture, Japanese Government, (Grant-in-Aid No 403022) is acknowledged.

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