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Author's Review

Nonactin and the Coupe du Roi*

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The macrolide antibiotic nonactin is the first example of a natural product with S_4 symmetry. It is now pointed out that the synthesis of nonactin by dimerization-cyclization of (-)-nonactyl-(+)-nonactic acid, reported by Ulrich Schmidt in 1975, is also the first example of a chemical combination of two homochiral molecules to give an achiral product.

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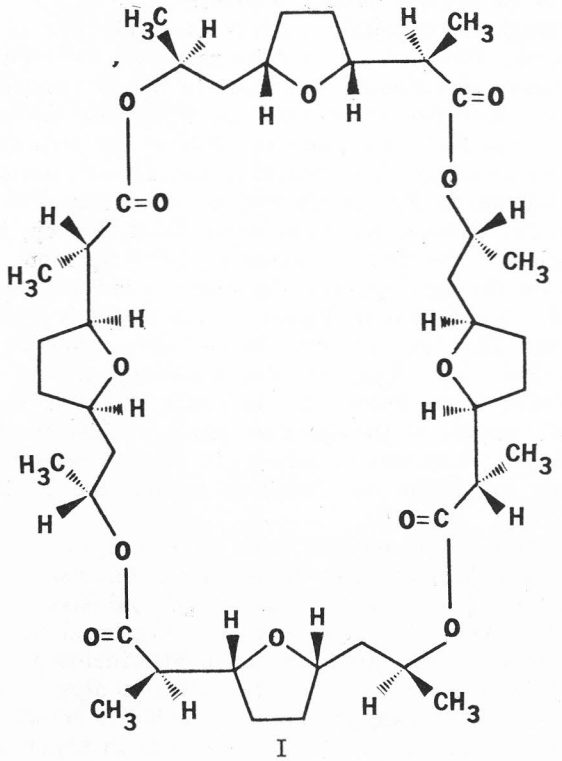
Back in 1957—58, Miša Mihailović and I shared a memorable year at the E.T.H. in Zürich, and the topic of this paper may evoke the spirit of those times: it was at the E.T.H., in the late fifties, that the structure of the macro-

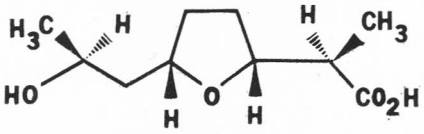


I

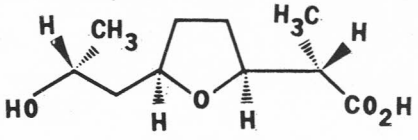
* Dedicated to Mihailo Lj. Mihailović on the occasion of his 60th birthday.

tetrolide antibiotic nonactin was being worked out by Vladimir Prelog and his colleagues[1] in what has since been characterized as »a classic application of stereochemical logic and chemical analysis.«[2]

Nonactin (I) is comprised of two subunits of (—)-(2*R*,3*R*,6*S*,8*S*)-nonactic acid (II) and two subunits of (+)-(2*S*,3*S*,6*R*,8*R*)-nonactic acid (III), arranged in an alternating order and linked by four lactone bonds to form a 32-membered ring. This arrangement imparts S_4 symmetry to nonactin, a meso compound without a plane or center of symmetry. Only two meso compounds



II



III

with this symmetry had previously been reported,[3] and nonactin was the first natural product in this class. Indeed, although many examples of S_4 symmetry have subsequently been discovered, in all but a few cases this is attained through conformational distortion of a structure of higher symmetry, normally D_{2d};[4] the remaining few examples are oddities belonging to the realm of inorganic or organometallic chemistry.[5]

But even though its unusual structure is surely one of nonactin's most striking features, this does not exhaust its role as a stereochemical curiosity: one of the syntheses of nonactin turns out to be, in retrospect, a landmark in stereochemistry. In order to provide the necessary background, we need to digress to an event that took place in 1965, at the first Bürgenstock Conference on Stereochemistry. To entertain his fellow stereochemists, Alain Horeau of the Collège de France showed us a curious way of bisecting an apple. A vertical cut is made half-way down from the top, a second vertical cut, at right angles to the first, is made halfway up from the bottom, and two horizontal cuts through opposite equatorial quadrants complete the operation. The results are shown in Figure 1: the apple is segmented into two homochiral halves. That is, the two halves are either both right-handed or both left-handed, depending on the direction of the horizontal cuts. Although this parlor trick, known as »la coupe du roi«, is no more than a three-dimensional version of the familiar yin-yang bisection of a circle into two two-dimensionally homochiral halves,[6] it rarely ceases to amaze, because it seems somehow to violate our intuitive notion that achirality should be conserved.

Many years later I showed this trick to Frank Anet, who was visiting Princeton from U.C.L.A. This after-dinner diversion inspired a collaborative enterprise that included our students, Jay Siegel and Steve Miura, and whose principal goal was a critical examination of the general problem of dividing finite geometric objects into isometric segments, including the special case of the coupe du roi.[7] In completing our theoretical analysis, which incidentally triggered a far-reaching reexamination of classical stereochemical concepts,[8] we also addressed the general problem of reactions in which achiral molecules are cleaved into homochiral fragments in the manner of the coupe du roi, as well as those in which homochiral molecules are combined to form an

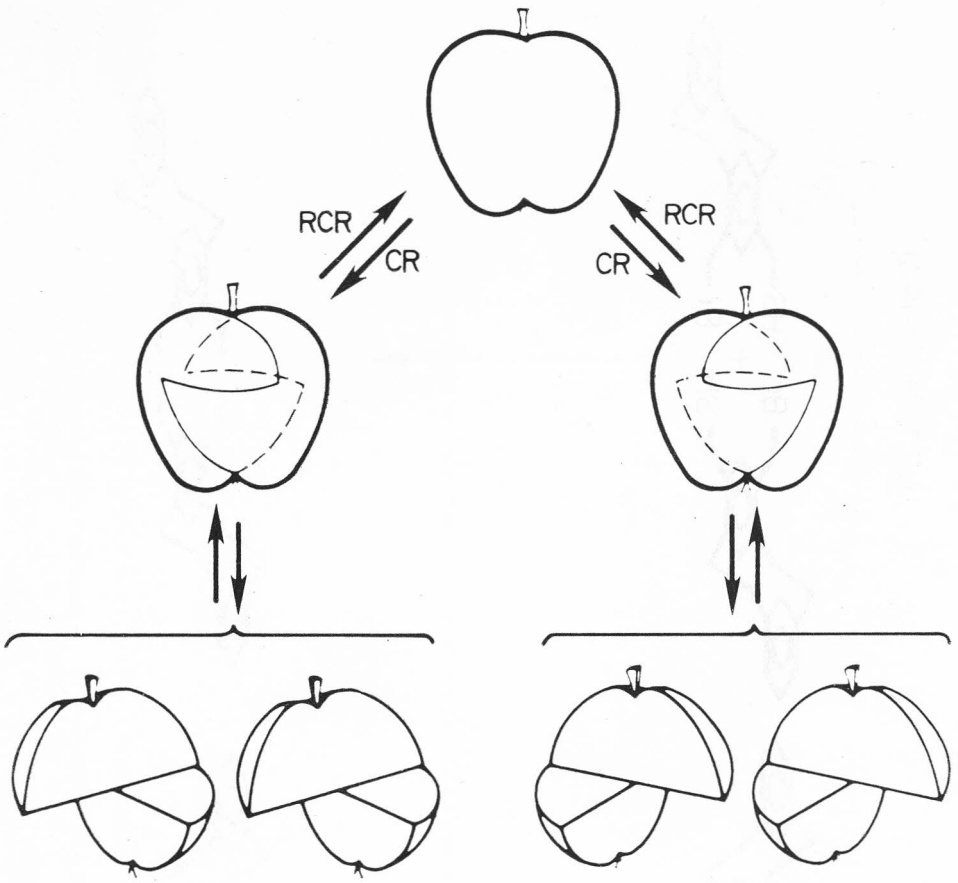


Figure 1. The coupe du roi (CR). The homochiral segments on the left are enantiomorphs of the homochiral pair on the right. The reconstitution of the apple from its segments is the reverse coupe du roi (RCR).

achiral product, the reverse coupe du roi (Figure 1). To put our arguments on a more practical footing, we decided to emphasize chemical relevance by providing an example of a reaction that would be a chemical analog of the reverse coupe du roi. Accordingly, we prepared and resolved racemic 4-carboxy-6-(hydroxymethyl)[2.2]metacyclophane, converted the (+)-acid into (+)-4-(bromomethyl)-6-(mercaptomethyl)[2.2]metacyclophane, and self-coupled the (+)-bromothiol. The product of this coupling reaction was the achiral cis dimer shown in Figure 2. In contrast, coupling of two enantiomeric molecules of bromothiol yields the achiral trans dimer (Figure 2). The two molecules of (+)-bromothiol are thus chemically analogous to two right-handed (or left-handed) apple halves (Figure 1), and their combination into the cis dimer yields a chemical analog of an apple.

Although we were unaware of it at the time, our chemical demonstration of a reverse coupe du roi was in fact not the first. And this brings us back to nonactin.

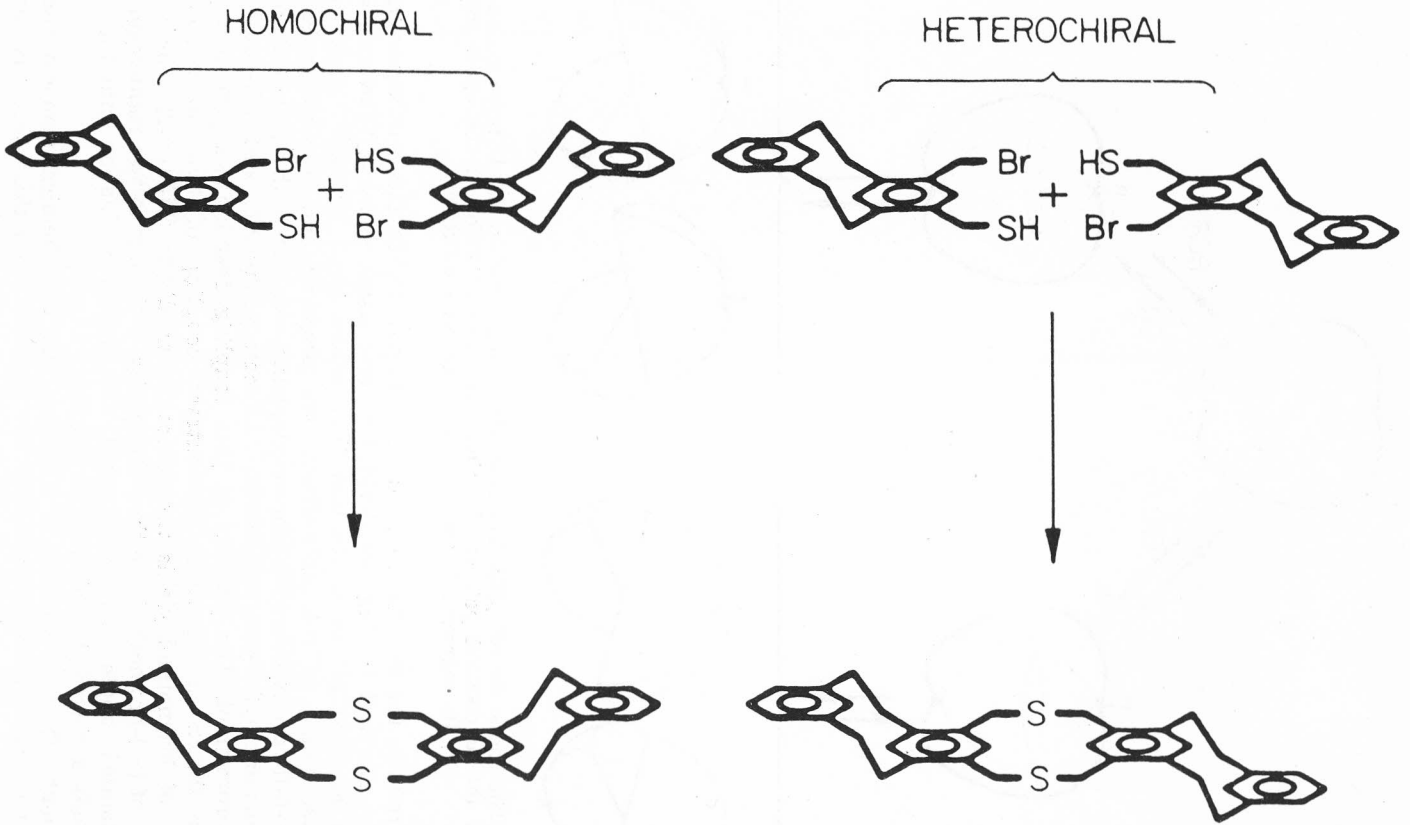
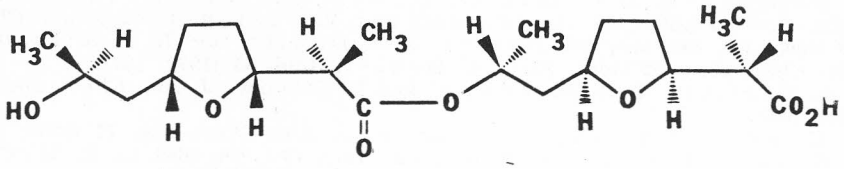


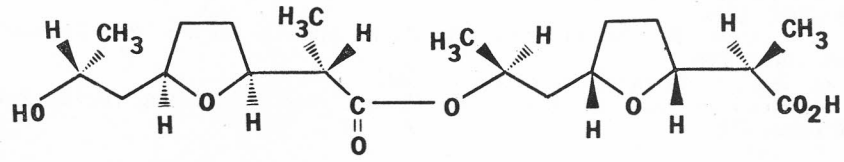
Figure 2. Left: Self-coupling of two homochiral molecules of 4-(bromomethyl)-6-(mercaptomethyl)[2.2]metacyclophane gives an achiral (C_{2v}) molecule of cis dimer. This is the chemical analog of a reverse coupe du roi. Right: Coupling of two heterochiral molecules of the same bromothiol gives an achiral (C_{2h}) molecule of trans dimer. Because an apple cannot be bisected into heterochiral halves, this reaction has no pomaceous analog.

No fewer than ten syntheses of nonactin have been described.[2] Among these is one that has attracted surprisingly little attention. In 1975, Ulrich Schmidt and his coworkers in Vienna briefly reported on a synthesis of nonactin.[9] Starting from (+)- and (—)-nonactic acid, which had previously been synthesized from optically active propylene oxide,[10] they prepared (—)-nonactyl-(+)-nonactic acid (IV). Dimerization-cyclization of IV by intermolecular double lactonization via the intermediate *N*-acylimidazolide or 2-pyridinethiol ester yielded nonactin, albeit in low yield.[11] This self-coupling of two homochiral molecules constitutes the first example of a chemical analog of the reverse coupe du roi.



IV

Prior to the publication of our paper,[7] this dimerization-cyclization was briefly discussed in the literature on only three occasions, according to Science Citation Index; two references came from the Vienna group[11,12] and one was buried in a review article on the synthesis of macrocyclic lactones.[13] Nowhere was there the slightest suggestion that this synthetic approach might have more general stereochemical significance. A year after the appearance of our paper,[7] Paul Bartlett and his coworkers at Berkeley[2] reported the synthesis of (+)-nonactyl-(—)-nonactic acid (V) and its cyclization-dimerization to nonactin by another macrolactonization procedure, again without mentioning the relationship to the coupe du roi. Finally, in 1985, Andrée Nouaille and Alain Horeau,[14] in a discussion of chemical reactions analogous to the coupe du roi, drew attention to the relevance of Bartlett's work to ours, though without reference to the earlier work of Schmidt.



V

Thus there are now two chemical examples of the reverse coupe du roi, ours and that of Schmidt and Bartlett. But there are still no chemical analogs of the coupe du roi itself. In principle one could imagine an enzymatic hydrolysis of nonactin into two molecules of IV or two molecules of V: as we pointed out,[7] given an object with S_4 symmetry, any bisection along the C_2 axis yields two homochiral halves, and while a cut perpendicular to this axis yields heterochiral halves, such a cut is of course chemically unfeasible in the case of nonactin. Alternatively, Horeau's proposed[14] enzymatic hydrolysis of a cyclic tetraester with C_{2v} symmetry promises to lead to the desired

goal. This approach is consistent with our view[7] that a central cyclic array is a structural necessity for the cleavage of an achiral molecule into homochiral fragments, and that C_{2v} symmetry, which is also the symmetry of the cis dimer in Figure 2, is the simplest for which bisection can only lead to achiral or homochiral fragments, in analogy to the bisection of an apple. I end my story on this note of hopeful anticipation.

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Nonaktin i »Coupe du Roi«

Kurt Mislow

Makrolidni antibiotik nonaktin predstavlja prvi primer jednog prirodnog proizvoda sa simetrijom S_4. Ovaj rad ukazuje da sinteza nonaktina dimerizacionom ciklizacijom (—)-nonaktil-(+)-nonaktinske kiseline, koju je 1975. godine opisao Ulrich Schmidt, predstavlja takođe prvi primer hemijske kombinacije dva homohilarna molekula koja daje ahilarni proizvod.