C, 90.48; H, 9.52. Found: C, 90.70; H, 9.50.

The reaction of **1f** (3 mmol) with **20** (15 mmol) in ether was performed in the presence of TMEDA (3.6 mmol) or HMPA (30 mmol) at 20 °C for 5 h. By colum chromatography on silica gel, 1,1-diphenyl-3-(1-adamantyl)-1-propene (**22**) was isolated together with dimer **6f**. **22**: a solid; mp 102–104 °C (from hexane); *m/e* 328 (M^+); ^1H NMR δ 1.7 (m, 17 H), 6.12 (t, J = 8.1 Hz, 1 H), 7.2 (m, 10 H). Anal. Calcd for $C_{25}H_{28}$: C, 91.16; H, 8.81. Found: C, 91.60; H, 8.70.

The Competitive Reaction between Two Alkyl Bromides. The reaction of **1a** with a mixture of *tert*-butyl bromide (3 equiv) and 1-bromoadamantane (3 equiv) was undertaken in ether in the presence of TMEDA (1.2 equiv) at 20 °C for 1 h. By column chromatography on silica gel, a mixture of 40% **2a** and 60% **3a** was isolated in 45% yield, together with dimers **6a–8a** (8% yield). The reaction in the presence of HMPA (10 equiv) also gave only the two *tert*-butylation products **2a** and **3a** in 40% yield, the ratio being 74:26.

The reaction of **1a** with a mixture of *tert*-butyl bromide (3 equiv) and isopropyl bromide (3 equiv) was undertaken in ether in the presence of TMEDA (1.2 equiv) at 20 °C for 1 h. By column chromatography on silica gel, a mixture of 3-phenyl-4-methyl-1-pentene[8b] and 1-phenyl-4-methyl-1-pentene[8b] was obtained in 60% yield, the ratio being 96:4.

Acknowledgment. The donation of (*S*)-(+)-2-butyl alcohol by Daisel Chemical Industries Ltd. is greatly appreciated.

Conformational Cycloenantiomerism in 1,2-Bis(1-bromoethyl)-3,4,5,6-tetraisopropylbenzene

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Abstract: The concept of cycloenantiomerism is critically reexamined. It is shown that suitably substituted derivatives of hexaisopropylbenzene (**1**) illustrate a novel type of stereoisomerism, in which enantiomers are distinguished by the sense of conformational orientation of side chains for a given configurational distribution pattern of stereocenters. Such isomers, which may be described as conformational cycloenantiomers, have now been synthesized for the first time. Photobromination of 1,2-diethyl-3,4,5,6-tetraisopropylbenzene yields a mixture of the two diastereomeric 1,2-bis(1-bromoethyl)-3,4,5,6-tetraisopropylbenzenes (**2**), from which the (1′*RS*,2′*SR*) isomer (**2a**) is isolated by HPLC. This isomer is a racemic mixture of conformational cycloenantiomers. VT-NMR measurements yield a lower limit of $\Delta G^{\ddagger}$ = 24 kcal mol^{-1} for the enantiomerization of **2a**.

Recently it was shown that the tightly interlocking cyclic tongue-and-groove arrangement of isopropyl groups in hexaisopropylbenzene (**1**) leads to nonbonded interactions which effectively immobilize these groups on the laboratory time scale.[2] Arnett and Bollinger[3] had previously conjectured that such conformational rigidity might stabilize enantiomers of suitably derivatized hexaisopropylbenzenes.[4] We now show that certain substitution patterns do indeed give rise to a novel type of stereoisomerism,[5] and we report the synthesis of a derivative of **1** that fits this description.

Cyclostereoisomerism. This concept was introduced by Prelog and Gerlach[6] in 1964.[7] As described in their paper, cyclostereoisomers are composed of an equal number of enantiomeric building blocks ("Bauelemente"), possess the same arrangement of stereocenters, i.e., the same cyclic distribution pattern of configurational descriptors ("Verteilungsmuster"), and differ only in the sense of direction of the ring ("Ringrichtung").[8,11]

Cyclostereoisomerism in a broad sense deals with isomerisms that arise when cyclic arrangements of stereocenters are associated with ring systems. In the problems that we will be addressing, the stereocenters can be attached externally to the ring or incorporated as members of the ring, and the ring itself can be either directed or undirected. Ring directionality in the present context depends on the sequential order of bonded atoms, i.e., on the constitution of the ring, so that an undirected ring is characterized by a palindromic sequence of atoms, i.e., by a sequence with bilateral symmetry. There are thus four basic combinations of stereocenters with ring systems (Figure 1) which may be exemplified by *N,N′*-di-*sec*-butylpiperazine (type A), 2,5-diketo-*N,N′*-di-*sec*-butylpiperazine (type B), 2,5-diketo-3,6-dimethylpiperazine (type C), and inositol (type I).

(1) Government of India Scholar, on leave from Manipur University.
(2) Siegel, J.; Gutiérrez, A.; Schweizer, W. B.; Ermer, O.; Mislow, K. *J. Am. Chem. Soc.* **1986**, *108*, 1569.
(3) Arnett, E. M.; Bollinger, J. M. *J. Am. Chem. Soc.* **1964**, *86*, 4729.
(4) "A natural consequence of this [conformational rigidity] would be the existence of stable enantiomers related to hexaisopropylbenzene in which the symmetry, with respect to the ring, is destroyed, provided that the average time for rotation [of the isopropyl groups] is long enough to allow resolution."[3]
(5) Portions of this work were reported in preliminary communications: (a) Siegel, J.; Mislow, K. *J. Am. Chem. Soc.* **1983**, *105*, 7763. (b) Mislow, K. *Chimia* **1986**, *40*, 395.
(6) Prelog, V.; Gerlach, H. *Helv. Chim. Acta* **1964**, *47*, 2288. See also: Prelog, V. *Science* **1976**, *193*, 17.
(7) For an extensive discussion of cyclostereoisomerism see: Cruse, R. In Eliel, E. L. *Stereochemie der Kohlenstoffverbindungen*; Verlag Chemie: Weinheim, 1966; pp 215–225.
(8) Cruse's treatment of cycloenantiomerism[7] differs from that of Prelog and Gerlach in the implicit application of the Neumann–Curie principle,[9] and in the requirement for constitutional equivalence of the stereocenters. Cruse dissects Ringrichtung from Verteilungsmuster and abstracts each to its point group symmetry; from this he is able to demonstrate that the achiral symmetries of Ringrichtung (C_{2nh}) and Verteilungsmuster (C_{nv}) with a common C_n axis intersect in two enantiomorphous ways to yield two enantiomers, i.e., two cycloenantiomers. Cruse also notes that the absence of a C_2 axis perpendicular to the principal axis (i.e., the absence of dihedral ring symmetry) is a necessary condition for cycloenantiomerism. However, Cruse's insistence on the *constitutional* equivalence of stereocenters imposes an unnecessary limitation on his treatment: as has been shown in another connection, such a constraint is irrelevant in analyses of symmetry properties.[10]
(9) See: Shubnikov, A. V.; Koptsik, V. A. *Symmetry in Science and Art*; Plenum Press: New York, 1974; pp 328–336. Donaldson, J. D.; Ross, S. D. *Symmetry and Stereochemistry*; Halsted Press Div., Wiley: New York, 1972; p 132.
(10) Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.
(11) In speaking of the *sense of direction* in a ring, it is of course essential to specify the side or face from which the ring is being viewed.

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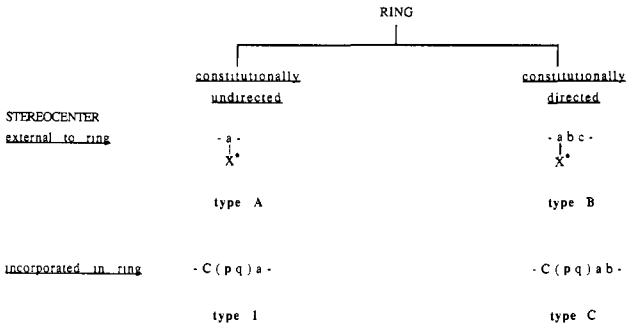

Figure 1. Four combinations of ring systems with stereocenters. In types A and B, the stereocenters (X*) are attached externally to a ring which may be constitutionally undirected (A) or directed (B). Ring members are indicated by a, b, etc. In types I and C, the stereocenters (C(pq)) are themselves members of a ring which may be constitutionally undirected (I) or directed (C).

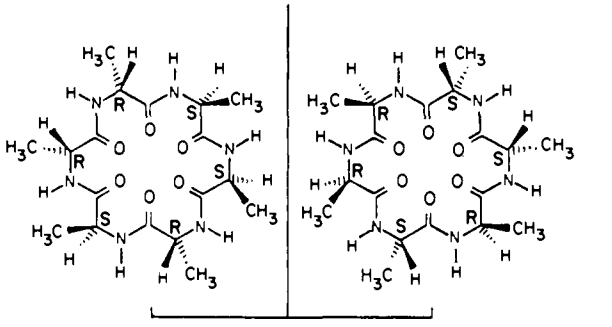

Figure 2. The cycloenantiomeric cyclohexaalanyls.

On the basis of the initially stated restrictions, Prelog and Gerlach defined certain pairs of members belonging to types B or C as cycloenantiomers and cyclodiastereomers and this general phenomenon as cyclostereoisomerism. Cycloenantiomers of type B are exemplified by a derivative of cyclohexaglycyl $(-N(X^*)-CH_2CO-)_6$ in which the six nitrogen atoms are substituted by three pairs of enantiomeric groups (e.g., (*R*)- and (*S*)-*sec*-butyl) attached to the six nitrogen atoms in a configurational distribution pattern that gives rise to two enantiomers differing in the sense of direction of the peptide bonds, i.e., $(R\rightarrow R\rightarrow S\rightarrow S\rightarrow R\rightarrow S)$ vs. $(R\leftarrow R\leftarrow S\leftarrow S\leftarrow R\leftarrow S)$. Cycloenantiomers of type C are exemplified by the cyclohexaalanyls in Figure 2.

Ring Directionality and Stereoisomerism. In discussing the number and kinds (enantiomers, diastereomers) of cyclostereoisomers possible for a given number of stereocenters, Prelog and Gerlach made no distinction between cyclostereoisomers of types B and C, which they considered to be closely related ("nahe verwandt"). In fact, however, the two types differ profoundly from the point of view of stereochemical theory. For example, two achiral (S_6 and C_i) and two enantiomeric (C_1) constructions of cyclohexaalanyl (type C) are possible from three molecules of (*R*)- and three of (*S*)-alanine.[12] Similarly, two achiral (D_{3d} and C_{2h}) and two enantiomeric (C_2) constructions of $(-NHCH_2CH(CH_3)CH_2-)_6$ (type I) are possible from three molecules of (*R*)- and three of (*S*)-1-amino-3-bromo-2-methylpropane. Ring directionality is absent in the second example, and yet the cyclooligomerization leads to the same number and type, achiral and chiral, of stereoisomers as in the first example. On the other hand, while chiral (C_1) constructions of $(-N(X^*)CH_2CO-)_6$ (type B) are possible from three molecules of (*R*)- and three of (*S*)-X^*NHCH_2COOH, combinations of three molecules of (*R*)- and three of (*S*)-$X^*NHCH_2CH_2Br$ can only yield achiral isomers of $(-N(X^*)CH_2CH_2-)_6$ (type A). In the last example, ring directionality is seen to function as an independent stereoelement. It follows that ring directionality is essential for enantiomerism only in cyclooligomers of type B and that cycloenantiomerism in cyclooligomers of type C, e.g., in certain cyclopolypeptides, does not differ in substance from ordinary enantiomerism.[13]

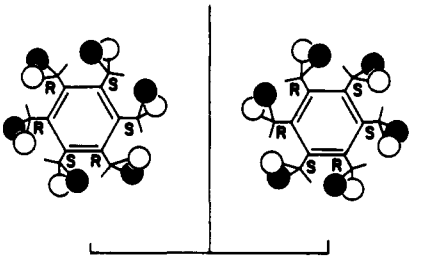

Figure 3. Schematic representation of enantiomeric hexaisopropylbenzene derivatives in which one CH_3 in each of the six isopropyl groups is replaced by a CD_3. Tertiary hydrogens are symbolized by short lines and CH_3 and CD_3 groups by open and filled circles, respectively.

Cycloenantiomerism of type B, but not of type C, thus meets what might be called the "meso condition", i.e., achirality in the absence of ring directionality. The same condition can also be expressed by the correspondence between cycloenantiomers of type B with meso compounds of type A (Figure 1). A comparison of cycloenantiomers of type C with meso compounds of type A is inappropriate, since *two* key structural features are simultaneously varied, i.e., ring directionality and location of stereocenters relative to the ring (Figure 1); the proper comparison is between cycloenantiomers of type C and corresponding structures of type I. These are not, however, achiral (meso) compounds, and *all* cycloenantiomers of type C therefore fail the meso condition.

The inherent contrast between cyclostereoisomers of type B and type C also finds expression in the consequences of ring directionality reversal. There are at least two fundamentally different ways of mechanically changing the direction of a ring in, for example, a cyclic peptide: by transposition of the NH and CO groups, or by a more "chemical" process in which the peptide bonds are first cleaved, the amino acid residues, i.e., the building blocks, are then flipped over while their relative positions in the cycle are left undisturbed, and finally the peptide bonds are reconnected. In the latter process the sense of direction of the ring is thus reversed while the Verteilungsmuster remains intact. Adapting a term introduced by Shemyakin et al.,[15] we call the second process *retromerization* and refer to the product as the *retromer*. In the literature dealing with cyclic peptides,[6,7,15-18] reversal in the direction of peptide bonds is invariably associated with retromerization, whether the comparison is between stereoisomers, including cycloenantiomers and cyclodiastereomers,[19] or constitutional isomers, including cycloisomers.[20] The first process is thus

(12) Constructions of cyclooligopeptides with S_{2n} ($n > 1$) symmetry from homochiral starting materials, e.g., the hypothetical synthesis of (S_6)-cyclohexaalanyl from three molecules of (*R*)-alanyl-(*S*)-alanine or from three molecules of (*S*)-alanyl-(*R*)-alanine, are examples of the reverse coupe du roi. See: Anet, F. A. L.; Miura, S. S.; Siegel, J.; Mislow, K. *J. Am. Chem. Soc.* **1983**, *105*, 1419. In particular, the hypothetical synthesis of (S_4)-cyclotetraalanyl from two molecules of (*R*)-alanyl-(*S*)-alanine or from two molecules of (*S*)-alanyl-(*R*)-alanine parallels the synthesis of nonactin from (−)-nonactyl-(+)-nonactic acid or (+)-nonactyl-(−)-nonactic acid. See: Mislow, K. *Croat. Chem. Acta* **1985**, *58*, 353.

(13) Similar results are obtained when removal of ring directionality is considered. Destruction of ring directionality in cycloenantiomers of type B, e.g., by excision of the six ring carbonyls in $(-N(X^*)CH_2CO-)_6$, results in achiral (meso) compounds of type A, i.e., (1′*R*,2′*R*,3′*S*,4′*S*,5′*R*,6′*S*)-$(-N(X^*)CH_2-)_6$ in the chosen example. On the other hand, destruction of ring directionality in cycloenantiomers of type C, e.g., by excision of the six carbonyls in the enantiomeric cyclohexaalanyls, results in ordinary enantiomers, i.e., the enantiomers of chiral $(-CH(CH_3)NH-)_6$ (type I) in the chosen example. Ring directionality is thus no more responsible for enantiomerism in cyclohexaalanyl than it is for enantiomerism in chiral hexamethylcyclohexane, inositol, and related homosubstituted cyclohexanes,[14] none of which possess ring directionality.

(14) Farina, M.; Grassi, M.; Di Silvestro, G. *J. Am. Chem. Soc.* **1985**, *107*, 5100 and references therein.

(15) Shemyakin, M. M.; Ovchinnikov, Yu. A.; Ivanov, V. T.; Ryabova, I. D. *Experientia* **1967**, *23*, 326.

(16) Gerlach, H.; Owtschinnikow, J. A.; Prelog, V. *Helv. Chim. Acta* **1964**, *47*, 2294.

(17) Gerlach, H.; Haas, G.; Prelog, V. *Helv. Chim. Acta* **1966**, *49*, 603.

(18) Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1 and references therein.

(19) Cyclic diastereomers with the same Verteilungsmuster and opposite ring directionality.[6]

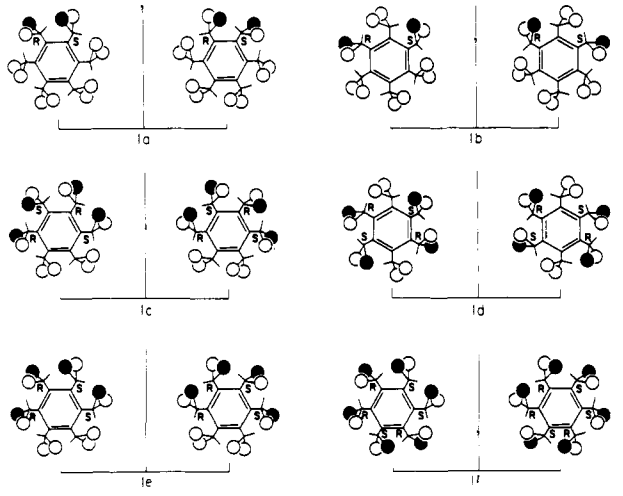

Figure 4. Conformational cycloenantiomerism based on hexaisopropylbenzene (**1**). The six possible substitution patterns are shown as racemic pairs, with CH_3 and CD_3 groups symbolized as in Figure 3.

equivalent to a retroenantiomerization.[15,18] When applied to cycloenantiomers of type B, either process leads to the enantiomeric structure (enantiomerization). By contrast, when applied to cycloenantiomers of type C, only the second process results in enantiomerization, while the first results in a product whose structure is indistinguishable from the starting one (homomerization).[21]

Conformational Cycloenantiomerism. Imagine a derivative of **1** in which one CH_3 in each of the six isopropyl groups is replaced by CD_3 so as to yield the configurational distribution pattern (1′*R*,2′*R*,3′*S*,4′*S*,5′*R*,6′*S*), where the primed positional descriptors refer to the newly created stereocenters at the methine carbons (C_I) attached to the correspondingly numbered ring carbons (C_{ar}). According to the configurational distribution, this hypothetical derivative should be an achiral meso compound. However, rotation about the six C_{ar}–C_I bonds is frozen in **1** on the laboratory time scale, and it may be safely assumed that the modified isopropyl groups in the derivative are similarly immobilized. The derivative is therefore expected to exist in two enantiomerically stable forms (Figure 3). If the molecular model is viewed along the normal to the benzene plane, it will be observed that reflection leaves the cyclic (*R*-*R*-*S*-*S*-*R*-*S*) pattern of configurational descriptors undisturbed while the sense of direction of the six C_I–H vectors is opposite for the two enantiomers. This relationship between the enantiomers in Figure 3 bears a striking resemblance to the relationship between the cycloenantiomeric cyclohexaalanyls (Figure 2). An obvious distinction between the enantiomers in Figure 2 and those in Figure 3 lies in the manner in which ring directionality is indicated: in the former it is given by the sequential order of *bonded* atoms, whereas in the latter it is given by the relative conformational orientation of *nonbonded* atoms.[22] Accordingly, it seems appropriate to designate the pair in Figure 3 and, by extension, the other hypothetical derivatives of **1** in Figure 4[23] *as conformational cycloenantiomers.*

In principle, the enantiomers in Figure 4 are interconvertible by internal rotation about the C_{ar}–C_I bonds, whereas bonds must be broken to interconvert the cycloenantiomers in Figure 2. Internal rotation leaves the configurations of the individual stereocenters intact, and this process thus effectively parallels retromerization in cycloenantiomeric peptides of type C in that reversal of ring directionality is accompanied by a switch of labeled substituents from one side of the ring to the other. Now imagine an alternative and entirely hypothetical process in which, under conditions of frozen internal rotation, the tertiary hydrogens are detached from the C_I atoms and then reattached to the other side, a process equivalent to having the tertiary hydrogens pass through the C_I atoms and emerge on the other side. This process interconverts homomers while inverting the configurations of all stereocenters and effectively parallels the hypothetical transposition of NH and CO groups in cycloenantiomeric peptides of type C. There is thus a clear parallel between the cycloenantiomers in Figure 4 and those of type C; the corresponding undirected system may be pictured as the transition structure for inversion at C_I by the second process, in which the ring is bisected by a C_2 axis. In the example given above, the first process is chemically feasible and the second is not, but the reverse is quite conceivable for other, related structures. That is, chemical feasibility is not at issue in this classification scheme. Consider, for example, a set of hypothetical hexakis(dimethylamino)benzene derivatives in which the CH_3's are selectively replaced by CD_3's in the pattern of Figure 4. If the conformation is such that the benzene ring bisects the dimethylamino bond angles and if the nitrogen atoms are pyramidal, directionality is imposed on the ring system. At room temperature, a process analogous to inversion at C_I is most likely to be dominant, with homomerization by inversion at nitrogen occurring far more easily than enantiomerization by rotation about the C_{ar}–N bonds. In this example the undirected ring system is the transition structure for inversion at nitrogen.

In short, cycloenantiomerism of the type depicted in Figure 4 is related to type C, and ring directionality is therefore no more responsible for enantiomerism in these compounds than it is in cyclohexaalanyl.[24]

Finally, we note that enantiomerization by internal rotation is not the decisive operational test for conformational cycloenantiomerism. Imagine, for example, a hypothetical molecule in which six 1,1′-binaphthyl groups are attached at their 4-positions to the six nitrogen atoms of cyclohexaglycyl, and in which the configurational sequence is (1′*R*,2′*R*,3′*S*,4′*S*,5′*R*,6′*S*). This molecule is enantiomerized by rotation about the 1,1′-binaphthyl bonds, yet the cyclic sense of orientation in this molecule is still given by the ordered sequence of *bonded* atoms in the ring, i.e., by the direction of the peptide bond vectors.

Synthesis of Conformational Cycloenantiomers. In considering the synthesis of systems that are capable of existing as stable conformational cycloenantiomers, an attractive approach is the transition-metal catalyzed cyclotrimerization of an appropriately substituted dialkylacetylene,[27] such as *meso*-3,6-dimethyloct-4-yne,

(20) Cyclic constitutional isomers with the same Verteilungsmuster and opposite ring directionality.[17]

(21) Transposition of ring atoms at stereocenters and retromerization are bound to give different stereochemical results: both processes reverse ring directionality, but the second corresponds to a *double* transposition, i.e., of a pair of ligands that are ring atoms and of another pair that are not. Note that in a chiral cyclostereoisomer of type C, transposition at all stereocenters in the ring of ligand pairs that are not themselves ring members (e.g., CH_3 and H in cyclohexaalanyl) always yields the enantiomer.

(22) A distinction is thus drawn between directionality based on ring constitution and directionality based on side-chain conformation. It is possible to formulate an alternative and independent definition of directionality based on the symmetry of the molecular model. This definition applies to all cyclic arrays, whether they are rings in the chemical sense (i.e., made up of bonded atoms) or not. Because undirected cycles are symmetric about the midline, the two halves are symmetry-equivalent; accordingly, a cycle is undirected if and only if it is bisected by a molecular C_{2n} axis or by a molecular σ plane perpendicular to the best-fit plane of the cycle. Otherwise it is directed. Thus, constitutionally directed rings (types B and C, Figure 1) are also directed by symmetry. The converse, however, need not obtain, since a constitutionally undirected ring (type A or I, Figure 1) may be directed by symmetry if it lacks the requisite C_{2n} axis or σ plane.

(23) The structures in Figure 3 correspond to **1f** in Figure 4. In Figure 3 of ref 5a, the labeling at positions 2 and 4 of the isomer corresponding to **1d** should be reversed.

(24) Conformational cycloenantiomers need not, however, be invariably related to type C. Consider, for example, a hypothetical derivative of 1,2,3,4-tetraisopropylbenzene in which the 5- and 6-positions are occupied by CHDT groups. In this compound ring directionality is fixed by the array of statically geared isopropyl groups on the time scale of rapid rotation about the C_{ar}–CHDT bonds.[25] Enantiomers are now interconverted by reversal of isopropyl group directionality, and the meso condition is fulfilled. The compound can thus be related to type B.

(25) By analogy to 1,2-diethyl-3,4,5,6-tetraisopropylbenzene.[26]

(26) Weissensteiner, W.; Gutiêrrez, A.; Radcliffe, M. D.; Siegel, J.; Singh, M. D.; Tuohey, P. J.; Mislow, K. *J. Org. Chem.* **1985**, *50*, 5822.

(27) For reviews on the oligomerization of acetylenes, see: Bird, C. W. *Transition Metal Intermediates in Organic Synthesis*; Logos Press: London, 1967; Chapter 1. Yur'eva, L. P. *Russ. Chem. Rev.* (*Engl. Transl.*) **1974**, *43*, 48.

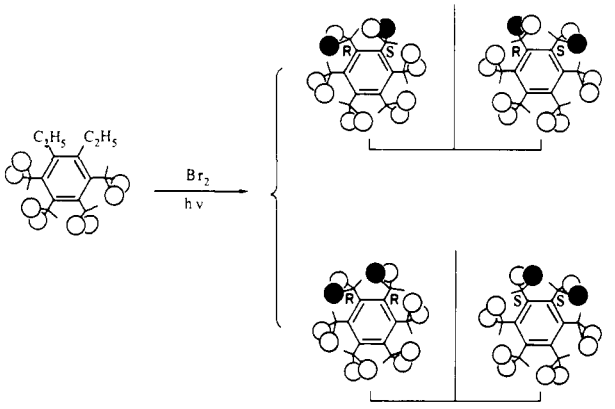

Figure 5. Photobromination of 1,2-diethyl-3,4,5,6-tetraisopropylbenzene to a diastereomeric mixture of 1,2-bis(1-bromoethyl)-3,4,5,6-tetraisopropylbenzene (**2**). Filled and open circles represent Br and CH_3, respectively. Tertiary hydrogens are indicated by short lines. Enantiomers are related by vertical mirror lines. Top: (1′*S*,2′*R*)- and (1′*R*,2′*S*)-enantiomers.[33] Bottom: (1′*R*,2′*R*)- and (1′*S*,2′*S*)-enantiomers.[33]

which in principle should lead to a racemic pair of type **1f** along with only one of the two achiral diastereomers.[28] However, an attempt to cyclotrimerize a mixture of the meso and dl acetylene[29] in the presence of $Hg[Co(CO)_4]_2$ yielded no product under conditions similar to those employed in the synthesis of **1** from diisopropylacetylene,[2] and even heating the reagents in a sealed tube at 150 °C for a week afforded no trace of the desired product. Attempts to cotrimerize 3,6-dimethyloct-4-yne and diisopropylacetylene were similarly unsuccessful, only **1** being formed in this reaction. Evidently the steric requirements of the cyclotrimerization reaction are exceptionally demanding. Because the synthesis of **1** by this route is thus not easily extended to higher alkyl derivatives, we were forced to abandon this approach and to consider an alternative strategy.

The observation[30] that hexaethylbenzene can be photobrominated or photochlorinated in all six α-positions suggested a way of creating suitably altered isopropyl groups *after* formation of the aromatic ring. Vicinal α-chloroethyl or α-bromoethyl groups, generated by α-halogenation of vicinal ethyls, meet two essential requirements: they contain stereocenters, and they are expected to be rigidly gear-locked in analogy to the isopropyl groups in **1**.[31,32] The eight diastereomers of hexakis(α-haloethyl)benzene are conveniently described by considering a mapping onto the eight diastereomers of hexaethylbenzene. Such a mapping becomes possible if the relative *R*/*S* configurations at the stereocenters in $C_6(CHXCH_3)_6$ are matched to the relative up/down dispositions of the ethyl groups in the synthetic precursor. Thus, using previously introduced notation,[2] the five conventional dl pairs of $C_6(CHXCH_3)_6$ are mapped onto R_0, R_1, R_{12}, R_{13}, and R_{14} ((1′*RS*,2′*RS*,3′*RS*,4′*RS*,5′*RS*,6′*RS*) : R_0; (1′*RS*,2′*SR*, 3′*SR*,4′*SR*,5′*SR*,6′*SR*) : R_1; etc.),[33] the two meso isomers[28] are mapped onto R_{123} (C_i) and R_{135} (S_6), and the pair of conformational cycloenantiomers corresponding to **1f** is mapped onto the enantiomeric pair R_{124}/R_{125}. There being no reason to believe that the desired product (**1f**) would be found in significant quantity among the eight possible diastereomeric products of photohalogenation,[34] we focused our efforts on a far less complex system.

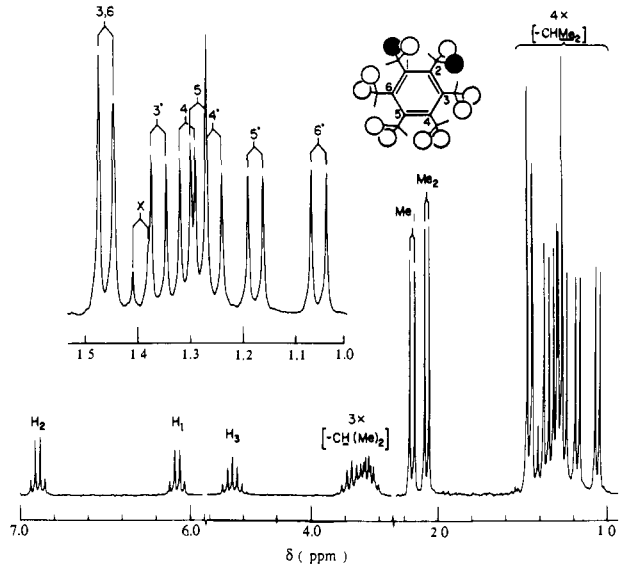

Figure 6. ^1H NMR spectrum of one of the two diastereomers of 1,2-bis(1-bromoethyl)-3,4,5,6-tetraisopropylbenzene (**2a**). Inset: isopropyl methyl region. The formula depicts the (1′*R*,2′*S*) isomer, with filled and open circles representing Br and CH_3, respectively. Resonances are assigned as described in the text.

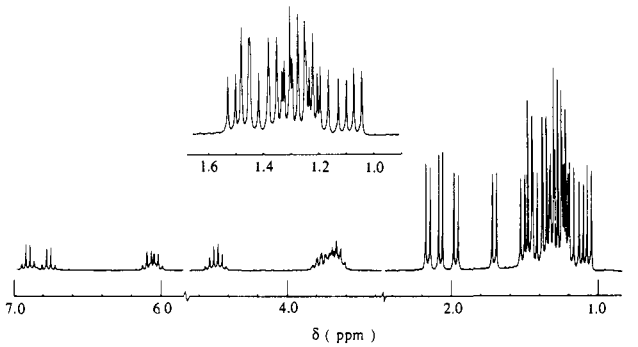

Figure 7. ^1H NMR spectrum of a diastereomeric mixture (**2a** + **2b**) of 1,2-bis(1-bromoethyl)-3,4,5,6-tetraisopropylbenzene. Inset: isopropyl methyl region.

1,2-Bis(1-bromoethyl)-3,4,5,6-tetraisopropylbenzene (**2**) can exist in only two diastereomeric forms: (1′*RS*,2′*SR*)-**2**, which consists of a pair of conformational cycloenantiomers of type **1a**, and (1′*RS*,2′*RS*)-**2**, which consists of a pair of conventional enantiomers.[33,35] Photobromination of 1,2-diethyl-3,4,5,6-tetraisopropylbenzene[36] yielded a mixture of the two diastereomers, **2a** and **2b** (Figure 5). Each is asymmetric on the NMR time scale, and each methyl or methine proton in the mixture should therefore give rise to a distinct NMR signal, barring accidental isochrony. This expectation is fully borne out in the α-bromoethyl

(28) In analogy to comparable cycloenantiomers,[6] the two achiral diastereomers of **1f** have C_i and S_6 symmetry.

(29) This mixture was obtained in 57% yield by reduction of the commercially available 3,6-dimethyloct-4-yne-3,6-diol. See: Nicholas, K. M.; Siegel, J. *J. Am. Chem. Soc.* **1985**, *107*, 4999.

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(31) The steric requirements of CH_3, Cl, and Br are of comparable magnitude. See: Hounshell, W. D.; Iroff, L. D.; Iverson, D. J.; Wroczynski, R. J.; Mislow, K. *Isr. J. Chem.* **1980**, *20*, 65 and references therein.

(32) NMR experiments are consistent with conformations of 1,2-bis(dichloromethyl)benzenes in which the $CHCl_2$ groups are statically geared, with the plane of the benzene ring bisecting the Cl–C–Cl angles. See: Mark, V.; Pattison, V. A. *Chem. Commun.* **1971**, 553. Hutton, H. M.; Hiebert, W. E.; Mark, V. *Can. J. Chem.* **1978**, *56*, 1261.

(33) The convention adopted for configurational descriptors of racemates is the one recommended by the IUPAC Commission on Nomenclature of Organic Chemistry, Section E (Stereochemistry), *Pure Appl. Chem.* **1976**, *45*, 13. Thus (1′*RS*,2′*RS*) denotes a racemate of (1′*R*,2′*R*) and (1′*S*,2′*S*), while (1′*RS*,2′*SR*) denotes a racemate of (1′*R*,2′*S*) and (1′*S*,2′*R*). Note that in comparing a pair of enantiomers, centers that are interconverted by reflection must carry the same number. See: Hirschmann, H.; Hanson, K. R. *Tetrahedron* **1977**, *33*, 891.

(34) According to Hopff and Wick,[30] the product of photohalogenation is the S_6 isomer. In preliminary experiments we found that photobromination of hexaethylbenzene (300 w, 5 h reflux in CCl_4) yields a product (90%, hexagonal plates, mp 208–212 °C dec after recrystallization from 3:1 CCl_4–C_6H_6) which consists of at least five components (TLC on silica, CCl_4–hexane eluent). Presumably these are all diastereomers of hexakis(α-bromoethyl)benzene.

(35) (1′*R*,2′*R*)- and (1′*S*,2′*S*)-**2** (Figure 5) are not cycloenantiomers because the pattern of configurational descriptors is not the same. Nevertheless, they fulfill the meso condition: reversal of ring directionality by transposition of ligands equivalent to inversion at C_t interconverts enantiomers. Rotation about the C_{ar}–C_t bonds results in homomerization.

(36) This hydrocarbon was isolated from the mixture obtained by cotrimerization of 3-hexyne and diisopropylacetylene in the presence of $Hg[Co(CO)_4]_2$.[26]

region of the ^1H NMR spectrum, which features four nicely separated methyl doublets at δ 1.70, 1.96, 2.06, and 2.15, and four methine quartets at δ 6.02, 6.07, 6.75, and 6.89. The isopropyl region is less well resolved: the 16 methyl doublets (eight from each diastereomer) at δ 1.04–1.52, the six methine septets (three from each diastereomer) at δ 3.6–3.9, and the two methine septets (one from each diastereomer) at δ 4.48 show up as overlapping multiplets.[37]

Attempts to separate the two diastereomers by HPLC or by recrystallization from a variety of solvents invariably resulted in selective decomposition of one (**2b**) with concomitant enrichment of the other (**2a**);[38] we were thus able to obtain **2a** free of **2b**, but not vice versa. Given the ^1H NMR spectrum of **2a** (Figure 6) the remaining lines in the spectrum of the mixture (Figure 7) could thus be assigned to **2b**. In general, the signals for **2a** are found downfield of the corresponding signals for **2b**. A ratio of **2a**:**2b** = 0.52:0.48 was found by integration of the methyl signals in the α-bromoethyl region (**2a**: δ 2.06, 2.15; **2b**: δ 1.70, 1.96) of the NMR spectrum in Figure 7.

The assignment of individual resonances in the ^1H NMR spectrum of **2a** (Figure 6) was made possible by the key observation that one of the isopropyl methine septets (δ 4.46) is shifted significantly downfield relative to the other three (δ 3.62–3.79). Undoubtedly this signal arises from the unique methine proton which is tucked into the cleft of a neighboring α-bromoethyl group and is thus strongly deshielded. Accordingly, this methine proton is assigned to the isopropyl group at position 3 (H_3). Irradiation of the signal at δ 4.46 collapses two doublets in the isopropyl methyl region, which can thus be assigned to the two methyls in the same isopropyl group (Me_3 and Me_3'), and results in NOE enhancement of the doublet at δ 2.06, which can thus be assigned to the methyl in the neighboring α-bromoethyl group (Me_2). The signal at δ 2.15 is therefore due to the methyl in the other α-bromoethyl group (Me_1). Irradiation of the quartet at δ 6.89 collapses the doublet at δ 2.06 and results in NOE enhancement of the doublet at δ 2.15; this quartet is therefore assigned to H_2. Irradiation of the quartet at δ 6.07 collapses the doublet at δ 2.15 and results in NOE enhancement of two doublets in the isopropyl methyl region; the quartet is therefore assigned to H_1 and the doublets to Me_6 and Me_6'. Irradiation of the most downfield of the doublets in the isopropyl methyl region (Me_3 + Me_6) results in NOE enhancement of the downfield septet in the group of three at δ 3.62–3.79, which is therefore assigned to H_4. Finally, irradiation of the signal due to H_4 collapses two doublets in the isopropyl methyl region, which are thus assigned to Me_4 and Me_4'. The remaining pair of isopropyl doublets are assigned to Me_5 and Me_5', and the two upfield septets in the region δ 3.62–3.79 are assigned to H_5 and H_6.

The preceding analysis, though made with reference to the (1′*R*,2′*S*) isomer depicted in Figure 6, applies with equal force to the (1′*RS*,2′*RS*) isomer. A distinction between the two diastereomers is therefore not possible on this basis. An attempt to identify the diastereomers by X-ray diffraction was vitiated by disorder in the crystal structure of **2a**,[39] and other NOE experiments designed to differentiate between **2a** and **2b** also proved unsuccessful. However, it was possible to assign configurations to the isomers on the basis of aromatic solvent-induced shifts (ASIS). It is well-known[40] that preferential shielding of protons trans to a polar group, relative to those located cis, leads to a positive differential shift. That is, $\Delta_{trans} - \Delta_{cis} > 0$, where $\Delta = \delta_{CHCl_3 \text{ or } CCl_4} - \delta_{C_6H_6}$. In Table I are listed solvent-induced shifts for protons in the α-bromoethyl groups of **2a** and **2b**. Inspection of the data clearly shows that the Δ's, especially those of the methyl protons, are significantly more positive in **2b** than they are in **2a**. These results indicate that the CH_3 in one α-bromoethyl group of **2b** is anti to the Br in the other, whereas in **2a** the CH_3 in one α-bromoethyl group is syn to the Br in the other. Accordingly, **2b** is identified as the (1′*RS*,2′*RS*) and **2a** as the (1′*RS*,2′*SR*) isomer (see Figure 5).

Table I. Aromatic Solvent Induced Shifts (ASIS) in Diastereomers of 1,2-Bis(1-bromoethyl)-3,4,5,6-tetraisopropylbenzene (**2**)

nucleus[a]	frequency[b] $CDCl_3$	frequency[b] C_6D_6	shift[c]
	2a		
H_2	1628.92	1725.36	−96.44
H_1	1505.99	1520.05	−14.06
Me_2	504.11	517.55	−13.44
Me_1	538.69	539.10	−0.41
	2b		
H_2	1621.70	1690.23	−68.53
H_1	1503.67	1508.18	−4.51
Me_2	519.40	491.45	+27.95
Me_1	485.87	426.64	+59.23

[a] Labels refer to the (1′*R*,2′*S*) isomer depicted in Figure 6 and to the corresponding (1′*R*,2′*R*) or (1′*S*,2′*S*) isomer. [b] In Hz at 250 MHz. [c] $\Delta = \delta_{CDCl_3} - \delta_{C_6D_6}$, in Hz.

This configurational assignment is consistent with the lower polarity of **2a**, the isomer with the higher rf value and the lower dipole moment (Experimental Section). A strong case can therefore be made that **2a** is a racemic mixture (or compound) of two conformational cycloenantiomers.

There is no sign of signal coalescence in the ^1H NMR spectrum of **2a** up to 180 °C, although extensive decomposition takes place at that temperature. With use of the Gutowsky–Holm approximation, a lower limit of $\Delta G^{\ddagger} = 24$ kcal mol^{-1} is calculated[41] for the conformational enantiomerization process. This result leaves no doubt that the conformational cycloenantiomers of **2a** are in principle separable and stable at room temperature.

Experimental Section

Solution 250.13-MHz ^1H and 62.83-MHz ^{13}C NMR spectra were recorded in benzene-d_6 at ambient temperature on a Bruker WM-250 spectrometer, unless otherwise indicated. Residual solvent resonances were used as an internal reference. Mass spectra were measured on an AEI MS-9 high-resolution mass spectrometer. High-performance liquid chromatography was done on a Waters Associates Prep LC/System 500 instrument with prepak 500 silica columns. Melting points were recorded on a Thomas Hoover melting point apparatus and are corrected. The elemental analysis was performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

1,2-Bis(1-bromoethyl)-3,4,5,6-tetraisopropylbenzene (2). A solution of bromine (0.32 g) in 5 mL of CCl_4 was added to a solution of 1,2-diethyl-3,4,5,6-tetraisopropylbenzene[36] (0.30 g) in 10 mL of CCl_4, and the well-stirred mixture was irradiated with a 60 w incandescent lamp at room temperature. A white precipitate of the dibromo product appeared within minutes, accompanied by vigorous evolution of hydrogen bromide. The reaction mixture was filtered after 10 min, and the residue was washed with CCl_4 (10 mL) and hexane (10 mL). Recrystallization from CCl_4 yielded white, shiny hexagonal plates (0.35 g, 77%), mp 198–200 °C dec. ^1H NMR δ 1.04–1.52 (multiplet of doublets, 24 H, $CH(CH_3)_2$), 1.70, 1.96, 2.06, 2.15 (quadruple doublets, 6 H, J = 7.27, 7.30, 6.97, 7.33 Hz, $CHBr(CH_3)$), 3.6–3.9 (m, 3 H, $CH(CH_3)_2$), 4.48 (overlapping septets, 1 H, J = 7.2 Hz, $CH(CH_3)_2$), 6.02, 6.07 (dq, 1 H, J = 7.30, 7.33 Hz, $CHBrCH_3$), 6.75, 6.89 (dq, 1 H, J = 7.28, 6.99 Hz, $CHBrCH_3$). See also Figure 7. ^{13}C NMR δ 21.47, 21.55, 22.47, 22.6–23.3, 23.44 ($CH(CH_3)_2$), 26.14, 26.70, 27.35, 27.78, 28.15 ($CH(CH_3)_2$ and $CHBrCH_3$), 45.57, 46.13, 47.48, 47.71 ($CHBrCH_3$), 138.56, 139.01, 140.38, 144.65, 147.62, 147.80, 147.90, 148.08, 149.19 (aromatic carbons). Mass spectrum (high resolution m/e 381.1968 ± 0.0038 (381.1981 calcd for

(37) The overlap of signals is much more pronounced in the ^{13}C NMR spectrum. Thus the α-bromoethyl methine carbons are the only ones to show the expected number of signals, in this case four, under the conditions of measurement.

(38) The lability of **2** is reminiscent of observations on (1-chloroethyl)-pentaethylbenzene: the ease with which this compound undergoes dehydrohalogenation has frustrated repeated attempts at isolation by chromatography on alumina or silica gel. See: Illuminati, G.; Mandolini, L.; Arnett, E. M.; Smoyer, R. *J. Chem. Soc. B* **1971**, 2206.

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$C_{22}H_{36}Br_2$). An analytical sample was prepared by recrystallization from hexane. Anal. Calcd for $C_{22}H_{36}Br_2$: C, 57.39; H, 7.83; Br, 34.78. Found: C, 57.97; H, 7.96; Br, 34.35.

The product mixture (rf values 0.5 (**2a**) and 0.4 (**2b**) by analytical TLC, eluent hexane) was subjected to HPLC, using 3% ethyl acetate-hexane (v/v) as eluent. This procedure resulted in the isolation of pure **2a** in addition to unidentified decomposition products of the other isomer. After recrystallization from benzene, **2a** had mp 203-205 °C dec. ^{1}H NMR δ 1.04-1.47 (multiplet of doublets, 24 H, $CH(CH_3)_2$), 2.06 (d, 3 H, J = 6.98 Hz, $CHBrCH_3$), 2.15 (d, 3 H, J = 7.35 Hz, $CHBrCH_3$), 3.62-3.79 (m, 3 H, $CH(CH_3)_2$), 4.46 (septet, 1 H, J = 7.19 Hz, $CH(CH_3)_2$), 6.07 (q, 1 H, J = 7.32 Hz, $CHBrCH_3$), 6.89 (q, 1 H, J = 6.99 Hz, $CHBrCH_3$). See also Figure 6. ^{13}C NMR δ 21.50, 22.49, 22.59, 22.71, 22.77, 23.16, 23.37 ($CH(CH_3)_2$), 26.17, 26.71 ($CHBrCH_3$), 27.81, 28.19 ($CH(CH_3)_2$), 47.49, 47.73 ($CHBrCH_3$), 139.04, 140.41, 144.67, 147.81, 148.11, 149.23 (aromatic carbons).

Both diastereomers decompose slowly in $CHCl_3$ or CH_2Cl_2 solutions, and more rapidly in tetrachloroethene or on exposure to light. They are relatively stable in CCl_4 or hydrocarbon solutions, but repeated recrystallization of the mixture invariably resulted in preferential decomposition of **2b**.

Dipole moments were determined for two solutions of mixtures of **2a** and **2b** in benzene at room temperature.[42] Mixtures containing 64 and 84% of **2a** had μ = 2.92 and 2.81 D, respectively. The calculated dipole moments of **2a** and **2b** are therefore 2.72 and 3.25 D, respectively.[43]

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(42) We thank Professor E. N. DiCarlo for these measurements.

(43) Dipole moments calculated by the empirical force field method (MM2) are 1.71 and 3.45 D for (1'*RS*,2'*SR*)- and (1'*RS*,2'*RS*)-**2**, respectively.

Total Synthesis of (±)-Granaticin

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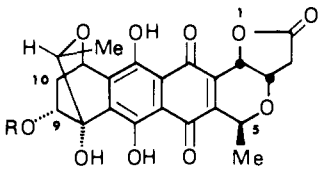
Abstract: A 20-step total synthesis of (±)-granaticin from tetralone **8** is described. Conversion of **8** to allylic alcohol **15** followed by a catalytic osmylation afforded triol **16** in a highly stereoselective manner, which was then cyclized to benzooxabicycle **18** through the agency of benzylic bromination with NBS. The intermediate **18** was efficiently converted to cyanophthalide **22**, and its annulation with 5-*tert*-butoxy-2-furfurylideneacetone afforded naphthyl ketone **25**. Reduction of **25** to a carbinol and subsequent pyranocyclization provided a diastereomeric mixture of hexacyclic compounds, **26a,b** and **27a,b**, which could be separated by HPLC. The predominant isomers **26a** and **26b**, whose structures were determined by X-ray crystallography and NMR spectroscopy, were subjected to two-step *O*-demethylation (oxidation with ceric ammonium nitrate to dimethoxy-1,4-naphthoquinones and subsequent treatment with $AlCl_3$-Et_2S) to provide (±)-granaticin (**1**) and its diastereomer **30**, respectively.

The antibiotic granaticin (**1**) was first isolated in 1957 from the culture of *Streptomyces olivaceus*[1a] and since has been detected in a number of other actinomycetes along with granaticin B (**2**),[1b] the α-L-rhodinoside of **1**, and dihydrogranaticin (**3**).[1c-e,2] Granaticin is highly active against Gram-positive bacteria and protozoa and exhibits some activity against P-388 lymphocytic leukemia in mice (T/C 166% at 1.5 mg/Kg) and cytotoxicity against KB cells (ED_{50} 1.6 μg/mL).[1d,3] The glycoside **2** shows a distinct inhibition of various transplanted tumors in rodents after intraperitoneal application.[4] Granaticin has been reported to inhibit RNA synthesis in bacteria by the failure to charge leucyl-*t*RNA.[5a] The cytotoxicity of **1** is attributed to inhibition of ribosomal RNA maturation.[5b]

A novel feature of the molecular structure of **1**, which had been determined by a combination of chemical degradations and an X-ray crystallographic analysis in 1968,[6] is the attachment of two oxygen-containing heterocycles at each side of the naphthazarin ring. These residues, the 2-oxabicyclo[2.2.2]oct-5-ene system



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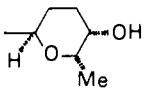
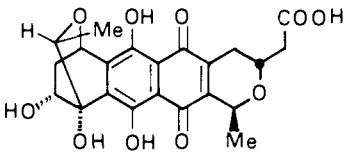
2, R = 



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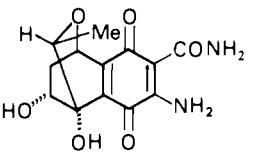

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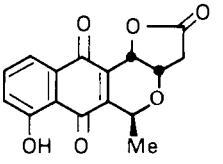

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