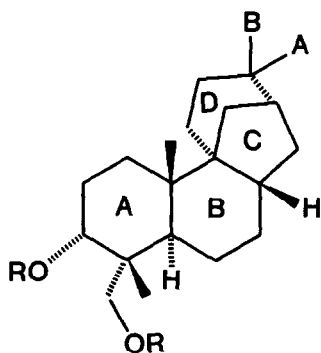


REACTION OF UNSYMMETRICAL DIENOPHILES WITH A KEY DIENOID INTERMEDIATE
FOR APHIDICOLIN SYNTHESIS

Eugene E. van Tamelen* and Steven R. Zawacky
Department of Chemistry, Stanford University
Stanford, California 94305

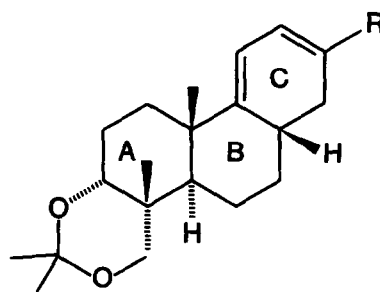
Summary: The Diels-Alder reactions of diene (6) with α -chloroacrylyl chloride and nitroethylene afford adducts (11) and (12), as proven by X-ray crystallographic analysis of a key transformation product (10), supplemented by appropriate correlation experiments. Formation of these adducts, rather than the less sterically congested isomers (7) and (9), can be rationalized using frontier molecular orbital theory.

In our recently completed total synthesis of the antiviral agent aphidicolin (1) (+),¹ the diene (2) served as an important intermediate, being converted by a Diels-Alder reaction with maleic anhydride to an adduct which in turn was transformed to the bicyclo[2.2.2] octene (3). Epoxidation of the latter, followed by sodium metal reduction, yielded the alcohol (4),



(1) R = H; A = α CH₂OH, B = β OH

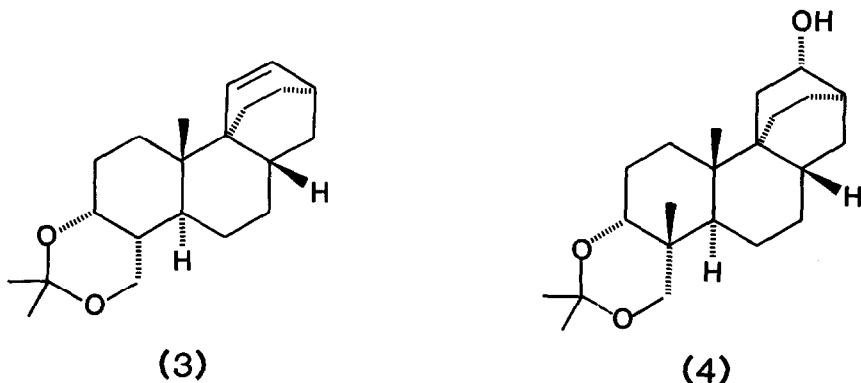
(5) R, R = C(CH₃)₂; A = H, B = OH



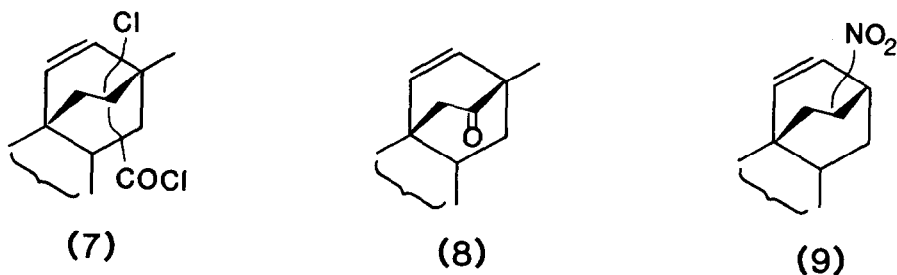
(2) R = H

(6) R = CH₃

the mesylate of which underwent solvolytic rearrangement to the desired bicyclo[3.2.1] octanol (5), precursor of the (+) natural product. In an endeavor to find more efficient routes to aphidicolin the reaction of the symmetrically alkyl substituted diene (6)² with unsymmetrical dienophiles was investigated.

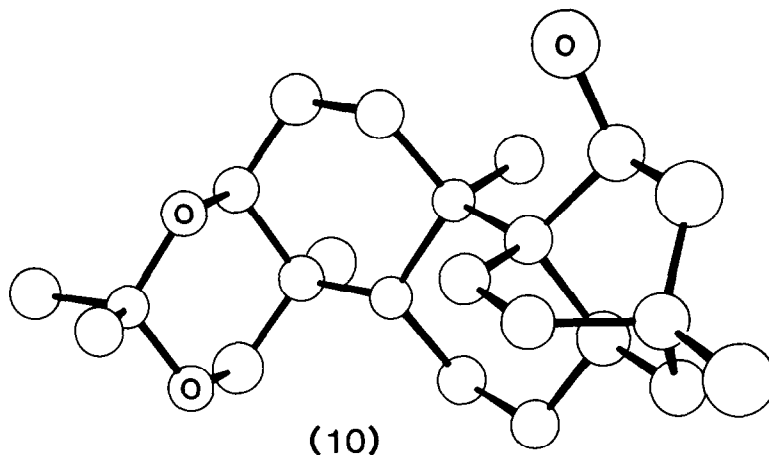


In this particular case, it was hoped that dienophiles of the type $\text{CH}_2=\text{CHA}$ or $\text{CH}_2=\text{CAB}$ would not only approach diene (6) from the more exposed β -face¹ but also with the comparatively bulky activating function(s) A/B farther from the highly substituted B-ring, thus avoiding formation of severely sterically compressed product. In one set of experiments, α -chloroacrylyl chloride and diene (6) reacted, in the presence of *N,N*-diisopropyl-*N*-ethylamine and CH_2Cl_2 at room temperature for 4 days, to give an adduct expected to possess structure (7). Degradation of this adduct via Curtius rearrangement of the corresponding azide to the α -chloroisocyanate followed by aqueous acid hydrolysis of the latter function,³ yielded a ketone (overall 20% from diene) believed to possess structure (8). Similarly, the reaction of

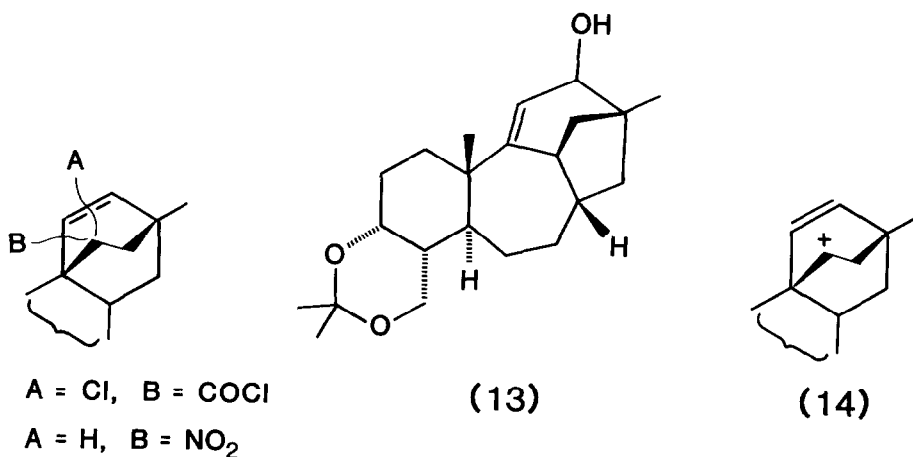


nitroethylene and diene (6) in refluxing CH_2Cl_2 for 3 days generated a 50% yield of adduct, thought to consist of the endo (47%) and exo (3%) forms corresponding to structure (9). Sodium borohydride reduction of the tetracyclic ketone (8) provided essentially a quantitative yield of a single alcohol; while $\text{Al}(\text{O}i\text{C}_3\text{H}_7)_3$ in refluxing xylene produced in 90% yield two isomeric alcohols in a 60:40 ratio, the major material being identical to that generated in the borohydride reduction. All efforts to utilize these alcohols, or sulfonate esters of them, for bicyclo[2.2.0] \rightarrow [3.2.1] octane rearrangements and eventual generation of (+)aphidicolin, were unsuccessful, and we eventually concluded that the above structural preconceptions were incorrect.

In order to clarify this structural turbidity, an X-ray crystallographic analysis⁴ was carried out on the alcohol formed by borohydride reduction of ketone (8), which effort estab-

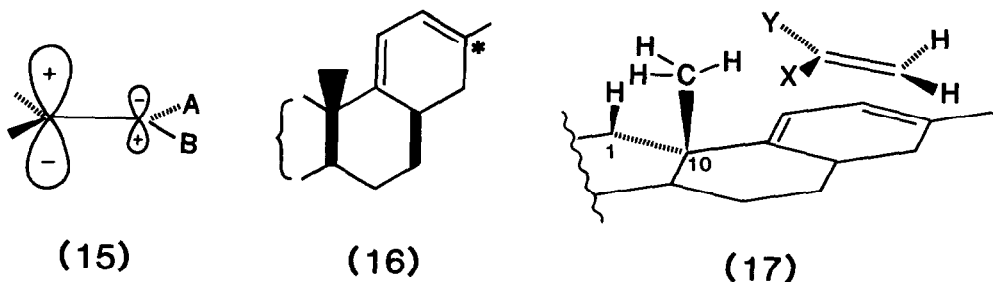


lished the constitution and stereochemistry depicted in (10). This assignment in turn indicated that the original Diels-Alder reaction leading to this group of substances had proceeded in the alternate mode (11). That the corresponding reaction with nitroethylene had taken a similar course was demonstrated by the following correlation. Reduction of the nitroethylene adduct (12) by means of iron and hydrochloric acid produced the corresponding pri-



mary amine, which upon diazotization with *i*-amyl nitrite-acetic acid in benzene yielded, via the diazonium cation, a secondary allylic acetate, the alcohol corresponding to which was identical to the allyl alcohol obtained by aqueous acetone solvolysis of the mesylate derived from the alcohol of known structure (10). On the basis of oxidation to an α,β -unsaturated ketone and other, spectral behavior, the alcohol so produced was assigned structure (13), formed in both cases by skeletal rearrangement of the carbocation (14) (or equivalent). Thus, both Diels-Alder reactions under study must have taken the same general course, generating regio isomer type (11, 12).⁵

The above results appear to be subtle manifestations of the frontier molecular orbital composition of the diene.⁶ In general, the gross structure of the adduct would be determined by the interaction involving the dienoid carbon atom with the largest HOMO coefficient and the carbon atom of the dienophile with the largest LUMO coefficient,⁷ the degree of bond-forming between these two carbons being more advanced, thereby altering correspondingly the symmetry



of the transition state. The β carbon in nitroethylene or α -chloroacrylyl chloride should possess the largest LUMO coefficient (15). Although superficially an electronically symmetrical, tetrasubstituted 1,3-diene, the HOMO coefficient of C^* seems to be greater in fact than those of the other carbons in the diene framework, by virtue of hyperconjugation involving as many as three single bonds (16).⁸ The partitioning of contributions from these bonds would depend on the dihedral angles to the π system, which is probably non-planar because of the *trans* AB ring juncture; and in the lowest energy conformation, the hyperconjugative contribution of the angular methyl would be dominant. In any case, the favored transition state for the reactions, portrayed in (17), then leads to the products actually formed, processes in which pronounced steric factors are overridden by esoteric orbital effects.

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References and Notes

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3. Cf. E. J. Corey, D. Ranganathan and A. K. Mehotra, *J. Am. Chem. Soc.*, **96**, 5261 (1974).
4. Carried out by Molecular Structure Corporation, College Station, Texas. For experimental details, see reference 2, p. 206.
5. All structural assignments were supported by appropriate, satisfactory elemental and spectral analysis. Chromatographic (tlc, gc, and/or hplc) inspection of Diels-Alder products or derived substances failed to reveal materials resulting from formation of (7) or (9).
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