the Hoffmann-La Roche Foundation.

Registry No. L-Asparaginylglycine, 67576-72-1; carbobenzoxy-L-asparaginylglycine benzyl ester, 20902-64-1; Boc-cyano-L-alanylglycine, 72378-46-2; Boc-cyano-L-alanine, 45159-34-0; glycine, 56-40-6; isoasparaginylglycine, 72378-47-3; Boc-*i*-Asn, 72390-11-5; Boc-Gly, 23650-19-3; Boc-Asn, 7536-55-2; Boc-Asn(Mbh), 72378-48-4; β-aspartamidinoacetic acid, 72378-49-5; β-Asp-Gly, 3790-52-1; α-Asp-Gly, 3790-51-0; aspartoyl-Gly, 72378-50-8; Ala(en)-Gly, 72378-51-9; β-aspartimidinoacetic acid, 72378-52-0; HF, 7664-39-3; TFA, 76-05-1.

Cambridge Data File in Organic Chemistry. Applications to Transition-State Structure, Conformational Analysis, and Structure/Activity Studies

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A description of the Cambridge Crystallographic Data File (CCDF) is illustrated with applications to organic chemistry. The use of chemical substructure searching techniques for the retrieval of three-dimensional coordinates for the more than 24 000 published organic crystal structures allows for inexpensive computer graphics and molecular modeling. Simple editing procedures and readily available programs from the X-ray crystallography literature allow the generation of transition-state models, the examination of bond lengths, etc., and direct molecular comparisons by least-squares fitting. The CCDF is a data base with a vast store of molecular information readily available to the organic chemist.

X-ray crystallography is widely recognized by organic chemists as the single most powerful structural tool currently available. A wealth of structural information can be obtained from a single-crystal X-ray diffraction experiment. However, once the stereochemical or other structural detail of interest to the organic chemist is established, the crystal structure itself is usually relegated to the archives. Little use of crystallographic information is made by most organic chemists despite the long and successful experience of biochemists, who use X-ray crystal structure data as a starting point for a multitude of structural studies.[1]

Part of the problem has been that structural data of the type useful to organic chemists is not readily accessible. Manual searches for suitable model compounds are laborious to impossible. A convenient method for *substructure searching*[2] is necessary in order to find molecular fragments of interest which may be buried in more complex molecules. Such techniques are now available. The Cambridge Crystallographic Data File (CCDF)[3-5] is a computer-readable data base containing the more than 24 124 published organic crystal structures. Substructure search techniques can be used to access both bibliographic information and molecular coordinates. A vast amount of data *as yet unrevealed* is readily accessible. We now discuss some uses of the CCDF in organic chemistry.

Molecular Models. Organic chemists have always been model builders.[6] The importance of molecular models to the organic chemist is particularly evident since Barton's contributions to conformation analysis[7] only 30 years ago.[8] How often has one seen in the literature rationalization of results "by inspection of models"?[9] The CCDF is a unique source of accurate geometric data for the easy construction by computer of molecular models. Although many computer techniques for building structures exist,[10] most programs are too complex for the average organic chemist. The CCDF allows rapid access to "real" molecules and rapid generation of stereoscopic pairs with essentially no prior knowledge of computers.[3] Moreover, many programs are readily available to obtain hard copies

(1) Gurd, F. R. N.; Rothgeb, T. M. *Adv. Protein Chem.*, in press.

(2) A method of substructure searching using Wisswesser line notation (WLN) is available from ISI. Granito, C. E.; Rosenberg, M. D. *J. Chem. Doc.* **1971**, *11*, 251. See also: Graf, W.; Kaindl, H. K.; Kniess, H.; Schmidt, B.; Warszawski, R. *J. Chem. Inf. Comput. Sci.* **1979**, *19*, 51.

(3) Available on-line through the NIH-EPA Chemical Information System, Interactive Sciences, Corp., 918 16th St. NW, Suite 500, Washington, DC 20006. The most recent update (July 1979) contains 24 124 compounds. The Cambridge Crystallographic Data Centre (Cambridge, England) maintains the file and makes every effort to obtain the data for any X-ray crystal structure referred to in the literature. Authors should expect to be contacted regarding X-ray data and should make every effort to cooperate by providing such data to the Centre. Every year, the NIH leases the crystal data base from the Crystal Data Centre in Cambridge, England. This lease is on behalf of the entire U.S. and permits the NIH to distribute the data base within the U.S. If you would like to obtain a copy of the Cambridge Crystal Data Base on tape, please contact Fein-Marquart Associates, 7215 York Rd, Towson, MD 21212.

(4) (a) Kennard, O.; Allen, F. H.; Brice, M. D.; Hummelink, T. W. A.; Motherwell, W. D. S.; Rodgers, J. R.; Watson, D. G. *Pure Appl. Chem.* **1977**, *49*, 1807. (b) Murray-Rust, P.; Motherwell, S. *Acta Crystallogr., Sect. B* **1978**, *34*, 2518. (c) Murray-Rust, P.; Bland, R. *Ibid.* **1978**, *34*, 2527. (d) Murray-Rust, P.; Motherwell, S. *Ibid.* **1978**, *34*, 2534.

(5) "Molecular Structure and Dimensions, Guide to the Literature 1935-1976. Organic and Organometallic Crystal Structures"; Kennard, O., Allen, F. H., Watson, D. G., Eds.; Cambridge Crystallographic Data Center: Cambridge, England, 1977.

(6) Perhaps the earliest molecular models were constructed of sticks and croquet balls by A. W. Hofmann (*Proc. R. Inst. G.B.* **1865**, *4*, 421) and used in a lecture delivered before the Royal Institution in 1865. This reference (found in: Ihde, A. J. "The Development of Modern Chemistry"; Harper and Row: New York, 1964) was kindly provided by E. E. Campaigne.

(7) (a) Barton, D. H. R. *J. Chem. Soc.* **1953**, 1027. (b) Construction of "Barton Models" was described [Barton, D. H. R. *Chem. Ind. (London)* **1956**, 1136], and photographs of such models appeared in the literature: Nare, H. R.; Turner, R. B. *J. Am. Chem. Soc.* **1953**, *75*, 4063.

(8) One point which should be emphasized is that not only are most "common" molecular fragments present in the CCDF but also many unusual and unique fragments are present. This is, of course, true because molecules which are unusual or unique are the ones which are more likely candidates for single-crystal X-ray studies.

(9) Fieser, L. F.; Fieser, M. "Steroids"; Reinhold: New York, 1959; p 7 and a multitude of papers.

(10) Wipke, W. T.; Heller, S. R.; Feldmann, R. J.; Hyde, E. "Computer Representation and Manipulation of Chemical Information"; Wiley: New York, 1974.

0022-3263/80/1945-0560$01.00/0

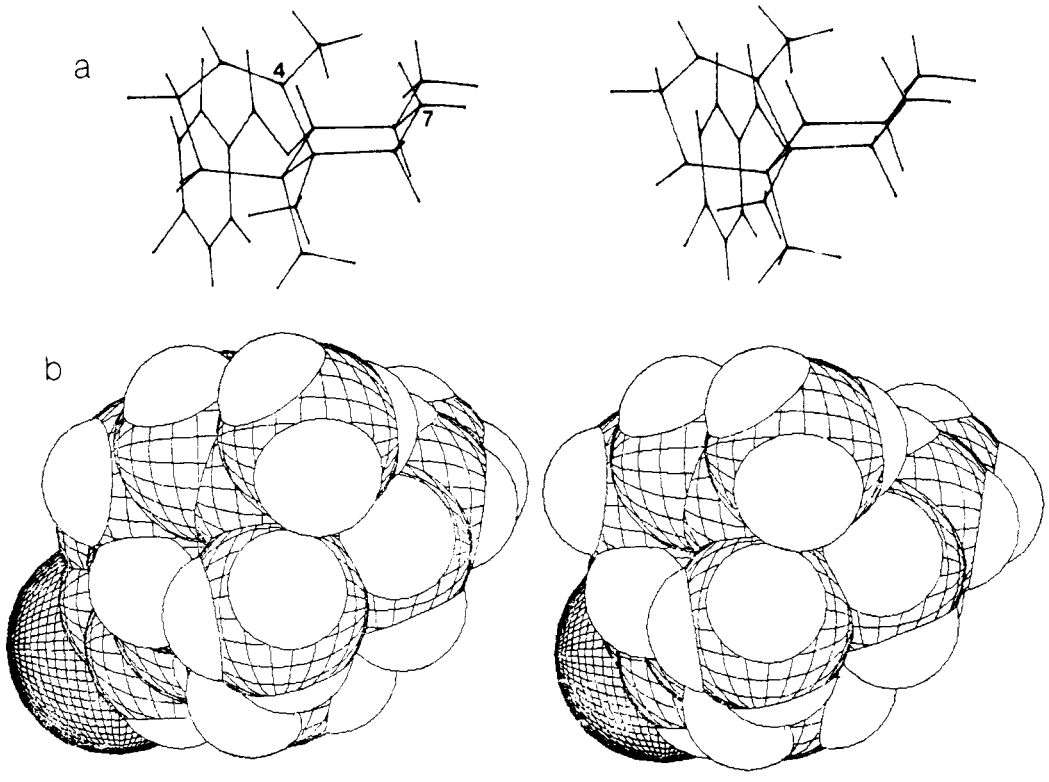


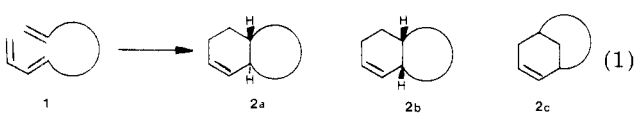
Figure 1. (a) Stereopair of molecule **6**. (b) Stereoscopic space-filling model of molecule **6**.

of stereodrawings as well as listings of bond distances, angles, and interatomic distances. Often by inspection of stereopictures of suitable model compounds, even more information is obtainable than examination of framework or space-filling[11] models. In addition, other "real" data for comparison purposes are usually available for the model compounds, such as IR and NMR.

X-ray structures, of course, represent solid-state conformations which are not necessarily identical with those in solution. Crystal-packing forces and solvent effects on conformation are obviously important.[12a,b] This problem is of particular importance in biological compounds, where activity is intimately related to conformation. Whereas most rigid molecules are likely to maintain the same conformation in solution, the solid-state conformations of flexible organic compounds can still provide useful information. The application of such crystallographic models in various aspects of organic chemistry is now described.

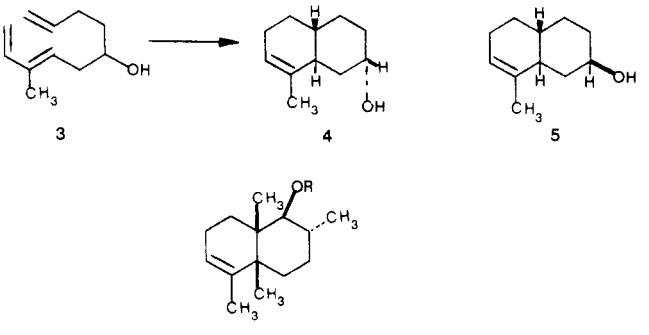
Transition-State Structure. While crystal structures are obviously "static", structural insights often are provided which allow predictions of reaction pathways to be made. We have applied[13] the use of model compounds, obtained from the CCDF, to the examination of stereochemical control in the intramolecular Diels–Alder reaction.

At present, factors[14] controlling the cyclization stereochemistry of 1 → **2a–c** (eq 1) are not well understood, and



(1)

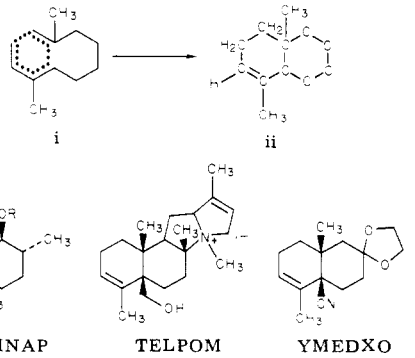
examples of all three modes of reaction are known. It is likely that subtle conformational and steric constraints play an important role. The Diels–Alder reaction[13] of **3**



yields compounds **4** and **5** (24% **4**, 33% **5**). The structure of **4** was determined by X-ray crystallography confirming the trans ring fusion. A search of the CCDF however found the related cis compound **6**.[15,16]

(11) The Merck molecular modeling system (MMS) for the generation of space-filling stereopictures has been described: Smith, G. M.; Gund, P. *J. Chem. Inf. Comput. Sci.* **1978**, *18*, 207.
(12) (a) Bernstein, J.; Hagler, A. T. *J. Am. Chem. Soc.* **1978**, *100*, 673 and references cited therein. (b) Review: Liljas, A.; Rossman, M. G. *Annu. Rev. Biochem.* **1974**, *43*, 475.
(13) Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 5289.
(14) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.

(15) First a suitable transition state (i) is drawn, and a representative substructure (ii) containing that molecular fragment is generated. Note that one can define carbons as fully bonded or leave the question open. Next a search of the CCDF leads to a list of REFCODES (in this case, 3 hits). These are DTMNAP,[16] TELPOM, and YMEDXO.



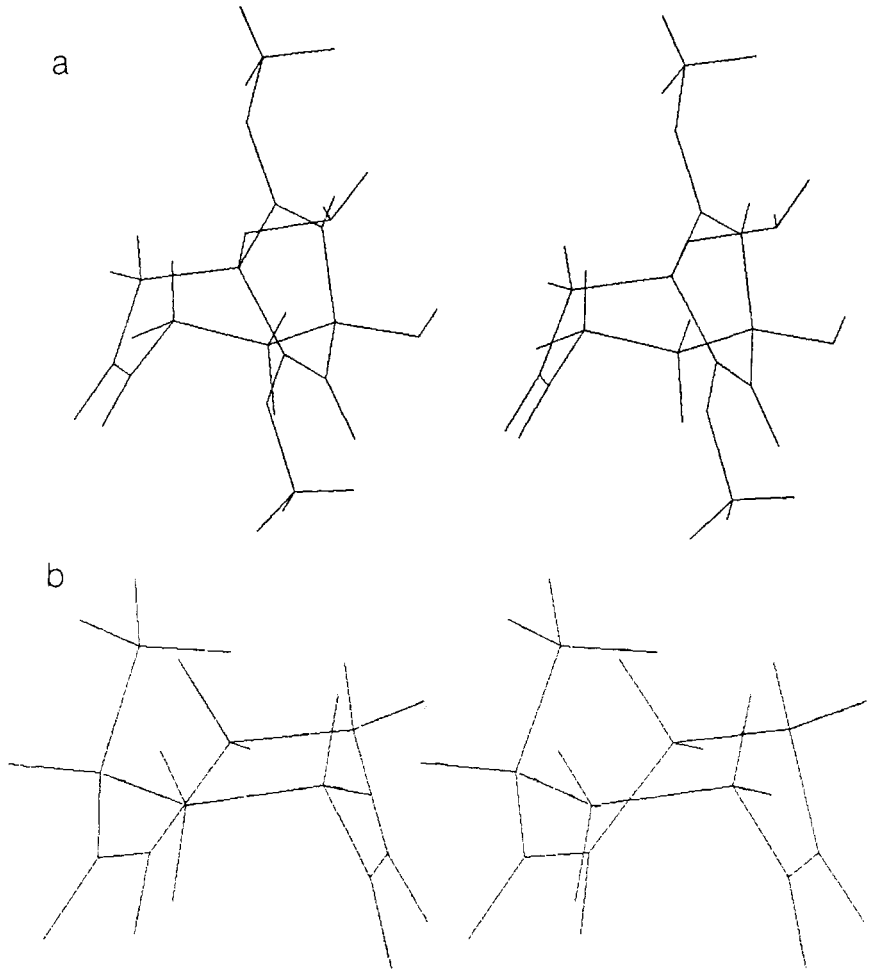
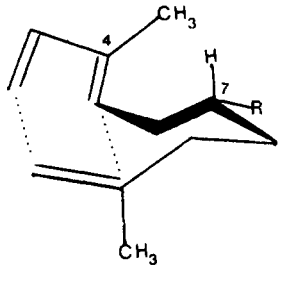


Figure 2. (a) Stereopair of molecule **28**. (b) Stereopair of conformer "A" of **25** constructed from molecule **28**.

The stereoscopic pair (Figure 1a) clearly shows a feature which had previously escaped our attention, i.e., that carbon C(4) is *axial* with respect to ring B, and therefore the vinylic methyl suffers a nonbonded interaction with the axial hydrogen on C(7). This interaction can also be seen in the stereoscopic space-filling model[11] (Figure 1b). The suggestion was therefore made[13] that the almost exclusive formation of trans isomers **4** and **5** was the result of this interaction in transition state **7** (vs. **8**). Thus, the



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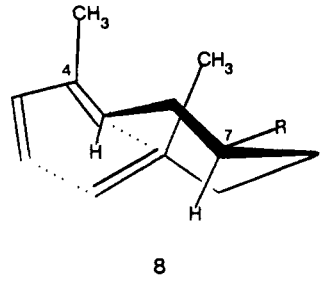


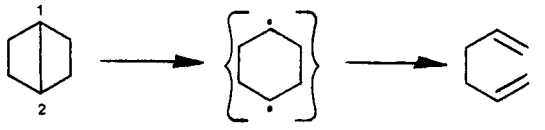
8

prediction is that if the methyl group were omitted, Diels–Alder cyclization via transition-state **8** would not be as favored. This has proven to be the case. Whereas **3** undergoes intramolecular Diels–Alder cyclization to give 94% trans product, compound **9** gives a 55:45 ratio of trans/cis product **10** (eq 2) under the same conditions.[17b]

(2)

9 10

Another use of the CCDF involves a structural examination of bicyclo[2.2.0]hexane derivatives. Compound **11** undergoes thermolysis to 1,5-hexadiene (**12**) via the well-known[18] thermal cleavage of the central C–C bond (eq 3). We have incorporated this reaction in a synthesis[19]



(3)

11 12

of the terpene skeleton **13**, which is obtained by heating **14** at 180 °C.

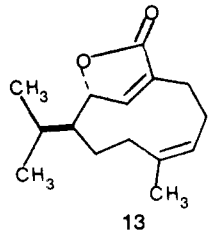
A substructure search of the CCDF using the connectivity of **15** gave a surprisingly large number of "hits".

(16) Saucy, G.; Ireland, R. E.; Bordner, J.; Dickerson, R. E. *J. Org. Chem.* **1971**, *36*, 1195.

(17) (a) Wilson, S. R.; Mao, D. T. *J. Org. Chem.* **1979**, *44*, 3093. (b) Wilson, S. R.; Mao, D. T., unpublished results.

(18) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1978**, *100*, 6268 and references cited therein.

(19) Wilson, S. R.; Phillips, L. R.; Pelister, Y.; Huffman, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 7373.



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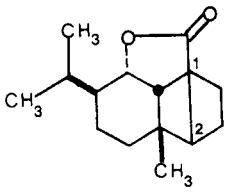

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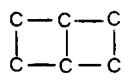

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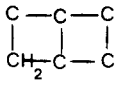
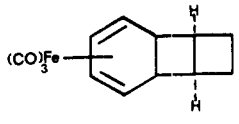


16

Examination of the bibliographic information showed that most of these were either homocubanes or Dewar benzenes. When the additional criterion of CH_2 was added (**16**), only four structures were found. One of the structures did not have coordinate data in the file.[20] The remaining three structures, **17**, **18**, and **19**, were compared with compounds



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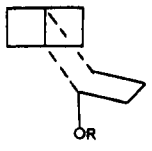

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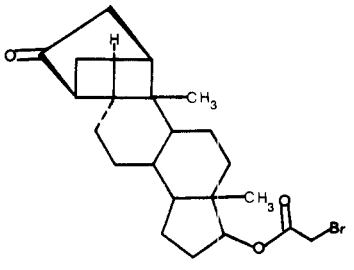

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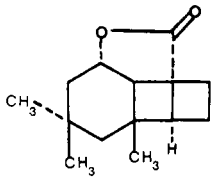

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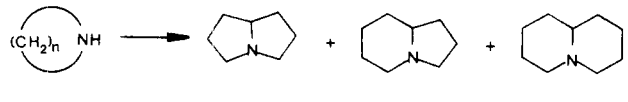
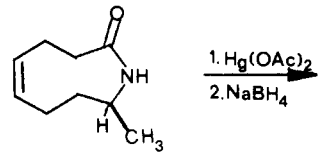
20 and **14**[19] and the electron diffraction structure of **11**.[21] The power of the connectivity search technique is clear if one ponders how the bicyclo[2.2.0]hexane **19** could have been found manually.

Clearly the longest C–C bond is the C_1–C_2 bond (1.55–1.59 Å), precisely the bond which first suffers cleavage in the thermolysis. This "principle of structural correlation"[22,23] is presently being applied to other thermal processes involving C–C bond cleavage in the rate-determining step.[24]

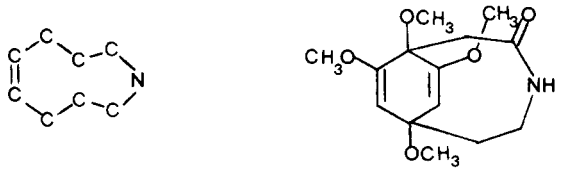
Conformational Analysis. As part of a general investigation of transannular reactions of medium-ring amines such as **21** as a route to pyrrolizidines **22**, indolizidines **23**, or quinolizidines **24**, we have studied[25] compound **25** which shows a temperature-dependent NMR spectrum, indicating two major conformers of equal population.[26] Mercuric acetate induced cyclization is stereospecific (**25** →**26**). We searched the CCDF for the



21 n = 7,8,9 22 23 24

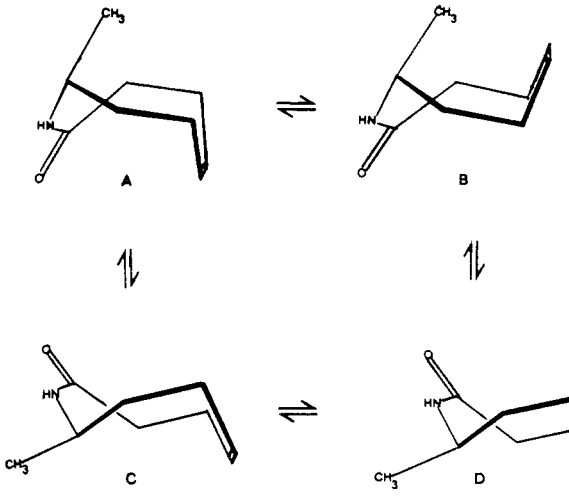


25 26



27 28

substructure **27**. A suitable model structure was found in **28**.[27] The stereopair of **28** (Figure 2a) shows the proper relationship of double bonds and amide. By deleting extra groups (OCH_3, CH=CH, and OH) and by adding a methyl group in a calculated position, we observe that all four conformers of **25** in dynamic equilibrium are generated (eq 4). The stereochemical outcome of cyclization **25** → **26** can now be seen to be due to a nonbonded interaction of the quasi-axial methyl group and axial hydrogens in conformer A relative to D (Figure 2b).



(4)

Molecular Comparisons. The use of molecular geometric information to *compare* molecules is quite easy once precise geometric coordinates are obtained. We have used a "best molecular fit" program[28] (BMFIT, see Experimental Section) to match molecules or parts of molecules to compare stereochemistry. (It is, of course, essential that the molecules are of the same chirality.[29]) The BMFIT program has been used to compare **11**, **14**, **17**, **18**, **19**, and

(20) The Jan 1, 1978, version of the CCDF which was used in these studies contains 19 113 entries of which 13 980 have atomic coordinates.
(21) Anderson, B.; Srinivasan, R. *Acta Chem. Scand.* **1972**, *26*, 3468.
(22) Murray-Rust, P.; Bürgi, H. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1975**, *97*, 921.
(23) Dunitz and co-workers have applied such techniques to examination of carbonyl addition reactions [Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563] and the S_N1 reaction.[22]
(24) For example, a substructure search of the CCDF for 1,5-hexadienes gave a set of 388 compounds which may provide information on the Cope rearrangement.
(25) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 330.
(26) The conformations of azacyclononanone have been discussed by using crystallographic coordinates. Winkler, F. K.; Dunitz, J. D. *Acta Crystallogr., Sect. B* **1975**, *31*, 276.
(27) Karle, I. L.; Karle, J. *Acta Crystallogr., Sect. B* **1970**, *26*, 1276.
(28) Nyburg, S. C. *Acta Crystallogr., Sect. B* **1974**, *30*, 251.
(29) If the molecules are not of the same enantiomeric series, the signs of appropriate coordinates must be changed.

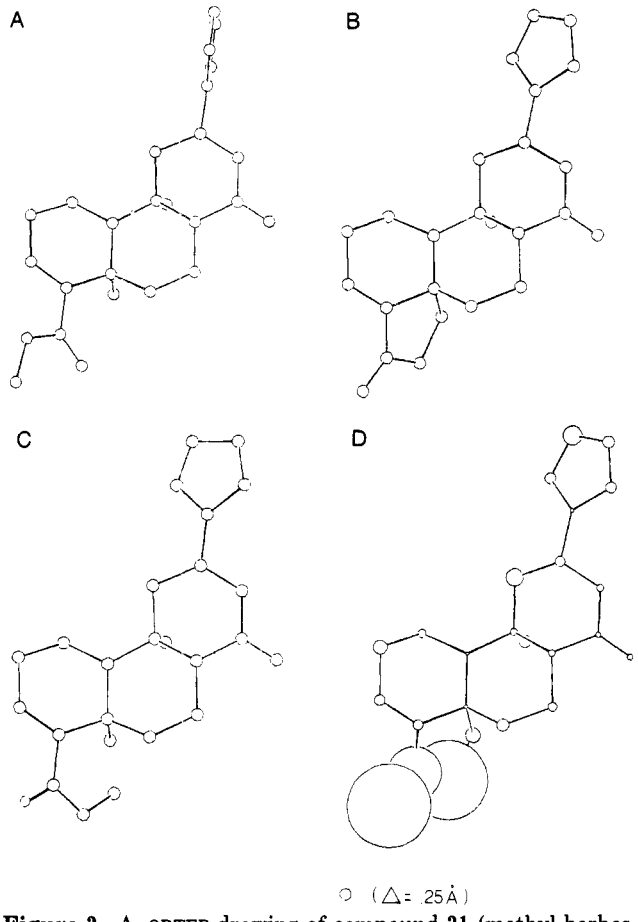


Figure 3. A, ORTEP drawing of compound **31** (methyl barbascoate); B, ORTEP drawing of compound **32**; C, compound **31** with the ester and furan groups rotated; D, BMFIT of B and C (ball sizes indicate goodness of fit).

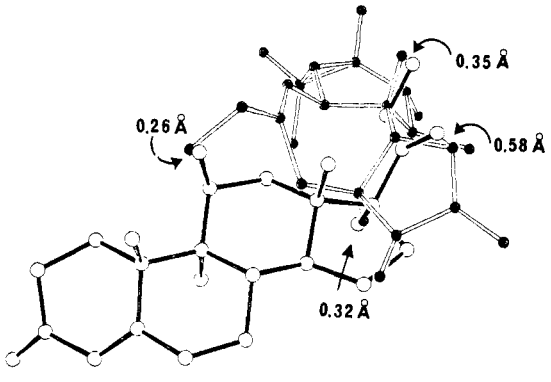
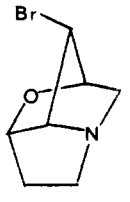


Figure 4. Superposition of cortisol (**33**) and phorbol (**34**). Goodness-of-fit of the functional groups is indicated.

20[19] as well as our synthetic lolium compound **29** with loline **30**.[30]



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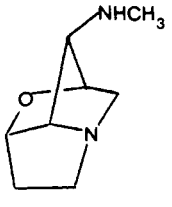

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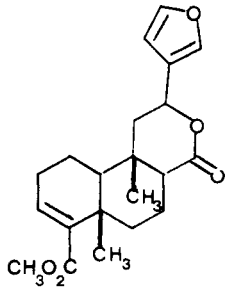
(30) Wilson, S. R.; Sawicki, R. A.; Huffman, J. C., submitted for publication.

An example of the use of this program can be seen in the comparison of methyl barbascoate (**31**)[31] with the lactonized diterpene **32**, whose structure was recently re-



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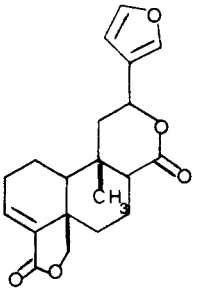
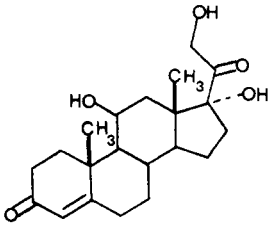


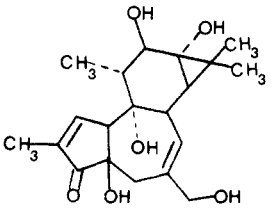
32

ported[32] (Figure 3). The deviations (Δ) in superposition are shown by the size of the atoms. (For better overlap the furan and ester group were rotated to the same approximate geometry.) Clearly, only subtle changes in *skeletal* conformation are required in going from **31** to **32**.

Structure/Activity Relationships. We should emphasize that all or part of the molecules can be compared by using BMFIT. In fact, it is *not necessary for the molecules to have any apparent similarity*. The comparison of functional-group overlap led to our observations that the antiinflammatory steroid cortisol (**33**) and the tumor



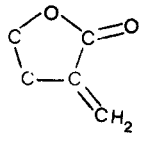
33



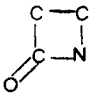
34

promoter phorbol (**34**) have complementary groups (Figure 4) which suggested a mechanism for phorbol's biological activity: alkylation of a steroid hormone receptor.[33]

Other studies currently in progress include examination of conformational factors in α-methylene lactones and β-lactams. A search of the CCDF using **35** as a sub-



35



36

structure gave 64 hits. Figure 5 shows the first structure from this search. The output gives the bibliographic information, two stereoviews (the second one rotated 90°) and a numbering scheme. Most are known antitumor agents as one would expect. A substructure search using **36** gave 51 hits. This list of data for all crystal structures of β-lactams contains an enormous amount of information on molecular geometry vs. structure. The use of such crystallographic data for chemical and biological inference

(31) Wilson, S. R.; Neubert, L. A.; Huffman, J. C. *J. Am. Chem. Soc.* **1976**, *98*, 3669.
(32) Wagner, H.; Seitz, R.; Lotter, H.; Herz, W. *J. Org. Chem.* **1978**, *43*, 3339.
(33) Wilson, S. R.; Huffman, J. C. *Experientia* **1976**, *32*, 1489.

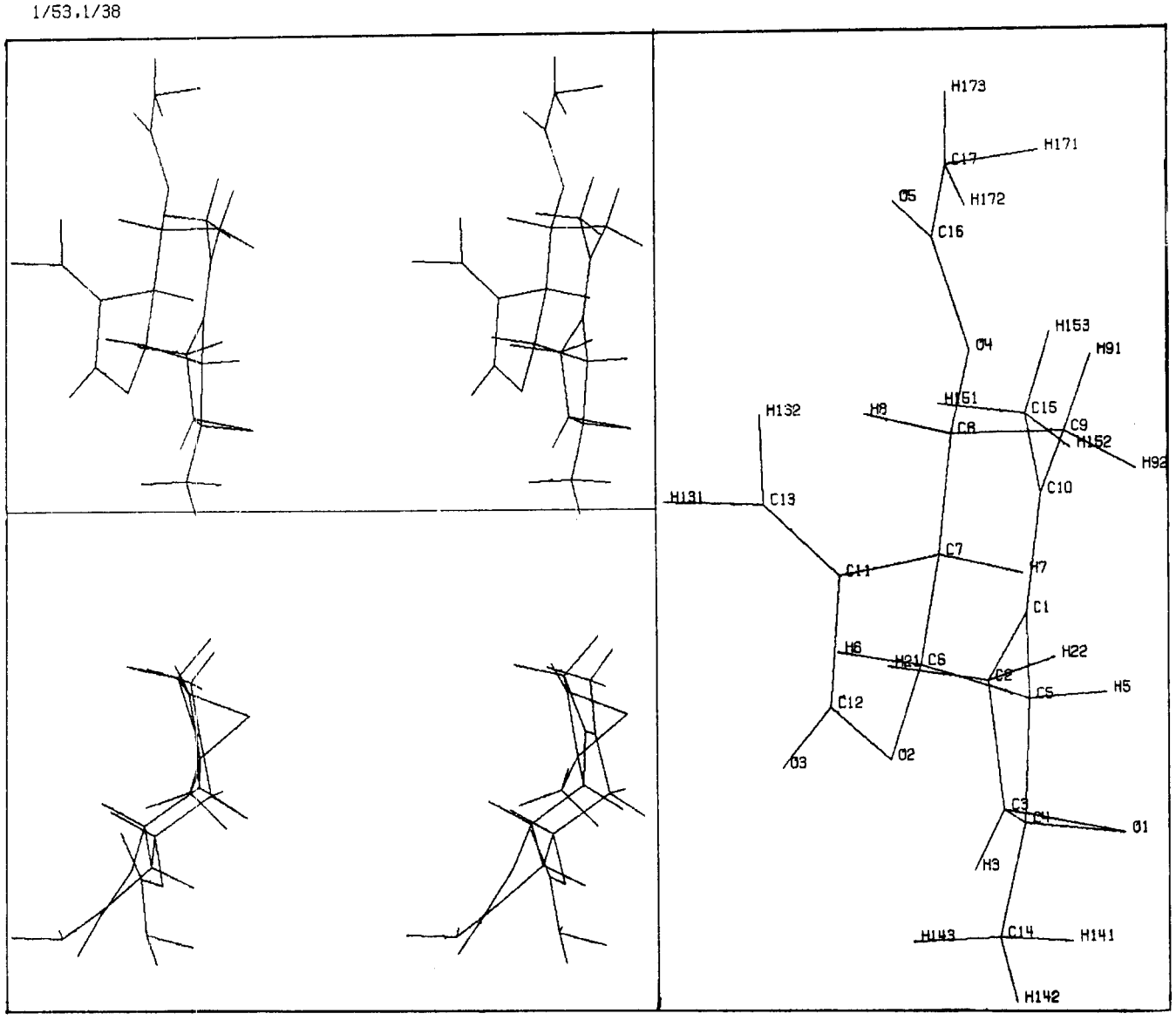


Figure 5. Example of α-methylene lactone substructure search.

in a small set of β-lactams has been reviewed.[34]

In summary, we have described how the molecular-coordinate data in the CCDF can be conveniently found by substructure searching and three dimensional models easily generated by computer and examined. The widespread use of the CCDF could mark a turning point in the use of crystallographic data in structural organic chemistry.

Experimental Section

Nearly all the programs used in this study are commonly available in most crystallography laboratories. The primary difference is in the fact that a systematic effort has been made to convert most of the programs to operate in an interactive mode on the computers available to the Molecular Structure Center.

The computations were all performed on a CYBER172-CDC6600 multimain-frame computer system with a KRONOS operating system and TELEX time-sharing facilities. The authors point out that even "low-speed" interactive computing (i.e., 300 baud) is highly advantageous when working with molecules. Inexpensive terminals are now available for graphics, and most major computing centers now support interactive computing. Since molecules can be easily represented as simple stick figures, a stereopair of a relative complex molecule can be transmitted in a reasonably short time (a molecule with 30 bonds, for example, can be displayed as a stereopair in less than 15 s). It is thus possible for the operator to manipulate molecular data and rapidly examine the results.

Of main concern for this paper is the local implementation of the Cambridge Crystal Data Centre structure files (CCDF).[4] The CCDF consists of three data files containing bibliographic, connectivity, and primary crystallographic data for nearly all organic and organometallic compounds for which the structural data has appeared in the literature. The files are being developed and continually updated by the Cambridge Crystal Data Centre in England and are available in the United States through the NIH-EPA Chemical Information System (CIS).[3] The files can be accessed directly through the CIS system for users who do not wish to implement them on their local computers and are available for a nominal fee for those who wish to devise their own systems. In general, the use of the CCDF at the IUMSC is identical with

(34) Sweet, R. M. In "Cephalosphorins and Penicillins"; Flynn, E. H., Ed.; Academic Press: New York, 1972; p 281.

that available through the CIS, and the input is nearly identical. To illustrate the use and structure of the files, we give two examples of the input and results obtained.

The bibliographic file consists of all pertinent bibliographic information for each of the compounds contained in the file. It is thus possible to search for compound names, authors, and elemental composition as well as certain classes of compounds. A typical query might be phrased as follows: Q *AUTHOR "HUFFMAN" OR "WILSON" AND *FORMUL "C20-22" AND "O2-4" The above question would list the "REFCODES" for all compounds in the CCDF which contained between 20 and 22 carbons and two to four oxygens and which were authored by either Huffman or Wilson.

The connectivity file use is illustrated by the formulation of the search question for substructure **27** shown below:

```
Q CONNECTIVITY SEARCH FOR C8N RING

    ALLBOND C
    NOLN
    AT1 N 2
    AT2 C 2
    AT3 C 2
    AT4 C 2
    AT5 C 2
    AT6 C 2
    AT7 C 2
    AT8 C 2
    AT9 C 2
    BO 1 2 1
    BO 2 3 1
    BO 3 4 1
    BO 4 5 1
    BO 5 6 2
    BO 6 7 1
    BO 7 8 1
    BO 8 9 1
    BO 1 9 1
    END
```

The input consists of the question identifier (Q CONNECTIVITY), followed by the keywords "ALLBOND C" and "NOLN". The first indicates that all bonds identified by the bonding cards (BO n_1 n_2 ...) are cyclic in nature. This information could have been entered on the individual bonding cards if in fact some of the bond types were to be acyclic. The "NOLN" card indicates that for the fragment requested, no bonds are allowed between any of the designated atoms other than those specified.

Following these cards, the individual atoms are identified by using the atom cards. The general form of the atom card is ATn_1 n_2 n_3 n_4 n_5, where n_1 is the sequence number as referenced by the bonding cards, n_2 identifies the element (carbon or nitrogen in our example), n_3 is the number of connectives which will be given in the bonding table, and n_4 and n_5, when present, indicate the number of hydrogens present and the number of functional groups allowed. In the coding for **27** all atoms are specified only as being connected to two other atoms, and n_4 and n_5 are omitted. This will allow any type of functional group to be present on the atoms (i.e., H or R).

Once the atoms are specified, the bonding pattern is given. The bonding card format is BO n_1 n_2 n_3 n_4, where n_1 and n_2 indicate which atoms are to be connected, n_3 indicates the type of bond (1 = single bond, 2 = double bond, etc.), and n_4 indicates whether the bond is cyclic or acyclic. In the example given all bonds are single with the exception of the C5–C6 bond which is required to be double.

Once the connectivity search is run, a list of "REFCODES" is again generated. At this stage one can do one of three things with the REFCODE file. Complete bibliographic data can be obtained, plots of the molecule can be generated off-line (see Figure 2a), or the crystallographic data for the compounds can be extracted and data tapes created for later use. We point out here that the CCDF which is available through the NIH-EPA CIS system will perform most of the functions thus far discussed, although a terminal capable of recording data would be necessary in order to retrieve the crystallographic data for later use.

The system in use at the IUMSC creates a local "standard data tape" (SDT) which is identical in format with those used as input to all crystallographic programs in our library. Thus it is possible to search the CCDF for molecules of interest and then manipulate, plot, or examine them by using the crystallography programs.

The BMFIT program which generated Figure 3D is a local version of Nyburg's[28] BMFIT and differs only in that the "thermal" parameter usually drawn in crystallography programs is scaled so that the size of the "atom" is proportional to the deviation from one atom to the corresponding atom in the other molecule. The program itself transforms the crystallographic coordinates of one molecule to the unit cell of the other and then translates and rotates the first molecule so that the square of the distances between corresponding atoms is minimized.

Problems can occur when molecules contain "flexible" groups such as the furan in Figure 3A,B. In order to overcome the gross errors which would occur in such cases, two local programs, GENCART and CART21, were written to allow manipulation of the crystallographic parameters. GENCART transforms the crystallographic data to a set of molecular parameters so that the atoms are described as a series of distances, angles, and torsion angles. CART21 will then allow manipulation of any of these parameters and will generate a new data tape with the "adjusted" molecule transformed back to crystallographic coordinates (Figure 3C). CART21 can also be used to generate and add molecular fragments to existing molecules or to generate hypothetical molecules.

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Synthesis of (24*R*,28*R*)- and (24*S*,28*S*)-Fucosterol Epoxides. Revision of C-24,28 Configurations[1]

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A facile synthesis of (24*R*,28*R*)- and (24*S*,28*S*)-24,28-epoxyfucosterol from fucosterol via the 24,28-glycols is described. The C-24,28 configurations were established by chemical correlation with sitosterol and clionasterol and show that previous assignments should be corrected.

Fucosterol epoxide (**1**) is a key intermediate in the dealkylation of sitosterol to cholesterol in insects.[2] For the detailed investigation of the mechanism of this dealkylation, it became necessary to develop a large-scale synthetic

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