Asymmetry in Organic Chemistry: A Left-handed Molecule Looks at the World

An analysis of asymmetry and its biochemical ramifications.

Steven Benner

As he interacts daily with his environment, man tends either to overlook or to forget altogether the conspicuous and the commonplace. So it is with the symmetry which pervades our activities, pleasures and tools, forms the structural basis of our arts, and is largely responsible for our biological existence. But symmetry and asymmetry are important in science as well, and the ability to perceive symmetry (and its absence) has been the foundation for several important advances in science in the past century and a half. What is symmetry? What happens when it is present? What are the effects of its absence?

In nature, a wide variety of symmetry forms are represented in the mineral kingdom. Mineralogists have long recognized six basic crystal forms, each defined in terms of the number of axes a crystal has and the relative lengths and directions of those axes. For example, the cubic form is characterized by three axes all of the same length and all set at right angles to each other. As early as 1664 Robert Hook noticed this regularity in form and speculated that it resulted from an ordered arrangement of subunits in the crystal, or in more modern terms, of the atoms in the crystal.

Symmetry as an artistic conception has been with us at least since the time the first man attempted to construct buildings and communicate with other men. Egyptian structures, such as the pyramids at Giza or the temples near the Aswan dam, are all exemplary of the use of symmetry in architecture. Symmetry and selected absence of symmetry have pervaded art and architecture ever since. In art, symmetry refers to a special balance around the central point or line, or a repetition of a structural feature. When present, symmetry represents form, stability, and in a classical sense, beauty. Its absence indicates instability and action. Judicious use of asymmetry in the arts, like dissonance in music, can be effective in catching the attention and stimulating the thought of perceptive viewers.

It is not surprising, then, that Louis Pasteur was attracted to one peculiar form of asymmetry that appeared in the crystals formed from a solution of racemic sodium ammonium tartrate at 24 degrees Centigrade. Pasteur, always with an eye for detail, noted not only that two different shapes of crystals were formed, but also that one shape was the mirror image of the other. Separating the two types of crystals with tweezers and a magnifying glass and dissolving each type in water yielded two solutions identical in every respect except that one rotated the direction a beam of light was polarized in a clock-

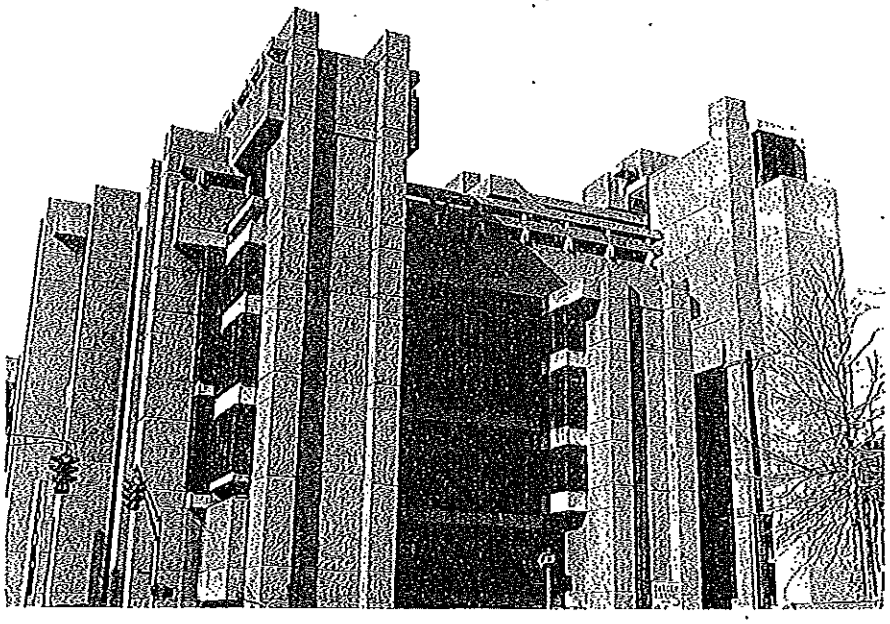

Fig. 1. The Art and Architecture building at the Yale University has extensive regions of asymmetry. We may safely assume that this indicates instability and action inside.

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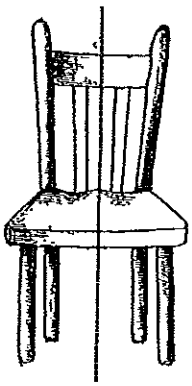

Fig. 2. A mirror plane divides an object so that every point on one side of the plane is matched with an equivalent point on the opposite side of the plane.

wise direction while the other rotated it counterclockwise (Fig. 7).

Isomers, two compounds having the same numbers and types of atoms but differing in physical properties, were well-known to Pasteur. Usually isomers differed in many physical properties including melting point, solubility, chemical reactivity and even color. But isomers identical in every way except the shape of their crystals and the direction they rotated polarized light were unheard of at that time, and Pasteur named this phenomenon "optical isomerism". Pasteur was unable to explain optical isomerism except by postulating that the molecules of the two types of tartaric acid were mirror images of each other—perhaps as left-handed and right-handed helices are mirror images of each other. It was not until 1874, when optical isomerism was better understood, that J.H. van't Hoff and J.A. LeBel independently introduced the idea of asymmetry, or "chirality", into organic chemistry. Chirality (from the Greek word meaning "hand") has since become one of the most useful concepts in chemistry.

To understand chirality the reader must consider one special form of symmetry—symmetry around a mirror plane. A mirror plane is a cut through the object such that every point and feature on one side of the plane is matched with an equivalent point or feature spaced similarly on the opposite side of the plane. We can define an object that has a mirror plane of symmetry as containing a "symmetry element," and hence it is "symmetrical." In contrast, an object that does not have any symmetry element, i.e., one that has no plane of symmetry, is "chiral". A chiral object is therefore an object that lacks a mirror plane of symmetry. This definition of chirality is the most accurate, but for most people, deciding that an object lacks some quality is difficult. Fortunately, there is another approach.

Every object (except, of course, a vampire) has a mirror image, and that mirror image can be constructed as in Fig. 4. If one treats an object A and its mirror image A' as two separate entities, one can now see if A and A' are distinguishable from each other. Can the two objects be superimposed, that is, can A be put "on top of" A' so that all features of each object match? If so, the object and its mirror image are "identical." As a rule, the mirror images of objects that are not chiral—objects that possess a mirror plane of symmetry— are identical to the object

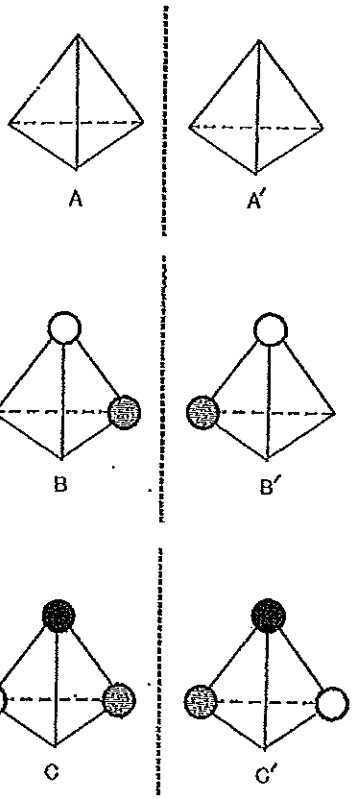

Fig. 4. Tetrahedrons A and B, each with at least two identical corners, are precisely like their mirror images, A' and B'. But tetrahedron C, with each of its four corners unique, is not identical to its mirror image C'. Tetrahedron C is chiral. Tetrahedrons A and B are not.

itself. The mirror image of a chiral object, in contrast, is never identical with the object itself. This makes available an easy test to determine if an object is chiral. Construct a mirror image of the object and see if it is impossible to rotate, turn, or otherwise manipulate the mirror image so as to superimpose it on the original object.

The best way to get a feel for chirality is to examine a very familiar chiral object, one's left hand. That the left hand is in fact a chiral object can be demonstrated by comparing a left hand with its mirror image, a right hand. It is clear that a left hand is not identical to a right hand, that is, a left hand could not be superimposed on the right hand. Thus, a left hand is chiral, and a left and right hand form a pair of mirror image objects. Such a pair is termed a pair of "enantiomers," and similar pairs of enantiomers can be shown to be the left and right feet,

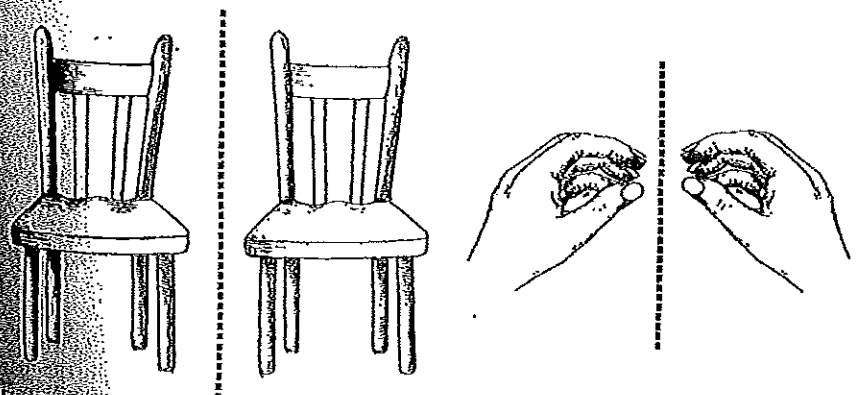

Fig. 3. The mirror image of a chair is just the same chair. The chair is not chiral. The mirror image of a left hand, however, is not another left hand, but is instead a right hand, which cannot be superimposed on the left hand. The left hand is therefore chiral.

the left and right ears, and so on. As an excursion into the geometry of three dimensions, the reader might convince himself that in addition to a left hand not being identical to its enantiomer, a right hand, the left hand by itself also lacks a mirror plane of symmetry. In other words, there is no way the human hand can be sliced so that the two halves of the hand on either side of the slice are mirror images of each other.

The postulate of van't Hoff and LeBel in 1874 was that carbon atoms, which normally exhibit a valence of four, have bonds directed in space towards the four corners of a tetrahedron as long as the carbon atom is attached to no double bonds. (Substituents attached to a carbon atom connected by one or more double bonds usually lie in a plane.) It can be seen that a tetrahedron by itself has a mirror plane of symmetry, and therefore is non-chiral, if all of the points of the tetrehedron are the same (Fig. 4). In fact, this type of tetrahedron can be seen to have several planes of symmetry. Even if some of the corners are made different (in Fig. 6 by attaching balls to some of the corners), the tetrahedron will have at least one plane of symmetry as long as at least two of the corners are the same. However, if the four points of a tetrahedron are all different, there is no plane of symmetry. The tetrahedron is therefore chiral. Its mirror image will not be superimposable on the original tetrahedron.

Since the four bonds of a carbon atom are pointed towards the four corners of a tetrahedron, we can analyze the chirality of carbon compounds by analogy with a tetrahedron; the carbon atom lies at the center and the four substituents bonded to the carbon atom are situated at the four corners of the tetrahedron. By this analogy it is easy to see that a carbon atom bonded to four identical substituents, as in methane, is not chiral. Nor is a carbon chiral if it is bonded to two or three different types of substituents. However, if a carbon atom is bonded to four different substitutents the carbon atom will be a chiral center. It can be shown that two different enantiomers of the chiral carbon exist, with these enantiomers being mirror images of each other, and not able to be superimposed. Van't Hoff and LeBel postulated that tartaric acid molecules were chiral in this manner, and thus came in a pair of enantiomers. Since the individual molecules were mirror images of each other, the enantiomers crystallized in crystal forms that were mirror images of each. And in solution the asymmetric molecules reacted with light asymmetrically, resulting in one enantiomer rotating polarized light in one direction and the other in the other direction.

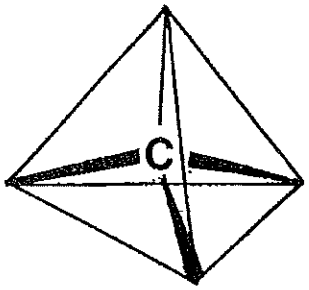

Fig. 5. The four bonds of a carbon atom are directed to the four corners of the tetrahedron, with the carbon at the center. If four different chemical groupings are attached to the carbon, it becomes a chiral center.

The discussion of stereochemistry, the three dimensional shape of organic molecules, is hindered because it is difficult to portray three-dimensional objects in two dimensions on paper. One method commonly used to portray three dimensions is used in Fig. 6. Bonds coming out of the plane of the paper are represented as solid lines while bonds going back beyond the plane of the paper are represented as dotted lines.

Chiral centers can also be named as either R or S, the designation being determined by assigning each of the substituents attached to the center a priority. The priority depends on the atomic weight of the substituent; the higher the atomic weight, the lower the priority. The molecule is then turned so that the substituent with the lowest priority is away from the observer, and the remaining substituents are examined from this perspective. If the substituents' order of priority decreases in a clockwise fashion, the center is labeled R. If the order of priority decreases in a counterclockwise fashion, the center is labeled S. An example of a simple chiral compound named in this fashion is fluorochlorobromomethane (Fig. 6). The reader should examine this figure carefully if he still is not convinced that this compound is chiral.

Tartaric acid (Fig. 7) is readily seen to have two chiral carbon atoms, each of the two middle atoms being attached to four different substituents. Thus it represents a more complicated case of chirality. Putting two asymmetric carbon atoms into one molecule creates at most four different stereoisomers, or "diastereomers." It is easy to see that if there are n chiral centers in a molecule, the maximum number of diastereomers is 2^n. Diastereomer, however, is the general term for stereoisomers. Some of the diastereomers are also enantiomers (and therefore chiral); some are not. In the case of tartaric acid, the RR and SS isomers are enantiomers (and chiral). But the RS isomer is identical to its mirror image, the SR isomer; these two diastereomers are therefore called "meso." Meso compounds, despite the fact that they contain chiral carbons, are not chiral as a whole because the chiral centers balance each other. A common example of a meso object is a whole human being. Although a human has chiral hands, feet, ears, and so on, each chiral member is balanced by another member of the opposite chirality on the opposite side of the body. Thus, while each part of the body by itself has no mirror plane of symmetry, the body as a whole does and is therefore not chiral. Thus looking at feet only, there are in principle four types of diastereotopic people, one with two left feet, one with two right feet, one

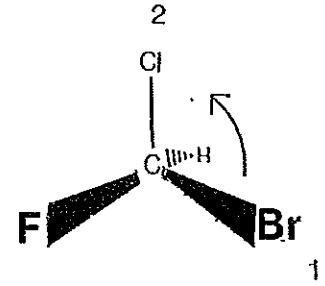

Fig. 6. S-bromochlorofluoromethane. The central carbon is bound to four different atoms, bromine (Br), chlorine (Cl), fluorine (F), and hydrogen (H), listed here in decreasing priority based on atomic weight. With the hydrogen pointing away, the substituent atom's priority decreases in a clockwise fashion. The carbon atom is therefore the S enantiomer.

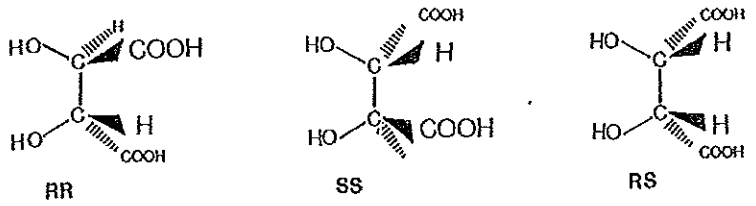

Fig. 7. The tartaric acid crystallized by Pastour was the RR isomer. It rotates a beam of polarized light in a clockwise direction, while the SS isomer rotates a beam of polarized light in a counterclockwise direction. The RS isomer, however, has a horizontal mirror plane of symmetry. It is a "meso" form, and displays no optical activity.

with a left foot on the left and a right foot on the right, and a fourth with a left foot on the right and a right foot on the left. It should be noted in particular that two of the diastereomers (a and b of Fig. 8) are also enantiomers. Furthermore, it should be seen that human beings of type c and d are "meso."

A word finally should be said about the chemical identity of enatiomers and diastereomers. As a rule, the only way to tell one enantiomer from its mirror image is to use another chiral object as a point of reference. This is true for chemicals as well as objects. Thus, the RR and SS enantiomers of tartaric acid will react identically with all compounds and reagents, unless those reacting compounds or reagents are chiral themselves. On the other hand, diastereomers have already built in another chiral center, and therefore pairs of diastereomers that are not pairs of enantiomers can be distinguished without reference to another chiral object. Pairs of diastereomeric compounds, such as RR and RS tartaric acids, as a rule, have different chemical and physical properties, including different melting points of crystals and solubilities in solvents.

These chemical principles can be illustrated again by looking at common chiral objects. A left foot can only be identified as a left foot (and not a right foot) if one compares the foot with a third chiral object, a left shoe (or some other appropriate standard for "leftness"). In contrast, using our diastereomeric people for illustration, it is possible to identify a as distinct from c without making reference to "left" and "right," e.g., c is the man with two big toes next to each other.) Thus it can be seen that unless a pair of diastereomers is also a pair of enantiomers, a pair of diastereomers can be identified by a non-chiral observer in a non-chiral environment.

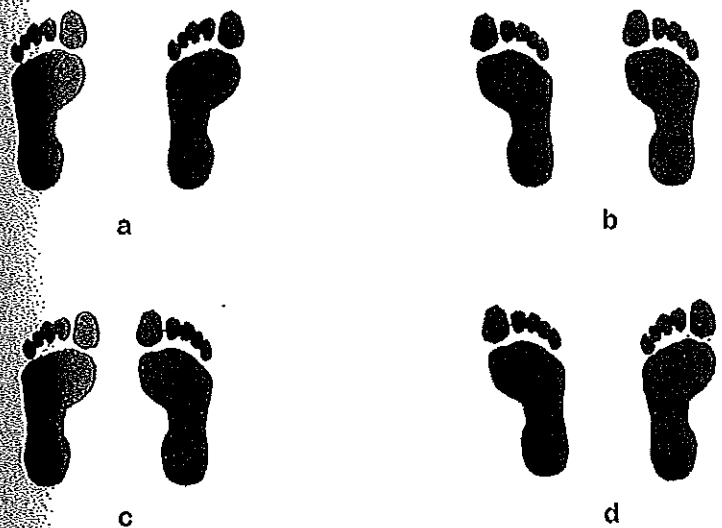

Fig. 8. Footprints from diastereomeric people.

It would be presumptuous to guide the reader through this analysis of stereochemistry without subsequently putting it to some kind of use. This is not difficult to do. Much of the elegance of chemistry and biochemistry is derived from the ability of these sciences to correlate function and reactivity of compounds with their shapes; in fact, how molecules react depends in large part on what they look like. This is particularly true in biological systems.

The most common example of the importance of chirality in biological systems appears in enzyme catalyzed reactions. Enzymes are extremely sensitive to the shapes of organic molecules that it uses as substrates. This is not surprising, particularly if one views the enzyme-substrate interaction as analogous to a lock and key interaction. Picture for example a macroenzyme that cuts fingernails. The "enzyme" accepts the left hand of a willing subject as a substrate into a cavity the shape of a left hand; at the end of each of the five branches of the cavity are little blades that neatly trim the substrate's nails. Needless to say, should the subject attempt to insert instead his right hand into the cavity, a substrate that is identical in every way with the left hand except in its chirality, the hand would not fit any more than the left foot would fit. The same is true for real enzymes. To a chiral enzyme a set of chiral compounds is more than just enantiomers; it is a pair of entirely different compounds altogether. Usually only one will serve as a substrate.

The degree of selectivity that enzymes make between enantiomers is remarkable. No S amino acids have ever been found as part of a normal animal protein, for example. In all vitamins and in most drugs that are chiral, one and only one enantiomer (or diastereomer) has full activity, while the others have greatly reduced activity or no activity at all. In insect pheromones, compounds used as sex attractants, the overall shape of the molecule is very important, and very

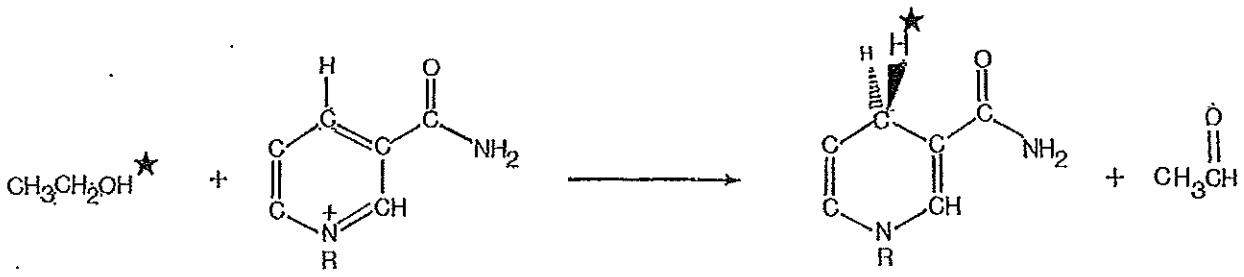

Fig. 9. Alcohol dehydrogenase transfers the hydrogen from ethanol exclusively to the top side of the NAD ring.

little change in shape is tolerated by the insect.

But even more striking is the ability of enzymes to make stereochemical distinctions between molecules that are not chiral, but rather are "prochiral." Prochiral centers are carbon atoms attached to three different types of groupings. (Chiral centers, it will be remembered, are attached to four different types of groupings.) An enzyme, by virtue of the fact that it is a chiral object, can selectively react with only one of two seemingly identical substituents on a prochiral atom.

A good example of the ability of enzymes to differentiate between atoms and groupings that look alike is a reaction involving the cofactor nicotinamide, or niacin (Fig. 9). Nicotinamide (in NAD) acts as a hydrogen atom acceptor in biological reactions, the hydrogen atom going on and off of the starred carbon atom of the ring to form NADH. The two hydrogens attached to the tetrahedral carbon in NADH are attached to a prochiral center. Thus although they seem identical a chiral enzyme can and does distinguish between them. Alcohol dehydrogenase, the enzyme that interconverts ethanol and acetaldehyde by the transfer of a hydrogren atom on and off of NAD in fact transfers only the hydrogen on the top of the molecule. This can be demonstrated by giving the enzyme ethanol labeled with deuterium, an isotope of hydrogren. No matter how many times the ethanol is converted to acetaldehyde and back again, deuterium and only deuterium is transfered in the reaction. There is never any transfer of the hydrogren originally bound to the nicotinamide molecule.

To synthetic chemists, asymmetry in organic chemistry represents a particularly difficult challenge. At Yale, several members of the Chemistry department, most notably those in the laboratories of Dr. Frederick E. Ziegler, are currently synthesizing natural products—compounds isolated from living systems. These compounds (Fig. 10) are often of medicinal interest, having shown biological activity against cancer or some other disease. They are also usually scarce, and are often found in rare or exotic plants and animals. It therefore is of great interest to devise a procedure by which these compounds can be synthesized in the laboratory. However, the stereochemistry of these compounds is crucial, and any design for a synthetic scheme to put these compounds together must also insure that the stereochemistry is correct. Unfortunately, the tools of a synthetic chemist are relatively unsophisticated and unselective compared with the enzymes described above. While biological reactions are close to 100 per cent stereospecific, most synthetic reactions are far less efficient, yielding usually a mixture of stereoisomers, only one of which is desired. Thus one of the principal obstacles to synthesis in the laboratory of biologically active compounds is producing the correct chirality at the molecule's asymmetric centers.

The ultimate synthesis of a biological compound is the synthesis of a whole enzyme. An enzyme is merely a chain of amino acids—each amino acid containing one chiral center. Although the amino acid starting materials can be isolated from nature (and therefore are entirely of the proper enantomer), the reactions used to link the amino acids one by one must be delicate enough not to racemize the amino acids, i.e., not to destroy this chirality. Clearly if only one percent of the chirality of an amino acid segment is lost in each step in the synthesis of a protein the size of ribonuclease (with 124 amino acids), only $(0.99)^{124}$ or 28% of the final product will have the correct stereochemistry at all of the chiral centers. Thus even with this high stereochemical yield, only 28% of the synthesized enzyme would be expected to be biologically active.

In synthetic procedures a good yield is considered to be anything above 80%. (If each step of the ribonuclease synthesis had gone with this efficiency, less than 10^{-12} of the product would have had the desired stereochemistry.) Considering that chirality is found in all types of compounds in living systems and not just in proteins, it is clear that the complete synthesis of life "in a test tube" is a long way off.

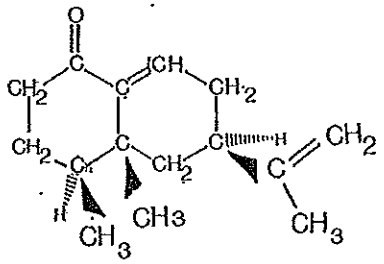

Fig. 10. Dr. Ziegler's group at Yale has been able to snythesize the natural product epleremophilone, shown above.