THE CONFORMATIONALLY CONTROLLED

ALKYLATION OF 15-HEXADECANOLIDE

By

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B.Sc., The University of British Columbia, 1987

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES

DEPARTMENT OF CHEMISTRY

We accept this thesis as conforming

to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

August 1989

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ABSTRACT

The 16-membered lactone 17 was synthesized and alkylated to yield a 4:1 ratio of 20 and 19 respectively. The product ratio was rationalized by molecular mechanics calculations on 18.

A new polar map convention was developed for conformational analysis of cyclohexadecane.
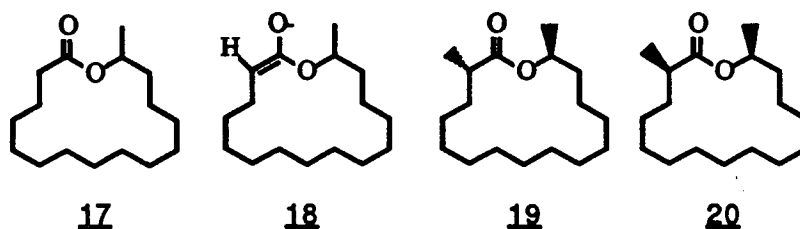
17   18   19   20

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LIST OF ABBREVIATIONS

ODP	oviposition-deterring pheromone
TBDMS	*tert*-butyldimethylsilyl
Ph	phenyl
Bn	benzyl
PMP	*para*-methoxyphenyl
Py	pyridine
THF	tetrahydrofuran
HMPA	hexamethylphosphoric triamide
DMH	*N,N*-dimethylhydrazone
LDA	lithium diisopropylamide
d.e.	diastereomeric excess
glc	gas-liquid chromatography
MCPBA	*meta*-chloroperoxybenzoic acid
LTMP	lithium 2,2,6,6-tetramethylpiperidide
pref	priority reflective
parf	priority antireflective
NMR	nuclear magnetic resonance
tlc	thin layer chromatography
IR	infrared
FT-IR	Fourier transform-infrared
LRMS	low resolution mass spectra
Anal. calcd	analysis calculated
DMPU	*N,N'*-dimethyl-*N,N'*-propylene urea
J	coupling constant
[H]	reducing agent

Me	methyl
ppm	parts per million
m	multiplet
t	triplet
d	doublet
s	singlet

ACKNOWLEDGEMENTS

I would like to thank Professor Larry Weiler for his guidance and support during this project.

The dedicated and friendly help of the NMR, mass spectroscopy and microanalysis staff were greatly appreciated.

Lastly, I would like to thank Dr. Charles Marais for performing the computer calculations.

INTRODUCTION

The plan for a natural product synthesis must contain a strategy for constructing the absolute and relative configuration of all chiral centers present. The oviposition-deterring pheromone (ODP) in the European cherry fruit fly, *Rhagoletis cerasi* L.,[1] illustrates a common problem (see Figure 1). As drawn, the starred chiral centers have the absolute configuration (8*S*, 15*R*). If two chiral centers are close, the synthetic strategy could involve asymmetric induction, but if the chiral centers are
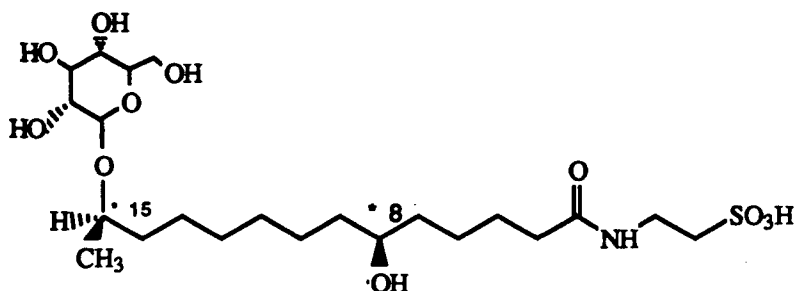
Figure 1. The oviposition-deterring pheromone in *Rhagoletis cerasi* L..[1]

far apart, the strategy usually involves coupling optically active fragments which may be made from optically active starting materials, from resolution of racemic intermediates, or from asymmetric synthesis using optically active reagents. In Ernst and Wagner's synthesis of ODP, two optically active fragments were coupled (see Figure 2).[1] The asymmetry in fragment A was derived from poly-(*R*)-3-hydroxybutanoate and the asymmetry in fragment B through the Sharpless epoxidation.[2] Although absolute asymmetric synthesis will produce the desired stereoisomers, it can be lengthy if no convenient, chiral starting

material or convenient, chiral reagent is available, and wasteful if 50% of a racemic mixture is discarded after a resolution.
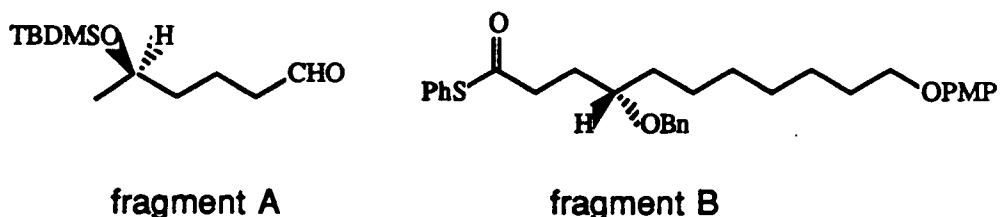

fragment A   fragment B

Figure 2. Fragments used in the synthesis of ODP by Ernst and Wagner.[1]

In 1981, Still and Galynker reported an alternative to absolute asymmetric synthesis for the construction of widely separated chiral centers.[3] This approach uses the conformational bias of macrocycles to transmit chiral information across many atoms. Barton used the term "long-range conformational transmission of chiral information" to describe steroidal reactions in which a chiral center controlled the reactivity at another center many atoms away.[4] The chiral center forced the steroid ring system to adopt a conformation which affected the reactivity at a distal center. Macrocycles with rigid conformations can transmit stereochemical information in a similar manner. This strategy is versatile because racemic starting materials and achiral reagents can be used.

Before we can predict which reactions will be stereoselective, we must understand the effect a chiral center has on the conformation of a functionalized macrocycle. Electrophilic and nucleophilic additions to sp^2 centers are the conformationally controlled reactions studied the most. Molecular mechanics calculations indicate that an existing chiral center forces a macrocycle to adopt conformations in which π-systems

are perpendicular to the plane of the ring.[3] These conformations are favoured because non-bonded, transannular interactions are eliminated if a hydrogen atom pointing to the interior of the ring is replaced by a π-bond perpendicular to the ring. Achiral reagents are able to differentiate the faces of a π-system because one face is blocked by the ring. Still and Galynker have referred to this phenomena as "peripheral attack of the reagent".[3]

The following examples of long-range conformational transmission of chiral information were taken from the recent literature. Each of the four reactions discussed proceeded with large diastereomeric excess which was rationalized by conformational analysis of a macrocycle.

The synthesis of (+)-aspicilin by Quinkert et al. involved a rare 1,8-asymmetric induction to setup the required configurations at C-1 and C-6.[5] Diisobutylaluminum 2,6-di-tert-butyl-4-methylphenoxide (Yamamoto's reagent)[6] reduced ketone 1 to alcohol 2 with a large diastereomeric excess while lithium tri-sec-butyl borohydride (L-Selectride) yielded alcohol 3 almost exclusively (see Figure 3).

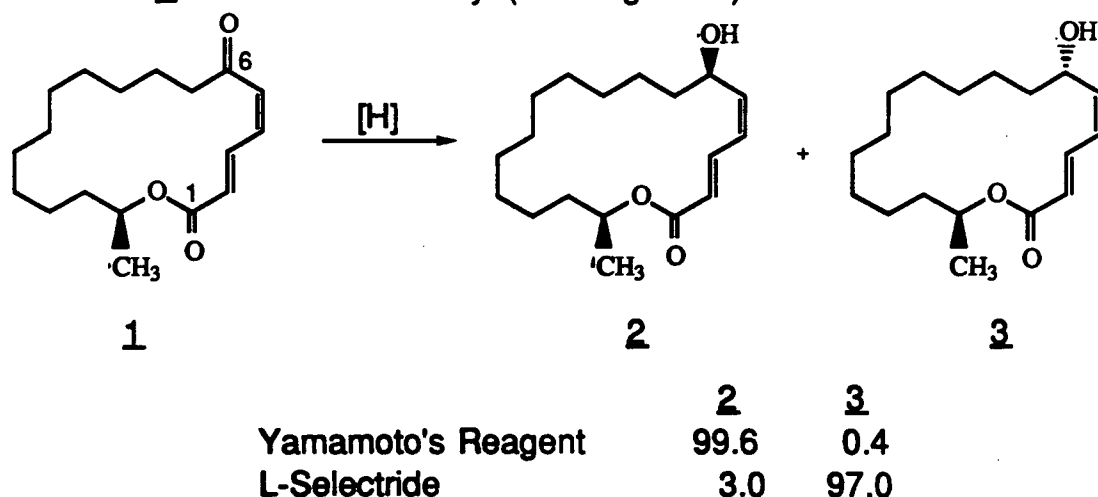|	2	3
Yamamoto's Reagent	99.6	0.4
L-Selectride	3.0	97.0

Figure 3.   Asymmetric induction in the synthesis of (+)-aspicilin by Quinkert et al.[5]

To explore the cause of this stereoselection, Quinkert et al. performed a computer-aided conformational search of 1.[5] Figure 4 shows the lowest energy conformer found. The next conformer was 4.2 Kcal mol^{-1} higher in energy and not considered further. Since the ketone *re* face of 1 is blocked by the transannular methylene groups, it was rationalized that reagent attack would occur from the less hindered, *si* face. L-Selectride did approach from the *si* face, but Yamamoto's reagent did not, indicating that the transition states for the two reactions must be very different.
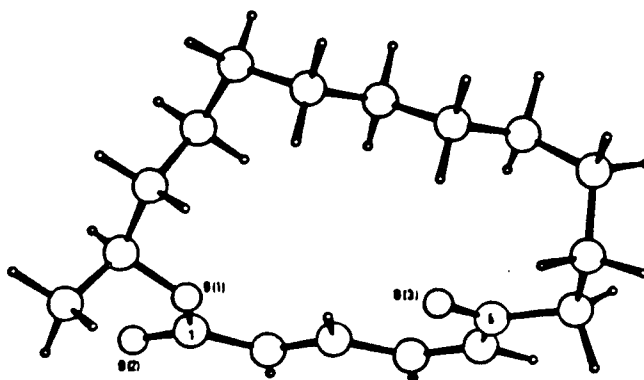

Figure 4. The major conformer of 1 determined from MM2 calculations by Quinkert et al.[5]

The synthesis of (±)-asperdiol by Kato et al., involved an oxidation-reduction sequence to adjust the hydroxyl group configuration at C-1 (see Figure 5).[7] Lithium aluminum tri-*tert*-butoxyhydride reduced ketone 4 to alcohol 5 exclusively.

Although the conformation of ketone 4 was not determined, Kato et al. proposed that the ring segment surrounding the carbonyl group adopted a preferred local conformation.[7] For the purpose of rationalizing the

stereochemical outcome of the hydride reduction, only the local conformation was modeled in detail. Approach of the hydride reagent towards the more open carbonyl face of the local conformer model accounted for the observed product **5**. Local conformer models have proven useful for understanding stereoselective reactions in large rings without knowing the details of the ring conformation.[8]
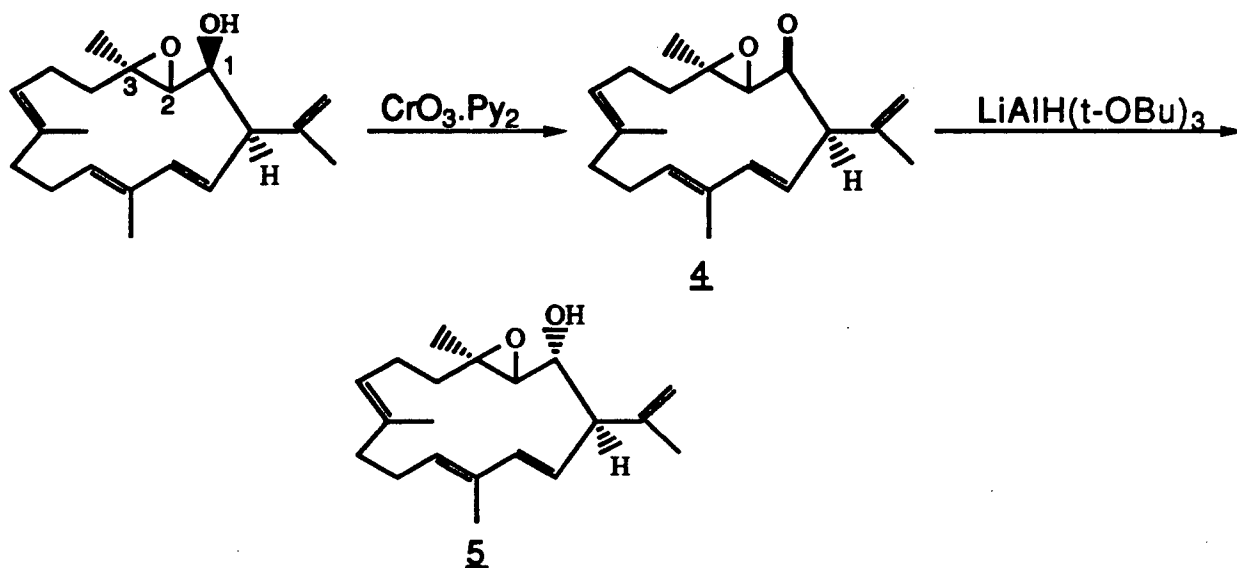

Figure 5. Stereoselective hydride reduction in the synthesis of (±)-asperdiol by Kato et al.[7]

Still et al. used the conformational properties of a 16-membered lactone as a framework for a 1,6-asymmetric induction in their synthesis of nonactic acid.[9] The synthetic strategy involved tying the ends of a molecular chain into the appropriate 16-membered macrocycle, introducing the desired stereochemistry and then cleaving the ring. An auxiliary segment was used to tie the ends of the molecular chain. Still et al. defined auxiliary segments as "strategic elements which may be varried to change the conformational properties of a substrate without changing the segment destined to become part of the final product".[9]
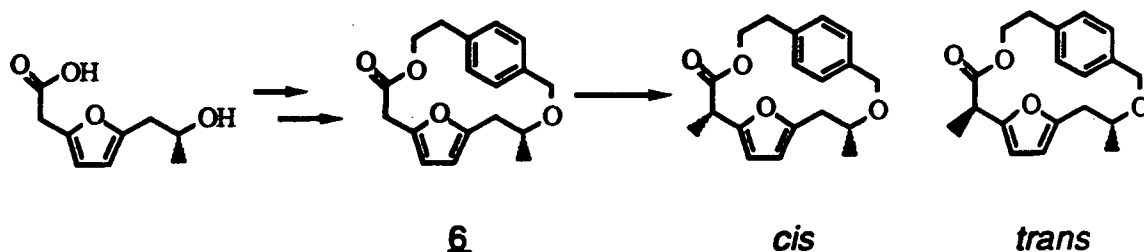
Figure 6. Asymmetric induction in the synthesis of nonactic acid by Still et al.[9]

Formation of the Z-enolate of **6** with potassium bis(trimethylsilyl)amide in toluene and subsequent addition of methyl iodide led to a 15:1 ratio of the *cis* and *trans* dimethyl products respectively. Formation of the E-enolate of **6** with lithium bis(trimethylsilyl)amide in THF/HMPA[10] and subsequent addition of methyl iodide led to a 4:1 ratio of the *trans* and *cis* dimethyl products respectively. In an effort to understand this stereoselectivity, Still et al. performed a conformational analysis of the Z- and E-enolates of **6** using the MACROMODEL[9] computer program. Inspection of the low energy, enolate conformers revealed that reagent attack from the ring periphery would lead to the observed products.

In 1981, Still and Galynker reported that lactones **7-11** could be kinetically alkylated to yield predominantly one product (see Figure 7).[3] This large diastereomeric excess contrasts with the small diastereomeric excess found in the reaction of a nucleophile with the chiral alcohol ester of an α-ketoacid.[11] The chiral information in this reaction is not efficiently transmitted across the ester group, but in the alkylation of **7-11**, efficient asymmetric induction is possible because of conformational control associated with the large ring.
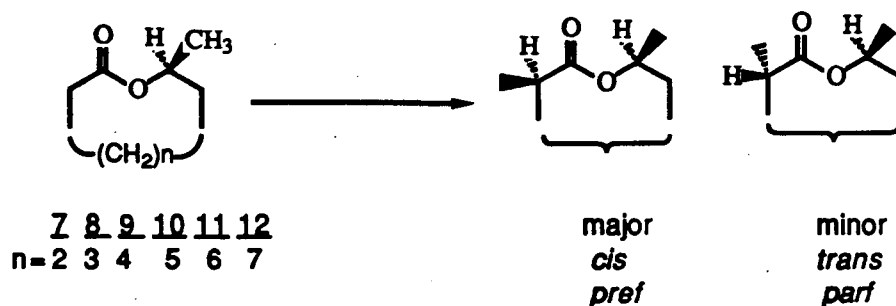
Figure 7. The major and minor products from the kinetic alkylation of 9- through 14-membered lactones.[3,14]

Still and Galynker performed molecular mechanics calculations to explain the observed stereoselectivity.[3] Conformational analysis of the Z-enolates of 7-11 revealed that the π-systems were perpendicular to the plane of the ring and that one enolate face was effectively blocked.

When we discussed our results in relation to Still and Galynker's, a problem arose because these authors used the cis/trans descriptors to define the relative configuration in the alkylated lactones. Communicating three-dimensional information with two-dimensional descriptors is ambiguous, henceforth, the priority reflective (pref) /priority antireflective (parf) system is used in this thesis when defining the relative configuration of alkylated lactones.[12] We chose the pref/parf system over others[13] because it is convenient for comparing relative configuration in rings of different size. A brief review of the pref/parf system is in the appendix.

Our group was interested to see if the reactivity pattern could be extended to include the 14-membered lactone. Kinetic alkylation of 13-tetradecanolide (12) proceeded with large diastereomeric excess and the stereoselectivity was rationalized by conformational analysis of the Z-enolate.[14] Encouraged by this result, our group began an extensive

investigation into the conformationally controlled reactions of 14-membered lactones. In general, the reactions of 14-membered lactones produced one major diastereomeric product.[15]

How large can a ring be and still maintain useful, predictable asymmetric induction? What is the greatest distance over which chiral information can be transmitted effectively? These questions came to mind and we sought to investigate the reactivity pattern of a still larger ring. We chose to study the 16-membered ring because it may exist in a strain-free, diamond-lattice conformation.[16] We hoped that this conformation would predominate, thereby, simplifying conformational analysis. We also chose to study this ring size because of our interest in the 16-membered macrolide antibiotics.[17] Studying the kinetic alkylation of 15-hexadecanolide will lay the ground rules for a complete investigation of this ring size and will help to answer the aforementioned questions.

To further illustrate the potential usefulness of studying 16-membered rings, a retrosynthetic analysis of ODP which would setup the C-8 hydroxyl group stereochemistry by long-range conformational transmission of chiral information, is outlined in Figure 8. The results from the alkylkation of 15-hexadecanolide will help future researchers to ascertain if the 16-membered lactone 13 could provide the conformational bias required for 1,8-asymmetric induction. If the low energy conformer(s) of 13 exposed only the *re* ketone face, then reagent attack from the ring periphery could set up the desired relative configuration in a synthesis of ODP.
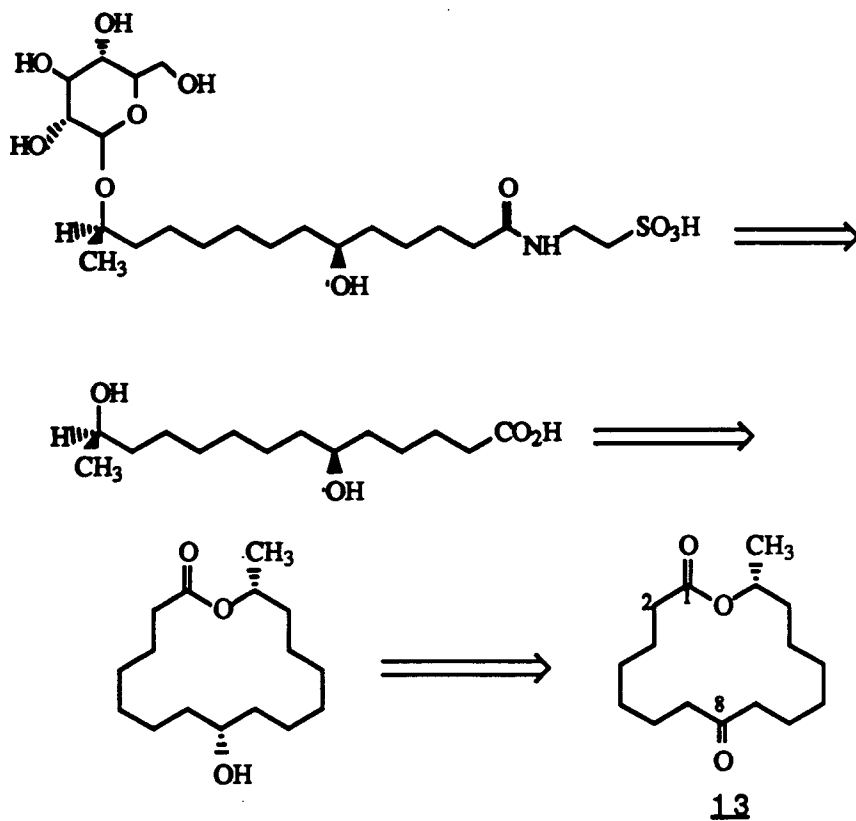
Figure 8. A retrosynthetic analysis of ODP.

RESULTS AND DISCUSSION

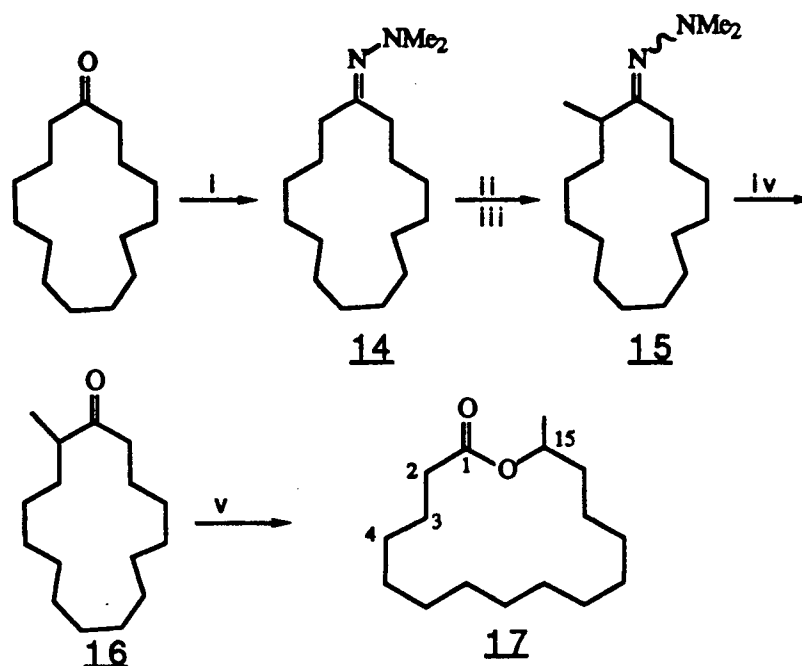### The Synthesis and Alkylation of 15-Hexadecanolide (17)

Figure 9. The synthesis of 15-hexadecanolide. i) H_2NNMe_2;
ii) LDA, THF, 0 °C; iii) MeI, 0 °C; iv) $NaIO_4$, THF, H_2O, pH 7;
v) CF_3CO_3H, Na_2HPO_4, CH_2Cl_2, -10 °C.

15-Hexadecanolide (17) was prepared as shown in Figure 9.[18] Kinetic methylation of readily available cyclopentadecanone produced a mixture of starting material, and monomethylated and dimethylated products. Since purification by flash chromatography[19] was unsuccessful, another synthetic route was attempted. Cyclopentadecanone was converted into its *N,N*-dimethylhydrazone (DMH) derivative 14, for it is well established that DMH's cleanly undergo monoalkylation.[20] Gas-liquid chromatography (glc) showed the presence of two components in the alkylated DMH 15 one of which had the same retention time as the unalkylated DMH 14. The

mechanism for DMH deprotonation and alkylation is outlined in Figure 10.[21] Treatment of a DMH with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at 0 °C and addition of methyl iodide results in the exclusive formation of the *syn* alkylation product which rearranges on standing to an equilibrium mixture which consists predominately of the more stable *anti* isomer. Thus, we tentatively assigned the two glc components as the *syn* and *anti* diastereomers. Oxidative hydrolysis of this mixture produced only the monoalkylated ketone, and no cyclopentadecanone, as shown by glc.
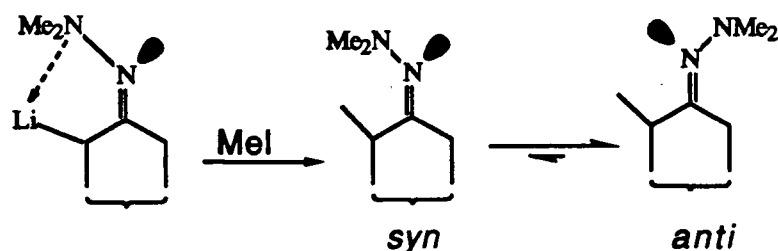
Figure 10. Alkylation and isomerization of a deprotonated DMH.[21]

Baeyer-Villiger oxidation of ketone 16 using *meta*-chloroperoxybenzoic acid (MCPBA) in chloroform at 0 °C took one week and there were many side products in the reaction mixture. Furthermore, the large excess of MCPBA required made this reagent unappealing. Trifluoroperoxyacetic acid oxidation at -10 °C was complete in one hour with few side products. Gas-liquid chromatography showed that MCPBA produced 1% of 17's regioisomer while trifluoroperoxyacetic acid produced 3-4% of this regioisomer.

Deprotonation of 15-hexadecanolide (17) with lithium 2,2,6,6-tetramethylpiperidide (LTMP) followed by addition of methyl iodide

produced a 4:1 mixture of diastereomers. The kinetic nature of the product distribution was verified by potassium *tert*-butoxide equilibration to an approximate 1:1 ratio of isomers.
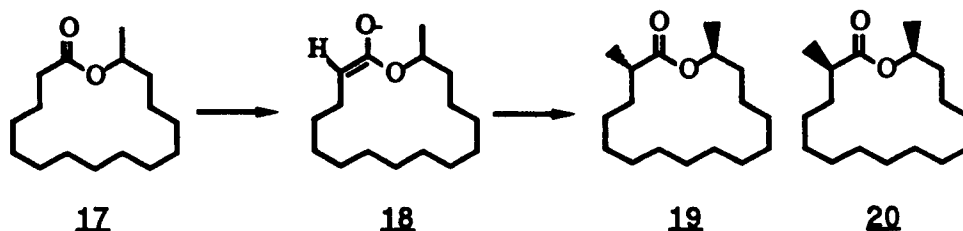
Still and Galynker reported a ^{1}H NMR chemical shift trend for assigning the relative configuration of methylated lactones.[3] This empirical rule states that for the 2-methyl lactones of secondary alcohols, the proton chemical shift difference between the two methyl substituents in 9 to 11-membered lactones is always larger in the *parf* case. Our group found that this rule applied to the 14-membered lactones[22] and it remained to see if the rule applied to the 16-membered lactones also.

Although the ^{1}H NMR spectra of 19 and 20 were clearly different, we wished to confirm their configuration by a synthetic method. We reduced the problem to determining the relative configuration of ketones 21 and 22 by realizing that they could be oxidized to the corresponding lactones 20 and 19. Deprotonation of ketone 16 with LTMP followed by addition of methyl iodide resulted in a 2:1 mixture of 21 and 22 respectively. Flash chromatography or tlc completely separated compounds 21 and 22.

21   22
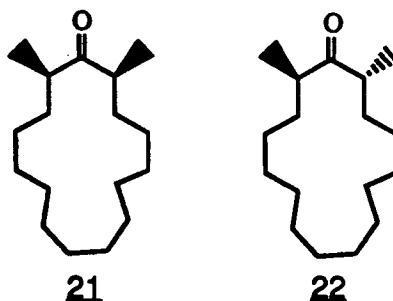
Since the faces of the carbonyl group in 21 are diastereotopic, hydride reduction could yield the two alcohols 24 and 25, whereas epimer 22 would yield only alcohol 26 since its carbonyl faces are equivalent. Lithium aluminum hydride reduction of 21 did produce the alcohols 24 and 25, and 22 did produce the alcohol 26 which clearly established their relative configuration. Thin layer chromatography completely separated alcohols 24 and 25.

21   24   25

22   26
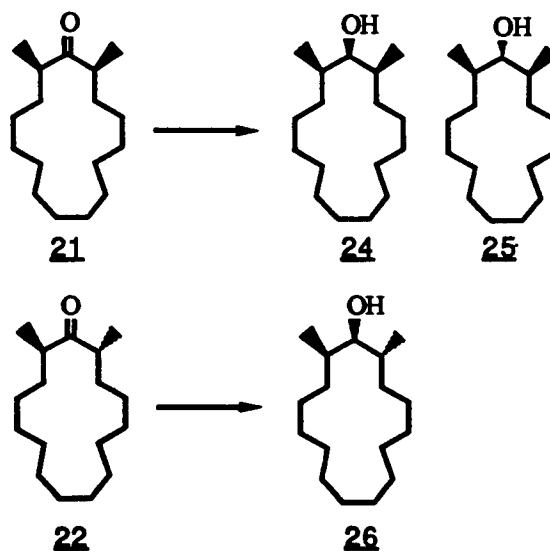
Baeyer-Villiger oxidation of 21 and 22 to the corresponding lactones proved the major diastereomer from the 15-hexadecanolide alkylation was 20.
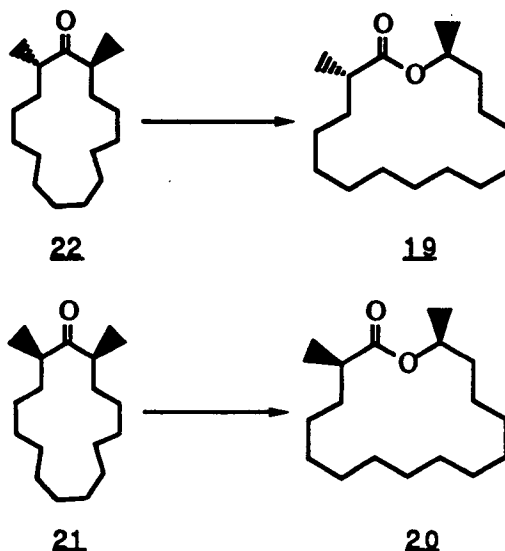
Conformational Analysis of 16-Membered Rings

We began our conformational analysis of 16-membered rings with a study of the hydrocarbon. There were two reasons for doing so: first, few molecular mechanics calculations have been carried out on 16-membered rings[23,24] and we wanted to investigate how the calculations on cyclohexadecane would correlate with experimental data; second, to understand how a conformational bias is imposed by a functional group or chiral center, one must compare the conformations of a functionalized macrocycle with that of the hydrocarbon.

Since the diamond-lattice is the unique way of extending a carbon skeleton indefinitely with "ideal" bond lengths, bond angles and dihedral angles, any "ideal" carbon skeleton is superimposable on the diamond-lattice. In searching for the preferred conformations of cyclohexadecane, one can therefore begin by finding all the closed paths on the diamond-

lattice.[25] Using a computer program, Uiterwijk et al. found 51 diamond-lattice conformers for cyclohexadecane.[26] Of these, only one, the [4444] conformer, occurred with no "overlap". "Overlap" is a severe non-bonded interaction which occurs when two hydrogen atoms formally occupy the same lattice position.[25] Conformational analysis is complicated because conformers can distort from their "ideal" parameters in order to relieve overlap. The resulting structure is related to the diamond-lattice, although not directly superimposable on any diamond-lattice structure.

Saunders recently carried out an extensive computer search for cyclohexadecane conformers. Trial structures were generated using a stochastic method[27] and then minimized using a combination of the STRFIT[28] and MM2[29] force fields. So far, Saunders has found 82 cyclohexadecane conformers within 5 Kcal mol^{-1} of the lowest [4444] conformation.[30] Using the BATCHMIN computer program (see appendix) we found an additional three conformers within a 3 Kcal mol^{-1} range of the lowest energy conformation, one of which turned out to be the second lowest energy conformer found yet. It should be noted that our search missed the eighth lowest energy conformer which Saunders found. This illustrates a problem in using computer calculations to determine all of the conformations of a large ring compound.[27,31] The polar maps and relative strain energies of the 85 lowest energy conformations are in the appendix. So far, nine conformers within 3 Kcal mol^{-1} of the lowest energy [4444] conformation have been found, but no other conformers have been found within 2.1 Kcal mol^{-1} of this conformer. The Boltzmann distribution indicates that 82% of cyclohexadecane molecules exist in the [4444] conformation at 25°C.

Although force field calculations indicate one cyclohexadecane conformer predominates, there is some disagreement about the measured distribution of conformers. Shannon et al. concluded on the basis of IR spectral data that cyclohexadecane in the solid state at -266 °C exists solely in the [4444] conformation, but in the liquid state at 45 °C a maximum of 15% of the conformers are [4444].[32] Allinger et al. have interpreted the IR data differently and concluded that cyclohexadecane exists exclusively in the [4444] conformation at 25 °C.[33] Anet and Cheng found the ^{13}C NMR spectra in solution at -152 °C was consistent with the [4444], but not the [3535] conformer which they calculated to be 1.9 Kcal mol^{-1} higher in energy.[34] Lastly, Yamanobe et al. concluded on the basis of ^{13}C NMR data that the low temperature solid state conformation of cyclohexadecane is retained in solution at 25°C.[330] Although most of the experimental work suggests the lowest energy conformation in solution is the [4444], which is consistent with our calculations, we were unable to evaluate the accuracy of our cyclohexadecane calculations because of the conflicting experimental results of Shannon et al..

The Dale nomenclature system used to name cyclotetradecane conformers[36] proved inadequate for naming cyclohexadecane conformers because some of the conformers had the same name and some could not be named at all. Modification of the Dale system or development of a new system was not attempted; the lowest energy conformer retained its [4444] designation and all others were simply referred to by a bracketed number found in the appendix.

The large number of cyclohexadecane conformers provided a good opportunity to test the utility of polar maps. The generation of polar maps and their usefulness in conformational analysis of large rings

have been reported elsewhere.[37] What follows is a brief discussion of the problems encountered in the conformational analysis of cyclohexadecane using polar maps.

The first feature of polar maps recognized was that mirror image plots represent the same conformer--not mirror image conformers. By numbering the dihedral angles in the reverse direction, one generates mirror image polar maps (see Figure 11).

1) 80		1) 80	
2) -170		2) 65	
3) 55		3) -165	
4) 70		4) 170	
5) -175		5) -170	
6) 170		6) 60	
7) -70		7) 70	
8) -60		8) -170	
9) 170		9) 170	
10) -170		10) -60	
11) 70		11) -70	
12) 60		12) 170	
13) -170		13) -175	
14) 170		14) 70	
15) -165		15) 55	
16) 65		16) -170	
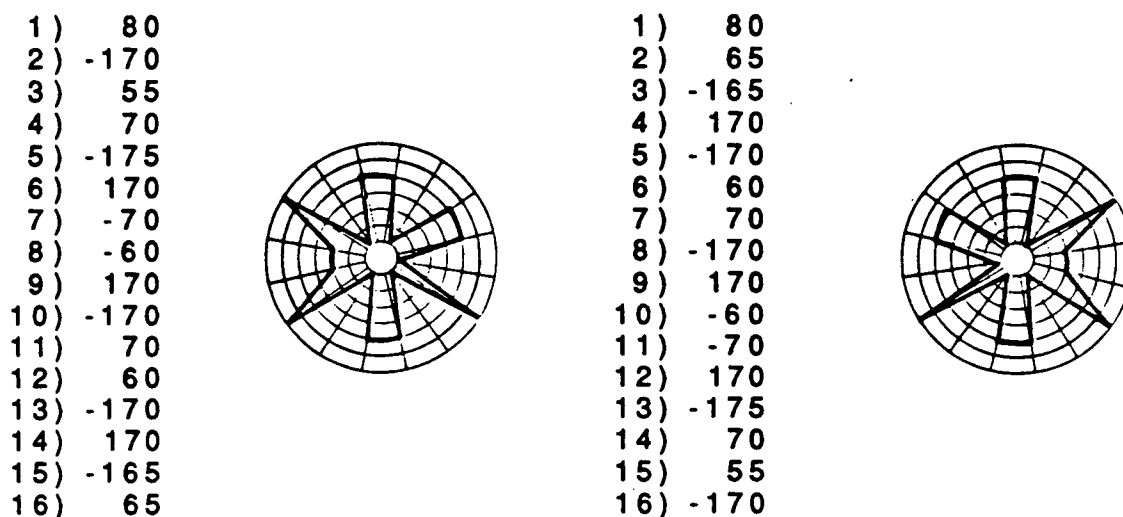
Figure 11. The dihedral angles and mirror image polar maps of cyclohexadecane conformer {4}.

The above observation may seem trivial, but it led to a second, more important observation. At first sight, the polar maps of enantiomers look very different (see Figure 12). In fact, to see that the polar maps are related one must look very carefully. The polar maps look different because the dihedral angles are related by a multiple of minus one.[37] The polar maps are not mirror images even though they represent mirror image conformations. With so many chiral cyclohexadecane conformations to study, the comparison of polar maps was slow.

Figure 12. Polar maps for the enantiomers of cyclohexadecane conformer {4}.

Lastly, a problem arose because of the convention for determining the sign of trans dihedral angles. To determine the sign, one looks at a Newman projection of the endocyclic bond. The dihedral angle is positive if the direction of rotation from the front plane to the rear plane is clockwise. The dihedral angle is negative if the direction of rotation from the front plane to the rear plane is counterclockwise (see Figure13).[37] With so many cyclohexadecane conformations to study, polar map generation was very slow.
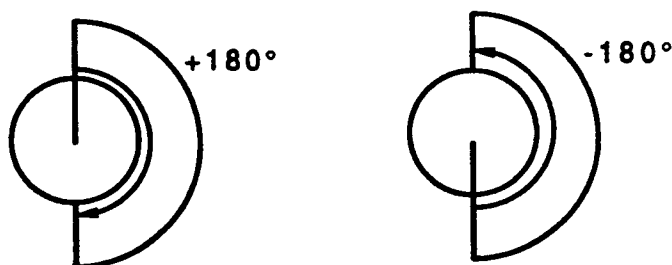
Figure 13. The rule for determining the sign of dihedral angles.[37]

A new polar map convention is proposed in order to speed up generation and comparison of cyclohexadecane polar maps. The relative sign of the gauche dihedral angles is important for identifying conformations, but the relative sign of the trans dihedral angles is not. Stating that a dihedral angle is trans is all that is necessary, therefore, all trans dihedral angles are to be plotted with positive sign. The resulting polar plots maintain all the advantages of the previous plots and are faster to generate. In addition, it is faster to see that two cyclohexadecane polar maps are plots of enantiomer conformations because only the signs of the gauche dihedral angles differ in the two maps, whereas in the previous convention the signs of both the trans and gauche dihedral angles differed.

Figure 14. New convention polar maps for the enantiomers of cyclohexadecane conformer {4}. The outermost circle is +180° and the innermost circle is -120°.

If both trans and gauche dihedral angles were plotted with positive sign then the polar maps of enantiomer conformations would be identical, but this was not done for the following reason. Dale and coworkers defined the sequence of dihedral angles, 180°,60°,60°,180° and 180°,

-60°,-60°,180° as corner positions,[38] and the sequence, 180°,60°, -60°,180° as a pseudo-corner position.[39] The four corner positions in the {4} conformer are easy to spot in the new convention polar map (see Figure 14). It is important to be able to identify these positions for the purpose of conformational analysis of macrocycles and this is why gauche dihedral angles are not all to be plotted positive as well.

We sought to rationalize the stereoselectivity of the 15-hexadecanolide alkylation using molecular mechanics calculations. Since force field parameters were not available for the alkylation transition state, calculations were carried out on the enolate. We assumed that the energy of the enolate was reflected in the transition state (early transition state) and that the electrophile would approach the enolate from the less hindered, peripheral face. As long as the electrophile is small and there is sufficient flexibility in the ring to minimize transannular effects as rehybridization occurs, then the same factors which govern the energy of enolates should be reflected in the transition state geometries.

The calculations were performed using the BATCHMIN computer program. We assumed the Z-enolate geometry because it is well documented that esters yield the Z-enolate exclusively upon kinetic deprotonation with LDA in THF at -78 °C.[10] In addition, the enolate of lactone 12, generated under the same conditions, was proven to have the Z-geometry.[14] Nineteen conformations of Z-enolate 18 were found within 2.0 Kcal mol^{-1} of the lowest energy one. By inspecting computer drawn structures it was concluded that 14 of the Z-enolate conformers would lead to the major product 20, while 5 conformers would lead to the minor product 19. The Boltzmann distribution of the 19 conformational states

predicts a 24:1 ratio of products 20 and 19 respectively. The experimentally observed ratio of products is 4:1. The likely cause for this discrepancy is an incomplete conformer search. To be confident that most of the large ring conformers had been found would require a very large amount of computer time. Our conformer search should only be considered as preliminary. Although other low energy conformers probably exist, our calculations, nonetheless, qualitatively explain the stereoselectivity of the reaction.

In earlier work on 14-membered lactones, members of our group assumed that the low energy conformations of a functionalized macrocycle may be found by introducing the functional group into the low energy hydrocarbon conformations.[22,40] This assumption proved useful in the conformational analysis of 14-membered lactones, but it was not clear that functionalized 16-membered rings would follow the trend. Every low energy conformation of Z-enolate 18 was, in fact, found to have a corresponding low energy hydrocarbon conformation (see Table 1).

The above new convention for polar maps proved useful for determining which Z-enolate conformer corresponded to which hydrocarbon conformer. Since the Z-enolate geometry has steric constraints not found in hydrocarbons, no hydrocarbon polar map matched exactly. If 11-13 of the 16 dihedral angles matched then the Z-enolate and hydrocarbon were said to have similar conformations. The 3-5 dihedral angles that differed always contained the functional group.

Table I. The nineteen lowest energy conformations of Z-enolate 18.

Z-enolate	strain energy (Kcal mol⁻¹)ᵃ	configuration of productᵇ	hydrocarbon conformer	strain energy (Kcal mol⁻¹)ᵃ
1	0.0		12	3.1
2	0.2		3	2.4
3	0.2		25	3.9
4	0.3		6	2.8
5	0.6		2	2.1
6	0.7		10	3.1
7	0.9		63	4.8
8	1.1		27	3.9
9	1.1		14	3.4
10	1.2	*parf*	5	2.4
11	1.3	*parf*	7	2.9
12	1.5		6	2.8
13	1.5	*parf*	79	4.9
14	1.6	*parf*	78	4.9
15	1.6		1	0.0
16	1.7		59,60	4.7
17	1.7		35	4.2
18	1.8	*parf*	44	4.4
19	1.9		12	3.1

ᵃ Strain energy is reported relative to the lowest energy conformation.
ᵇ Product configuration refers to 20 (*pref*) or 19 (*parf*). All Z-enolates led to 20 (*pref*) except where noted.

To recapitulate, the alkylations of lactones 7-12 and 17 all produced the *pref*-dimethyl lactone as the major product, and calculations indicated that in each reaction several Z-enolate conformations gave rise to the same product. Although this situation could arise fortuitously, it may also be related to the presence of low energy local structures in the lactone enolates. The enolate model in Figure 15 was suggested by Still and Galynker to be one such local structure.[3] When the 19 conformations of Z-enolate 18 were compared at the functionalized part of the molecule, 4 different local conformations were found. Three of the four local conformations were similar to Still and Galynker's model.

As stated earlier, Still and Galynker noted that the difference between the proton chemical shifts of the two methyl substituents was always larger for the *parf*-dimethyl products (from the alkylation of lactones 7-11), and now our group has demonstrated that the 14- and 16-membered dimethyl lactones also follow this trend. It is possible that this phenomenon may also be related to the presence of fixed local conformations, but no attempt was made to characterize them.
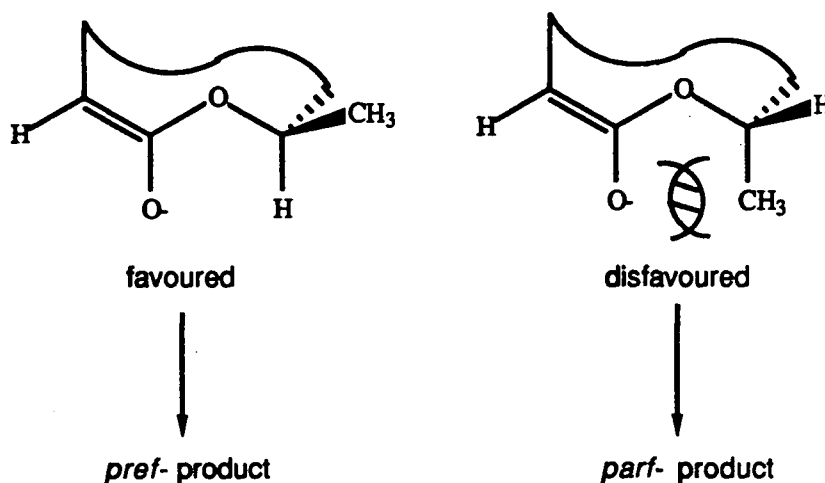
Figure 15. Still and Galynker's local conformer model for lactone enolates.[3] The disfavoured conformer has a steric interaction between the methyl group and the oxyanion.

CONCLUSION

15-Hexadecanolide (17) was synthesized in four steps in 72% overall yield. When alkylated, 15-hexadecanolide yielded a 4:1 ratio of diastereomers. A simple synthetic method proved the relative configuration of the products. Molecular mechanics and a local conformer model were useful for rationalizing the reaction stereoselectivity.

A new convention was developed to speed up generation and comparison of polar maps.

EXPERIMENTAL MATERIALS AND METHODS

General

Unless otherwise stated, all reactions were performed under dry nitrogen gas in flame-dried glassware. Cold temperature baths were maintained as follows: -78 °C (dry ice-acetone); -10 °C (ice-saltwater); and 0 °C (ice-water). Anhydrous reagents and solvents were prepared according to literature procedures.[41] Flash chromatography[19] was performed using silica gel 60, 230-400 mesh, supplied by E. Merck Co..

Infrared spectra (IR) were recorded on a Bomem, Michelson 100, FT-IR connected to an IBM compatible microcomputer. IR spectra were recorded in carbon tetrachloride solution using sodium chloride cells of 0.2 mm thickness. The resolution of the IR spectra is 4 cm^{-1}. All ^{1}H NMR spectra were recorded in deuterochloroform solution on a Bruker WH-400 spectrometer (400 MHz). All ^{13}C NMR spectra were recorded in deuterochloroform solution on a Varian XL-300 spectrometer (75 MHz). NMR signals are reported as chemical shifts with chloroform (^{1}H-7.24 ppm; ^{13}C-77.3 ppm) as an internal standard. ^{1}H NMR signal multiplicities, coupling constants, and integration ratios are indicated in parentheses. Low resolution mass spectra (LRMS) were recorded on a Kratos-AEI model MS 9 spectrometer using electron impact ionization with an ionization potential of 70 eV. The LRMS peaks are reported in mass to charge ratios with relative peak intensity listed in parentheses. Carbon and hydrogen elemental analyses were performed by Peter Borda, Department of Chemistry, U.B.C., on a Carlo Erba elemental analyzer, model 1106. Analytical glc analyses were performed on a Hewlett-Packard gas chromatograph, model 5880, containing a DB-210 capillary column. In all

glc analyses a flame ionization detector and helium carrier gas were used.

Preparation of cyclopentadecanone-DMH (14)

13
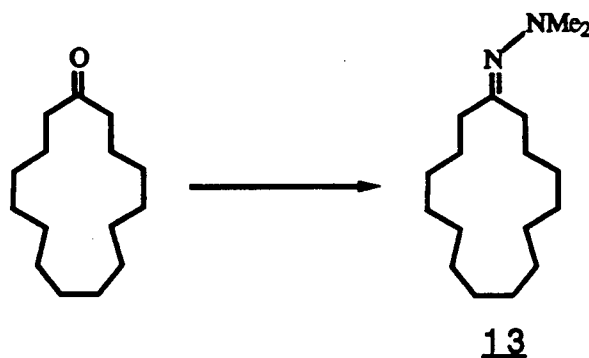
A solution of cyclopentadecanone (0.85 g, 3.8 mmol) and *N,N*-dimethylhydrazine (1.43 mL, 18.9 mmol) was heated at 50 °C for 24 hours. Anhydrous benzene was added and the reaction mixture was azeotropically distilled for a further 24 hours. The benzene and excess *N,N*-dimethylhydrazine were evaporated under reduced pressure leaving 1.0 g of 14 (100% yield). The brown oil 14 was used immediately in the next reaction because it readily hydrolyzed in the presence of water or silica gel.

IR:(cm⁻¹) 2924, 2853, 2815, 2778, 1636, 1465.

¹H NMR:δ 2.43 (t, J=7.0 Hz, 2H), 2.41 (s, 6H), 1.55 (m, 4H), 1.45-1.30 (m, 20H) ppm.

LRMS:(m/z) 266 (m+, 18), 222 (39), 113(11), 100 (50), 97(13), 96(14), 84(13), 83(15), 82(17), 81(12), 71(24), 70(21), 69(23), 67(14), 60 (100), 59(16), 58(41), 57(24), 56(14), 55(55), 46(14), 45(46), 44(69), 43(44), 42(28), 41(61), 39(11).

Preparation of 2-methylcyclopentadecanone (16)

To a solution of diisopropylamine (0.85 mL, 6.0 mmol) in anhydrous THF (5 mL) at 0 °C was added 1.6 N *n*-butyllithium solution in hexanes (3.75 mL, 6.0 mmol). After stirring for 10 minutes at 0 °C a solution of 13 (1.0 g, 3.8 mmol) in anhydrous THF (10 mL) was added via cannula. The yellow mixture turned brown after stirring for 15 hours at 0 °C. Methyl iodide (0.47 mL, 7.6 mmol) was added and within 4 minutes the solution became cloudy yellow. After stirring for 15 minutes at 0 °C, the reaction was quenched with water (3 mL) and diluted with petroleum ether (15 mL). The organic layer was concentrated under reduced pressure and dissolved in THF (83 mL). Gas-liquid chromatography showed the presence of two compounds. A solution of sodium *meta*-periodate (4.0 g, 19 mmol) in water (20 mL) and pH 7 phosphate buffer (10 mL) was added. The yellow, heterogeneous mixture was stirred at 25 °C for 6 hours or until completion of oxidative hydrolysis as determined by tlc. The cloudy orange mixture was filtered and extracted with petroleum ether. The crude product was obtained by combining the organic extracts, drying with magnesium sulphate and concentrating under reduced pressure. The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (30:1) as eluent. Gas-liquid chromatography showed

the presence of only one compound. The reaction produced 2-methylcyclopentadecanone (0.72 g, 3.0 mmol, 79% yield) as a yellow oil.

IR:(cm^{-1}) 2928, 2860, 1713, 1458.

^{1}H NMR:δ 2.59 (m, J=7.0 Hz, 1H), 2.49 (m, J=7.0, 16.0 Hz, 2H), 2.34 (m, J=7.0, 16.0 Hz, 2H), 1.69 (m, 2H), 1.54 (m, 2H), 1.29 (m, 20H), 1.02 (d, J=7.0 Hz, 3H) ppm.

LRMS:(m/z) 238 (m+, 29), 209(14), 139(17), 125(15), 112(10), 111(18), 98(26), 97(29), 96(14), 85(33), 84(19), 83(31), 82(14), 81(15), 73(13), 72(53), 70(18), 69(44), 68(12), 67(20), 57(20), 56(28), 55 (100), 43(38), 42(23), 41(85), 39(16).

Anal. calcd for $C_{16}H_{30}O$: C, 80.61; H, 12.68. Found: C, 80.61; H, 12.55.

Preparation of 15-hexadecanolide (17)

16   17
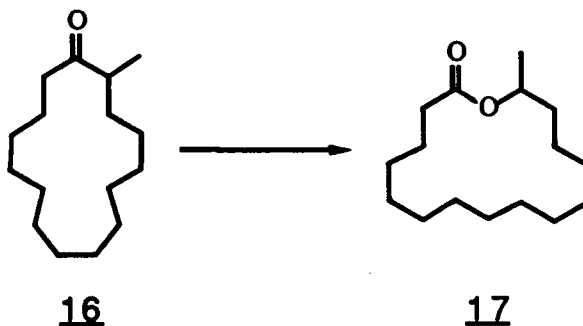
Trifluoroacetic anhydride (0.75 mL, 5.3 mmol) was slowly added to 90% hydrogen peroxide (0.15 mL) in anhydrous dichloromethane (2 mL) at -10 °C. The heterogeneous solution was stirred at -10 °C for 45 minutes and then a solution of 16 (102.0 mg, 0.44 mmol) in anhydrous dichloromethane (5 mL) was slowly added. Immediately afterwards, sodium hydrogen phosphate (0.31 g, 2.2 mmol) was added and the resulting

heterogeneous solution was stirred for 1 hour at -10 °C. The reaction mixture was filtered, concentrated under reduced pressure and diluted with petroleum ether (5 mL). The organic phase was washed with a 10% potassium hydroxide/10% sodium sulphite aqueous solution (1 mL), concentrated under reduced pressure and flash chromatographed using petroleum ether/ethyl acetate (50:1) as eluent to yield 17 (101.0 mg, 0.40 mmol, 91% yield) as a yellow oil. Thin layer chromatography could not separate a mixture of 16 and 17.

IR:(cm^{-1}) 2935, 2860, 1735, 1461.

^{1}H NMR:δ 4.94 (m, J=4.0, 6.0, 8.4 Hz, 1H), 2.28 (m, 2H), 1.70 (m, 2H), 1.55(m, 2H), 1.40-1.25 (m, 20H), 1.19 (d, J=6.0 Hz, 3H) ppm.

LRMS:(m/z) 254(m+, 8), 238(17), 236(24), 210(13), 139(12), 125(17), 112(13), 111(24), 110(16), 109(10), 98(38), 97(41), 96(29), 95(17), 85(23) 84(32), 83(46), 82(25), 81(21), 73(13), 72(29), 71(29), 70(28), 69(59), 68(18), 67(19), 58(17), 57(35), 56(36), 55(100), 54(11), 43(61), 42(22).

Anal. calcd for C$_{16}$H$_{30}$O$_2$: C, 75.60; H, 11.80. Found: C, 75.43; H, 12.01.

Preparation of *Parf*-and *Pref*-2-methyl-15-hexadecanolide (19) and (20)

16   18   19
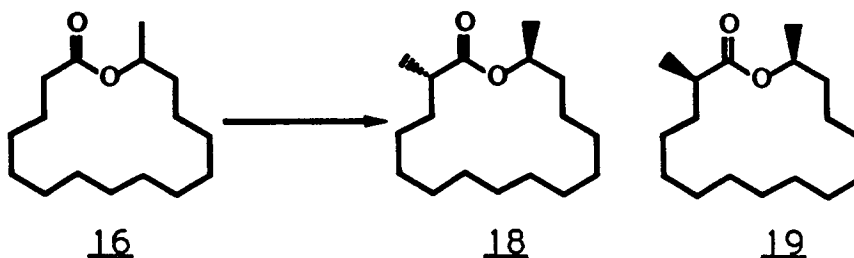
Lithium 2,2,6,6-tetramethyl piperidide was generated at -78 °C by adding 2,2,6,6-tetramethyl piperidine (0.11 mL, 0.67 mmol) to 1.6 N *n*-butyllithium solution in hexanes (0.40 mL, 0.64 mmol) in anhydrous THF (1 mL). After stirring for 10 minutes, a solution of <u>17</u> (107.0 mg, 0.42 mmol) and one crystal of 1,10-phenanthroline in anhydrous THF (2 mL) was added. The dark, red solution was stirred at -78 °C for 2 hours and then a solution of methyl iodide (50 μL, 0.84 mmol) in *N,N'*-dimethyl-*N,N'*-propylene urea (DMPU, 0.2 mL) was added. After stirring the reaction mixture for 1 hour at -78 °C, the cloudy yellow solution was concentrated under reduced pressure, dissolved in petroleum ether (5 mL) and washed with water (1 mL). The organic layer was concentrated under reduced pressure and flash chromatographed using petroleum ether/ethyl acetate (100:1) as eluent to yield <u>19</u> (20.4 mg, 76 μmol) and <u>20</u> (81.5 mg, 0.304 mmol). The yield of the reaction was 90%.

<u>19</u>

IR:(cm^{-1}) 2933, 2859, 1708, 1462, 1381.

^{1}H NMR:δ 4.93 (m, J=3.2, 6.2, 7.9 Hz, 1H), 2.40 (m, J=4.1, 6.8, 7.9 Hz, 1H),1.70-1.20 (m, 24H), 1.19 (d, J=6.2 Hz, 3H), 1.10 (d, J=6.8 Hz, 3H) ppm.

LRMS:(m/z) 268(m+, 9), 250(21), 224(16), 195(14), 194(10), 139(15), 125(23), 112(24), 111(45), 110(20), 109(11), 98(33), 97(64), 96(22), 95(21), 88(34), 85(22), 84(30), 83(70), 82(27), 81(25), 74(87), 71(35), 70(55), 69(84) 68(21), 67(32), 57(69), 56(71), 55(100), 43(87), 42(50), 41(95), 39(26).

Anal. calcd for C$_{17}$H$_{32}$O$_2$: C, 76.12; H, 11.94. Found: C, 76.01; H, 12.02.

20

IR:(cm⁻¹) 2961, 2928, 2856, 1729, 1465.

¹H NMR:δ 4.92 (m, J=3.5, 6.2, 7.9 Hz, 1H), 2.43 (m, J=4.7, 7.0, 8.5 Hz,

  1H),1.75-1.24 (m, 24H), 1.21 (d, J=6.2 Hz, 3H), 1.15 (d, J=7.0 Hz, 3H)

  ppm.

LRMS:(m/z) 268(m+, 7), 250(23), 125(33), 112(35), 111(55), 110(29),

  98(52), 97(72), 96(31), 95(29), 87(26), 85(33), 84(48), 83(76),

  82(37), 81(36), 73(86), 72(24), 71(50), 70(61), 69(87), 68(32),

  67(40), 58(15), 57(72), 56(72), 55(100), 54(24), 43(88), 42(56),

  41(90), 39(30).

Anal. calcd for $C_{17}H_{32}O_2$: C, 76.12; H, 11.94. Found: C, 75.95; H,

  12.03.

Preparation of 2,2-dimethyl-15-hexadecanolide (27)
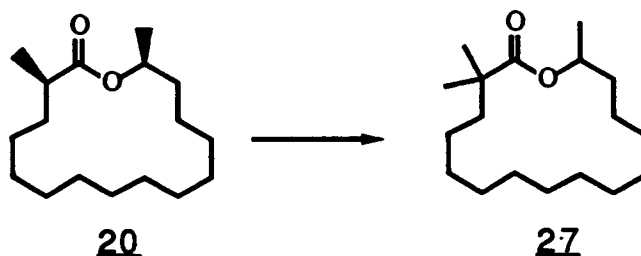
A solution of **20** (49.7 mg, 0.19 mmol) and one crystal of 1,10-phenanthroline in anhydrous THF (1.5 mL) was syringed into a solution of LDA (0.37 mmol) in anhydrous THF (0.5 mL) at 0 °C. After stirring the dark, red solution for 2.5 hours, a solution of methyl iodide (35 μL, 0.56 mmol) in DMPU (0.2 mL) was added. The reaction mixture immediately turned bright yellow. The solution was stirred for 5 minutes at 0 °C and then warmed to room temperature over a 15 minute period. The solution

was concentrated under reduced pressure, dissolved in petroleum ether (5 mL) and washed with water (1 mL). The organic layer was concentrated under reduced pressure and flash chromatographed using petroleum ether/ethyl acetate (50:1) as eluent to yield 2,2-dimethyl-15-hexadecanolide (48.2 mg, 0.17 mmol, 89% yield).

IR:(cm⁻¹) 2980, 2931, 2857, 1720, 1165.

¹H NMR:δ 4.87 (m, J=3.8, 6.2, 7.9 Hz, 1H), 1.65-1.20 (m, 24H), 1.16 (d,J=6.2 Hz, 3H), 1.14 (s, 3H), 1.11 (s, 3H) ppm.

LRMS:(m/z) 282(m+, 10), 264(7), 238(15), 195(25), 111(39), 97(53), 88(100), 85(21), 84(33), 83(60), 82(26), 81(21), 71(40), 70(57), 69(78), 68(22), 67(27), 57(79), 56(86), 55(80), 43(75), 42(38), 41(76), 29(50).

Anal. calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13. Found: C, 76.71; H, 12.17.

Preparation of *Pref*-and *Parf*-2,15,-dimethylcyclopentadecanone (21) and (22)

A solution of 16 (133.1 mg, 0.56 mmol) and one crystal of 1,10-phenanthroline in anhydrous THF (1 mL) was syringed into a solution of LTMP (0.84 mmol) in anhydrous THF (1.5 mL) at -78 °C. After stirring for

2 hours at -78 °C, a solution of methyl iodide (70 μl, 1.1 mmol) in DMPU (0.5 mL) was added. The red solution slowly turned yellow. After stirring at -78 °C for 30 minutes, the reaction was worked up as in the previous alkylations. Flash chromatography using petroleum ether/ethyl acetate (100:1) as eluent, yielded 21 (88.2 mg, 0.35 mmol) and 22 (45.4 mg, 0.18 mmol, 95% yield).

21

IR:(cm^{-1}) 2931, 2857, 1708, 1465, 1386.

^{1}H NMR:δ 2.70 (m, 2H), 1.71 (m, 4H), 1.37-1.17 (m, 20H), 1.20 (d, J=7.2Hz, 6H) ppm.

LRMS:(m/z) 252(m+, 36), 112(54), 111(33), 99(39), 98(44), 97(63), 86(99), 85(26), 84(50), 83(71), 82(27), 81(24), 71(46), 70(67), 69(86), 68(24), 67(36), 57(80), 56(81), 55(100), 54(21), 43(91), 42(63), 41(98), 39(34).

Anal. calcd for $C_{17}H_{32}O$: C, 80.95; H, 12.70. Found: C, 80.86; H, 12.80.

22

IR:(cm^{-1}) 2935, 2860, 1702, 1465.

^{1}H NMR:δ 2.65 (m, 2H), 1.69 (m, 4H), 1.50-1.20 (m, 20H), 1.65 (d, J=7.2 Hz, 6H) ppm.

^{13}C NMR:δ 219.24 (C=O), 43.64 (CH), 32.42 (CH$_2$), 26.54, 26.34, 26.23,25.94, 25.79 (CH$_2$s), 16.47 (CH$_3$) ppm.

LRMS:(m/z) 252(m+, 61), 126(30), 125(37), 113(22), 112(65), 111(51), 100(26), 99(56), 98(61), 97(71), 96(37), 95(32), 87(34), 86(100), 85(50), 84(64), 83(75), 82(46), 81(44), 72(35), 71(61), 70(73), 69(85), 68(44), 67(51), 58(23), 57(82), 56(81), 55(97), 54(40), 53(35), 43(87), 42(67), 41(93), 39(52)

Anal. calcd for $C_{17}H_{32}O$: C, 80.95; H, 12.70. Found: C, 80.96; H, 12.63.

Preparation of *Parf*-2.15-dimethylcyclopentadecanol (26)

22   26

A solution of **22** (45.0 mg, 0.18 mmol) in anhydrous THF (1 mL) was slowly added to lithium aluminum hydride (3.4 mg, 89 µmol) in anhydrous THF (0.5 mL) at 0 °C. The reaction mixture was stirred for 15 minutes and then quenched with saturated, sodium sulphate solution (2 mL). The aqueous phase was extracted with petroleum ether and the combined extracts were concentrated under reduced pressure to yield alcohol **26** (36.2 mg, 0.14 mmol, 77% yield).

IR:(cm⁻¹) 2935, 2860, 1465.

¹H NMR:δ 3.14 (m, 1H), 1.80-1.20 (m, 26H), 1.00 (d, J=6.0 Hz, 3H), 0.9 (d,J=7.0 Hz, 3H) ppm.

Preparation of *Pref*-2.15-dimethylcyclopentadecanols (24) and (25)
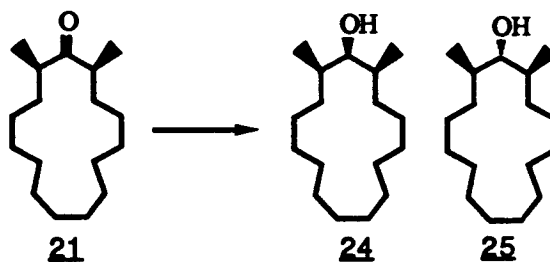
A solution of 21 (45.0 mg, 0.18 mmol) in anhydrous THF (1 mL) was slowly added to lithium aluminum hydride (3.4 mg, 89 µmol) in anhydrous THF (0.5 mL) at 0 °C. The reaction mixture was stirred for 15 minutes and then quenched with saturated, sodium sulphate solution (2 mL). The aqueous phase was extracted with petroleum ether and the combined extracts were concentrated under reduced pressure to yield 24 and 25 (36.2 mg, 0.14 mmol, 77% yield).

IR:(cm^{-1}) 2932, 2863, 1465.

^{1}H NMR:δ 3.35 (q, 1H), 3.17 (q, 1H), 1.75-1.20 (m, 26H), 0.96 (d, J=6.0Hz, 3H), 0.94 (d, J=8.0 Hz, 3H) ppm.

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(40)   (a) Ounsworth, J. Ph.D Thesis, University of British Columbia, **1985**. (b) Keller, T. Ph.D. Thesis, University of British Columbia, **1988**.   (c) Hu, Q. M.Sc. Thesis, University of British Columbia, **1988**.   (d) Spraklin, D.K. M.Sc. Thesis, University of British Columbia, **1988**.

(41)   Perrin, D.D.; Armarego, W.L.F.; Perrin, D.R. *Purification of Laboratory Chemicals;* Pergamon Press: New York, **1966**.

APPENDIX

The *Pref/Parf* System[12]

The term priority reflective (*pref*) is used when the path of decreasing, Cahn-Ingold-Prelog, sequence-rule priority a,b,c reflects the path of decreasing sequence-rule priority x,y,z.
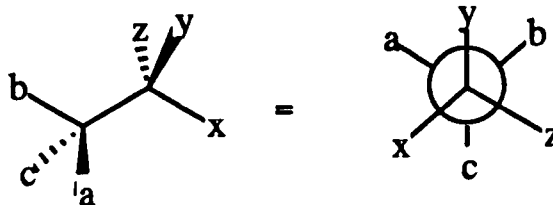
The term priority antireflective (*parf*) is used when the path of decreasing sequence-rule priority a,b,c does not reflect the path of decreasing sequence-rule priority x,y,z.
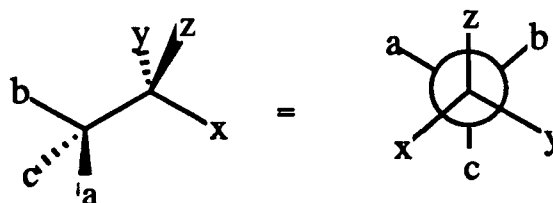
The BATCHMIN Computer Program

The BATCHMIN version 2.6 computer program[31] is the property of Columbia University and was kindly supplied by Professor Clark Still. The program was run on a Personal Iris computer.

Cyclohexadecane Polar Maps and Relative Strain Energies (Kcal/mol)
(maps plotted with new convention)
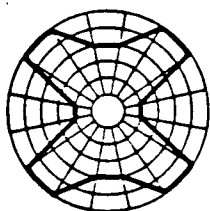
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0.00 Kcal/mol
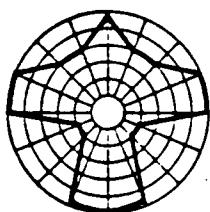
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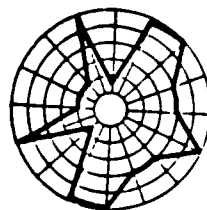
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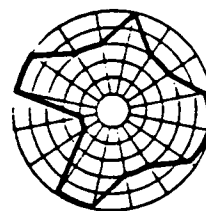
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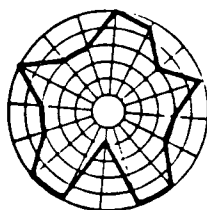
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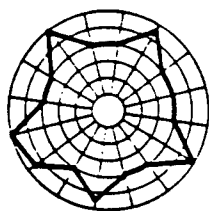
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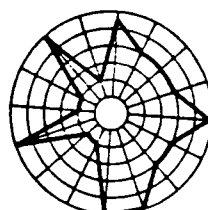
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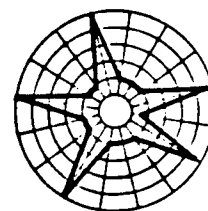
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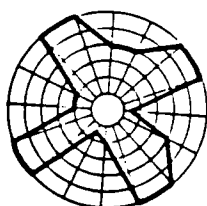
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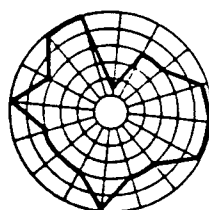
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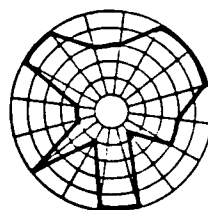
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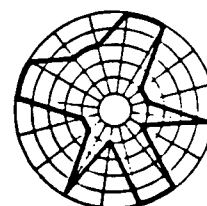
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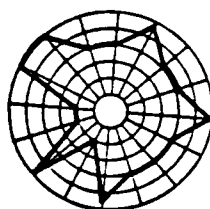
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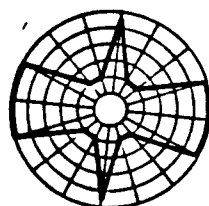
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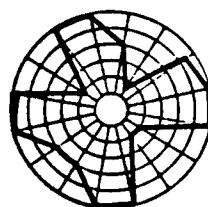
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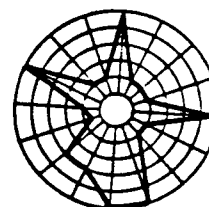
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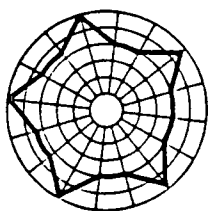
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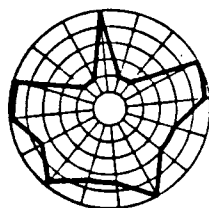
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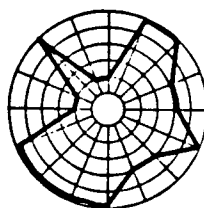
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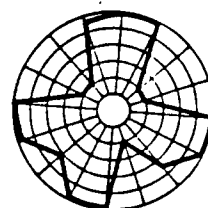
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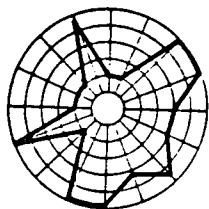
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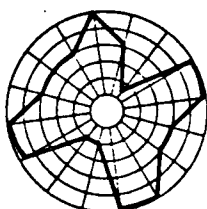
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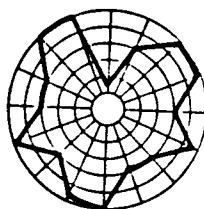
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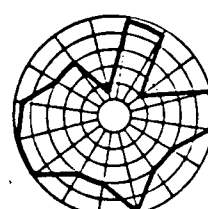
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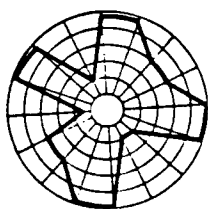
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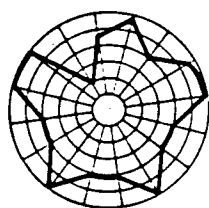
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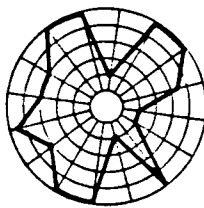
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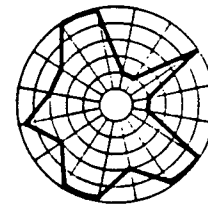
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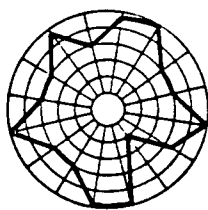
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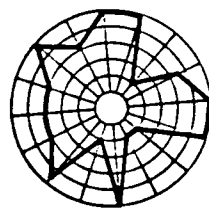
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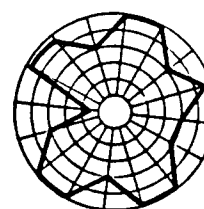
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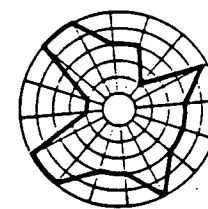
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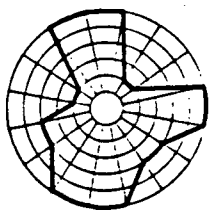
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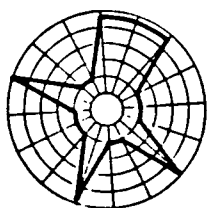
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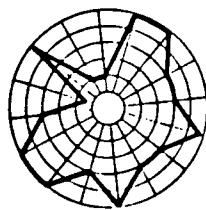
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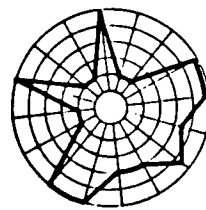
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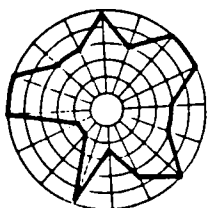
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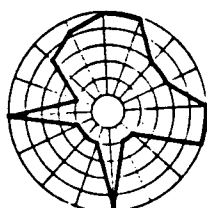
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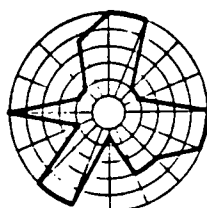
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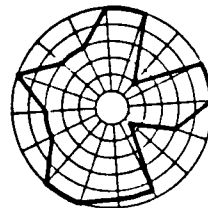
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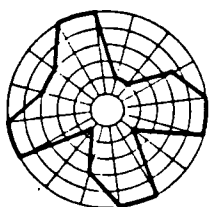
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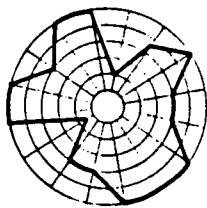
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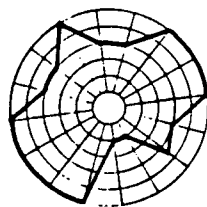
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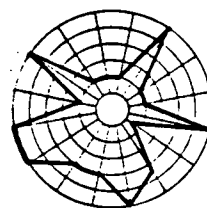
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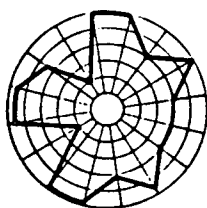
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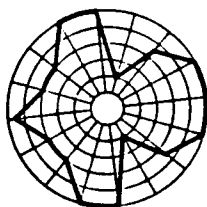
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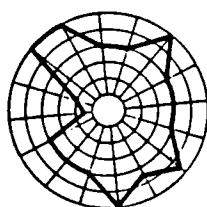
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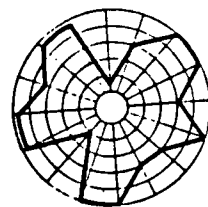
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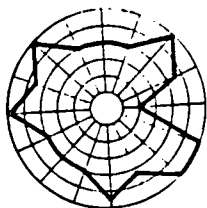
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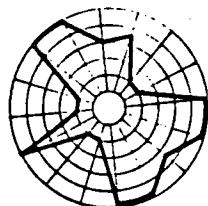
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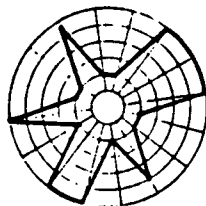
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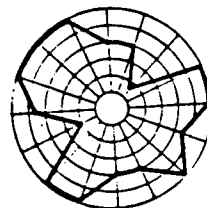
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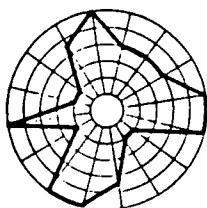
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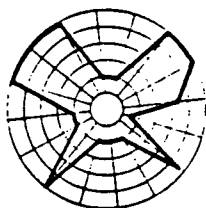
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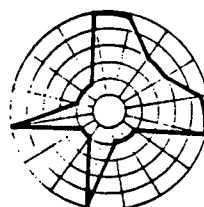
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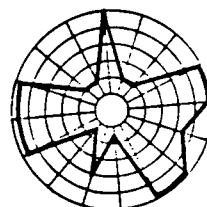
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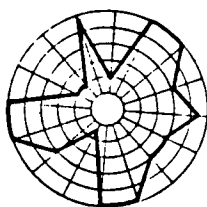
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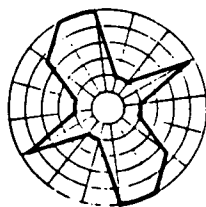
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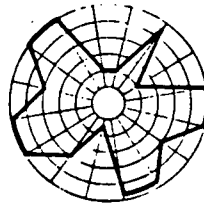
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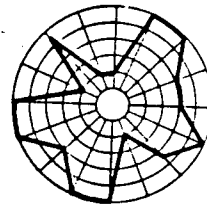
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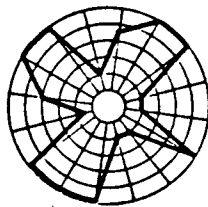
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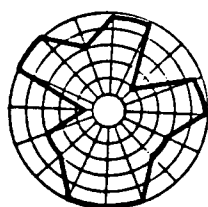
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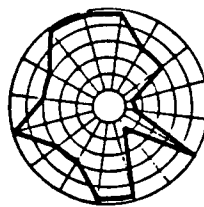
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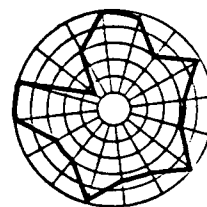
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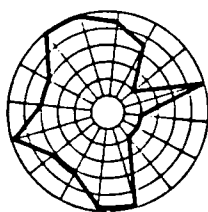
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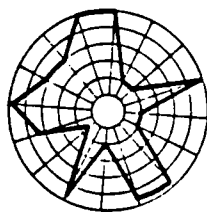
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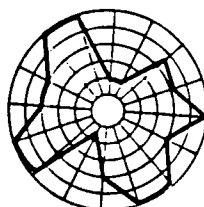
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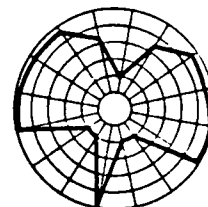
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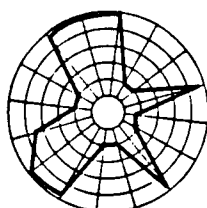
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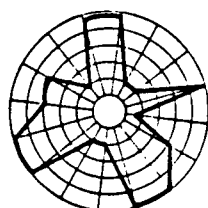
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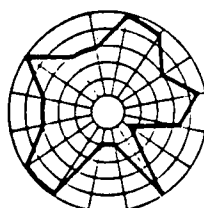
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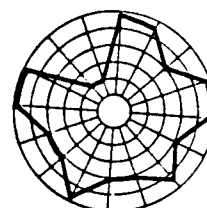
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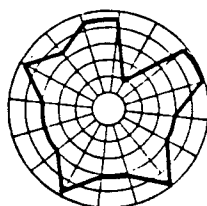
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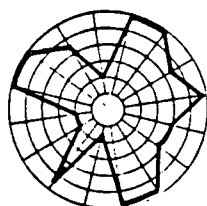
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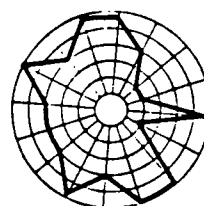
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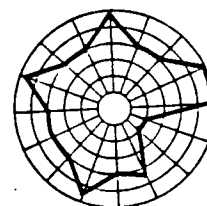
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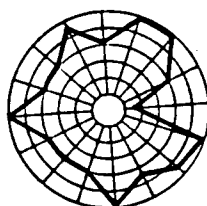
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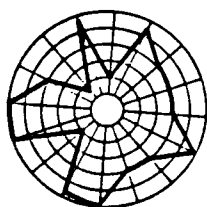
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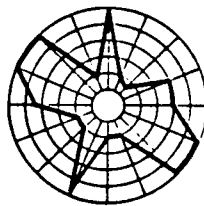
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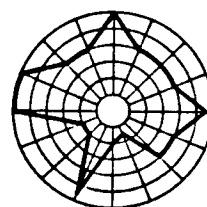
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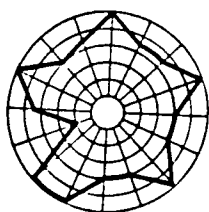
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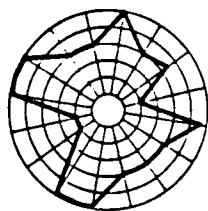
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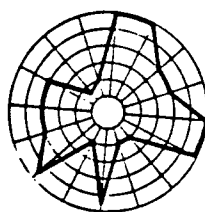
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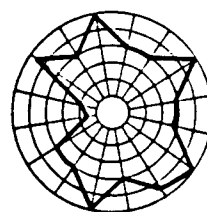
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4.98

SPECTRAL INDEX

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PPM

5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5

% TRANSMITTANCE

4000. 3400. 2800. 2200. 1600. 1000. CM-1