

Compounds **16d/17d** and **16e/17e** were isolated in 95% yield after filtration through a short silica pad (light petroleum bp 40–60 °C).

Compound **19** was obtained essentially pure in 18% yield as a low melting solid (mp 25–28 °C) after two recrystallizations (light petroleum, bp 40–60 °C) of the oily crude reaction product from 1-hexadecene and 2 equiv of *N*-bromosuccinimide (cooling to –15 °C and rapid filtration). On the basis of IR data (965 cm⁻¹ s, 720 w) the product has been assigned the *E* configuration.

NMR 0.88 (t, 3 H), 1.26 (broad s, 20 H), 1.90 (m, 2 H), 3.95 (d, 2 H), 4.49 (m, 1 H), 5.86–5.93 (several peaks, 2 H).

General Procedure for the Preparation of Conjugated Dienes. Sodium borohydride (10% in 0.1% aqueous NaOH) was added dropwise under N₂ at ambient temperature to a solution of the appropriate allylic dibromide in methanol or tetrahydrofuran (1.5–2 mmol/15 mL solvent) containing bis(2-thienyl) ditelluride (5–10 mol %) until the orange-red color of the ditelluride disappeared. Two equivalents of NaBH₄ were usually required in the MeOH runs whereas the THF reactions required up to 3 equiv (due to formation of a two-phase system with incomplete phase transfer of the borohydride).

The reaction mixture was then poured into water and extracted with pentane. During this process the catalyst was usually reformed and extracted into the organic phase. In some cases (synthesis of terminal dienes) the catalyst was not reformed during the workup procedure. The formation of a white insoluble precipitate was observed in these cases. The combined organic extracts were washed several times with water, dried, and evaporated. The diene product was then purified by means of distillation or column chromatography and compared with authentic samples (compounds **4**, **6**, **9**, **11**, **13**, **15**, **18a**). Methanol was usually a good solvent for the debromination reactions. However, in the synthesis of terminal dienes methoxylated products were formed as undesired byproducts. Tetrahydrofuran was therefore the solvent of choice for these reactions.

In the synthesis of terminal olefins 10% of the catalyst was used in order to obtain good yields of product dienes.

The yields of C₆, C₇, and C₈ dienes were determined by GLC. The isomeric composition of the terminal olefins was determined by using ¹H NMR spectroscopy. In order to successfully isolate a sample of 1,3-hexadiene (**18a**), (preparative GLC was unsuitable) a slow stream of N₂ was passed through the reaction mixture (diluted with 6 volumes of H₂O after the completion of the borohydride addition) into a cold trap (–78 °C). The condensate

was then dissolved in CDCl₃ and washed several times with water to remove most of the THF.

NMR data for terminal dienes.

18a: 1.01 (t, 3 H), 2.11 (m, 2 H), 4.95 (d, 1 H), 5.09 (d, 1 H), 5.75 (m, 1 H), *J*_{H,H olefinic} = 15.2 Hz), 6.04 (m, 1 H), 6.32 (m, 1 H).

18b: 0.90 (t, 3 H), 1.26–1.44 (several peaks, 4 H), 2.08 (m, 2 H), 4.95 (d, 1 H), 5.08 (d, 1 H), 5.71 (m, 1 H), *J*_{H,H olefinic} = 15.0 Hz), 6.04 (m, 1 H), 6.31 (m, 1 H).

18c: 0.88 (t, 3 H), 1.28 (broad s, 8 H), 2.08 (m, 2 H), 4.95 (d, 1 H), 5.08 (d, 1 H), 5.71 (m, 1 H), *J*_{H,H olefinic} = 15.1 Hz), 6.04 (m, 1 H), 6.29 (m, 1 H).

18d: 1.33 (broad s, 8 H), 1.60 (m, 2 H), 2.05 (s, 3 H), 2.07 (m, 2 H), 4.05 (t, 2 H), 4.95 (d, 1 H), 5.09 (d, 1 H), 5.70 (m, 1 H), *J*_{H,H olefinic} = 15.2 Hz), 6.05 (m, 1 H), 6.32 (m, 1 H).

20: 0.88 (t, 3 H), 1.26 (broad s, 20 H), 2.08 (m, 2 H), 4.95 (d, 1 H), 5.08 (d, 1 H), 5.71 (m, 1 H), *J*_{H,H olefinic} = 15.0 Hz), 6.04 (m, 1 H), 6.32 (m, 1 H).

The NMR data of compounds **14**⁴⁰ and **18e**⁴¹ were in excellent agreement with published data.

Acknowledgment. We thank Chemische Werke Hüls A.G. for a generous gift of 11-dodecen-1-yl acetate. Financial support by the Swedish Natural Science Research Council is gratefully acknowledged.

Registry No. 1, 82093-40-1; 2, 66697-24-3; 3, 97112-42-0; 4, 16939-57-4; 5, 42086-53-3; 6, 592-57-4; 7, 97102-18-6; 8, 6044-73-1; 9, 513-81-5; 10, 34804-71-2; 11, 2548-47-2; 12, 97102-19-7; 13, 4054-38-0; 14, 97102-20-0; 15, 54162-19-5; **16a**, 97102-21-1; **16b**, 97102-22-2; **16c**, 97102-23-3; **16d**, 97102-24-4; **16e**, 97102-25-5; **17a**, 97102-26-6; **17b**, 97102-27-7; **17c**, 97102-28-8; **17d**, 97102-29-9; **17e**, 97102-30-2; (*E*)-**18a**, 20237-34-7; (*Z*)-**18a**, 14596-92-0; (*E*)-**18b**, 39491-65-1; (*Z*)-**18b**, 39491-64-0; (*E*)-**18c**, 58396-45-5; (*Z*)-**18c**, 66717-33-7; (*E*)-**18d**, 97102-31-3; (*Z*)-**18d**, 97102-32-4; (*E*)-**18e**, 50767-78-7; (*Z*)-**18e**, 51760-35-1; 19, 97102-33-5; 20, 97102-34-6; **23**, 97102-35-7; **29**, 18214-55-6; CH₂=CHCH₂CH₂CH₂CH₃, 592-41-6; CH₂=CH(CH₂)₅CH₃, 111-66-0; CH₂=CH(CH₂)₉OAc, 112-19-6; 11-dodecen-1-yl acetate, 35153-10-7; 1,1,2,2-tetrakis(bromomethyl)ethylene, 30432-16-7; 1-decene, 872-05-9; 1-hexadecene, 629-73-2; methyl benzoate, 93-58-3.

(40) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.
(41) Schechter, H.; Hsiao, C.-N. *Tetrahedron Lett.* **1984**, *25*, 1219.

Computer-Assisted Mechanistic Evaluation of Organic Reactions. 10. Stereochemistry

Catherine E. Peishoff and William L. Jorgensen*

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

Received December 11, 1984

The emphasis of CAMEO, an interactive computer synthesis program, is the application of mechanistic reasoning to the prediction of organic reaction products. In addition to intrinsic chemical reactivity, the question of stereochemical and physical limitations must be addressed in assessing overall reactivity. The program has been significantly improved in this area by the addition of algorithms which cover inversion of configuration, identification of stereorelationships, and steric-accessibility limits for intramolecular reactions. The paper begins with a review of stereoperception in CAMEO. Reactions from the base-catalyzed and nucleophilic module are then used to illustrate pertinent stereochemical and physical restrictions. Implementation of the algorithms is discussed, and reactions from a synthesis of longifolene are reviewed from a stereochemical perspective.

Introduction

CAMEO, an interactive computer synthesis program which predicts the products of organic reactions given starting materials and conditions, is under continued develop-

ment.¹⁻⁷ In its initial stages, the predictive ability of the program focused on base-catalyzed and nucleophilic

(1) Salatin, T. D.; Jorgensen, W. L. *J. Org. Chem.* **1980**, *45*, 2043.

Table I. Requirements for Intramolecular S_N2 and Addition Reactions when the Pertinent Stereocenters Are in One Ring

case	nucleophile (J)	electrophile (I)	other features	S _N 2	addn	example ^{1,3}
1a	off ring	off ring	nonadjacent stereocenters	J&L cis	J&L cis	
1b	off ring	in ring	nonadjacent stereocenters	J&L trans		
2a	off ring	off ring	adjacent stereocenters	J&L cis unless 6:4 or better, then either		
2b	off ring	in ring	adjacent stereocenters	J&L trans unless 6:4 or better, then either		

chemistry which covered proton transfer and standard addition, substitution, and elimination reactions by using a mechanistic approach for reaction evaluation.¹ With the addition of organometallic² and organosilicon³ chemistries, the module was refined to consider the competitions between organometallic addition, proton transfer, and halogen-metal exchange as well as the strong affinity of oxy and halo anions for silicon. More recently, modules have been added to treat thermal pericyclic reactions including cycloadditions and sigmatropic and electrocyclic rearrangements,^{4,5} electrophilic processes involving carbonium ion intermediates,⁶ and aromatic substitution.⁷

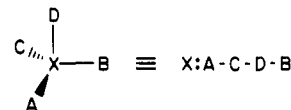
To merely know that two or more substrates are capable of interacting chemically is often insufficient for predicting the likelihood of the interaction. A fundamental problem which must be considered in CAMEO and which is the topic of this paper is the effect of stereochemistry and intramolecular accessibility on the course of an organic reaction. Although sophisticated methods are available for predicting conformational stability which may bear on reactivity, our approach is to use empirical rules based on stereorelationships, positional effects, and relative distances to help gauge reaction feasibility.

The paper begins with a review of stereoperception in CAMEO. Next, reactions proceeding through mechanisms in the base-catalyzed and nucleophilic module are used to illustrate inversion of configuration, identification of stereorelationships, and accessibility limits for intramolecular reactions. Stereoselectivity in both unimolecular and bimolecular elimination reactions is then considered. At the conclusion of each section, the incorporation of these characteristics into CAMEO is discussed. The paper finishes with a look at a synthesis of the sesquiterpene longifolene. The predicted products from the reactions of both the observed intermediates and alternative stereoisomers are described.

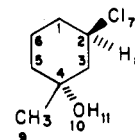
Stereoperception

The linear representation developed by Petrarca and co-workers to define a stereocenter is also used in CAMEO.^{8,9}

Briefly, it is the clockwise ordering of the atoms about a stereocenter sighting down a wedged or dotted bond.



There are 12 equivalent linear representations for a tetrahedral center that can be interconverted by double permutations of the indices for the four attachments. Manipulations of such stereorepresentations can then be used to perceive structural data such as cis/trans and R/S relationships or the identity of appendages.¹⁰ For each bond, one word is used in CAMEO to store the first atom in the bond, the second atom in the bond, the bond order, the bond number, and a stereoindex. A stereoindex of zero indicates no stereochemistry has been designated; one, that the wedge originates at the first atom; two, that the wedge originates at the second atom; three, that the dotted bond originates at the first atom; four, that the dotted bond originates at the second atom; five, that the bond is axial; six, that the bond is equatorial; and seven, that the stereochemistry about a double bond is undefined.^{7a} The linear representations are stored in a 4 × 12 array (STEREP) such that STEREP(1,1) is the atom number of the attachment located on the defining wedged bond of the first stereocenter in the molecule. The remaining three attachments are stored in a clockwise order sighting down the wedge. In the absence of a wedge, a dotted bond is used as the defining bond. In this case, a counter-clockwise ordering of the other attachments is needed as illustrated below.^{8,9}



STEREP(1,1) = 7	STEREP(1,2) = 10
STEREP(2,1) = 1	STEREP(2,2) = 3
STEREP(3,1) = 8	STEREP(3,2) = 5
STEREP(4,1) = 3	STEREP(4,2) = 9

(2) Salatin, T. D.; McLaughlin, D.; Jorgensen, W. L. *J. Org. Chem.* 1981, 46, 5284.

(3) Peishoff, C. E.; Jorgensen, W. L. *J. Org. Chem.* 1983, 48, 1970.

(4) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* 1983, 48, 3923.

(5) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* 1984, 49, 3001.

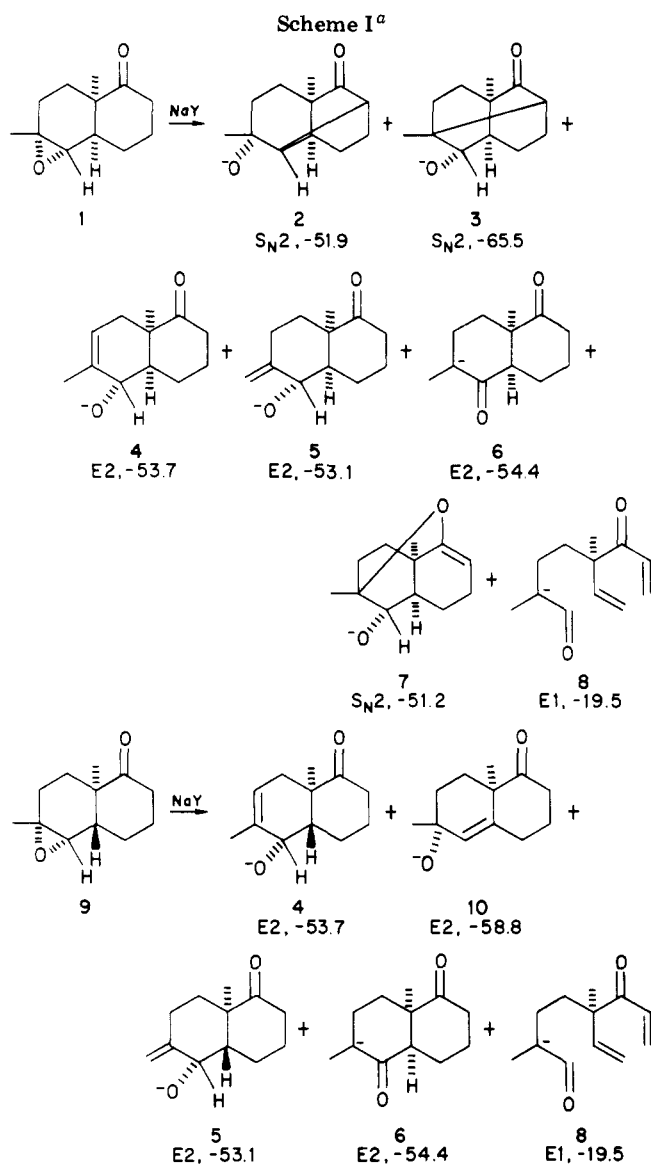
(6) McLaughlin, D.; Jorgensen, W. L. to be submitted for publication.

(7) (a) Roos-Kozel, B. L. Ph. D. Thesis, Purdue University, 1981. (b) Bures, M. G.; Roos-Kozel, B. L.; Jorgensen, W. L. *J. Org. Chem.*, in press. (c) Peishoff, C. E.; Jorgensen, W. L. *Ibid.* 1985, 50, 1056.

(8) Petrarca, A. E.; Lynch, M. F.; Rush, J. E. *J. Chem. Doc.* 1967, 7, 154.

(9) See also: Corey, E. J.; Howe, W. J.; Pensak, D. A. *J. Am. Chem. Soc.*, 1974, 96, 7724. Wipke, W. T.; Dyott, T. M. *J. Am. Chem. Soc.* 1974, 96, 4825.

(10) Corey, E. J.; Jorgensen, W. L. *J. Am. Chem. Soc.* 1976, 98, 189.



Only one stereobond is required in CAMEO to define a stereocenter; it is assumed that the bond opposing the stereobond has the same stereotype (wedged or dotted).



A maximum of two stereobonds is allowed on one atom to avoid ambiguity. All stereochemical changes and evaluations in CAMEO are made via manipulations of the linear representations or stereobonds. Although the program has the capacity to recognize a saturated stereocenter having only three explicit attachments, it is imperative that all four attachments be explicit if the stereochemical manipulations at that center are to be reliable.

Nucleophilic Substitution and Addition Reactions

A. Intermolecular S_N2 Reactions. Inversion of configuration at a carbon stereocenter undergoing an S_N2 reaction is well documented¹¹ and is illustrated by eq 1.¹²



(97% inversion)

the proportion of inversion to retention of configuration depends on the leaving group, the strength of the nucleophile, and the steric environment about the electrophilic site.³ Because the stereochemical outcome of substitution reactions at silicon is uncertain, the products are displayed as racemic mixtures in CAMEO.

Implementation. The inversion of a stereocenter in a substitution reaction is accomplished using the stereobonds. A brief discussion of this process has been reported.³ In the drawing of the product, the bond between the electrophilic atom and the leaving group is severed and the fragments are separated. The nucleophilic atom is then positioned so that it occupies the original coordinates of the leaving atom. A new bond between the nucleophilic and electrophilic sites is drawn with the same stereochemical character as that of the electrophilic site-leaving group bond. Since the assignment of stereobonds is directly related to the direction in which the initial bond is drawn, i.e., a → b or a ← b, it is possible that assigning the index of the electrophilic site-leaving group bond to the electrophile-nucleophile bond will not reproduce the original stereochemistry. To ensure that this does not occur, the stereobond of the electrophilic site-leaving group bond is reset when necessary to the index that would be assigned if the initial bond was drawn from the electrophilic site to the leaving group. The new bond between the electrophile and nucleophile is drawn in the same direction, i.e., starting at the electrophilic site. Now, assigning the new bond the same index as the old bond will reproduce the initial stereochemistry. Then, to invert the center, if there were dotted bonds, one is redrawn wedged, and all other stereochemistry is removed from the center. If there were only wedged bonds, one is redrawn as dotted, and again all other stereochemistry at this center is removed. In the case of a silicon electrophile, all stereochemistry is removed.

B. Intramolecular Addition and S_N2 Reactions. The feasibility of intramolecular addition and S_N2 reactions is often limited because of the physical constraints imposed by rings, bridges, fusions, or double bonds. It is necessary, therefore, to evaluate the stereochemistry of those obstacles located between the nucleophilic site and the leaving group when judging the likelihood of such reactions. The simplest case involves the double bond. The program recognizes as stable only those rings containing a trans double bond which have eight or more members. Thus, if the path from the nucleophilic atom to the leaving group contains a trans double bond and fewer than eight atoms, reaction is not allowed. A similar restriction is applied to prohibit formation of cycloalkynes with fewer than eight ring atoms.

Preexisting rings can require more extensive analyses. Five general cases with stereochemical restrictions may be identified involving different combinations of rings, bridges and fusions. These are listed in Tables I and II along with their requirements for addition or S_N2 reactions. In describing these systems, J and L are used to designate the nucleophilic site and the leaving atom, respectively, and I is the electrophilic site which always has the leaving group attached to it. Also, stereocenters pertinent to the analyses

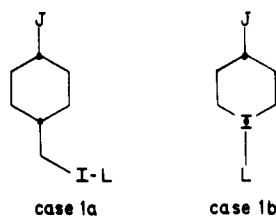
(11) Reviews: Bunton, C. A. "Nucleophilic Substitution at a Saturated Carbon Atom"; Elsevier: Amsterdam, 1963. Ingold, C. K. "Structure and Mechanism in Organic Chemistry", 2nd ed.; Cornell U. Press: Ithaca, N.Y., 1969. Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem.* 1977, 14, 1.

(12) Harvey, S. H.; Hoye, P. A. T.; Hughes, E. D.; Ingold, C. J. *Chem. Soc.* 1960, 800.

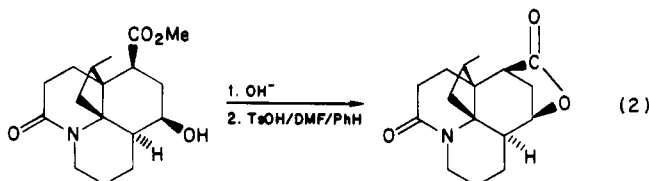
Table II. Requirements for Intramolecular S_N2 and Addition Reactions in Polycyclic Ring Systems

case	features	requirements	other requirements for S_N2 and addn	example ¹⁴
3	1 bridge/fusion atom in path	bridging atom or nonring system atom trans to nucleophile	see cases 1a, 1b for addn case 1b, J&L must be cis	
4	2 bridge/fusion atoms (belonging to same bond or bridge) in path	1. bridging atom or nonring system atom trans to nucleophile 2. possible mandatory cis fusion	see case 3	
5	1. nucleophile in ring 2. two bridge or fusion atoms (belonging to same bond or bridge) in path	see case 4	see cases 1a, 1b	

are dotted, and the symbol “≈” is used to indicate that either a bridge or fusion is present at the designated site. Six-membered rings are used generically to represent any ring size. The simplest situation is depicted in case 1 and



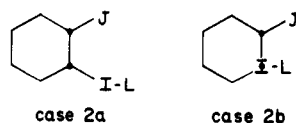
is the foundation of the remaining four. To gauge the feasibility of case 1 reactions such as in eq 2



(taken from a total synthesis of the alkaloid annotinine),^{13a} five questions must be answered: 1. Which ring atoms are the pertinent stereocenters? 2. Which ring is the common ring for determining stereorelationships? 3. What is the stereorelationship between the appropriate appendages on these stereocenters? 4. What type of reaction is being performed? 5. What is the position of the electrophilic site relative to the common ring?

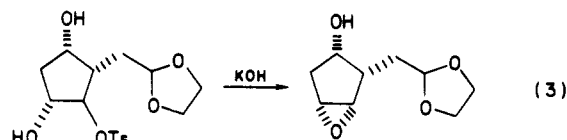
For the addition reaction in eq 2, the off-ring locations of the electrophilic and nucleophilic sites require a cis relationship of the ring appendages for lactone formation, as specified in Table I.

Cases 2 through 5 involve refinements of case 1 to consider the generation of fused systems and the steric problems in polycyclic systems caused by bridges and fusions. Case 2 considers the formation of ring fusions rather than the bridges of case 1 and thus is less restricted by the stereochemistry. The key issue for case 2 is the size lim-



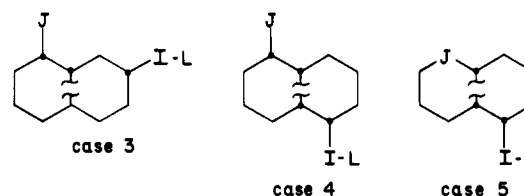
(13) (a) Wiesner, K.; Poon, L.; Jirkovsky, I.; Fishman, M. *Can. J. Chem.* 1969, 47, 433. (b) Sarett, L. H.; Arth, G. E.; Lukes, R. M.; Beyler, R. E.; Poos, G. I.; Johns, W. F.; Constantin, J. M. *J. Am. Chem. Soc.* 1952, 74, 4974. Johns, W. F.; Lukes, R. M.; Sarett, L. H. *Ibid.* 1954, 76, 5026. Poos, G. I.; Lukes, R. M.; Arth, G. E.; Sarett, L. H. *Ibid.* 1954, 76, 5031. (c) Fried, J.; Lin, C. H.; Sih, J. C.; Dalvin, P.; Cooper, G. F. *J. Am. Chem. Soc.* 1972, 94, 4342. Fried, J.; Sih, J. C.; Lin, C. H.; Dalvin, P. *Ibid.* 1972, 94, 4343. Fried, J.; Sih, J. C. *Tetrahedron Lett.* 1973, 3899.

itation on trans ring fusions. There are quite a few examples of trans-fused systems with an envelope ring of size 8 as in bicyclo[5.1.0]octanes, bicyclo[4.2.0]octanes, and bicyclo[3.3.0]octanes.¹⁵ The added strain due to the trans fusions in these systems is estimated to be 5–10 kcal/mol from molecular mechanics calculations.¹⁶ There are few examples of trans-fused systems with an envelope of seven atoms;¹⁷ the added strain is about 15 kcal/mol.^{16b} In view of this and the exclusion of trans-cycloalkenes and cycloalkynes with more than about 10 kcal/mol of strain, the current restriction in CAMEO is to disallow formation of trans-fused ring systems with an envelope of less than eight atoms. Simple epoxide formation, eq 3,^{13c} illustrates the



more limiting case. To form the product, the nucleophile and leaving group must have the trans orientation when the electrophilic site is in a ring; cis orientation would yield a very strained product.

Cases 3, 4, and 5 extend case 1 to polycyclic systems.



Here, either the nucleophilic and electrophilic sites or the pertinent stereocenters are located in separate rings, as judged by the smallest set of smallest rings (SSSR) criterion.¹⁸ As such, the bridges and/or fusions separating them must be analyzed. In all of these cases, the atom that

(14) (a) Sauers, R. R.; Parent, R. A. *J. Org. Chem.* 1963, 28, 605; *Chem. Commun.* 1965, 511. (b) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* 1956, 78, 2023, 2657; *Tetrahedron*, 1958, 2, 1. (c) Corey, E. J.; Watt, D. S. *J. Am. Chem. Soc.* 1973, 95, 2303.

(15) (a) Gassman, P. G.; Williams, F. J.; Seter, J. *J. Am. Chem. Soc.* 1968, 90, 6893. (b) Wiberg, K. B.; de Meijere, A. *Tetrahedron Lett.* 1969, 519. (c) Corey, E. J.; Bass, J. D.; Le Mahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* 1964, 86, 5570.

(16) (a) Wiberg, K. B.; Lupton, E. C., Jr.; Wasserman, D. J.; de Meijere, A.; Kass, S. R. *J. Am. Chem. Soc.* 1984, 106, 1740. (b) Jorgensen, W. L.; Gao, J., unpublished results.

(17) Meinwald, J.; Tufariello, J. J.; Hurst, J. J. *J. Org. Chem.* 1964, 29, 2914. Gassman, P. G.; Bonser, S. M. *J. Am. Chem. Soc.* 1983, 105, 667.

(18) Roos-Kozel, B. L.; Jorgensen, W. L. *J. Chem. Inf. Comput. Sci.* 1981, 21, 101.

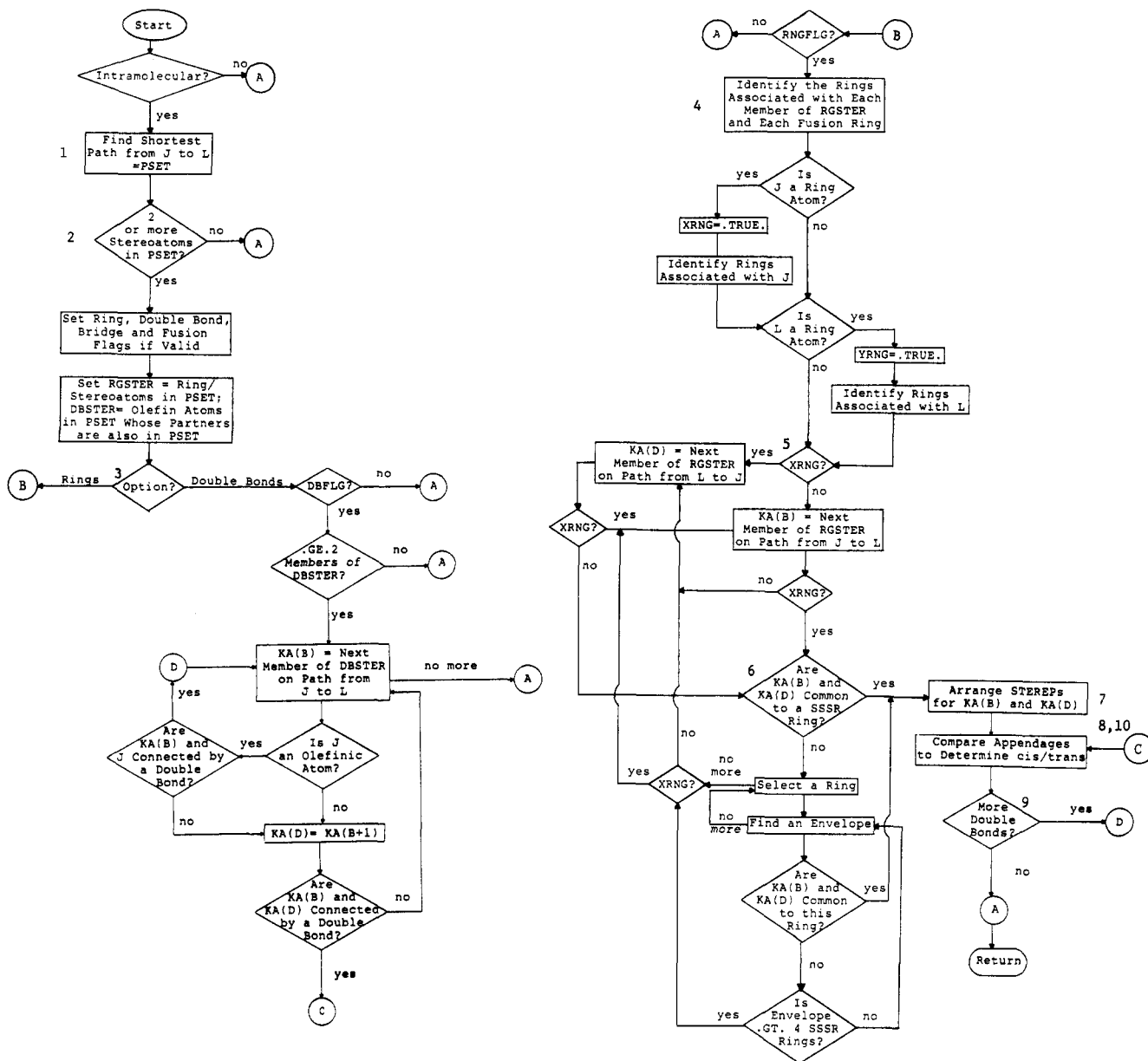
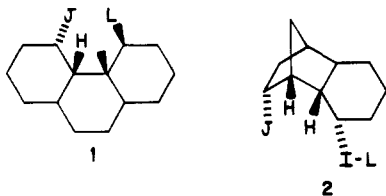


Figure 1. Flowchart for cis/trans perception.

is connected to the bridge or fusion atom closest to the nucleophile and that is not a member of the ring system common to the pertinent stereocenters (i.e., the hydrogen in 1) must be trans to the nucleophile for the reaction to



be considered viable. Similarly, *all* the bridges or fusions in extended systems must have this characteristic, as in 2. Additionally, a cis fusion may be necessary (cases 4 and 5) to achieve the proper conformation for reaction.

Implementation: Stereochemical Relationships. Four subroutines, IMSTER, CITRAN, FDPATH, and FUSION, are used to gauge the feasibility of intramolecular reactions. IMSTER is used specifically for addition and S_N2 reactions, while the others are general routines for cis/trans perception, path finding, and perception of cis- and trans-fused or bridged ring systems, respectively.

The first step in evaluating intramolecular reactions involving ring systems is to establish the stereorelationship of the appendages in question. This is accomplished in the subroutine CITRAN, a flowchart of which is depicted in Figure 1. In order to assure a completely general treatment, the program evaluates all stereochemical relationships via STEREP manipulations. The key to the identification of these relationships lies in placing known substituents of the stereocenters in positions 1 and 2 of the STEREP arrays and noting the relative positions of the remaining substituents in positions 3 and 4.¹⁹ The following points illustrate and/or clarify the corresponding sections of the diagram:

1. Intramolecular reactions generate new rings whose size may limit the viability of the reactions. Thus, the shortest path between the two atoms (nucleophile and leaving group) is used in cis/trans identification. The subroutine FDPATH finds the shortest path and stores the atoms sequentially from J to L as KA(1) to KA(c) where c is the pathlength. KA(1) to KA(c) are collectively the pathset (PSET).

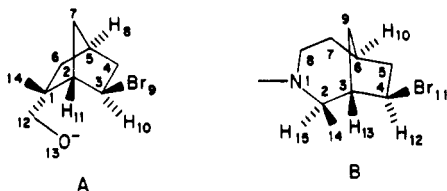
(19) The method used is an extension of that described in ref 9.

2. Currently, there must be at least two stereocenters in the path for cis/trans perception; however, in reactions such as an intramolecular addition, one stereocenter may influence the generation of a second. If only one stereocenter is in the path, the routine will find and store it for this consideration.

3. Since cis/trans perception is necessary in both cyclic and unsaturated systems, the routine is designed to handle both; however, since the returned information is used by other programs, separate calls are made from IMSTER.

4. In order to make the choices for pertinent stereocenters more manageable, only stereocenters that are in the path and in rings are considered. The rings containing each stereocenter in the set are identified and stored. The base ring of bridged systems, i.e., the six-membered ring for norbornane, is also included, though it is not in the smallest set of smallest rings (SSSR). This information is used to ascertain the presence or absence of an SSSR ring common to the pertinent stereocenters and, in the latter case, used to construct the proper envelope rings for further analyses. In the event that J or L is a ring atom, the rings associated with them are also identified and stored.

5. The direction of the search for pertinent stereocenters, i.e., J to L or L to J, is important to the identification of the correct stereocenters and the correct common ring. This is best understood by considering molecules A and B. The path from nucleophile to leaving group in A is

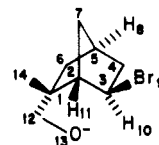


13-12-1-2-3-9; the set of possible stereocenters is (1,2,3). For B, the path is 1-2-3-4-11 with (2,3,4) the possible stereocenters. By inspection, the desired stereocenters in A are 1 and 3, and the ring common to them is the six-membered base ring; in B, 3 and 4 are the correct stereocenters with the five-membered bridging ring common to them. If the search for the first pertinent stereocenter in A begins at the nucleophile, atom 1 will be chosen for consideration since atom 1 is the first stereocenter in a ring encountered on the path from J to L. The second pertinent stereocenter, atom 3, is found by using the same criterion, but searching from L to J. Confirmation of the six-membered base ring as common to atoms 1 and 3 establishes them as the pertinent stereocenters [designated KA(B) and KA(D)]. When the same method is used for B, atom 2 is selected for consideration. Starting at L, atom 4 is selected as the second pertinent stereocenter, and as there is a ring common to these two centers, the search might end. Clearly, the common ring and pertinent stereocenters would have been identified incorrectly. To avoid this situation, two corrections must be made. First, when the nucleophile is also a ring atom, the search is begun at the other end of the path. Thus for B, the path is followed from L to J, yielding atom 4 as the first center for consideration. Second, in establishing the correct common ring, those rings containing the nucleophile must be ignored since, in this case, the atom can be considered to be on an appendage. For the same reason, in those addition reactions in which both the nucleophile and the electrophile are ring atoms, neither the rings associated with the nucleophile nor the rings associated with the electrophile may be considered when identifying the common ring. With this in mind, atom 2 is still found first

when starting at J, but is disregarded. Atom 3 is found next, and since there is a ring that does not contain the nucleophile but does contain atoms 3 and 4, they are established as the pertinent stereocenters.

6. If a ring common to KA(B) and KA(D) cannot be found by using the smallest set of smallest rings, fusion atoms in the path are taken individually, and their ring sets are used to construct envelope rings for consideration. The search is allowed to proceed to a maximum envelope consisting of four SSSR rings. If a common ring is still not evident, a new KA(B) or KA(D) is selected, and the search is repeated.

7. Using A as an example, the STEREPs for KA(B) and KA(D) are arranged in the following manner:

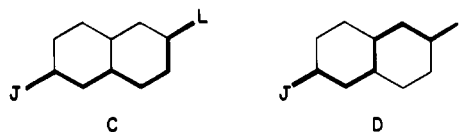


J = KA(1) = 13 L = KA(6) = 9 B = 3 D = 5
 KA(B-1) = 12 KA(B) = 1 KA(B+1) = 2
 KA(D-1) = 2 KA(D) = 3 KA(D+1) = 9
 original STEREPs: KA(B): 14-2-12-6
 KA(D): 9-2-4-10

(a) Permute so that the atoms in the common ring and on the path [KA(B+1), KA(D-1)] are in STEREP(1).

(b) Permute so that the atoms in the common ring and not on the path (atoms 6 and 4) are in STEREP(2).

(c) If an interchange was necessary to accomplish (a) or (b), maintain configuration by exchanging STEREPs (3) and (4) after each interchange. The revised STEREPs for KA(B) and KA(D) in A are then KA(B): 2-6-12-14 and KA(D): 2-4-9-10. The ordering of STEREPs (1) and (2) is based on the concept of a single ring in which the path connecting the two stereocenters follows the perimeter of the ring as in C. If the ring is fused and the path from



J to L crosses the fusion bond as in D, the effect is that of "inverting" KA(D) since the STEREP assignments of the ring atoms adjacent to KA(D) will be reversed. To accommodate this situation, the ordering for one of the stereocenters [KA(B)] must be reversed so that the atoms that are both ring and path atoms are in STEREP(2) and the atoms that are ring but not path atoms are in STEREP(1).

8. The stereorelationship between nucleophile and leaving group is found by comparing the positions in the STEREPs of the atoms KA(B-1) and KA(D+1); the same location indicates trans while different locations must obviously be cis. In example A, atoms 12 and 9 are in the same STEREP position; therefore the relationship is identified as trans.

9. Up to ten double bonds may be processed per path. The stereoinformation is stored in the array CTDB for each double bond as it is found in the path from nucleophile to leaving group.

10. In the generation of STEREPs for doubly bonded atoms, STEREP(1) is set as the other atom in the double bond with STEREPs (2) and (3) being the clockwise ordering of the remaining substituents. There is no need, therefore, to rearrange the STEREPs prior to comparing STEREP locations. The stereorelationship is trans if the path atoms KA(B-1) and KA(D+1) are in the same position; otherwise it must be cis.⁹ A problem that can arise

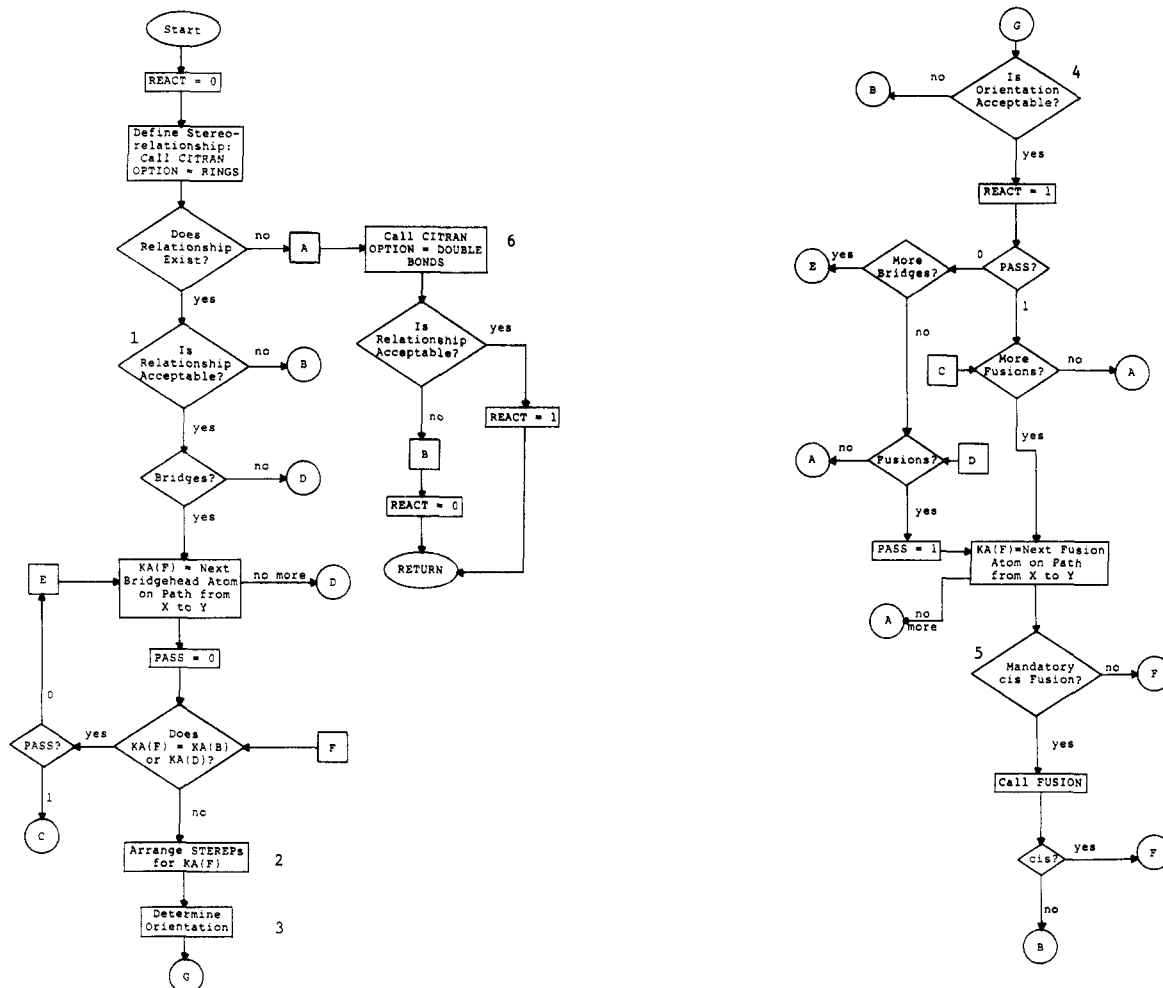
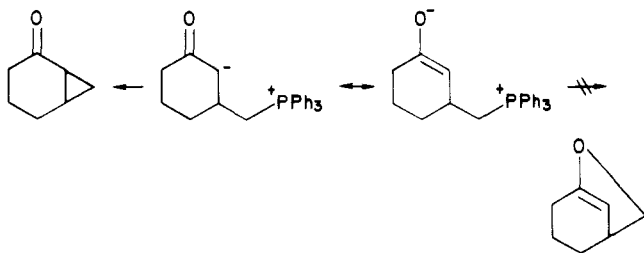


Figure 2. Intramolecular stereorelationships flowchart.

at this point is having the two olefinic atoms without any corresponding STEREPs. This occurs when the olefinic bond is generated via resonance as in the following example of an intramolecular alkylation.



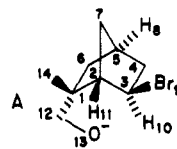
In the ketone starting material, there are no stereocenters, and thus no stereoperception is necessary. Resonance of the anion occurs during the mechanism phase of CAMEO, and the reaction is considered prior to any re-perception of the molecule. In this situation, the STEREPs obviously must be generated first and then the comparisons made for cis/trans identification.

Steric Accessibility. At this point, the pertinent stereocenters, the common ring to which they belong, and the stereorelationship of the nucleophilic site and leaving group have been determined. Identification of the acceptable relationships and any steric interference by bridges or fusions may now be completed in the subroutine IMSTER (Figure 2). Again, the following points correspond to the numbered boxes in the flow chart.

1. Ring systems are analyzed first, and the reaction is judged to be initially viable if it meets the criteria for

stereorelationships outlined in Table I.

2. In determining whether bridges or fusions would interfere in a reaction, bridgehead atoms in the path are chosen first for inspection. If a bridgehead atom is also KA(B) or KA(D), it is passed over since the cis/trans designation accounted for this bridge. Otherwise, the STEREP for this atom, labeled KA(F), is arranged as for A below. Permutation of the STEREP for KA(F) and



KA(B-1) = 12 KA(B) = 1 KA(B+1) = 2
 KA(F-1) = 1 KA(F) = 2 KA(F+1) = 3
 Original STEREPs: KA(B): 2-6-12-14
 KA(F): 11-3-1-7

comparison with that for KA(B) can then provide the required stereochemical information as follows:

(a) Permute so that the atom that is not a member of any of the rings containing KA(B), KA(D), and KA(F) is in STEREP(1).

(b) Permute so that KA(F-1) is in STEREP(2).

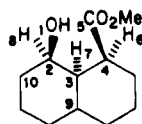
(c) If an interchange was necessary to accomplish (a) or (b), maintain configuration by exchanging STEREPs (3) and (4) after each interchange. The revised STEREPs for KA(B) and KA(F) in A are KA(B), 2-6-12-14, and KA(F), 11-1-7-3.

3. The position of the bridge relative to the nucleophilic site is found by comparing the STEREP locations of KA(B-1) and KA(F+1). If the positions do not match, as in

this case, these atoms are cis and the first atom on the bridge is trans to the nucleophile.

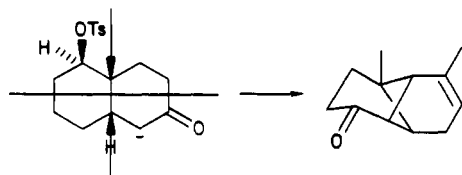
4. As long as the orientation is acceptable, i.e., the bridge is trans to the nucleophile, any additional bridgehead atoms on the path are processed. If one is not acceptable, the reaction is not allowed to occur.

5. Fusion atoms are processed identically to bridgehead atoms as can be seen in the following example:



KA(B-1) = 1 KA(B) = 2 KA(B+1) = 3
 KA(F-1) = 2 KA(F) = 3 KA(F+1) = 4
 Original STEREPs: KA(B): 3-10-1-8
 KA(F): 7-4-2-9
 Revised STEREPs: KA(B): 3-10-1-8
 KA(F): 7-2-9-4

Atoms 1 and 4 are found to be cis, so lactone formation is considered possible. There are instances, however, where a cis fusion is required for the reaction to be viable (cf. Table II; examples for cases 4 and 5). These cases can be defined as (1) having the coordinates of KA(B) and KA(D) in diametrically opposing quadrants given a line perpendicular to the fusion bond which bisects the ring system and a second line perpendicular to the first running along the fusion bond or (2) having the coordinates of the nu-

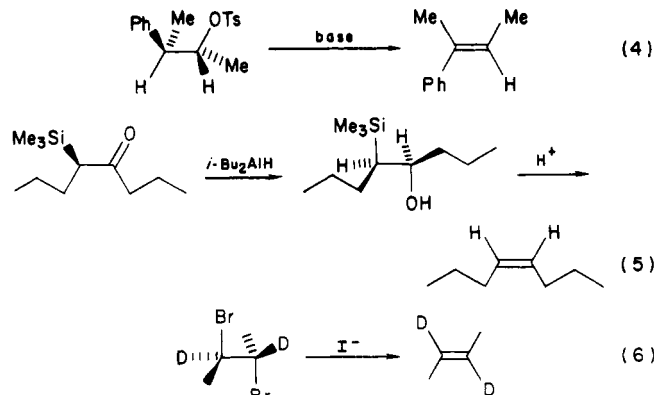


cleophilic site and KA(D) in diametrically opposing quadrants if the nucleophilic site is a ring atom. Again, the STEREPs are used to determine the stereochemistry of the fusion (subroutine FUSION). STEREP(1) contains those atoms that are not part of the ring envelope and STEREP(2) contains the fusion atoms. If the atoms that fall in STEREP(3) are members of the same ring (SSSR), the fusion is trans. Fused systems, then, are first checked for a mandatory cis fusion and then checked for proper orientation of the nucleophile.

6. If the reaction is still feasible, the path from nucleophile to leaving group is checked for the presence of double bonds. An allowed reaction has the path atoms in the cis configuration, or, if the new ring being formed is of size eight or larger, either configuration is acceptable.

Bimolecular and Pericyclic Elimination Reactions

A. Elimination Reactions Occurring with Anti Specificity. The anti rule for elimination reactions proceeding by the E2 mechanism was proposed on the basis of product studies of isomeric reactants.²⁰ The most common reactions of this type involve the removal of a proton and leaving group as in eq 4;²¹ however, silicon and some halides may take the place of the proton as evidenced in the acid-catalyzed Peterson olefination reaction, eq 5,²² and the dihalide elimination in eq 6.²³ For dihalide eliminations where at least one of the centers is primary,

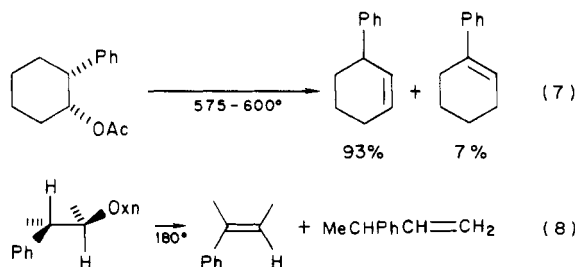


syn products have been found, but the mechanism actually involves an S_N2 displacement followed by the anti elimination of IBr. Although generally the rule, there are several factors that can disfavor an antiperiplanar orientation in E2 reactions. Normally, only products arising from anti elimination are displayed by CAMEO; however, the program recognizes two cases where syn eliminations are favored over the anti alternatives. Here, only the syn elimination products are produced.

The first case is found in small bridged-ring compounds. The conformational rigidity imposed by bridging impairs the ability of adjacent trans substituents on two-membered bridges to be coplanar. The dihedral angle is typically around 120°. Cis substituents, on the other hand, are constrained to be coplanar. Elimination in these systems tends to favor the syn orientation as evidenced in the 2,3-dihalonorbornanes. The trans-dichloride loses HCl about 80 times faster than the cis-dichloride with sodium pentoxide in 1-pentanol.²⁴

The second case occurs when β-activation is present. Functional groups which increase the acidity of the β hydrogens have been shown to effect a syn elimination over an unactivated anti elimination. Thus, both the cis and trans isomers of (2-phenylcyclohexyl)trimethylammonium hydroxide yield 1-phenylcyclohexene on heating.²⁵ The activated anti elimination is 2 orders of magnitude faster than the activated syn elimination; however, both are faster than the unactivated anti elimination to form 3-phenylcyclohexene, which was not an observed product. When β activation is present for the syn elimination, both the syn and anti products are displayed in CAMEO.

B. Elimination Reactions Occurring with Syn Specificity. Pyrolytic elimination reactions are the most often cited examples of eliminations proceeding with synperiplanar specificity.²⁶ Acetate and xanthate pyrolyses, eq 7²⁷ and 8,²⁸ are examples. Intramolecular elimi-



nation reactions with four- and five-membered transition

(20) For one such study see Cram, D. J.; Elhagez, F. A. A. *J. Am. Chem. Soc.* 1952, 74, 5851.

(21) Cram, D. J. *J. Am. Chem. Soc.* 1952, 74, 2149.

(22) Hudrik, P. F.; Peterson, D. J. *J. Am. Chem. Soc.* 1975, 97, 1464.

(23) Winstein, S.; Pressman, D.; Young, W. G. *J. Am. Chem. Soc.* 1939, 61, 1645.

(24) Cristol, S. J.; Hoegger, E. F. *J. Am. Chem. Soc.* 1957, 79, 3438.

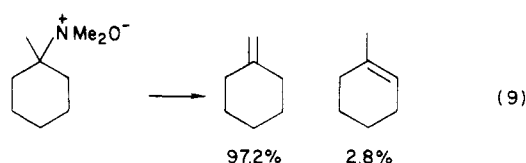
(25) Arnold, R. T.; Richardson, P. N. *J. Am. Chem. Soc.* 1954, 76, 3649.

(26) DePuy, C. H.; King, R. W. *Chem. Rev.* 1960, 60, 431.

(27) Alexander, E. R.; Mudrak, A. *J. Am. Chem. Soc.* 1950, 72, 3194; 1951, 73, 59.

(28) Cram, D. J. *J. Am. Chem. Soc.* 1949, 71, 3883.

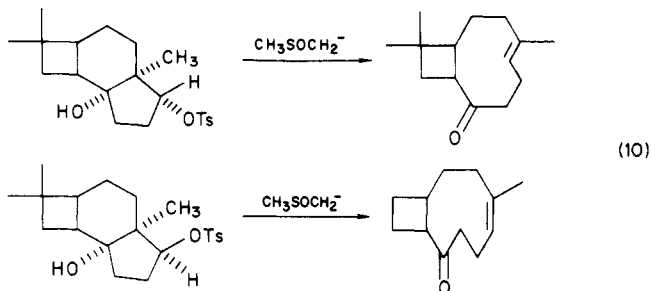
states as in the base-catalyzed Peterson olefination reaction or the decompositions of betaines in Wittig reactions and amine oxides in the Cope elimination (eq 9)²⁹ show greater syn selectivity.



C. Implementation. The manipulations necessary to identify syn/anti relationships have been detailed in a previous report.³ Briefly, the procedure involves ordering the STEREPs for the two stereocenters such that STEREP(1) is the other atom in the incipient double bond, STEREP(2) is the leaving atom, and the remaining elements in STEREP are the other substituents in the clockwise ordering. Unlike cis/trans systems which contain a rigid reference, syn/anti relationships cannot be determined by simply comparing STEREP positions for the two stereocenters. It is necessary to first produce the elimination product from the starting material as drawn. For this product, the clockwise ordering of the substituents is obtained and then compared to the STEREPs of the starting material. At this point, it can be determined whether the two leaving groups were originally drawn in a syn or anti orientation. If the orientation is correct for this reaction, no redrawing of the product is necessary; if not, the coordinates for the substituents on one of the stereocenters may be interchanged.

Unimolecular Elimination Reactions

A. E1cb Fragmentation Reactions. 1,4-Fragmentation reactions (Grob fragmentations) have been shown to be highly stereospecific, proceeding through a transition state in which the leaving group, breaking bond, and assisting orbital are aligned in an antiperiplanar orientation.³⁰ Grob fragmentations of polycyclic systems have been classified according to the relationship of the assisting orbital and leaving group terminus: location within the same ring is intraannular and within different rings is interannular, and if the assisting orbital is external to the ring system, the relationship is termed extraannular.³¹ In extraannular cases, the attainment of the antiperiplanar transition state is dependent in part on the geometric relationship of the leaving group and the assisting orbital and, in part, on the conformational flexibility of the molecule. Corey's syntheses of caryophyllene and isocaryophyllene illustrate the stereoselectivity as shown in eq 10.³²

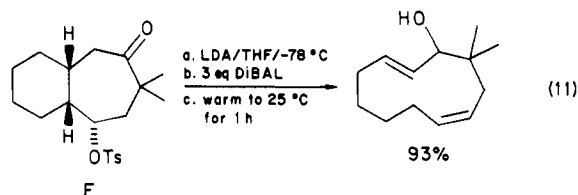


(29) Cope, A. C.; Baumgardner, C. L.; Schwetzer, E. E. *J. Am. Chem. Soc.* 1957, 79, 4729.

(30) Grob, C. A.; Scheiss, P. W. *Angew. Chem., Int. Ed. Engl.* 1967, 6, 1.

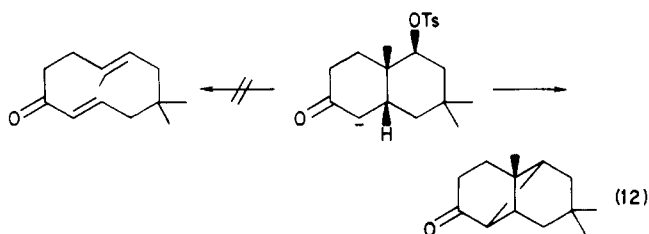
(31) Clark, D. A.; Fuchs, P. L. *J. Am. Chem. Soc.* 1979, 101, 3567.

Intraannular fragmentations show similar conformational dependencies. Studies of the four diastereomers of F (eq 11) and its trans-fused isomer indicate that the



molecule's ability to adopt a "folded" conformation dictates the mechanism of tosylate displacement. Specifically, the "folded" conformation leads to substitution while the "extended" conformation gives fragmentation.³¹

Interannular fragmentations are known to occur with boronate as the assisting group³³ and when the assisting orbital is a lone pair of electrons on nitrogen;³⁴ however, the report of an enolate-assisted fragmentation³⁵ was later disproven (eq 12).³⁶



Implementation. Until conformational analysis is treated more comprehensively in CAMEO, implementation of stereochemical restrictions for 1,4 fragmentation reactions is limited to those cases which involve scission of a fusion bond. Here, the geometric relationships involving the assisting group, the fusion, and the leaving group can be used to predict the viability of the fragmentation and the geometries for the incipient double bonds.

Table III summarizes the fragmentations currently being handled. Figure 3 contains a flowchart of the logic used with the numbered boxes corresponding to the following points.

1. In all cases where the stereochemistry is not completely specified, the reaction is assumed to be viable.
2. Interannular fragmentations are currently not restricted owing to the limited and conflicting data available as to their viability and the geometries of the incipient double bonds.
3. Conformational models indicate that a trans double bond should always be produced at the anion side during an intraannular fragmentation.

Baldwin's Rules

An assessment of the physical restraints on organic reactions would not be complete without the application of Baldwin's rules³⁷ to intramolecular ring-forming processes. The physical basis for these rules arises from the geometric requirements of the transition states which may be adversely affected by the chain linking the reactive sites. The

(32) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* 1963, 85, 362. *Ibid.* 1964, 86, 485.

(33) Marshall, J. A. *Synthesis* 1971, 71, 229.

(34) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* 1969, 8, 535.

(35) Mukharji, P. C.; das Gupta, T. K. *Tetrahedron* 1969, 25, 5275.

(36) Heathcock, C. H.; Gray, D. *Tetrahedron* 1971, 27, 1239.

(37) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* 1976, 734.

Table III. Geometric Requirements for Intramolecular 1,4-Fragmentations Treated by CAMEO

annular type	fusion	nucleophile/ leaving group	leaving group/ adjacent fusion group	product	example
extra	trans	trans		trans ene	
extra	trans	cis		E2 elimination	
extra	cis	cis		trans ene	
extra	cis	trans		cis ene	
intra	trans		trans	substitution	
intra	trans		cis	trans/trans enes	
intra	cis		cis	substitution	
intra	cis		trans	trans/cis enes	

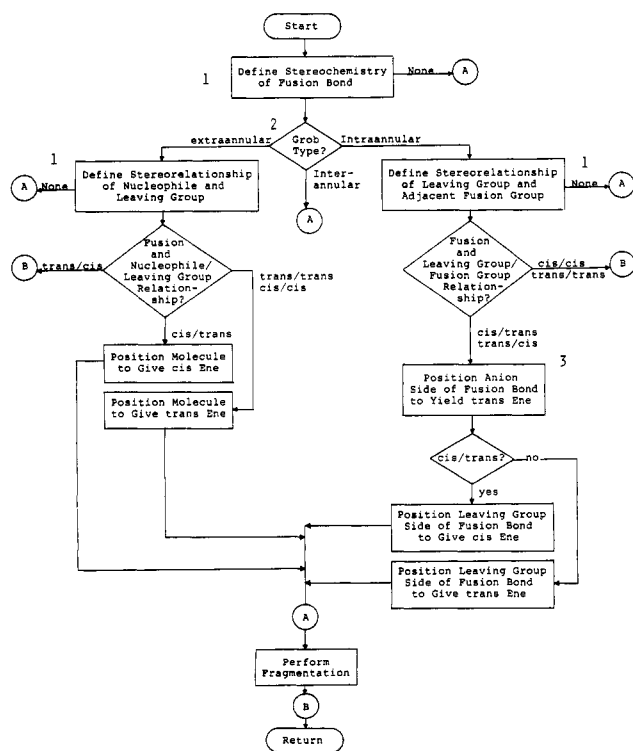


Figure 3. Flowchart for the formation of 1,4-fragmentation products.

systems are classified according to the hybridization of the electrophilic atom, the number of atoms in the ring being formed, and whether the breaking bond is exo- or endo-

cyclic to the new ring. The following rules are applied in CAMEO to reactions of first row elements:

	favored mode	disfavored mode
tetrahedral	3,4,5,6,7-exo-tet	5,6-endo-tet
trigonal	3,4,5,6,7-exo-trig	3,4,5-endo-trig
	6,7-endo-trig	
digonal	5,6,7-exo-dig	3,4-exo-dig
	3,4,5,6,7-endo-dig	

It should be noted that these rules are applied on a nonfatal basis; that is, disfavored reactions are allowed to occur; however, the products are displayed with a message which indicates the violation.

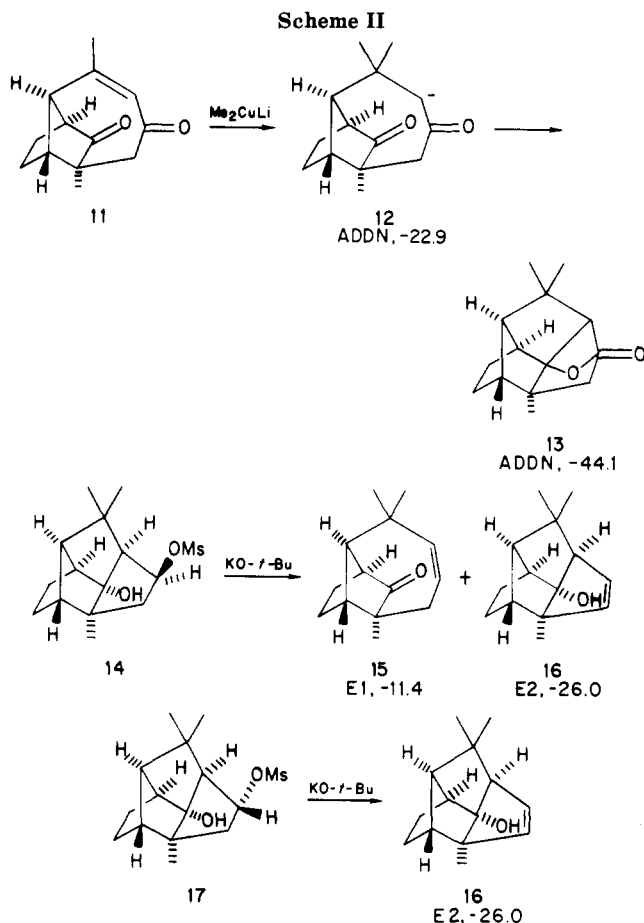
Sample Sequences

Several reactions from McMurry's synthesis of longifolene³⁸ have been chosen to illustrate the selectivity imparted to the program by the addition of the stereochemical package. For our purposes, the key to most stereoselective reactions is not that the desired product was produced but that competing reactions or reactions of the diastereomeric substrates were stereochemically forbidden. For contrast, the predicted products for reactions of some isomers are given. For each product, the program supplies the user with the mechanism by which the structure was generated and a rough ΔH in kcal/mol for the reaction.³⁹ These are included in the schemes under each structure.

Scheme I contains the intramolecular S_N2 reaction used as the key step toward the longifolene ring skeletons (1 →

(38) McMurry, J. E.; Isser, S. J. *J. Am. Chem. Soc.* 1972, 94, 7132.

(39) The ΔH computation includes changes in aromaticity, ring strain, total bond energy, steric interactions, and ion stabilities: Gao, J.; McLaughlin, D.; Jorgensen, W. L., to be submitted.



2). In addition to an O-alkylation (7), the program predicts both possible C-alkylation reactions (2, 3) to be viable. Although the six-membered ring product, 3, may be more thermodynamically favored, the reported product, 2 (93%),³⁸ contains the five-membered ring. Three E2 products (4, 5, 6) from anti eliminations and a less fa-

vorable E1 fragmentation product (8) are also output. Epoxy ketone 9, an epimer of compound 1, is predicted to give only elimination products under the same reaction conditions. The substitution reactions were considered, but were rejected because of the trans fusion which prevents the folded conformation necessary for the reaction to proceed. An additional product, 10, is predicted for this molecule as the fusion hydrogen and the epoxy leaving group are now anti. In Scheme II, the cis geometry of the nucleophilic site and carbonyl following dimethyl cuprate addition to compound 11 leads to an intramolecular addition product, 13. This product was reported in 96% yield;³⁸ it is the only product predicted by the program as is the 1,4-addition of dimethyl cuprate to 11.² Once functionalized to the hydroxymesylate 14, a Grob fragmentation occurs in the presence of base to yield product 15 (100%).³⁸ The program also predicts an elimination product, 16, but does not produce the intramolecular S_N2 product which, although stereochemically viable, does not compete with the facile fragmentation process. In contrast, epimer 17 is predicted to give only the E2 elimination product since neither the S_N2 nor the fragmentation has the proper stereochemical orientation.

Conclusion

The addition of stereochemical analysis to the computer synthesis program CAMEO has enhanced the sophistication of its predictions. Cis/trans and syn/anti relationships are recognized and used to ascertain stereochemical and/or physical restrictions on an organic reaction. Inversion of configuration is also addressed. Although illustrated with examples from base-catalyzed and nucleophilic chemistry, similar analyses have been incorporated throughout the mechanistic phases of the program.

Acknowledgment. Gratitude is expressed to the National Science Foundation for support of this work. The assistance of J. S. Burnier, D. R. McLaughlin, J. Gao, and B. L. Roos-Kozel is also appreciated.

Nucleophilic Attacks on Carbon-Carbon Double Bonds. 31.¹ Complete and Partial Stereoconversion in Vinylic Substitution of (*E*)- and (*Z*)- β -Chloro- α -phenylcinnamaldehydes and (*E*)-2-Iodo-1,2-diphenyl-1-nitroethylene by Nucleophiles

Zvi Rappoport* and Aviv Gazit

Department of Organic Chemistry, The Hebrew University, Jerusalem 91904, Israel

Received December 21, 1984

Substitution of the chlorine of (*E*)- and (*Z*)- α -chloro- β -phenylcinnamaldehydes ((*E*)- and (*Z*)-5) by *p*-toluenethiolate (ArS⁻), *p*-cresolate (ArO⁻), and MeO⁻ ions proceeds with complete or partial stereoconversion. With ArS⁻ both (*E*)- and (*Z*)-5 gave only the *E* product, whereas ArO⁻ and MeO⁻ gave different mixtures of *E* and *Z* products, where the *E* isomer predominates. With Cl⁻ no (*E*)-5 \rightleftharpoons (*Z*)-5 isomerization took place. Azide ion gave 2,4-diphenyloxazole (10) and 1-phenyl-5-benzyltetrazole (11). Reaction of (*E*)-2-iodo-1,2-diphenyl-1-nitroethylene with methoxide ion gave both *E* and *Z* substitution products and 1,2-dimethoxy-1,2-diphenylethylene. The stereochemistry of the substitution was discussed in terms of a multistep route via a carbanionic intermediate in relation to the nature of the activating group and the nucleophile. Comparison with literature cases shows that the present work extends the range of operation of the multistep substitution, as probed by stereochemistry, to systems less activated than those previously studied. The formation of the heterocycles 10 and 11 is ascribed to an initial formation of a vinyl azide followed by nitrogen loss and migration of phenyl to the nitrene formed. Cyclization with rearrangement gives 10 and reaction with another N₃⁻, decarbonylation, and cyclization gives 11. The crystal structures of (*E*)-PhC(Nu)=C(Ph)CHO, Nu = MeO, ArS, and of 10 and 11 were determined.

The stereochemistry of nucleophilic vinylic substitution via addition-elimination (eq 1, Y, Y' = electron withdraw-

ing groups, X = leaving group, Nu⁻ = nucleophile) is a strong tool in delineating the details of the mechanism of