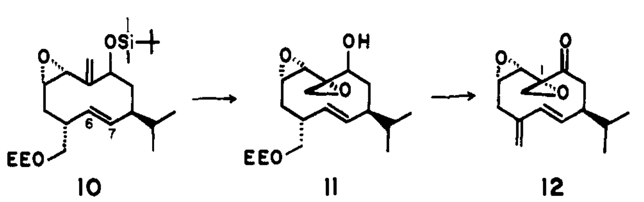
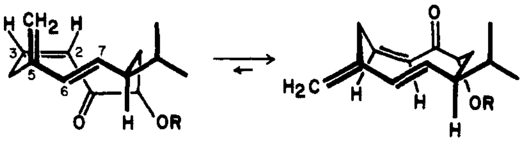
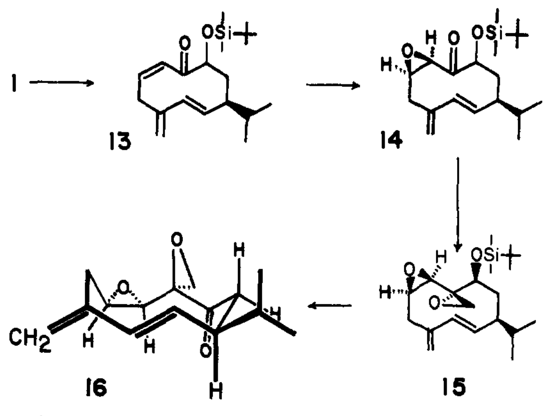


C_6H_6)[20] cleanly gave bisepoxide **11** (95%). Again the stereochemistry follows from peripheral attack and is supported by the observation that **11** is isomeric with desilylated **7**. Finally, oxidation ($CrO_3 \cdot 2Pyr$), deprotection (H_2O-HOAc), and elimination via the selenoxide as before gave **12**. Like **9**, this material was also found not to be the same as periplanone-B. Interestingly, the NMR of **12** shows it to be conformationally very different from **9** and periplanone-B. This is not unexpected. By inverting the C-1 exocyclic epoxide in the stereostructure **9**, a transannular -O- interaction is replaced by a more severe $-CH_2-$ interaction. This interaction coupled with the axial isopropyl could easily drive a deep-seated conformational change to give **12** a totally different ring geometry.

Preparation of the third diastereomer of i required a method for construction of the stereoisomeric C-2–C-3 cis epoxide. It will be seen that the desired epoxide is now the more hindered one and, other things being equal, would require the disfavored antiperipheral approach of an epoxidant to a C-2–C-3 olefin. Since this was clearly a difficult process, an alternative tactic was chosen. It appeared possible that, if the C-5–C-7 conjugated diene were constructed before epoxidation, the inherent preference[21] of 1,3-dienes for the s-trans conformation might be enough to drive the medium ring into a new conformation in which the opposite face of the C-2–C-3 olefin would be exposed for reaction. Peripheral epoxidation would then give the desired epimeric epoxide. These expectations appear to have been largely realized for, when silylated **1** was deprotected (H_2O-HOAc) and eliminated (1, o-$NO_2C_6H_4SeCN$, Bu_3P/THF; 2, H_2O_2/THF) to **13** (54%), epoxidation (t-BuOOH, KH^{22}/THF, −20 °C) gave a 4:1 mixture of epoxy ketones in which the major component was the desired isomer **14** (74%). The product was readily purified by crystallization (mp 113–114 °C) and treated with dimethylsulfonium methylide to give a single bisepoxide **15** (69%). Finally, deprotection ($Bu_4N^+F^-$/THF) and oxidation ($CrO_3 \cdot 2Pyr$) gave **16** (81%). Comparison of (±)-**16** with periplanone-B by 300-MHz NMR, IR, and mass spectra showed the two substances to be identical. Bioassay showed (±)-**16** to be very active.[23] This synthesis firmly establishes the gross structure i as that of the elusive American cockroach sex excitant and strongly suggests the relative stereochemistry and conformation shown above. As reported in the following communication,[24] these stereochemical and conformational assignments were fully confirmed by an X-ray crystallographic structure determination of the intermediate alcohol, periplanol-B.





Acknowledgment. I thank Dr. C. J. Persoons of TNO in Delft, Netherlands, for his invaluable aid in providing high-field NMR spectra and bioassays of our final products. Financial support was generously provided by the National Science Foundation, Research Corporation, and Eli Lilly.

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(25) Alfred P. Sloan Fellow, 1978–1980.

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Sex Pheromone of the American Cockroach: Absolute Configuration of Periplanone-B

Sir:

The identification of the sex pheromones of the American cockroach, *Periplaneta americana*, has been a long standing

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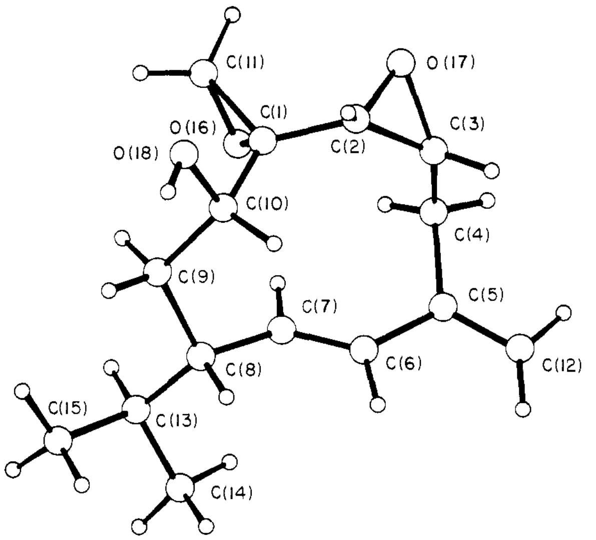
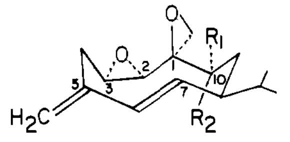
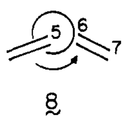


Figure 1. Computer-generated perspective drawing of periplanol-B.

problem. In 1962, Wharton and co-workers reported the isolation of an excitant from this insect;[1] isolation studies were also performed by Jacobson et al.[2] and more recently by Chen.[3] These structural studies were hampered by severe restrictions in the amount of pheromone available. After a tedious isolation procedure, Persoons et al. isolated about 200 μg of the major constituent[4] and proposed one out of six conceivable planar structures as the most plausible.[4-6] The recently completed synthesis of periplanone-B[7] not only confirmed the proposed planar structure but also strongly indicated, based on mechanistic considerations, that the relative configurations of the four chiral centers should be represented as in **1**.





8

1: $R_1, R_2 = O$
2: $R_1 = -O-Si(Me)_2-\underline{t}-Bu,\ R_2 = H$
3: $R_1 = -OH,\ R_2 = H$
4: $R_1 = -OMTPA,\ R_2 = H$
5: $R_1 = -OBz,\ R_2 = H$
6: $R_1 = H,\ R_2 = -OH$
7: $R_1 = H,\ R_2 = -OBz$

The relative configuration has been unambiguously established by an X-ray crystallographic study. Crystals of periplanol-B (**3**) were grown from CH_2Cl_2–heptane solutions and the preliminary X-ray photographs indicated that they belonged to the orthorhombic crystal class. Accurate cell constants, determined by a least-squares fit of 15 moderate-angle, diffractometer-measured 2θ values, were $a = 8.184$ (4), $b = 6.579$ (2), and $c = 26.547$ (9) Å. A reasonable density of 1.24 g/cm^3 required four molecules of $C_{15}H_{22}O_3$ in the unit cell and the systematic extinctions were consistent with the chiral space group $P2_12_12_1$. The correctness of this assignment of space group is shown by the successful solution and refinement discussed below. Since the crystals were grown from a solution of the racemate and belong to a chiral space group, periplanol-B is one of the moderately rare molecules that spontaneously resolves, although only on a microscopic scale. A total of 2301 unique diffraction maxima were surveyed using a computer-controlled four-circle diffractometer with graphite monochromated Mo Kα (0.71069 Å) radiation and a variable-speed ω scan. After correction for Lorentz, polarization, and background effects, 1970 (86%) were judged observed ($F_o \geq 3\sigma(F_o)$).[8]

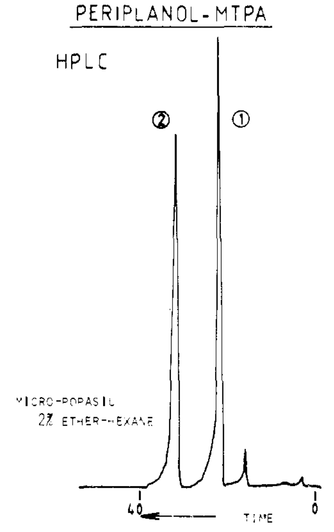


Figure 2. LC trace of diastereomeric MTPA esters of periplanol-B.

The structure was solved by a multisolution, weighted tangent formula approach using seven reflections from the centrosymmetric zones for the variable phases. A resultant weighted E synthesis revealed all of the nonhydrogen atoms and the hydrogens were located in a difference synthesis following partial refinement. Full-matrix least-squares refinements with anisotropic temperature factors for the nonhydrogen atoms and isotropic temperature factors for the hydrogens have currently converged to a standard crystallographic residual of 0.088 for the observed data.

Figure 1 is a computer-generated perspective drawing of the final X-ray model. The enantiomer shown was chosen to correspond to that indicated by the chiroptical studies to be discussed below. The C(12)–C(5)–C(6)–C(7) dihedral angle is −154°. There does not appear to be any intramolecular steric congestion and the closest transannular contact is between H(7) and H(10) of 2.1 Å. In general, bond distances and angles agree well with generally accepted values. There appears to be an intermolecular hydrogen bond between O(18) H–O(17) of 2.89 Å and no other intermolecular contacts less than 3.4 Å. Further crystallographic details are given in the supplementary material described at the end of this paper.

The absolute stereochemistry has been determined in the following manner. Racemic silyl ether **2**, an intermediate in the total synthesis of periplanone-B, was hydrolyzed to racemic periplanol-B (**3**), which was then converted to diastereomeric MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) esters **4** by acylation with (+)-MTPA chloride in pyridine.[9,10] A total of ~1 mg of the MTPA ester was resolved by LC separation (μ-Porasil, 2% ether in hexane, ~50 μg per injection, Figure 2). The CD spectra[11] (in hexane) of the two separated diastereomeric esters exhibited antipodal extrema at 227 nm, i.e., at the absorption maximum of the diene chromophore. Peak 1, which was subsequently identified as the alcohol corresponding to the natural pheromone, exhibited a negative CD. The facts that the intensities of the extrema due to the MTPA chromophore at ~260 nm were only 1% of the 227-nm extrema and that the 227-nm absorptions were antipodal show that there is no strong through-space interaction of the coupled oscillator type operating between the aromatic and diene chromophores.

The separated esters were hydrolyzed with 0.03 N NaOH in aqueous methanol to give resolved periplanol-B and its enantiomer which were then oxidized with CrO_3 in pyridine to

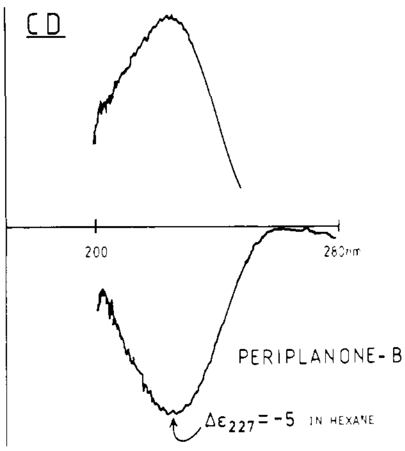


Figure 3. CD spectra of periplanone-B and its enantiomer.

periplanone-B and its enantiomer. Both the alcohol and ketone derived from the MTPA ester with the negative 227-nm Cotton effect similarly exhibited negative CD extrema at 227 nm, whereas the alcohol and ketone derived from the MTPA ester with the positive CD showed positive CD spectra (Figure 3).[12]

Bioassays of the resolved components were performed in the following manner. The resolved compounds were dissolved in hexane and their concentrations determined by gas chromatography. From these stock solutions, dilution series were made and amounts ranging from 10^{-1} to 10^{-9} μg of the test compounds were applied on pieces of filter paper (3.0 × 0.6 cm). After evaporation of the solvent, the filter papers were placed in a pasteur pipet and the samples were tested by blowing an air stream (±500 ml/min, duration 2-3 s) across the filter paper into a jar containing male cockroaches. A sample was considered to be active when at least 50% of the test insects showed the characteristic behavior (wing fluttering, copulatory attempts). Tests were repeated five times using five jars, each containing 10 male roaches. Test jars were randomized before each test. The sequence of sample testing was from lower to higher concentrations. The threshold activity of enantiomeric periplanone-B was found to be 10^{-2} μg (i.e., devoid of activity); for both synthetic and natural periplanone-B this value is 10^{-6}-10^{-7} μg. This latter value agrees very well with previous findings regarding the natural pheromone.[13]

The low level activity of the unnatural isomer may be explained upon careful examination of the LC trace in Figure 2. This shows that peak 1 tails toward peak 2; it is not unrealistic to expect that the enantiomeric periplanone-B derived from peak 2 is contaminated with a 10^{-5} portion of the natural isomer. Also, it is conceivable that the (+)-MTPA chloride used for the resolution was contaminated with a 10^{-5} portion of the (−)-MTPA chloride. Thus, even if the LC separation was 100% efficient, peak 2 would contain a small amount of the MTPA ester derived from natural periplanone-B and (−)-MTPA.

It was decided to determine the absolute configuration of periplanone-B by the exciton chirality method.[14] To this end, the 10-benzoate derivatives, **5**, of both enantiomeric alcohols were prepared in the expectation that the benzoate 223-nm absorption would couple with the diene 227-nm band. However, this was not the case; no split CD curve was observed for **5** or its enantiomer (Figure 4).

Inspection of molecular models constructed with our X-ray structure data revealed that the electrical transition moments of the diene chromophore and the equatorial benzoate group (which is parallel to the 10-C–O bond) lie in approximately the same plane; hence no split CD is observed. To circumvent this difficulty, 50 μg of the resolved periplanone-B was reduced with sodium borohydride in ethanol to give, in addition to a trace of **3**, a major new alcohol which regenerated periplanone-B upon oxidation. This new substance is the 10-*epi*-alcohol **6**, having an axial hydroxyl function produced by peripheral addition of hydride.[7] As expected, benzoate **7**, derived from the *epi*-alcohol, gave a typical exciton split double extrema (Figure 5) which indicates that the transition dipoles constitute a negatively twisted system **8**. Since the exciton chirality method is based on the nonempirical coupled oscillator theory;[14-16] these results establish the chirality of natural periplanone-B to be as shown in **1**.

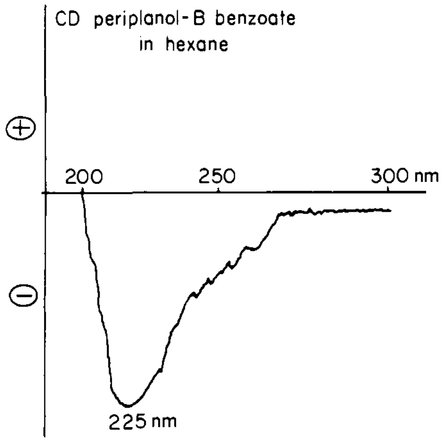


Figure 4. CD: periplanol-B benzoate in hexane.

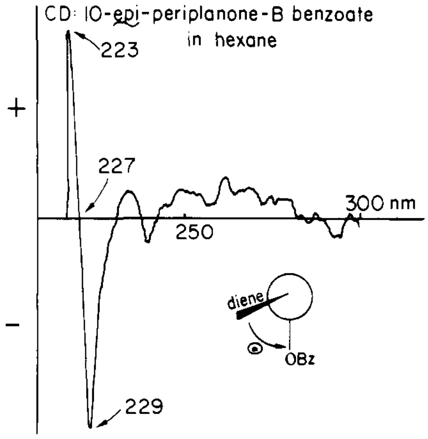


Figure 5. CD: 10-*epi*-periplanone-B benzoate in hexane.

The allylic chirality method developed by Burgstahler and co-workers[17] and the diene helicity rule[18] both predict the correct absolute configuration of periplanone-B as determined by the coupled oscillator method. In the allylic chirality method, the allylic bonds C(4)-C(3) and C(8)-C(9) make the dominant negative contributions.[19]

Therefore, in this case it appears that there is excellent agreement between the coupled oscillator-exciton chirality theory and the empirical chirality rules.[20]

Acknowledgment. K.N. is grateful to Dr. L. M. Roth for helpful discussions and generous gifts of material in the early stage of this research.

Supplementary Material Available: Fractional coordinates, bond distances, bond angles, and structure factors for periplanol-B (12 pages). Ordering information is given on any current masthead page.

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(20) These studies were supported by National Institutes of Health Grant AI 10187 (to K.N.) and by the Hoffmann-La Roche Corp. (to J.C.).
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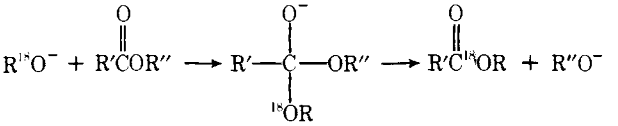
Effect of Solvation upon Carbonyl Substitution Reactions

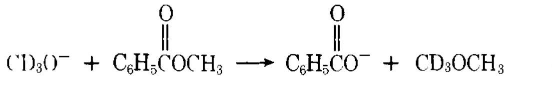
Sir:

Extensive mechanistic studies have established that alkaline hydrolysis of esters and transesterification proceed by attack of the nucleophile at the carbonyl carbon to form a tetrahedral intermediate followed by cleavage of the acyl–oxygen bond ($B_{AC}2$) (eq 1).[1] In addition to the direct evidence[2] which has been obtained by studies with ^{18}O, ester hydrolysis occurs at a rate which is unreasonably fast for an alternate mechanism, such as an S_N2 reaction at the alkyl carbon atom to produce alkyl–oxygen cleavage. These results are usually interpreted to mean that the carbonyl carbon atom is much more susceptible to nucleophilic attack than the alkyl carbon atom.



$$R^{18}O^- + R'\overset{O}{\overset{\|}{C}}OR'' \longrightarrow R'\!-\!\underset{^{18}OR}{\underset{|}{\overset{O^-}{\overset{|}{C}}}}\!-\!OR'' \longrightarrow R'\overset{O}{\overset{\|}{C}}{}^{18}OR + R''O^- \quad (1)$$

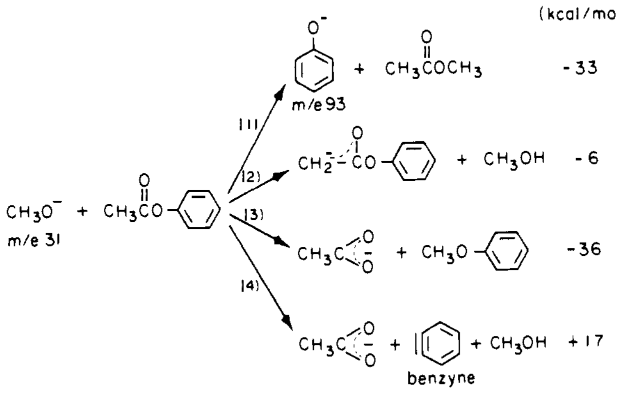
Recently, reactions of this type have been studied in the gas phase to elucidate how solvation effects nucleophilic reactivity. A surprising result of this work is that other reaction channels become competitive or dominant over the $B_{AC}2$ mechanism.[3] For example, in the absence of solvation, the reaction of deuteriomethoxide with methyl benzoate produces only benzoate (by the S_N2 mechanism) (eq 2).[4] Even attachment of electron-withdrawing groups to the carbonyl carbon fails to activate the carbonyl sufficiently to compete with the S_N2 channel.



$$CD_3O^- + C_6H_5\overset{O}{\overset{\|}{C}}OCH_3 \longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}O^- + CD_3OCH_3 \quad (2)$$

These discrepancies between the mechanisms in the gas phase and in solution prompted us to examine reactions of phenyl acetate with various nucleophiles. Phenyl acetate was chosen because it appeared to be a likely substrate for observing the $B_{AC}2$ mechanism in the gas phase. Presumably the S_N2 channel would be shut off because this would require nucleophilic aromatic substitution upon an unactivated benzene ring, and phenoxide would be expected to enhance the probability of the $B_{AC}2$ mechanism because it is a good leaving group. Using methoxide ion as an example, there are four possible reactions with phenyl acetate (Scheme I). Our estimates of the exothermicity for each channel are shown at the far right side.[5] On the basis of the thermochemistry, channel 1 ($B_{AC}2$), channel 2 (α-proton abstraction), and channel 3 (S_N2) are allowed. The large endothermicity for channel 4 (β elimination) removes it as a possibility because the reaction would be far too slow to be observed. Channel 2 is unusual from the point of view of solution chemistry; however, it is allowed in the gas phase because hydrogens α to a carbonyl group are more acidic than aliphatic alcohols.[9] Furthermore, since the only previous report of gas-phase nucleophilic aromatic substitution showed the rate to be very slow,[10] we expected carbonyl attack (channel 1) or proton abstraction (channel 2) to be the most likely reactions.

Scheme I



We have recently studied the gas-phase reactions of phenyl acetate with various nucleophiles using a pulsed ion cyclotron resonance (ICR) spectrometer,[11] and, surprisingly, the only reaction observed is channel 3, where $X^- = OH^-, CH_3O^-, CN^-, SH^-, CH_3S^-$, or $C_6H_5O^-$. The rate constants determined for the various nucleophiles are all close to the diffusion-controlled limit and range from 3 to 8 × 10^{-10} cm^3 molecule^{-1} s^{-1}. Neither the expected product of the $B_{AC}2$ channel,

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