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CHEMICAL CONSEQUENCES OF CONFORMATION IN MACROCYCLIC COMPOUNDS

AN EFFECTIVE APPROACH TO REMOTE ASYMMETRIC INDUCTION[1]

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Abstract—In this paper we show that the conformational properties of medium- and large-ring organic molecules have profound consequences on the stereochemical course of their chemical reactions. Kinetic enolate alkylations, dimethylcuprate additions and catalytic hydrogenations were examined on a variety of monosubstituted 8- to 12-membered macrocyclic ketones and lactones, and the diastereomeric composition of the products was determined. In many systems a single Me substituent provided enough conformational bias to allow highly stereoselective formation of new asymmetric centers. The diastereoselection exhibited by the reactions investigated appears to be intimately associated with the conformational properties of the macrocyclic substrates employed since simple molecular mechanics calculations allowed semiquantitative prediction of the product distributions in every case.

The intricate stereochemical relationships among the substituents which adorn the numerous complex acyclic and macrocyclic compounds found in nature have fascinated organic chemists ever since the structures of the compounds began to be elucidated in the 1950's. These compounds have attracted synthetic chemists in particular and, starting twenty or so years ago, researchers began to consider seriously the preparation of these molecules by total synthesis. Although great strides have been made in recent years, further development requires improved solutions to many of the problems associated with the synthesis of these compounds. One obvious concern is stereochemical control. Although vicinal asymmetric centers may be controlled effectively by internal or relative asymmetric induction, the establishment of correct relationships between widely separated or remote asymmetric centers presents more of a problem.

Almost without exception,[2] current synthetic approaches to stereochemically complex acyclic and macrocyclic natural products rely on some form of absolute stereochemical control to set up remote diastereomeric relationships. This absolute stereochemistry typically originates from some readily available enantiomerically pure starting material, from resolution of an intermediate, or more interestingly from asymmetric induction by an enantiomerically pure reagent. Although each of these approaches has its strengths, each also has inherent problems, and effective alternatives are clearly needed.

In this paper we describe a general and viable alternative to absolute stereocontrol methods for the construction of remote stereochemical relationships. This alternative involves the direction of reaction stereoselectivity by preexisting substrate chirality which may be quite distant from the reaction site.[3] Although such remote asymmetric induction would not be expected to be particularly effective if it operated by a direct interaction between widely separated centers of asymmetry, effective control might originate from a conformational bias which could be provided to a substrate by remote chirality. This type of control is of course common in cyclohexane-derived ring systems where axial-equatorial preferences are often used for stereochemical control in synthesis. We have been studying the reactions of simple monosubstituted medium- and large-ring compounds in the anticipation that conformationally controlled stereoselection might be a common feature of these systems.[4] In the remaining sections of this introduction some of the reasons for this expectation are presented and an appropriate reaction model with predictive capabilities is described.

Conformations of macrocycles. As revealed by dynamic NMR measurements,[5] X-ray crystallography[6] and semi-empirical molecular mechanics calculations,[7] the structures of medium- and large-ring molecules are very different from what is suggested by the floppy necklaces of atoms produced by conventional molecular models. Although macrocyclic compounds are usually capable of existence in a number of stable conformations, only a few of these conformations are low enough in energy to be appreciably populated at normal temperatures. Even-membered macrocycles have received the most study and, at least for the cycloalkanes, conformational near-homogeneity has been seen in rings as large as cyclohexadecane.[8] Odd-membered cycles tend to exist in less symmetrical forms with smaller energy differences between stable conformations.[9]

From the outset there are a number of things that can be stated about the geometries of simple macrocyclic compounds and their potential for the control of remote diastereomeric relationships. First of all, macrocycles tend to exist in conformations having as few transannular nonbonded repulsions and high-energy torsional arrangements as possible. A simplistic view of cyclooctane for example rationalizes its occurrence largely in a boat–chair (BC) conformation with two eclipsed ethane linkages (darkened) rather than the alternative chair–chair (CC) conformation having four such linkages or the boat–boat(BB) conformation having an additional serious transannular repulsion. Likewise cyclodecane prefers the

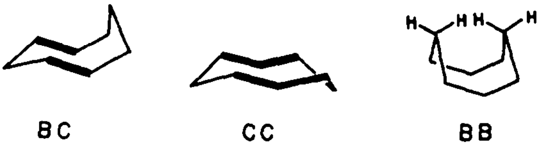


Fig. 1

boat–chair–boat conformation (BCB) having all staggered linkages over the all-chair conformation (CCC) which has four eclipsed ethane segments.

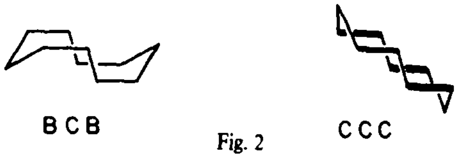


Fig. 2

Substituted or functionalized derivatives typically have very similar structures which may be rationalized by a closer look at cyclooctane and cyclodecane. Although replacement of a methylene by say a CO group could lead to five different conformations of BC-cyclooctanone and three different conformations of BCB-cyclodecanone, one conformation is significantly more stable in both cases.[10] That conformation is the one that replaces the C3 methylene by a CO group and thus relieves a particularly serious transannular nonbonded repulsion (shown in the structures below as dotted lines). As in six-membered rings, substituents usually prefer pseudoequatorial environments. However, some interesting and provocative differences between cyclohexane and macrocycles are apparent. The table below was calculated by molecular mechanics using Allinger's MM2 force field[11] and shows the energy cost of moving a Me group into the pseudoaxial position at each of the five nonequivalent sites on cyclooctane and the three nonequivalent sites on cyclodecane.

	Methyl position	Cyclooctane	Cyclodecane
Pseudo A-values	1	1.8	6.6
for Methyl	2	2.8	0.0
(Kcal/mole)	3	>4.5	9.2
	4	−0.3	
	5	6.1	

For most sites, energy differences are so large that axial substitution is effectively forbidden. Thus to the extent that a substituent can be localized at a particular site, the equilibrium conformation of the system may usually be predicted with confidence. Sites 4 and 6 in cyclooctane and sites 2, 5, 7 and 10 in cyclodecane are unusual in that no energetic penalty seems to be associated with axial substitution at those sites. This situation actually derives from the presence of a gauche–butane interaction in both the axial and the equatorial environments and results in the circumstance that gem-disubstitution strongly favors conformations having the two substituents at such corner sites.

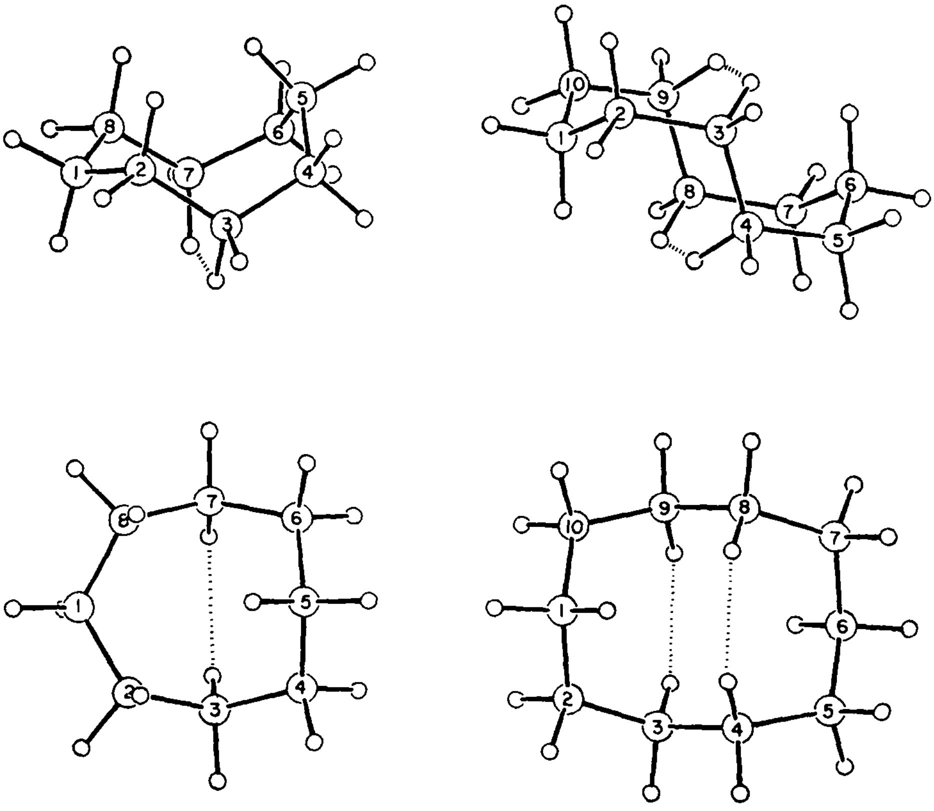


Fig. 3

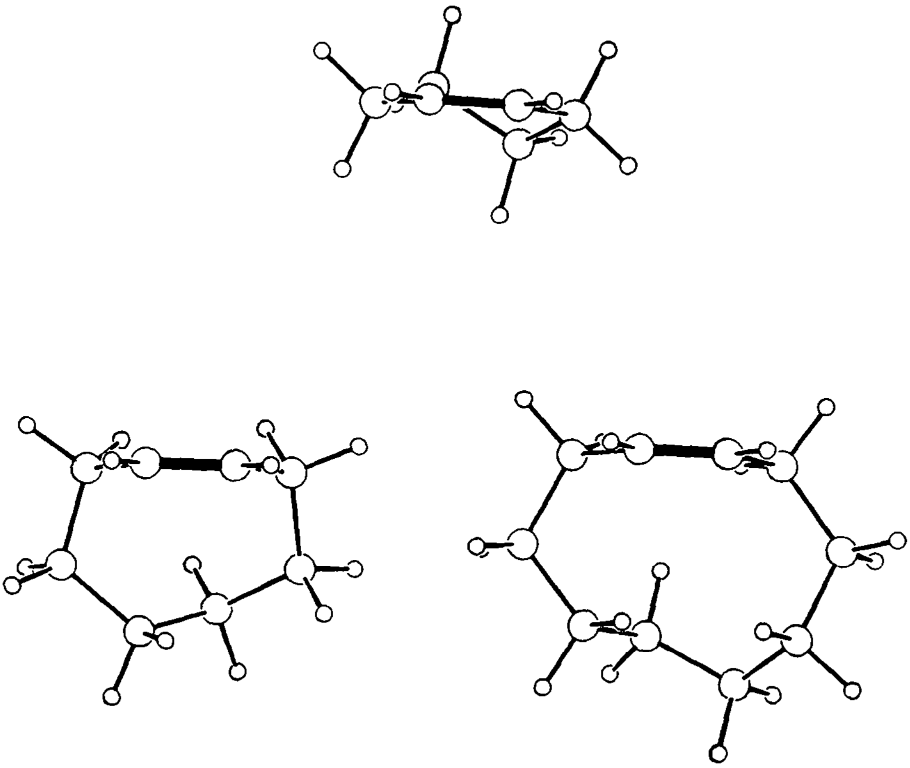


Fig. 4

The conformational biasing described above for the derivatives of cyclooctane and cyclodecane tends to be a general property of macrocyclic compounds and arises from the pronounced tendency of these molecules to minimize transannular nonbonded repulsions. Since, however, our primary interest here is relative asymmetric induction, we must now examine the relation of conformation to stereoselection in these systems. Experience tells us that while conformational biasing may be a necessary requirement for the control of nonadjacent stereochemistry, it is not a sufficient one. 6-Membered rings for example are generally well-biased by a single substituent; however, the stereoselectivity associated with their reactions is nearly always significantly less than that suggested by the A-value of the biasing substituent. This situation is often a result of the fact that the two diastereotopic faces of normal-sized rings are not overwhelmingly different, and thus most reactions do not tend to be stereospecific with regard to a particular conformation of the ring. Functionalized macrocycles on the other hand typically have 3-dimensional structures which are significantly different from normal rings in that sp^2 centers tend to stand perpendicular to the plane of the ring where important transannular nonbonded interactions are minimized. This conformational arrangement and its consequences may be seen by comparing the lowest energy structures of 6-, 8-, and 10-membered *cis*-cycloalkenes from a vantage point where the olefinic linkages (thickened) are viewed edge-on (Fig. 4).

It is clear from these views that the two faces of the olefinic π-systems in *cis*-cyclooctene and *cis*-cyclodecene are sterically very different. Since one face of the π-system is severely hindered by the disposition of the allylic C–C bonds as well as by transannular methylene groups, it would be expected that various addition reactions would occur largely or perhaps exclusively from the less hindered, peripheral face of the olefinic linkage.[12] This anticipated preference for peripheral attack of external reagents coupled with the expectation of efficient conformational biasing by ring substituents leads one to conclude that high relative asymmetric induction in the reactions of substituted macrocyclic compounds might be a general phenomenon. In the pages which follow, we test the above expectation by examining the stereoselectivity of several addition reactions on monosubstituted 8- through 12-membered ring compounds. It will be shown that high asymmetric induction is in fact a common feature of these systems.

Methods. The experiments we report here involve addition reactions of monomethylated 8-, 9- and 10-membered cyclic ketones and 9- through 12-membered lactones. The reactions examined most completely in these systems are the kinetic enolate alkylation (a. $LiNiPr_2$, b. MeI) of saturated ketones and lactones, and catalytic hydrogenation (H_2, Rh/Al_2O_3) and conjugate addition of dimethylcuprate (Me_2CuLi or $Me_2CuLi\text{-}BF_3$) to α,β-unsaturated ketones and lactones. Products were analyzed to determine diastereomer ratios by capillary VPC (25 meter flexible silica column, Carbowax 20M), ^{13}C NMR and high field (250 or 300 MHz) ^1H NMR. Assignments were made by either unambiguous synthesis via the coupling of enantiomerically pure fragments, by symmetry arguments from NMR, or by intercorrelations among products. Rationalization of the stereochemical identity of the observed products is another matter however. While high diastereoselection may be more the rule than the exception in macrocyclic rings systems, the important ability to predict product stereochemistry requires a detailed knowledge of perhaps unfamiliar substrate conformations and energies. For this purpose we propose computational molecular modeling by semiempirical molecular mechanics. The computational form of molecular model shares few of the deficiencies associated with its mechanical counterpart and can supply complete three-dimensional structural information as well as approximate energies. Although simple inspection of computed structures provides much insight into the observed stereoselectivities, we have opted for a slightly more complex scheme of modeling in order to be able to forecast product distributions semiquantitatively.

Since most of the reactions we have studied are kinetically controlled, transition state structures and energies ideally should be calculated. Molecular mechanics is not intended for this purpose however. Therefore, a very simple model was chosen for comparing stereoisomerically related transition states, which assumes that those pathways leading smoothly from relatively low-energy starting geometries to relatively low-energy product conformations will be preferred. We thus choose least motion reactions connecting a starting material conformation with a closely related product conformation and ignore those reaction pathways either starting from or leading to highly strained conformations of reactants or products. By assuming exclusive peripheral attack and calculating the strain energies of conformationally related starting materials and products (MM2 force field),[11] it is possible to predict product distributions based on starting material energies (early transition state) or product energies (late transition state).[13]

RESULTS

8-Membered rings. As indicated by the examples below, kinetic alkylation (a. $LiNiPr_2/THF$; b. MeI −60°) of simple cyclooctanone enolates proceeds with high stereospecificity and with yields greater than 90%. The molecules shown were measured by capillary VPC with standardization by authentic mixtures of diastereomers. The identities of the products were determined by reduction of 1 to a dl-alcohol ($LiAlH_4$, >90%), showing two different $CH{-}CH_3$ molecules in the proton NMR,[14] and by Baeyer–Villager oxidation of 2 to a 9-membered lactone (CF_3CO_3H, >90%) whose structure was proven by alternative synthesis from optically active fragments (see below). The kinetic nature of the product distributions was verified by base equilibration of 1 and 2 to 53:47 and 63:37 cis:trans diastereomeric mixtures respectively. The high diastereoselectivity observed in the reactions on these substrates stands in marked contrast to the 60:40 to 80:20 mixtures typically obtained in related to 6-membered ring alkylations. The results are also of considerable interest in relation to the various possible conformations of the enolates which lead to them. Shown below are the structures and strain energies of likely intermediates in the kinetic enolate alkylation of 2-methylcyclooctanone. It is clear that the relatively low energies of enolates 1A and 1C could be used to rationalize the observed preference for the formation of the trans product. A distinction between these two pathways cannot be made at this point but it would not be surprising if the transannular interaction which develops as 1C is alkylated would tend to promote reaction by enolate 1A. A similar analysis of the alkylation of 3-methylcyclooctanone sheds light on this point:

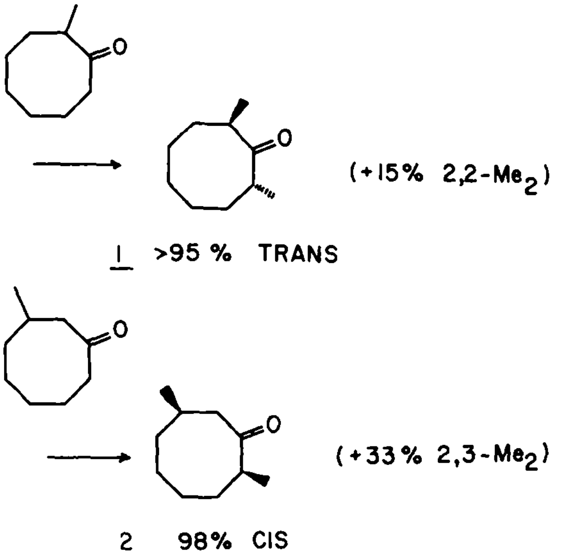


Fig. 5

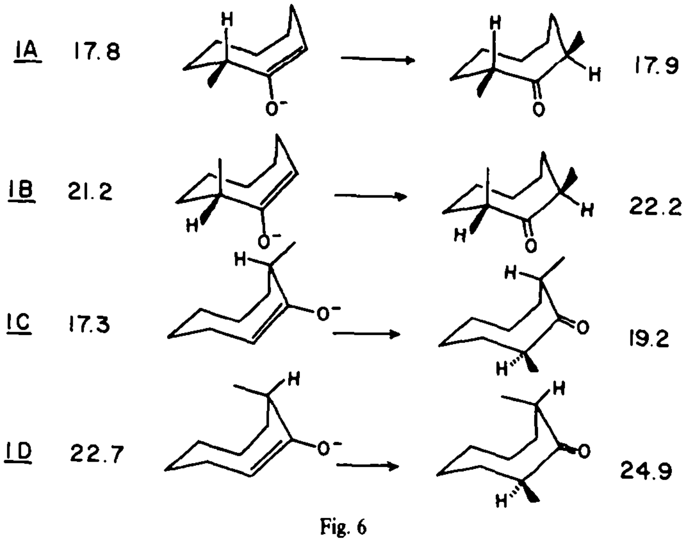


Fig. 6

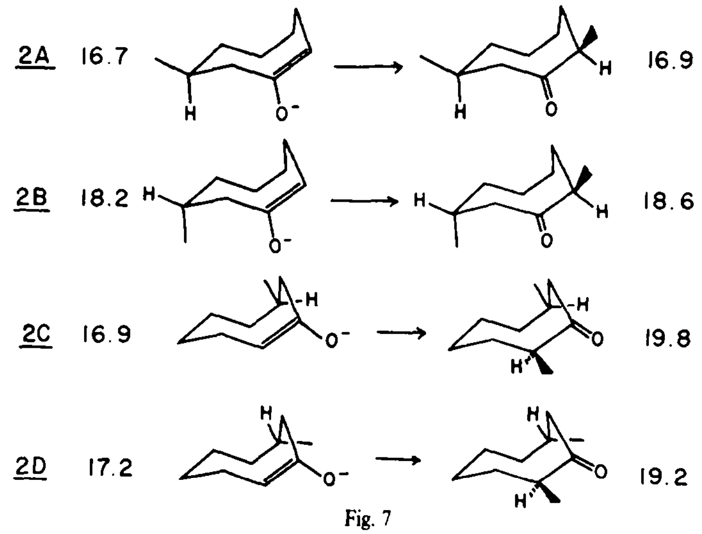


Fig. 7

It is clear that the 98% selectivity for the *cis* product is not adequately explained by starting enolate energies alone. If, however, the developing transannular strain associated with alkylation of **2C** and **2D** is taken into account either by considering the strain energies of enolates **2A** and **2B** only or by considering the energies of all the direct products, then a Boltzmann distribution at −60° gives the observed ratio exactly. Here we have chosen the former alternative for calculating product distributions in enolate alkylations for two reasons. First, previous studies of kinetic enolate methylations seem best interpreted in terms of an early reactant-like transition state[15] and second, the best fit of experiment to theory in other macrocycles is found when the diastereomer ratios are based on enolate strain energies. The stronger correlation of product distributions with enolate energies than with product energies should not be taken, however, to have mechanistic significance at this point, since it results in part from differences in the Van der Waals energy functions used for alkoxide and CO oxygen (experimental).

The addition of lithium dimethylcuprate (Et_2O, 0°) to 8-methylcyclooct-2-en-1-one results in the clean formation of a single adduct (72%) which is diastereomeric with **2**. This reaction may not be interpreted in terms of typical 8-ring boat-chair conformers discussed previously since these do not have sufficient overlap of the enone π-systems. The trans product may be formed however by peripheral attack on either of the two lowest conformations of cyclooctenone (below) which lead directly to relatively low energy conformations of the product enolates. Alternative conformations having pseudoaxial methyl substituents are essentially excluded by severe transannular nonbonded interactions (>4 kcal) in both starting materials and products.

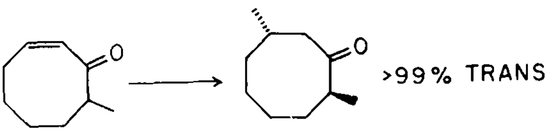


Fig. 8

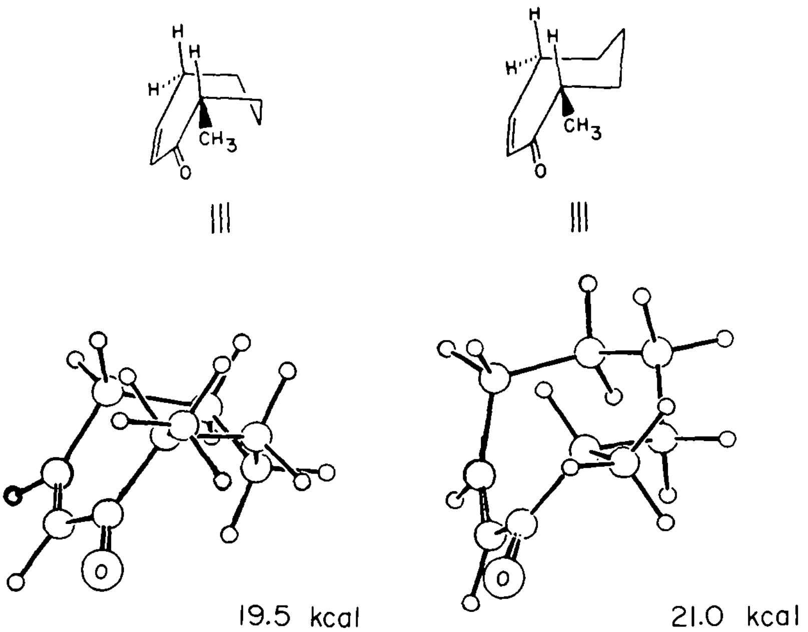


Fig. 9

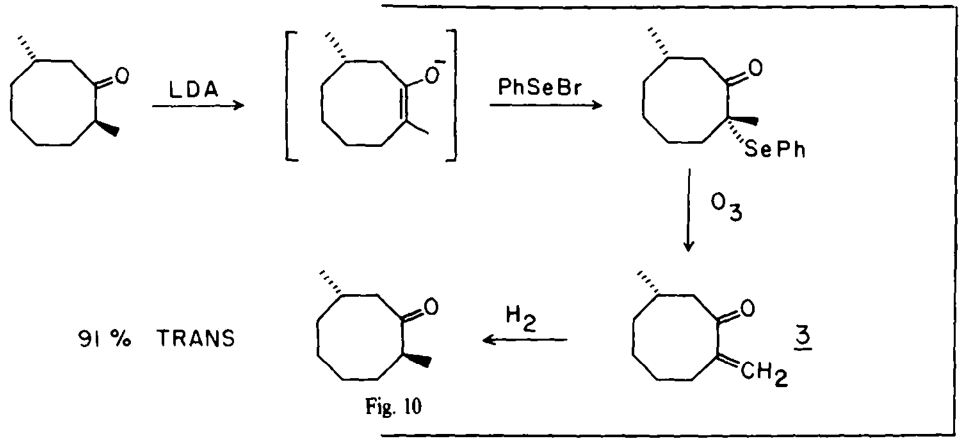


Fig. 10

The final reaction which we have examined in an 8-membered ring is catalytic hydrogenation of the α-methylene cyclooctanone **3**. The preparation of this material is of interest in itself. Under conditions believed to be kinetic (excess $LiNiPr_2$, THF, −40°), the major enolate formed turns out to be the more substituted one[16] which is subsequently treated with phenylselenenyl bromide (from PhSeSePh and Br_2) at −78° to give very largely a single α-ketoselenide. The *trans*-dimethyl stereochemistry is tentatively assigned by analogy with the alkylation leading to **2**. Kinetic selection for the more substituted enolate is obviously unusual but may be explained by consideration of low energy conformations of the starting ketone. If it is assumed that only hydrogens which are perpendicular to the C=O can be removed (thus H_α and $H_{\alpha'}$ are candidates) and furthermore that transition states leading to highly strained *trans*-cyclooctene structures will be strongly disfavored (thus $H_{\alpha'}$ may not be removed), then the low strain of the 16.4 kcal conformation would favor a reaction pathway leading to the more substituted enolate. Note also that the 19.9 kcal structure maintains its primary source of strain—a transannular H-Me interaction—along the entire reaction pathway and thus would be relatively strained regardless of the position of the transition state. This conformational effect would therefore appear to largely override the usual 1.5–3 kcal kinetic bias for deprotonation at the less substituted site.[17]

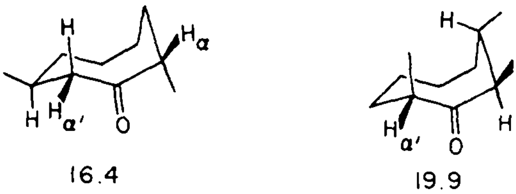


Fig. 11

Hydrogenation of the enone **3** with rhodium on alumina proceeds almost quantitatively and yields a 10:1 mixture of *trans*:*cis* 2,7-dimethylcyclooctanones. The four relevant conformations of the starting material **3** are shown along with their calculated strain energies, and a Boltzmann distribution over these four states would predict a product ratio of 70:30 *trans*:*cis*. This relatively poor correspondence does not however take into account the fact that hydrogenation of **3C** and **3D** proceeds with development of a severe transannular H-Me interaction during rehybridization of the methylene group. A similar rehybridization of **3A** or **3B** on the other hand leads smoothly to a product-like species having axial substitution at an energetically favorable corner site on the ring. A Boltzmann distribution between **3A** and **3B** only then leads to an expected product ratio of 93:7 *trans*:*cis*.

9-*Membered Rings*. Kinetic alkylation of 2-methylcyclononanone (a. $LiNiPr_2$, THF; b. MeI) leads without appreciable stereoselection to a 52:48 mixture of the *cis*- and *trans*-dimethylcyclononanones.[18] In contrast, dimethylcuprate adds to both the *cis*- and *trans*-cyclononenones[19] shown to yield largely *trans*-2,8-dimethylcyclononanone[20] (yields 74% and 93% respectively).[21] These cuprate additions are particularly interesting reactions since it is quite difficult to rationalize formation of the *trans*-dimethyl product using mechanical molecular models. Strain-energy minimized structures of low energy enone and product enolate conformations do lead however to the observed product distributions. For example, *trans*-enone **6** has the two lowest energy conformations shown in Fig. 14 (**6A** and **6B**). The strain energies of 27.8 and 29.9 kcal/mol are for the conformations shown while the values in parentheses, 30.4 and 30.5 kcal, are for closely related conformations in which the asymmetric C9 carbon has been inverted (i.e. the C9–Me and the C9–H are exchanged). Starting material energies are obviously not directly related to the stereochemistry of the products since peripheral cuprate addition to the most stable conformation of the enone would yield the *cis*-dimethylcyclononanone. However, if the identities of the atoms in the starting materials are redefined to give the product enolate with an added β-substituent (e.g. the darkened Me), then consideration of the resulting strain minimized structures does lead to the observed products. Thus while conformation **6B** is ap-

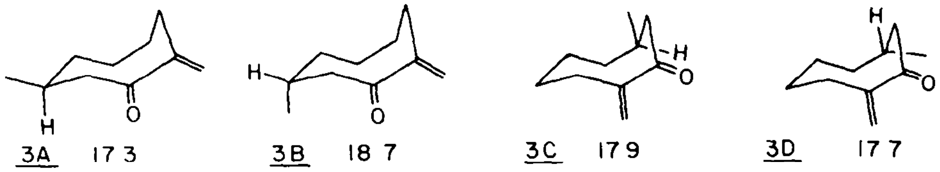


Fig. 12

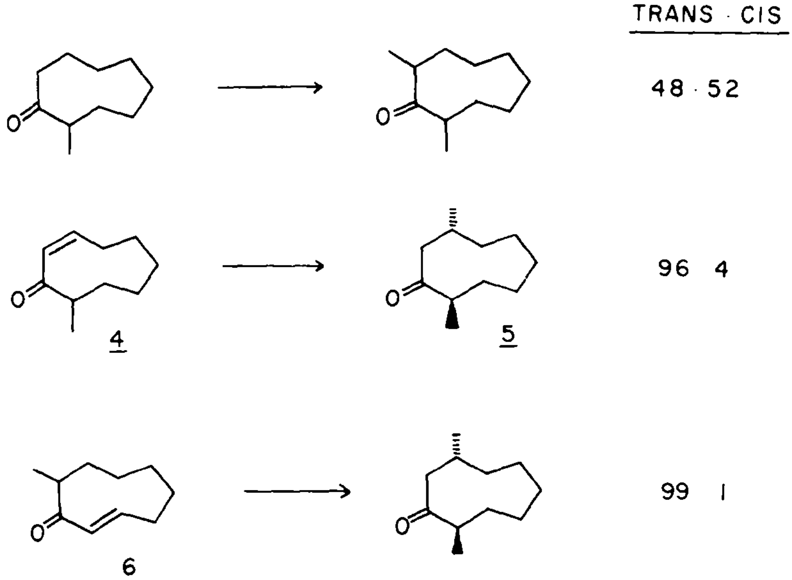


Fig. 13

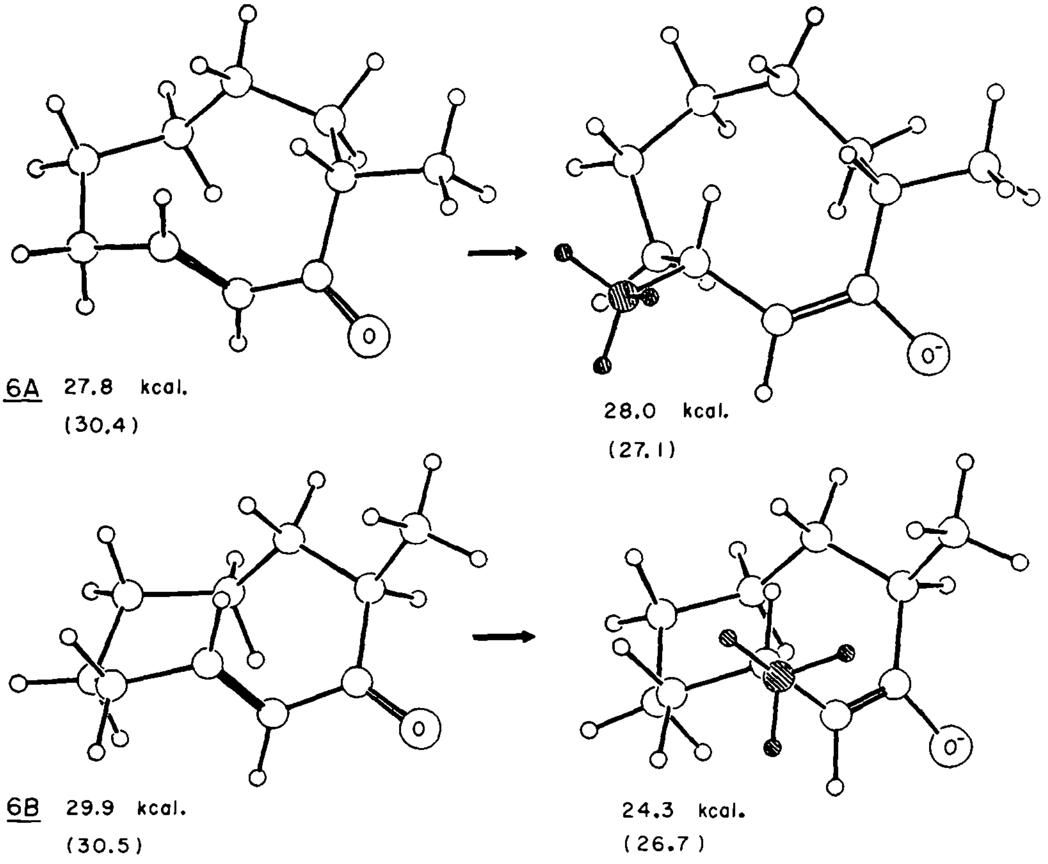


Fig. 14

proximately 2 kcal higher in energy than the lowest energy structure **6A**, its conjugate addition reaction is accompanied with the loss of 5 kcal more strain than is associated with a similar reaction of the more stable **6A**. The observed results (99% *trans*) are thus modeled here by a relatively late transition state with a Boltzmann distribution based on product enolate energies at 0° which predicts slightly greater than 99% *trans* product. In this paper, all calculations on cuprate addition reactions were modeled in this way—first by finding all low energy enone conformations (up to ≃4 kcal excess strain), then by redefining the conformation as the product enolate, by minimizing the strain energy once more, and finally by calculation of a Boltzmann distribution based on those product enolate energies. Assumption of exclusive peripheral attack then gives a product diastereomer ratio. Such a calculation for **4** predicts a 99:1 *trans*:*cis* product ratio. A potential alternative model based on the strain energy of either ground state starting enones or of starting enones having their π-systems forced into planarity does not lead to the observed product ratios.

9-Membered lactones also show substantial asymmetric induction in the systems we have examined. Lactone **7** (prepared from 2-methylcyclooctanone with CF_3CO_3H, 75% yield) gave exclusively the *cis*-dimethyl derivative **8** in better than 95% yield on treatment with lithium diisopropylamide and methyl iodide. The relative stereochemistry of **8** was determined by homologation[22] and correlation with a 10-membered lactone (**22**) whose structure was proven by unambiguous synthesis from enantiomerically pure fragments. Calculation of the product distribution for enolate alkylation based on the relative strain energies of the *Z*-enolates gives an expected *cis*:*trans* ratio of 99:1. Our calculations on this and other macrolactones suggest a large preference for kinetic formation of the enolate geometry which is *cis* with respect to the ring olefin. A similar preference is well-documented in acyclic ester deprotonations,[23] and in the present case the isomeric transoid enolate is calculated to be much more highly strained.

As will be demonstrated, cuprate additions and catalytic hydrogenations typically give complementary product stereochemistries in macrocyclic systems. This result would be expected if the reactions proceed by peripheral attack of Me on one hand and H on the other and involve the same basic conformation of the substrate. The reactions of **9** and **11** above provide an example of this situation. The relative stereochemistry of **10** and **12** follows from an alternative synthesis of the LAH reduction product of **10** in its optically active form starting from (*R*)-citronellol and (*S*)-propylene oxide[24] as shown below. The stereoisomeric diols could be distinguished by high resolution ^{13}C NMR.

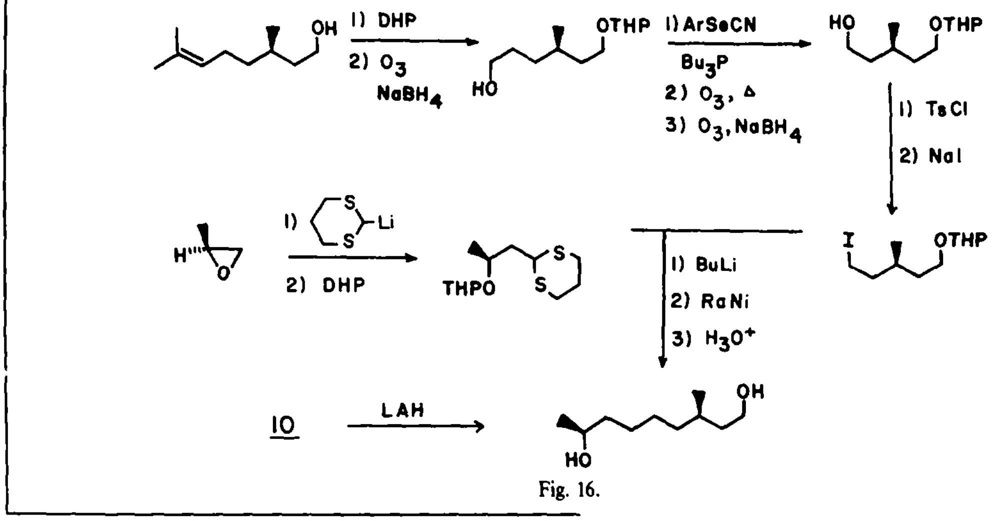


Fig. 16.

As with many other odd-membered rings, a number of relatively low energy conformations of *cis*-unsaturated 9-membered lactones seem to be possible. The most stable structures which we could find are shown in Fig. 17. Using the calculation procedure described above, this set of conformations leads to a 97:3 *cis*:*trans* prediction for the cuprate addition to **9** and a 90:10 *trans*:*cis* prediction for the hydrogenation of **11**. The hydrogenation ratio here and those to follow were calculated from the strain energies of the starting unsaturated carbonyl compounds which had their π-systems constrained to planarity. While there are other ways to calculate hydrogenation results, this method is the most simple and gives an acceptable correlation with experimental ratios in all the systems which we have examined thus far.

10-Membered Rings. Like 2-methylcyclononanone, 2-methylcyclodecanone gives very close to a 1:1 mixture of diastereomers on kinetic enolate alkylation with methyl iodide. Dimethylcuprate additions (Et_2O, 0°)

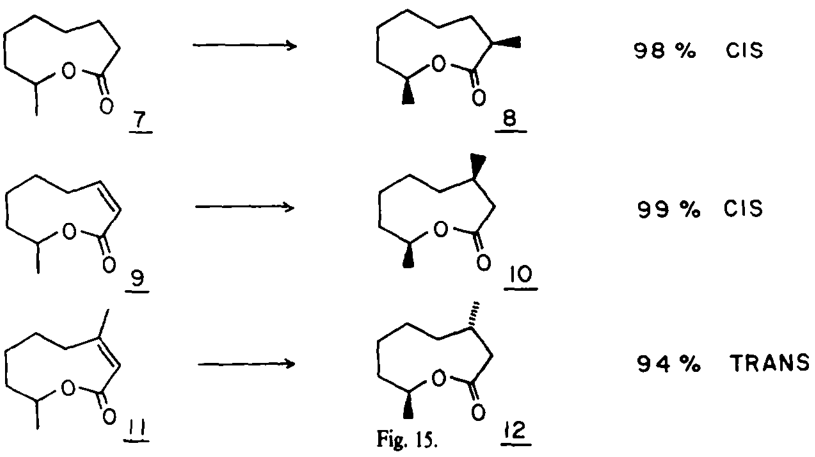


Fig. 15.

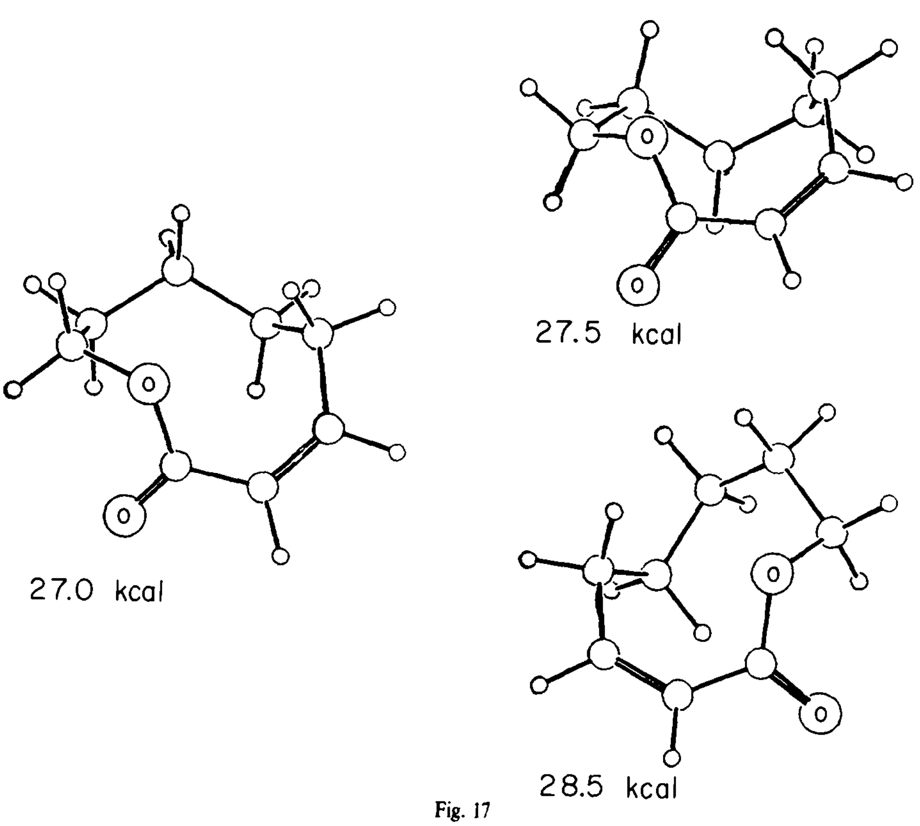
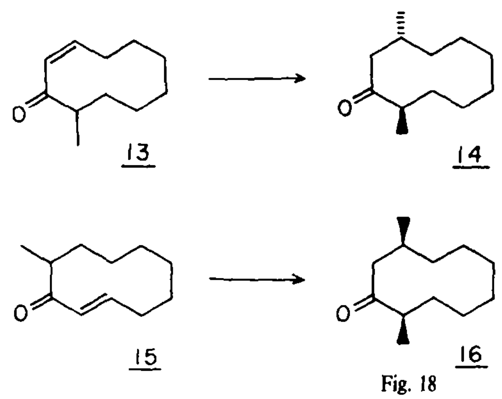


Fig. 17

however continue to provide high diastereoselection although the results are qualitatively different from those observed in the cyclononenone additions. Thus *cis*-10-methylcyclodecenone gives *trans*-2,9-dimethylcyclodecanone (76% yield) while *trans*-10-methylcyclodecenone gives the corresponding *cis* dimethyl product (75% yield). As with all the other dimethylcuprate addition reactions we have examined, it is possible to improve significantly the stereoselectivity of the addition by using a boron trifluoride-catalyzed variant[25] of the reaction at −78°. In the case of **15**, stereoselection for the *cis* isomer **16** increased to better than 99% (>95% yield). The stereochemical assignments follow from Baeyer–Villager oxidation of **16** with trifluoroperacetic acid in methylene chloride to an 11-membered lactone which was synthesized alternatively from (*R*)-citronellol and (*S*)-propylene oxide along lines[26] similar to those described in the structure proof of **10**. Calculated ratios show good correspondence with observation and reflect reaction largely by the usual BCB conformations of the cyclodecenones shown in Fig. 19. These systems are both interesting and relatively complex. While there are at least four conformations of **13** within 2 kcal of the lowest energy one, there are at least six relatively low energy conformations of **15** (and the most stable of these is 0.5 kcal less strained than the BCB structure shown below). It turns out however that the strain energy of most of these conformers rises substantially on conjugate addition, and the BCB structures (and to some



CIS : TRANS	
Exp	Calc
94:6	93:7
6:94	3:97

Fig. 18

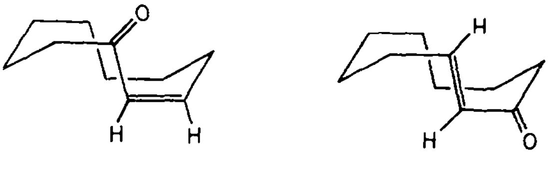
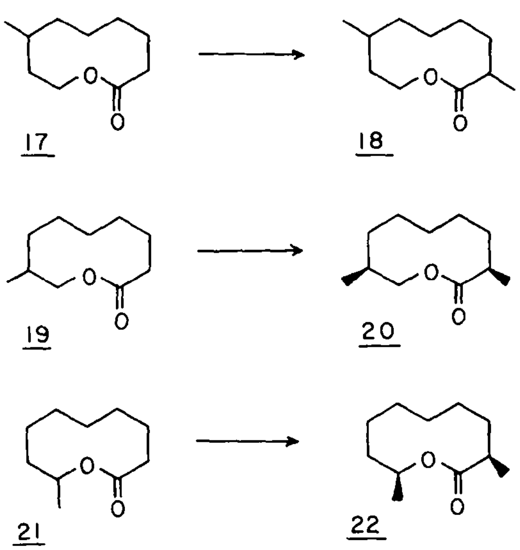


Fig. 19

extent their CCB cousins) thus seem to contribute overwhelmingly to the lowest energy reaction pathway.

In order to better define those conformations involved in our reactions, we have examined the diastereoselectivities associated with variously methylated derivatives of the same macrocycle much as we did with the cyclooctanones. These studies were carried out on 10-membered lactones. Kinetic enolate methylation of 7-, 8-, and 9-methylnonanolides prepared by the methods of Borowitz[27] and Wakamatsu[28] gives the results shown below with stereochemical assignments being made by alternative syntheses from optically pure materials.



CIS : TRANS Exp (yield)	Calc
~50 50 (>90%)	38:62
86 14 (>90%)	85:15
>99 1 (>90%)	99:1

Fig. 20

Although stereoselectivity clearly falls as the distance between the enolate and the controlling asymmetric center increases, molecular mechanics calculations provide further insight into the observed product ratios. First of all, it is possible to rationalize formation of the observed major products using the most stable conformation (BCB) of the 10-membered lactone enolate. For the 9-methylated enolate, axial substitution (1,3 Me–H interaction) is preferred over equatorial substitution (1,3 Me–O⁻ interaction), and the 2,9-dimethyl alkylation product is *cis*. The 8-methyl enolate clearly should favor equatorial substitution and would therefore give rise to the *cis* 2,8-dimethyl product. The 7-methylated derivative is an interesting case in that a Me at the C7 corner position has a single gauche-butane interaction whether it is axially or equatorially disposed. The negligible A-value at C7 would therefore imply the observed result of no stereoselectivity. Semiquantitative agreement with experiment requires the additional consideration of the slightly higher energy CCB conformation which molecular mechanics calculations indicate to contribute 5–15% of the product.

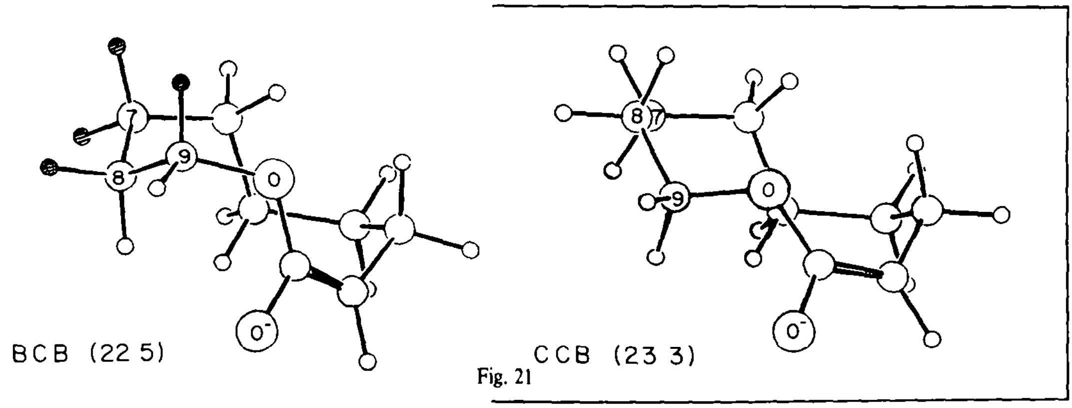
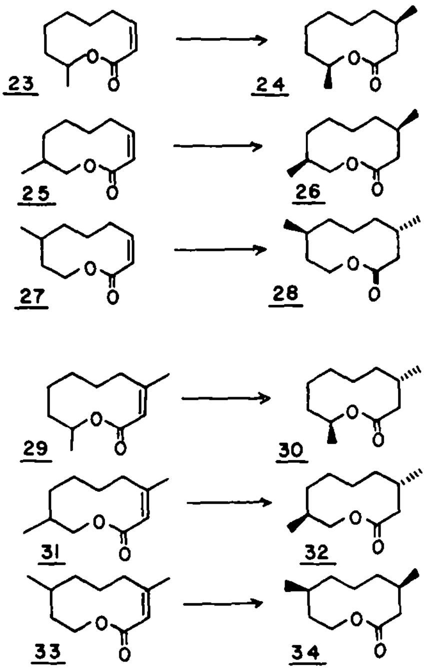


Fig. 21

The α,β-unsaturated lactones which are shown in Fig. 22 were prepared from their saturated analogs via enolate selenation, oxidation and selenoxide elimination.[29] These compounds on reaction with lithium dimethylcuprate (Et_2O, 0°) or with hydrogen (Rh/Al_2O_3, MeOH) gave the corresponding dimethyl lactones with the indicated stereochemistry. The assignments again follow unambiguously via alternative synthesis from (*S*)-propylene oxide and either (*R*)-citronellol or (*R*)-β-hydroxyisobutyric acid. Synthetically, the individual results are not particularly interesting except for the reactions of the 9-methylated substrates and for the single boron trifluoride-catalyzed dimethylcuprate addition (*). From a mechanistic standpoint, however, the uniformly complementary product distributions obtained from methylation and hydrogenation would again suggest uniformity both in the stereochemical mode of reagent attack and in the conformation(s) of the substrate. Strain energy calculations support this picture. As in some of the previous examples, the lowest energy conformations of the unsaturated lactones, the BCB and BCC forms shown below, appear not to contribute to the product distribution. The lack of reactivity toward both cuprate addition and, interestingly, catalytic hydrogenation probably results from the particularly poor enone π-overlap which is characteristic of these conformations. While overlap may be forced, the resulting loss of ester resonance and other distortions produce roughly 10 kcal of excess strain. Energetically less expensive alternatives are available, however, in the form of other low energy conformations of the enone which do have planar π-systems. After excluding the BCB and BCC forms below, the next two lowest energy conformations of the *cis*-nonenolide ring do have nearly planar π-systems and are shown below. Although higher energy forms may contribute to some extent, strain energy calculations for the cuprate addition and the hydrogenation over all the low energy forms we could find suggest that 85–95% of the product in each case is derived from the two structures shown in Fig. 24. The major product in each example may result from peripheral addition to the 25.9 kcal conformer with C7, C8 or C9 substitution in its most stable environment (darkened). Correspondence between experimental and calculated product distributions is quite acceptable within the context of our rather crude transition state models.



CIS : TRANS Exp (yield)	CIS : TRANS Calc
99:1 (82%)	94:6
80:20 (55%)	83:17
15:85 (68%) * 5:95 (70%)	28:72
9:91 (90%)	20:80
17:83 (90%)	14:86
83:17 (90%)	78:22

Fig. 22

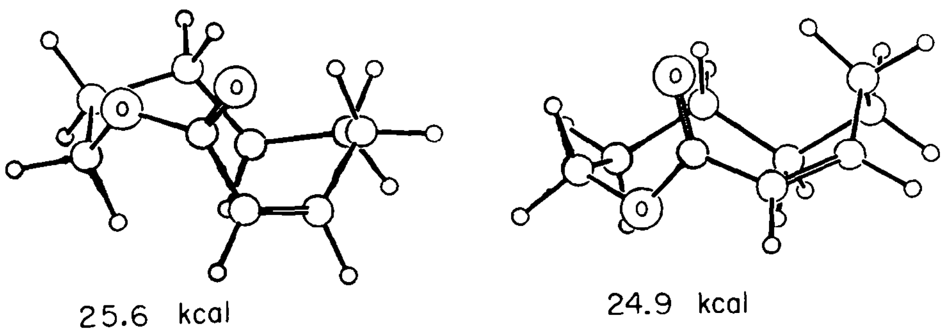


Fig. 23

Larger rings. In the examples above, our calculations suggest that the very high stereoselectivity associated with the reactions of 9-methyl 10-membered lactones is largely the result of several conformations giving rise to the

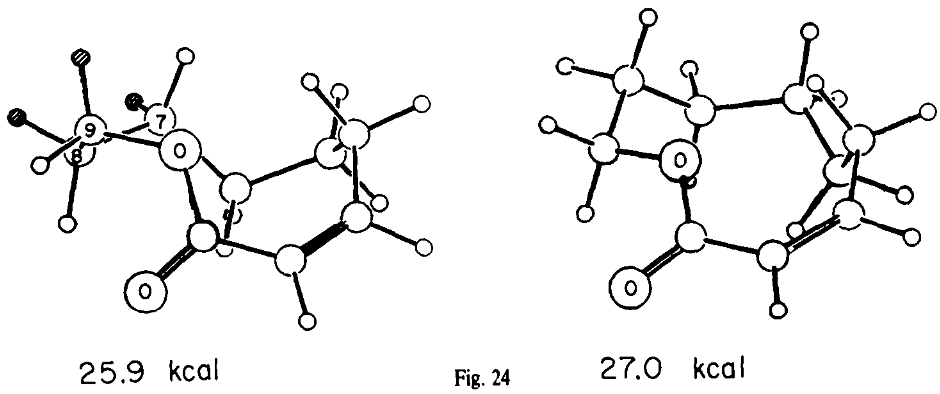


Fig. 24

same product. Although this situation could arise fortuitously, it may also be related to the presence of certain low energy conformational substructures in several reactive conformers which favor formation of some particular product. The substituted enolate below is

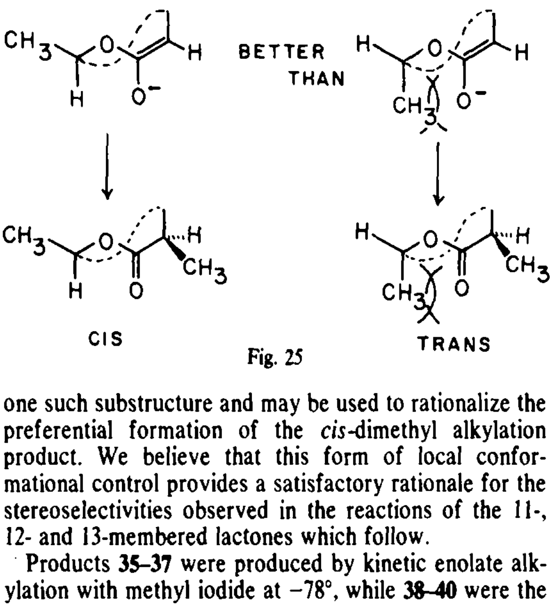


Fig. 25

one such substructure and may be used to rationalize the preferential formation of the *cis*-dimethyl alkylation product. We believe that this form of local conformational control provides a satisfactory rationale for the stereoselectivities observed in the reactions of the 11-, 12- and 13-membered lactones which follow.

Products **35–37** were produced by kinetic enolate alkylation with methyl iodide at −78°, while **38–40** were the result of a boron trifluoride-catalyzed dimethylcuprate addition also at −78°. Except for products arising from the 11-membered lactones, stereochemical assignments are tentative. Thus while **35** and **38** were identified by comparison with authentic materials prepared by Baeyer–Villager oxidation of *cis*-2,10-dimethylcyclodecanone and **16**, the remaining materials were assigned stereochemistry by trends established with the 9- through 11-membered lactones in diastereoselectivity and NMR chemical shifts. For lactone enolate alkylation products, the most obvious distinction was that the difference between the chemical shifts of the two Me substituents was always larger for the *trans*-dimethyl lactones. For dimethylcuprate adducts, the alpha methylene hydrogens typically appeared more widely separated in the trans-dimethyl isomer. These differences are tabulated below.

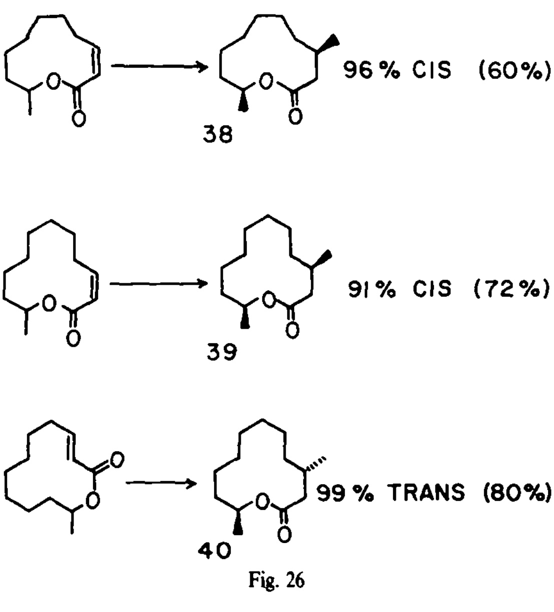


Fig. 26

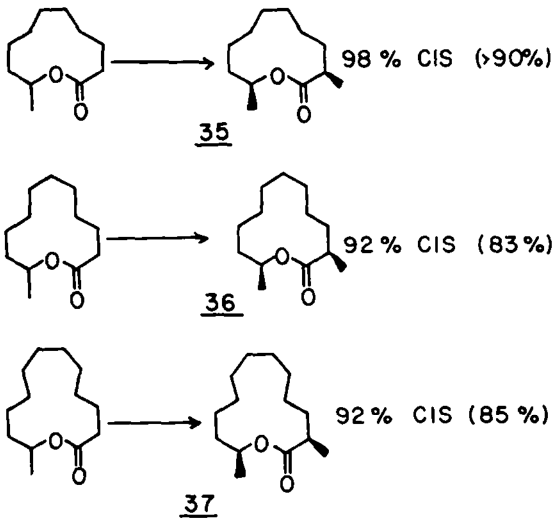
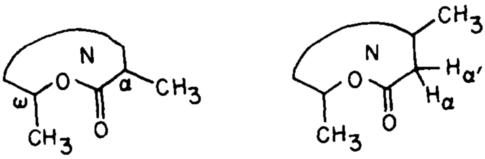


Fig. 27



	CH$_3$: $\delta_\omega - \delta_\alpha$		α-H: $\delta_\alpha - \delta_{\alpha'}$	
	cis	*trans*	*cis*	*trans*
			0.26	0.57
	0.11	0.19	0.24	0.50
	0.07	0.12	0.11	—
	0.01	0.09	0.05*	0.45*
N = 9	0.04*	0.10*		
= 10	0.01/	0.08*		
= 11				
= 12				

* = tentative assignment

Fig. 28

CONCLUSION

In the preceding paragraphs, we have described reactions which demonstrate that medium- and large-ring molecules have inherent conformational properties which make them valuable as a medium through which remote chiral centers may interact effectively. In the reactions outlined, this interaction has taken the form of kinetic diastereoselection which appears to rely on the conformational preferences of the substrate and on a uniformly high stereoselection of reagents for the peripheral mode of attack. Molecular mechanics calculations have proven useful in the rationalization of observed stereospecificities and appear to have predictive value for kinetic as well as thermodynamic (equilibration of ketones, enones, etc.) product distributions. Although the correspondence between calculated and experimental product diastereomer ratios is semiquantitative, our modeling of these kinetically controlled processes is quite crude and much improved ways for comparing stereoisomeric transition states with molecular mechanics are both needed and conceivable.

Synthetically, it is clear that macrocyclic intermediates have much potential as three-dimensional templates for use in the construction of complex arrays of asymmetric centers. Although the results described here involved only the simplest of substrates, elaboration of a substrate with additional chirality or other rigidifying elements (e.g. olefins, heteroatoms, gem-substituents) will generally reduce the number of low energy conformations available and thus improve stereospecificity. A great deal of control seems available and it should be possible to select strategically valuable conformations rationally by appropriate substitution and functionalization.

REPRESENTATIVE EXPERIMENTAL

8-Hydroxynonanoic acid lactone (**7**). To the mixture of 90% H_2O_2 (1 ml; 40 mmol) and 5 ml CH_2Cl_2 at 0° was added dropwise ($(CF_3CO)_2O$ 7 ml; 50 mmol). The resulting homogeneous soln containing trifluoroperacetic acid could be stored at −20° for several weeks. To a soln of 2-methylcyclooctanone (1.12 g; 8 mmol) in 8 ml of CH_2Cl_2 and buffered with anhydrous Na_2HPO_4 (7.1 g; 50 mmol) was added at 0° dropwise CF_3CO_3H solution (7 ml; 22 mmol). The resulting mixture was stirred at room temp for 5 hr, poured into water, washed with $NaHCO_3$aq and dried over $MgSO_4$. After removal of the solvents at reduced pressure, the oily residue was flash chromatographed using 4% EtOAc in petroleum ether to yield 890 mg (72%) of **7** as a transparent sweet-smelling oil (3% of starting material was recovered). IR (film) cm^{-1} 2940, 1730, 1450; PMR (CCl_4) δ 1.23 (d, 3H, J = 7 hz), 1.1–2.0 (m, 10H), 2.15 (m, 2H), 5.00 (m, 1H); MS (CI)*m/e* 157 (M + 1), 148 (M + 1 − H_2O), 111; tlc (silica gel, 5% EtOAc in pentane) R_f = 0.36.

2-Methyl-8-hydroxynonanoic acid lactone (**8**). To a soln of diisopropylamine (1.51 g; 15 mmol) in 20 ml THF at 0° was added 2.3 M BuLi soln in hexane (4.35 ml). After 10 min at 0° the mixture was cooled to −78° and a soln of **7** (930 mg; 5.95 mmol) in 1.5 ml of THF was added dropwise. To the resulting soln after 1 hr at −78°, a soln of MeI (1 ml; 15.5 mmol) in 2.5 ml anhyd HMPA was added all at once. The mixture was allowed to warm to 0°, poured into satd NH_4Claq and extracted with petroleum ether. The organic phase was washed with H_2O, brine, dried ($MgSO_4$) and evaporated to give 990 mg (98%) of **8** as a yellow oil, which was homogeneous by tlc and greater than 98% pure by VPC. IR (film) cm^{-1} 2940, 1725, 1455, 1260, 1080; PMR ($CDCl_3$)δ 1.153 (d, 3H, J = 7 hz), 1.260 (d, 3H, J = 7 hz), 1.2–1.9 (m, 10–12H), 2.52 (m, 1H), 5.11 (m, 1H); MS (CI) *m/e* 161 (M + 1), 153 (M + 1 − 18), 125; tlc (silica gel, 5% ethyl acetate in pentane) R_f = 0.42.

8-Hydroxynon-2-enoic acid lactone (**9**). To a soln of diisopropylamine (1.01 g; 10 mmol) in 10 ml THF at 0° was added BuLi in hexane (7.5 mmol). After 10 min at 0° it was cooled to −78° and a soln of **8** (780 mg; 5 mmol) in 2 ml THF was added dropwise. The resulting mixture was stirred at −78° for 1 hr and a soln of PhSeBr (7.6 mmol) [prepared from 1.56 g (15 mmol) of $(PhSe)_2$ and 620 mg (38 mmol) Br_2] in 10 ml THF was added in a single portion. A yellow soln formed and was allowed to warm to −40° and was poured into 100 ml sat NH_4Claq. The product was taken up in petroleum ether, washed with brine, dried ($MgSO_4$) and evaporated. The yellow residue was purified by flash chromatography on silica gel with 3% EtOAc in petroleum ether to give 1.92 g (93%) of the derived phenylselenide. 1.22 g of the phenylselenide was dissolved in 15 ml of CH_2Cl_2, cooled to −78° and ozonized until the blue color persisted. The soln was allowed to stand for 5 more min and then was purged with N_2 at −78° for 5 min, and then added gradually to 50 ml of refluxing CCl_4. After heating at reflux for 20 min the yellow soln was cooled, washed with dil HCl and dried with $MgSO_4$. After the removal of solvents at reduced pressure the oily residue was flash chromatographed on silica gel to give 441 mg (73%) of **9** as an oil. *Analytical*: IR (film) cm^{-1} 2920, 1700, 1450, 1260, 850, 730; PMR ($CDCl_3$) δ 1.0–1.8 (m, 6H), 1.35 (d, 3H, J = 7 hz), 1.8–1.3 (m, 1H), 3.05 (m, 1H), 4.95 (m, 1H), 5.80 (dd, 1H, J = 2, 11 hz), 6.45 (ddd, 1H, J = 7.9, 11 hz); MS (CI) *m/e* 155 (M + 1), 137 (M + 1 − 18), 109; tlc (silica gel, 5% EtOAc in pentane) R_f = 0.36.

3-Methyl-8-hydroxynonanoic acid lactone (**10**). To a suspension of CuI (1.52 g) in 10 ml anhydrous ether, 11 ml of 1.4M ethereal MeLi was added dropwise at 0°. The resulting fine yellow suspension was stirred at 0° for 20 min and a soln of **9** (308 mg; 2 mmol) in 1 ml anhydrous ether was added dropwise over a 1 hr period. After an additional hr at 0° the mixture was poured into 100 ml of sat NH_4Claq, and was extracted with petroleum ether. The organic extract was dried ($MgSO_4$), the solvents were removed, and the residue was flash chromatographed in 3% EtOAc in petroleum ether to give 282 mg of **10** as a transparent oil (89%). *Analytical*: IR (film) cm^{-1} 2940, 1740, 1450, 1250, 1040; PMR ($CDCl_3$) δ 1.020 (d, 3H, J = 7 hz), 1.274 (d, 3H, J = 7 hz), 1.2–1.85 (m, 9H), 2.001 (t, 1H, J = 12 hz), 2.261 (dd, 1H, J = 12.3 hz), 5.04 (m, 1H); MS (CI) *m/e* 171 (M + 1), 153 (M + 1 − 18), 111; CMR ($CDCl_3$) δ 20.82, 22.91, 24.49, 27.92, 32.65, 33.32, 34.77, 43.51, 71.78; tlc (silica gel, 5% EtOAc in pentane) R_f = 0.42.

3-Methyl-8-hydroxynon-2-enonic acid lactone (**11**). To a soln of diisopropylamine (202 mg; 2 mmol) in 2 ml THF at 0° was added 2.3Msoln of BuLi in hexane (0.65 ml). After 10 min at 0° the soln was cooled to −78°, and 158 mg of **10** in 0.5 ml THF was added dropwise. The resulting mixture was stirred at −78° for 1 hr and a soln of PhSeBr in 1 ml THF (from 375 mg (1.2 mmol) of $(PhSe)_2$ and 0.045 ml (0.8 mmol) of Br_2) was added as fast as possible. The yellow soln which formed was allowed to warm to −30° and was then poured into 50 ml sat NH_4Claq. After the usual workup and flash chromatography, 202 mg (63%) of a yellow phenylselenide was obtained. This phenylselenide (121 mg, 0.318 mmol) was dissolved in 10 ml CH_2Cl_2 and ozonized at −78° until the blue color appeared, and then it was allowed to stand for 5 additional min. The soln was then purged with N_2 at −78° for 5 min, added to 50 ml refluxing CCl_4, and refluxed for 20 min. After cooling to room temp it was washed with dil HCl, dried ($MgSO_4$) and the solvents were removed at reduced pressure. The residue was purified by flash chromatography in silica gel with 3% EtOAc in 97% petroleum ether to give 53 mg (85%) of **11**. *Analytical*: IR (film) cm^{-1} 2940, 1705, 1630, 1460, 1260, 980, 865; PMR ($CDCl_3$) δ 1.151 (m, 1H), 1.355 (d, 3H, J = 7 hz), 1.45–1.60 (m, 2H), 1.60–1.75 (m, 2H), 1.890 (m, 2H), 1.922 (d, 3H, J = 1.2 hz), 3.366 (broad t, 1H, J = 11 hz), 4.970 (m, 1H), 5.72 (t, 1H, J = 1.2 hz); MS (CI) *m/e* 169 (M + 1) tlc (silica gel, 5% EtOAc in pentane) R_f = 0.30.

Trans 3-methyl-9-hydroxynonanoic acid lactone (**12**). To a suspension of 5% Rh/Al_2O_3 (25 mg) in 1 ml MeOH was added **11** (17 mg). The mixture was hydrogenated at 14 psi for 2 hr at 0° and then was allowed to warm to 25°. The catalyst was filtered off and the solvent was removed at reduced pressure to give 17 mg (100%) of **12** (contaminated with 3.6% of *cis* isomer (VPC)). *Analytical*: IR (film) cm^{-1} 2950, 1735, 1450; PMR ($CDCl_3$) δ 0.981 (d, 3H, J = 7 hz), 1.261 (d, 3H, J = 7 hz), 1.31 (m, 1H), 1.35–1.70 (m, 6H), 1.80–1.95 (m, 1H), 1.965 (dd, 1H, J = 9, 13.5 hz), 2.270 (m, 1H), 2.540 (dd, 1H, J = 5, 13.5 hz) 5.119 (m, 1H); MS (CI) *m/e* 161 (M + 1), 153 (M + 1 − 18), 110 (M − 51); tlc (silica gel, 5% EtOAc in pentane) $R_f = 0.42$.

2-*Methylcyclodecanone* (**41**). To a soln of diisopropylamine (202 mg; 2.0 mmol) in 2 ml of THF at 0° was added a 2.4M solution of n-BuLi in hexane (0.63 ml; 1.5 mmol). After 10 min, the resulting LDA soln was cooled to −30° and a soln of cyclodecanone (308 mg; 2.0 mmol) in 0.5 ml THF was added dropwise. After 20 min at −30°, the soln was chilled to −60° and MeI(0.20 ml; 3.1 mmol) was added. The mixture was allowed to warm slowly to room temp and was partitioned between brine and petroleum ether. After drying ($MgSO_4$), the solvents were removed and the residue was purified by flash chromatography on silica gel with 2% EtOAc in petroleum ether to afford 204 mg (62%) of product and 94 mg (35%) of recovered cyclodecanone. *Analytical*: IR (film) cm^{-1} 2950, 1700, 1465, 1445, 1380; PMR ($CDCl_3$) δ 1.04 (d, 3H, J = 7 hz), 1.2–2.0 (m, 14H), 2.4–3.0 (m, 3H); MS (CI) *m/e* 169 (M + 1), 149, 109; tlc (silica gel, 5% ethyl acetate in pentane) $R_f = 0.42$.

(E)-10-*Methylcyclodec-2-en-1-one* (**15**) and (Z)-10-*methylcyclodec-2-en-1-one* (**13**). To a soln of diisopropylamine (404 ml; 4 mmol) in 3 ml THF at 0° was added dropwise a 2.4M BuLi soln in hexane (1.25 ml; 3 mmol). After 10 min at 0° the mixture was cooled to −30°, and a soln of 336 mg (2 mmol) of **41** was added. The resulting soln was chilled to −60°, and a soln of PhSeBr (from 936 mg of PhSeSePh (3 mmol) and 265 mg (1.6 mmol) of Br_2) in 2 ml THF was added in a single portion. The resulting mixture was allowed to warm to 0°. The yellow suspension was then partitioned between petroleum ether and brine. The organic phase was dried ($MgSO_4$) and the solvents were removed at reduced pressure. The residue was purified by flash chromatography on silica gel in 2% EtOAc—98% petroleum ether to afford 567 mg of a mixture of two phenylselenides (88%). A soln of 270 mg (0.89 mmol) of this mixture in 5 ml CH_2Cl_2 was treated with O_3 at −78° until the blue color persisted, and then it was allowed to stand at −78° for an additional 5 min. After purging with N_2 the resulting colorless soln was added to 20 ml refluxing CCl_4 and refluxed for 20 min. The resulting yellow soln was then washed with dil HCl, dried ($MgSO_4$) and the solvents were evaporated. The yellow oil residue was then purified by flash chromatography using EtOAc in petroleum ether (1:50), to afford 62 mg (45%) of (E)-10-*Methylcyclodec-2-en-1-one* (**15**) and 45 mg (33%) of (Z)-10-*methylcyclodec-2-en-1-one* (**13**).

Analytical (**15**): IR (film) cm^{-1} 2940, 1670, 1620, 1450, 970; PMR ($CDCl_3$)δ 1.087 (d, 3H, J = 7 hz), 1.2–1.9 (m, 10H), 2.1–2.25 (m, 1H), 2.25–2.4(m, 1H), 2.90 (m, 1H), 6.299 (d, 1H, J = 16.5 hz), 6.567 (dq, J = 6, 9, 16.5 hz); MS (CI) *m/e* 167 (M + 1), 149 (M + 1-H_2O); tlc (silica gel, 5% EtOAc in pentane) $R_f = 0.25$.

Analytical (**13**): IR (film) cm^{-1} 2950, 1685, 1625, 1460; PMR ($CDCl_3$) δ 1.0–1.6 (m, 8H), 1.131 (d, 3H, J = 7 hz), 1.70–190 (m, 1H), 1.90–2.05 (m, 1H), 2.397 (m, 1H), 2.560 (m, 2H), 5.762 (dq, 1H, J = 12, 9.5, 8 hz), 6.392 (d, 1H, J = 12 hz); MS (CI) *m/e* 167 (M + 1), 148 (M + 1 − H_2O); tlc (silica gel, 5% EtOAc in pentane) $R_f = 0.34$.

cis-2,9-Dimethylcyclodecanone (**16**). To a suspension of CuI (285 mg; 1.5 mmol) in 1.5 ml anhydrous ether at 0° was added dropwise 2M MeLi soln in ether (1.4 ml; 2.8 mmol). The resulting yellow suspension was stirred at 0° for 20 min and a soln of **15** (28 mg; 0.169 mmol) in 0.5 ml anhyd ether was added dropwise over 5 min. After 1 hr at 0° the mixture was poured into 50 ml sat NH_4Claq and extracted with petroleum ether. After the organic phase was dried with $MgSO_4$ and the solvents were removed under reduced pressure, the oily residue was purified by flash chromatography on silica gel using EtOAc in petroleum ether (1:50) to afford 25 mg (76%) of **16** contaminated with 5.7% of *trans* isomer. *Analytical*: IR (neat) cm^{-1} 2930, 1700, 1455, 1370; PMR ($CDCl_3$) δ 1.024 (broad d, 3H, J = 7 hz), 1.064 (d, 3H, J = 7 hz), 1.2–2.0 (m, 12H), 2.373 (m, 2H), 2.921 (m, 1H); MS (CI) *m/e* 183 (M + 1), 109; tlc (silica gel, 5% EtOAc in pentane)R_f = 0.42.

trans-2,9-*Dimethylcyclodecanone* (**14**). Following the procedure described in the previous section, **13** (39 mg; 0.236 mmol) gave **14** (33 mg; 75%) as an oil. *Analytical*: IR (film) cm^{-1} 2930, 1705, 1470, 1370. PMR ($CDCl_3$) δ 0.979 (d, 3H, J = 7 hz), 1.039 (d, 3H, J = 7 hz), 1.1–1.8 (m, 12H), 2.213 (dd, 1H, J = 4, 15.5 hz), 2.30 (m, 1H), 2.71 (dd, 1H, J = 10, 15.5 hz), 2.768 (m, 1H); MS (CI) *m/e* 183 (M + 1), 109 (M + 1 − 79); tlc (silica gel, 5% EtOAc in pentane) $R_f = 0.46$.

cis-2,9-*Dimethylcyclodecanone* (**16**) *via* BF_3Et_2O-*catalyzed* Me_2CuLi. To a suspension of CuI (95 mg; 0.5 mmol) in 0.5 ml anhyd ether at 0° was added a 2M MeLi soln in ether (0.37 ml; 0.75 mmol). After 20 min at 0° the yellow suspension was cooled to −78° and 141 mg (1 mmol) of BF_3Et_2O was added dropwise, followed by a soln of 16 mg (0.097 mmol) of 97.1:2.9 mixture of **15** and **13** in 0.2 ml anhyd ether. The mixture was then allowed to warm to 0°, and was partitioned between satd NH_4Claq and petroleum ether. The organic soln was dried with $NaSO_4$ and the solvents were removed under reduced pressure to afford 16 mg (98%) of 96.9:3.1 mixture of **16** and **14** by VPC. The spectral data of the major product were identical to those of **16** previously prepared.

trans-2,8-*Dimethylcyclooctanone* (**1**). To a soln of diisopropylamine (101 mg; 1 mmol) in 0.8 ml THF at 0° was added a 2.4M BuLi soln in hexane (0.31 ml; 0.75 mmol). After 10 min at 0° the soln was cooled to −30°, and 2-methylcyclooctanone (70 mg; 0.5 mmol) in 0.1 ml THF was added dropwise and the resulting soln was stirred at −30° for 30 min. After the mixture was chilled to −60°, MeI (0.14 ml; 2.16 mmol) was added and the soln was allowed to warm to 0° and was partitioned between satd NH_4Claq and petroleum ether. The organic phase was dried with $MgSO_4$ and the solvents were removed under reduced pressure to yield 72 mg (92%) of an 85:15 mixture of **1** and 2,2-dimethylcyclooctanone, from which **1** could be isolated in a pure state by careful flash chromatography using EtOAc in petroleum ether (1:50). *Analytical*: IR (film) 2940, 1700, 1450; PMR ($CDCl_3$) δ 1.057 (d, 6H, J = 7 hz), 1.3–1.8 (m, 10H), 2.664 (m, 2H); CMR ($CDCl_3$) δ 18.98, 24.49, 26.46, 34.56, 44.03; MS (CI) *m/e* 155 (M + 1), 127 (M + 1 − H_2O), 111; tlc (silica gel, 5% EtOAc in pentane) $R_f = 0.32$.

Calculation of product distributions. For the computation of diastereomeric ratios, two computer programs were used. The first of these was the MM2[11] molecular mechanics program written by N. L. Allinger and Y. H. Yuh and available from the Quantum Chemistry Program Exchange at Indiana University (QCPE Program No. 395). To the parameters supplied with the program were added the following constants for enolates and α,β-unsaturated esters:

Van der Waals: Stretching:

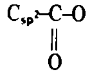
0^- $r^* = 2.20, e = 0.05$ C_{sp^2}–O^- $l_0 = 1.36, k_s = 6.0$

Torsion:	V1	V2	V3
$C_{sp^3}-C_{sp^2}=C_{sp^2}-O^-$	−0.2	16.25	0.0
$H-C_{sp^2}=C_{sp^2}-O^-$	0.0	16.25	0.0
$H-C_{sp^3}-C_{sp^2}-O^-$	0.0	0.0	0.54
$C_{sp^3}-C_{sp^3}-C_{sp^2}-O^-$	0.0	0.0	0.0
$C_{sp^2}-\underset{\substack{\Vert \\ O}}{C}-O-C_{sp^3}$	−2.5	1.4	0.0
$C_{sp^2}-C_{sp^2}-\underset{\substack{\Vert \\ O}}{C}-O$	1.0	1.0	0.0
$H-C_{sp_2}-\underset{\substack{\Vert \\ O}}{C}-O$	0.0	1.0	0.0
$C_{sp^3}-C_{sp^2}-\underset{\substack{\Vert \\ O}}{C}-O$	0.0	1.0	0.0

Bending

$C_{sp^2}{=}C_{sp^2}{-}O^-$ $\theta_0 = 120.0°$ $k_\theta = 0.50$

$C_{sp^3}{-}C_{sp^2}{-}O^-$ $\theta_0 = 124.0°$ $k_\theta = 0.50$


$C_{sp^2}{-}\underset{\underset{O}{\|}}{C}{-}O$ $\theta_0 = 120.0°$ $k_\theta = 0.50$

The constants above are not the result of an extensive parameterization and should only be considered as very crude. They were assigned to give the experimental barrier to rotation and conformer population to methyl acrylate[30] and also to fit equilibrium data for E, Z enolates of 3-pentanone[31], 2-methyl-3-pentanone and 4-methyl-2-pentanone.[32] For the enolates, Z, E energy differences are calculated to be 0.90, 1.0 and 0.80 kcal/mole respectively and compare to experimental values 0.90, 1.00, and 0.60. The only unusual value as we see it is our rather large Van der Waals value for alkoxide oxygen which attempts to take into account association with solvent, counterion, etc. A relatively large value for an anionic atom relative to the neutral counterpart has precedent in the relative A-values of $-SH$ and $-S^-$ (0.9 vs 1.3) and $-COOH$ and $-COO^-$ (1.3 vs 1.9).[33] It should be noted that use of the neutral oxygen radius (1.74) does not change any of the gross results here but only makes agreement with experiment slightly poorer in certain cases.

Initial geometries of macrocycles for energy minimization were either obtained from manual measurements on Dreiding molecular models or through the use of a ring-making computer program. This program exhaustively produces all combinations of sets of dihedral angles (resolution up to 10°) which result in formation of an N-atom cycle with reasonable closure bond distances and angles. The search for closure is a directed one which aborts most unproductive avenues of exploration (close contact of atoms, too few atoms to span remaining distance, etc) and thus can evaluate large sets of dihedral angles efficiently. Running on our PDP-11 VAX computer, the program can evaluate sets of dihedral angles at the rate of better than 500,000 conformations/sec for closure under various programmable constraints. Use of the program as it stands for searching out unfamiliar conformations of macrocyclic compounds has two problems. First, we do not have the ability to computationally remove near-duplicate conformations at this time. Second, the use of low resolution sets of dihedral angles to limit the generation of conformers can result in the missing of important conformations as can the use of too large transannular contact constraints. Although care was used in the search for initial conformations reported in this paper, we cannot be sure that other low energy conformers were not overlooked in some instances.

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[19] Compounds **4** and **6** were prepared by selenoxide elimination starting from 2-methylcyclononanone. The resulting mixture was separated by column chromatography on silica gel.

[20] The structure of **5** was assigned by Baeyer–Villager oxidation (CF_3CO_3H) to a 10-membered lactone (**30**) whose structure was proven by alternative synthesis from (*R*)-citronellol and (*S*)-propylene oxide.

[21] In the case of **6**, the reaction was effected using the boron trifluoride catalyzed dimethyl cuprate addition.[25]

[22] Homologation was effected as follows: (1) $LiAlH_4$; (2) $TsCl/C_5H_5H$; (3) NaCN/DMSO; (4) H_3O^+ and (5) thiopyridyl ester lactonization (E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.* **96**, 5614 (1974)).

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[26] Tetrahydropyranyl citronellol was treated with: (1) O_3, Me_2S; (2) $Ph_3P{=}CH_2$; (3) BH_3, NaOH, I_2; and (4) Jones reagent. The resulting iodoheptanoic acid was used to alkylate the anion prepared from (*S*)-propylene oxide[24] by reaction with: (1)

lithiodithiane; (2) dihydropyran; and (3) n-BuLi. The adduct was desulfurized (RaNi), hydrolyzed (HCl, H_2O), and lactonized as the thiopyridyl ester to give the Baeyer–Villager product of **16**.

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