SYNTHESIS AND CONFORMATIONAL STUDIES OF 11-(1,3-DITHIAN-2-YL)-13-TETRADECANOLIDE

BY

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B.Sc., The University of Toronto, 1986

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF
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We accept this thesis as conforming to the required standard

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Department of Chemistry

The University of British Columbia
Vancouver, Canada

Date 22 FEB 89
11-(1,3-Dithian-2-yl)-13-tetradecanolide (71) was synthesized in a ten step sequence in approximately 3% overall yield.

Alkylation of this compound with methyl iodide yielded a 6:1 mixture of diastereomers 72 and 73, the major isomer being 72. The stereochemistry at C-2 of these compounds was determined by their conversion to 74 and 75 respectively, whose stereochemistry was known.

Results of molecular mechanics calculations suggest that the alkylation reaction proceeds through either of the low energy [3335] or [3344] conformations, both of which give rise to the observed product ratio.
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<td>J</td>
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I would like to thank Professor Larry Weiler for his guidance throughout the course of this work. His timely advice and encouragement are greatly appreciated.

I would also like to thank my colleagues, past and present, who have made lab 320 a sometimes strange, but never dull place to work.

In addition, the help of the technical departments, especially the NMR group, for both routine and special experiments, is greatly appreciated.
This thesis is dedicated to my parents.
INTRODUCTION

GENERAL INTRODUCTION

Upon first examination, this work consists of two unrelated themes - synthesis and conformation - representing the way people have previously looked at the macrolide antibiotics. It is only relatively recently that people, including ourselves, have begun to examine the possibility of exploiting the conformational behaviour of these systems as a synthetic strategy itself.

While our ultimate goal is to use the conformational effects of the ring to develop a general method for stereocontrolled macrocycle synthesis, much of the fundamental work remains to be done. This thesis is a continuation of the efforts of our laboratory to study the effect of various ring substituents on the conformation of the macrocycle.

The reader may find the "structure sheet" (following this page) a useful guide during the reading of the thesis. In addition, Appendix I describes the nomenclature used in the conformational discussion, as well as the methodology employed in producing polar maps. Appendix II outlines how our MM2 calculations were performed and finally, Appendix III contains IR and $^1$H NMR spectra for the compounds prepared.
The macrolide antibiotics are compounds of historical, academic and clinical importance. Historically, they represent some of the more complex natural products whose structures have been determined without the benefit of modern techniques, such as NMR spectroscopy.\(^1\) Academically, the macrolides have been used to illustrate sophisticated methods of acyclic stereocontrol in synthesis, for example, the diastereoselective aldol chemistry.\(^2\) Clinically, they are used in the treatment of disorders such as Legionnaires' disease.\(^3\)

The practical uses of macrolide antibiotics, the demand for synthetic derivatives, and their stereochemical complexity continue to attract the attention of chemists today.

1.1 DISCOVERY OF MACROLIDES

In 1950, Brockmann et al.\(^4\) isolated the first macrolide antibiotic, pikromycin (1). It was obtained from a strain of the bacteria *Streptomyces* and was named for its bitter taste.

![Diagram of pikromycin](image)

Since this first discovery, more than 90 macrolide antibiotics have been isolated and characterized. In addition, many shunt metabolites and biosynthetic intermediates of these compounds have also been isolated.\(^5\)

The common feature in all these compounds is the macrocyclic lactone ring and it was Woodward\(^6\) who proposed the name "macrolide" to describe them. The
macrolides are classed according to the ring size of the aglycone moiety (i.e., the large ring without the sugar) and the majority contain an amino and/or a neutral sugar. They possess antibacterial activity, especially against Gram-positive bacteria, Gram-negative cocci and mycoplasms. Their production, isolation and biological activity have been reviewed in detail elsewhere.  

1.2 SYNTHESIS OF MACROLIDES

The macrolide antibiotics represent a great challenge to synthetic chemists. The associated stereochemical complexity, the variety of substituents and functional groups, and the biological significance have all generated synthetic interest in these compounds. These efforts were first reviewed in 1977 and updated in 1985. Clearly, there are two problems to overcome: (1) construction of the macrocyclic ring and (2) control of the sp² and sp³ stereochemistry in the aglycone.

1.2.1 CONSTRUCTION OF THE MACROCYCLE

Synthetic studies began in earnest in the mid-1970's with the development of large ring lactone chemistry. Below are a variety of documented examples representing a number of strategies for the macrolide ring formation.

Ozonolysis of double bonds in olefins such as 2 (Scheme 1), followed by reductive workup, gives the medium-sized rings 3. One drawback to this procedure is that it is not general because of the strong conditions required.

![Scheme 1. C=C Bond cleavage for ring formation.](image_url)
In the Baeyer-Villiger oxidation, an oxygen atom is formally inserted adjacent to the carbonyl of a ketone. It is well-known that the oxygen is inserted on the more substituted side of the carbonyl, so this is a good way to prepare unsymmetrical lactones (Scheme 2).\textsuperscript{11}

\begin{center}
\includegraphics[width=\textwidth]{Scheme2}
\end{center}

Scheme 2. C-O Bond formation (by oxygen insertion) for ring formation.\textsuperscript{11}

The Diels-Alder reaction is a useful way to form carbon-carbon bonds (Scheme 3) and it is more general than the previous two methods because the conditions are not as drastic.\textsuperscript{12} The stereochemistry of the newly formed asymmetric centers is controlled, and in the intramolecular variation, there is an entropic advantage. One disadvantage is that intermolecular dimerization may be a significant side reaction.
Although lactonization of a long, open chain hydroxy-acid is entropically disfavoured and polymerization is a significant problem, it is by far the most general method to form macrolides and has received considerable attention.

The double activation method (Scheme 4)\textsuperscript{13} provides a good leaving group at the carboxyl end of the molecule, while at the same time, increasing the nucleophilicity of the alcohol moiety. This technique works on the premise that proton transfer from the hydroxyl to the carboxylic oxygen is favoured and the driving force is the formation of the very stable 2-pyridthione (12). Since the initial report, a variety of carboxyl activating groups have been used, all of which work by the same double activation method.
Scheme 4. Corey-Nicolaou double activation method for lactonization.13
As with the double activation method, the Masamune method (Scheme 5)\textsuperscript{14} activates the carboxyl group. The acid is converted to the S-tert-butyl thiolester 13, and mercuric trifluoroacetate is used as an activating agent for the cyclization. Masamune favours the intermediacy of the mercury complex 14 over the mixed trifluoroacetic anhydride 15 in this cyclization, although this has not been proven.

Scheme 5. Masamune method for lactonization.\textsuperscript{14}
Mukaiyama has developed a method (Scheme 6) which is closely related to the Corey-Nicolaou procedure in that the carboxyl group is activated as a pyridine derivative. The formation of the stable 2-pyridone 17, is the driving force for the reaction.

In addition, a variety of other groups have been used to activate the carboxyl moiety, including the imidazole $^{18}$ and tosylate $^{19}$ groups.

\[(\text{CH}_2)_n \text{R} \quad \text{R=} \quad \text{N} \quad \text{O} \quad \text{Me} \quad \text{OSO}_2 \]

\[18 \quad 19\]

1.2.2 STEREOCONTROL OF THE AGLYCONE

With ample methodology available to achieve cyclization, the remaining problem was one of stereocontrol. There are four basic approaches to this problem at present:

1. The well-known conformational preferences of a small or medium-sized ring are used to control the asymmetric centers and the ring is subsequently opened or enlarged.

2. The natural product, such as a carbohydrate, defines the stereochemistry and after manipulation, the ring is opened.

3. The desired stereochemistry is obtained through a series of asymmetric reactions on acyclic compounds.

4. The new asymmetric centers are introduced onto the intact macrocyclic ring using the conformational bias of the large ring.

Below is a comparison of the first three approaches as applied to the erythromycins. Synthetic examples using the macrocyclic approach will be given later.
following a discussion of some of the conformational analyses of macrocyclic rings. It is this last approach with which our research has been concerned.

The ring cleavage approach was used by Woodward and co-workers in their synthesis of erythromycin A, published posthumously in 1981.\textsuperscript{18} Eight of the ten chiral centers were controlled via the rigid dithiane system, while the remaining two were secured by acyclic control (Scheme 7). The conjugate addition of phenylmethanethiolate to $20$ and the subsequent protonation, both from the convex face of the molecule, are good representative examples of this approach. Compound $20$ adopts a conformation such that $R_1$ is equatorial to minimize the 1,3-diaxial interactions in the dithiane system, and the phenylmethanethiolate approaches from the more accessible convex face of the molecule. Similarly, the protonation of the intermediate occurs from the same convex side, leading to the stereochemistry at C-7 and C-8 as shown in $21$.

The series of steps represented by multiple arrows are by no means trivial. For instance, the transformation $23$ to $24$ required inversion at the starred carbon in $23$ before cyclization could be effected and extensive manipulation of the protecting groups. In addition, the glycosidation was required to be stereo- and regio-selective. These demands were eventually met to culminate in a very ingenious synthesis.
Scheme 7. Ring cleavage approach to the erythromycin skeleton.\textsuperscript{18}
The carbohydrate approach to erythromycins was first proposed by Miljkovic et al.\textsuperscript{19} in 1974 and exploited by Hanessian and co-workers\textsuperscript{20} in their synthesis of the erythronolide A seco-acid derivative 29 (Scheme 8). It is based on the coupling of carbohydrate derived C1-C7 and C8-C13 units from the same precursor, D-glucose, (25). Unfortunately, they are not able to gain control of the stereocenters at C-6 and C-8.

Scheme 8. Carbohydrate approach to the erythromycin skeleton.\textsuperscript{20}
Although the acyclic approach has been used to construct segments of various macrolides, Masamune et al.\textsuperscript{2} were the first to build a complete seco-acid using "aldol" chemistry exclusively to secure all chiral centers. The synthesis of 6-deoxyerythronolide B (31) is shown in Scheme 9. The transition state geometry that determines the diastereoselectivity in the condensation step is shown in 30. The R\textsubscript{2} group of the aldehyde assumes a pseudo-equatorial position while the enolate assumes a position with the cyclohexyl and protected alcohol oriented to minimize the 1,3-diaxial interaction as shown.

Scheme 9. Acyclic stereochemical control approach to the erythromycin skeleton.\textsuperscript{2}
Scheme 9. Acyclic stereochemical control approach to the erythromycin skeleton.
To summarize, the ring and acyclic approach both permit control of all ten stereocenters in the erythromycin aglycone, in 56% and 85% overall stereoselectivity, respectively. The carbohydrate method achieves control of eight of the ten stereocenters in the aglycone.

1.3 THE CONFORMATION OF LARGE RINGS

The conformational effects on the properties of large ring compounds were first brought to light in 1961 by Huber et al. They showed, through X-ray structures, that several substituted cyclodecanes crystallized in essentially the same conformation and concluded that this conformation must represent some kind of energy minimum. Then in 1963, Dale demonstrated that the above-mentioned solid state conformations were similar to those found in the diamond lattice - a network of ideal C-C bond lengths and bond angles. Dale concluded that any conformation fitting the diamond lattice must represent a minimum in angular torsional strain. He went on to predict low energy conformations for all even-numbered carbon rings from the six- to the sixteen-membered. Although the predictions were made using only models, X-ray and theoretical analysis have since shown them to be remarkably accurate.

In 1965, Celmer completed the configurational assignment of oleandomycin (32), and suggested a conformation for the macrolides which was consistent with the known experimental data. He noted that this conformation closely resembled one of Dale's diamond lattice conformations (Figure 1-Model I). Another model was put forward by Perun and co-workers (Figure 1 -Model III) which was based on their work with erythronolide B (33). In 1969, Demarco studied the conformations of 9-dihydroerythronolides and by a combination of 1H NMR, chemical transformations and CD studies, he found support for Perun's model (Model III). In 1975, Ogura et al. proposed new diamond lattice conformations for kromycin (34) (Model IV), and oleandomycin (32) (Model V).

Upon examination of Figure 1, it is clear that two different conformations may be so similar that it is difficult to distinguish between them (cf. Model I and Model V). However, a plot of the torsional angles of the bonds within the ring results in a polar map (Appendix I), which easily distinguishes between two similar conformations (Figure 2).
Figure 1. Conformational models of 14-membered macrolides.
1.3.1 SYNTHESIS USING MACROCYCLIC CONTROL

In 1983, Vedejs et al.\textsuperscript{28} used the conformational preferences of a 9-membered ring for a stereocontrolled osmylation in the synthesis of erythronolide A. The olefin \textsuperscript{35} assumes a crown-like geometry such that alkyl substituents that are alpha to the double bond, occupy pseudo-equatorial positions if possible. Attack of the reagent from the least hindered face gives the product \textsuperscript{36}.
In 1983, Still and Novak\textsuperscript{29} reported the synthesis of 3-deoxyrosaranolide (41) in which they used 11 kinetically controlled reactions to establish the stereochemistry about the aglycone. Of significance is that eight of these reactions gave \(>15:1\) stereoselectivity (the rest gave 5-10:1 selectivity). Shown in Scheme 10 are three reactions used in this remarkable example of macrocyclic control in synthesis.
Scheme 10. Conformationally controlled reactions showing good selectivity in the synthesis of 3-deoxyrosaranolide (41).
Finally, a recent report by Baker et al.\textsuperscript{30} describes the synthesis of an erythromycin A derivative 43, via a stereoselective intramolecular Michael reaction (Scheme 11). In the product, a cyclic C\textsubscript{11}-C\textsubscript{12} carbamate, the stereochemistry at C-11 is controlled by the lowest energy conformation of the $\alpha$-$\beta$-unsaturated ketone 42, as determined by MM2 calculations. The isomer that has the same stereochemistry as the natural product at C-10 (shown in 43) was obtained in a 6:4 ratio over the diastereomer with respect to C-10 (cf. 24).

![Scheme 11. Synthesis of an erythromycin A derivative 43 via an intramolecular Michael reaction.\textsuperscript{30}](image)

As outlined above, there are relatively few syntheses based on macrocyclic control, hence our interest in this approach to the control of stereochemical centers on large rings.
1.4 OBJECTIVES OF THIS WORK

From these discussions, it is clear that synthesis of the macrolides via macrocyclic conformational control is a viable approach. However, more work is required to understand the factors of conformational control and this is the area on which we have focussed our efforts.

The question is what factors stabilize one conformation of the ring to enable predictable reactivity? The objective of this work is to explore the effect of substitution at the C-11 position of 14-membered lactones, where many natural products of synthetic interest have functionality. We chose the dithiane ring system as the C-11 functionality for this purpose. The reason for this choice is twofold: (1) it is a bulky, geminal substituent and thus its steric requirements should have a pronounced effect on the conformation of the ring, and (2) it is a masked carbonyl group and thus subsequent functional elaboration is possible.
RESULTS AND DISCUSSION

2.1 SYNTHESIS OF 11-SUBSTITUTED-13-TETRADECANOLIDES

The target molecule 44 and the retrosynthetic analysis are shown in Scheme 12. This plan offered a number of advantages, the first of which was that both of the starting materials - 1,7-heptanediol (45) and ethyl acetoacetate (46) - are inexpensive and readily available. The second advantage of this plan was the flexibility it offered for the cyclization. Formation of the macrolide via method I (Scheme 12) would utilize classical intramolecular esterification techniques, which although well-documented,8 give only moderate yields. If the macrolide were formed via method II (Scheme 12), the cyclization would be carried out using an intramolecular Wadsworth-Emmons reaction.31,32 This method offered hope for a higher yield and, in addition, the product of the cyclization, an α,β-unsaturated ketone, would be an interesting compound in itself for subsequent chemical studies. We then intended to protect the C-11 carbonyl of 44 as the cyclic 1,3-dithiane because, as mentioned in the introduction, we expected the dithiane group to significantly reduce the flexibility of the molecule. This would allow us to alkylate at C-2 in what we hoped would be a diastereoselective manner. Interestingly, both methods I and II were available from the identical starting materials and either of these routes would allow us to put an enantiomerically pure stereochemical marker in the molecule since the enzymatic reduction of ethyl acetoacetate (46) is known to be highly enantioselective.33 This would be useful in assigning the stereochemistry of any alkylation reaction products of 11-(1,3-dithian-2-yl)-13-tetradecanolide (71) (Scheme 22). With these factors in mind, we set out on the synthesis of fragment A.
Scheme 12. Retrosynthetic analysis for the preparation of 11-oxo-13-tetradecanolide (44).
2.1.1 SYNTHESIS OF FRAGMENT A

The proposed synthesis of fragment A is shown in Scheme 13. Monobromination of the diol 45 to give 47 was carried out using aqueous hydrogen bromide in a non-polar solvent. Protection of the bromo alcohol 47 as its tetrahydropyranyl ether gave compound 48 in good yield (~75% for two steps). Displacement of the bromine in 48 by the anion of dimethyl malonate, followed by hydrolysis and decarboxylation, gave the acid 49 (90% yield), which contained all of the carbon atoms required for fragment A.

Concurrently, work on fragment B was proceeding, and problems during its preparation made further work on fragment A unnecessary. These problems are described in the following section.
Scheme 13. Proposed synthesis of fragment A.
2.1.2 SYNTHESIS OF FRAGMENT B

The proposed route to the synthesis of fragment B is shown in Scheme 14. As expected, the enzyme catalyzed reduction of ethyl acetoacetate (46) proceeded in high chemical yield (>90%) with good enantioselectivity (85% ee as determined by $^{19}$F NMR and $^1$H NMR) to give ethyl (S)-(+)3-hydroxybutanoate (50). The next step was to protect the alcohol as its benzyl ether. The benzyl group was attractive because the acid in fragment A was protected as its benzyl ester, and both could be removed in one step under catalytic hydrogenation conditions. Unfortunately, we could not obtain the benzylation product 51a in reasonable yield, so we decided to simply protect the alcohol as its tetrahydropyranyl ether 51b. Although it added two steps to the synthesis, the addition and later removal of the THP group were both expected to proceed in high yield.

A recent report in the literature by Widmer,37 discovered subsequent to the successful preparation of 51b, might have offered a solution to our problem above. He found that the β-hydroxy ester 53 was benzylated in low yield with partial racemization of the β-stereocenter under basic conditions (Scheme 15). His solution was to use benzyl 2,2,2-trichloroacetimidate (55) under acid-catalyzed conditions to obtain the β-benzyloxy ester 54 in good yield, with no racemization. This procedure had previously been reported for carbohydrate chemistry.38

With the tetrahydropyranyl ester 51b in hand, the final carbon atom of fragment B was to be added via the lithium salt of dimethyl methylphosphonate according to the procedure of Dauben et al.39 Several attempts to achieve this transformation were made, but the desired product 52 could only be isolated in trace amounts with the major product being unreacted starting material. The reaction of the dimethyl methylphosphonate salt was also attempted with the anion from the β-hydroxy ester 50, with the same poor results.
Scheme 14. Proposed synthesis of Fragment B.
Scheme 15. Protection of an alcohol using benzyl 2,2,2-trichloroacetimidate.\textsuperscript{37}
Under the strongly basic conditions of the reaction, the phosphonate anion could abstract protons alpha to the ester in both compounds 50 and 51b. This would neutralize the phosphonate anion and lead to the stable enolates of compounds 50 and 51b respectively, as shown below.

Upon workup, these enolates would liberate the starting materials as observed, while the dimethyl methylphosphonate would remain in the aqueous phase. This is consistent with the previous observation that compound 53 (Scheme 15) underwent epimerization and could not be benzylated under basic conditions.
With fragment B unavailable to us by the anticipated route, neither of our proposed synthetic routes was now available. A new approach was devised where the dithiane was introduced prior to ring formation (Scheme 16). This plan had the benefit that the enzyme reduction of ethyl acetoacetate could still be utilized.

Before embarking on this route, a model study was proposed to determine if the alkylation of compound 59 with compound 57 could be carried out. Before using the enantiomerically enriched 58, we synthesized a racemic sample of 59 (Scheme 17).

The opening of propylene oxide by the anion of 60a went in surprisingly poor yield (30%), but because both starting materials were so inexpensive, we continued on. Alkylation with the lithium salt of the bromo-acid 57 with the anion from 59a (Scheme 18) gave no alkylation product. Before pursuing this reaction, further investigation of the dithiane chemistry revealed that the 5-membered cyclic 2-lithio-1,3-dithiolanes (60a) undergo facile elimination to form ethylene and dithiocarbonate, neither of which would be isolated under normal workup conditions. This may also explain the low yield of the initial epoxide opening. By employing the 6-membered 1,3-dithiane (60b), the epoxide was opened in >80% yield. Unfortunately, alkylation of 59b with the lithium salt of 57 still would not proceed.
Scheme 17. Preparation of model compound 59.

Scheme 18. Reaction conditions for the attempted alkylation of the model compound 59.
We considered the possibility that the dithiane anion was abstracting a proton alpha to the carboxylate in 57 and thus neutralizing itself. This was checked by quenching the reaction with D2O. There was no deuterium incorporation in the acid which would have been observed if this scenario were true. We then studied the alkylation of the unprotected hydroxyl moiety 61b.

We found a literature precedent\textsuperscript{41} for this reaction which suggested the use of the cation complexing agent N-hexamethylphosphoramide (HMPA) to facilitate alkylation, however, alkylation of 61b under the conditions shown in Scheme 19 gave only poor yields (10-30\%) of the desired product with recovery of the starting materials. We tried the alkylation with the bromo ester 62, as well as the bromo tetrahydropyranyl ether 63, with similarly disappointing results.
Scheme 19. Reaction conditions for the attempted alkylation of compound 61b.
At this point, we speculated that lack of deprotonation of the dithiane in 59 or 61 might be the reason for the poor yields in the alkylation. Previous work in our laboratory\textsuperscript{42} found that epoxide opening was accelerated significantly by the use of a complexing agent. Also, a report in the literature at this time\textsuperscript{43} suggested that in addition to the complexing agent, long reaction times might be necessary to deprotonate substituted dithianes.

Using the same alkylating agents as before, 57, 62, and 63, we tried increasing the reaction time (up to 24 h) as well as the temperature (up to room temperature), but with the same poor results.
The following experiment was then devised to systematically determine the optimum deprotonation conditions:

We wanted the deprotonation conditions to be as mild as possible so the temperature was to be kept low (-20 °C) for as long as possible, and the HMPA was to be added only after the temperature had been raised and the deprotonation had sufficient time to take place in the absence of the complexing agent. Aliquots from the reaction were taken at the times shown and quenched with D₂O. The progress of the reaction was followed by observing the integration ratio of the thioacetal proton signal in the ¹H NMR (δ 4.3 ppm), which was well resolved from any other signals in the spectrum of compound 61b.

The results show that after 4 h at -20 °C, deprotonation was complete and there was 100% deuterium incorporation in the aliquot taken. After raising the temperature to 0 °C and stirring for another hour, the amount of deuterium incorporation was reduced to 55%, indicating that the dithiane dianion is beginning to
abstract solvent protons. Finally, addition of the complexing agent makes the dianion so reactive that it is quantitatively neutralized by abstraction of solvent protons.

After determining the optimum deprotonation conditions, we tried the alkylation again with the bromo tetrahydropyranly ether 63, but were disappointed to find that the reaction still did not proceed (10% desired product and starting materials). Once again, a new strategy was devised (Scheme 20), where the order of alkylation was reversed, i.e., alkylation of 60b with the bromo tetrahydropyranly ether 63 was to be followed by the epoxide opening. Unfortunately, the enzyme reduction product would no longer be useful in this route. However, since the epoxide could be purchased in chiral form, we could still synthesize the optically active 71 by this route.

As expected, the alkylation of 1,3-dithiane (60b) with the bromo tetrahydropyranly ether 63 proceeded efficiently (80% yield). Under standard alkylation conditions, 60b is deprotonated with base and an excess of alkylating agent is then added. In this case, any excess n-butyllithium transmetallated the bromo tetrahydropyranly ether 63. This was alleviated by simply using an excess of the dithiane 60b. Next, propylene oxide was opened with the anion from 64 to give the alcohol 65 in 85% yield. Protection of the alcohol as its acetate (90%), followed by removal of the THP (85%) gave the alcohol 67. This compound was oxidized to the corresponding acid in two steps as attempts to carry out this transformation in a single step resulted in the loss of the dithiane ring. First, a Moffatt oxidation44 gave the aldehyde 68 and the corresponding acid was obtained by the AgNO3-NaOH method45 (50% for two steps). Hydrolytic removal of the acetate gave the cyclization precursor, the hydroxy-acid 70 in 53% yield.
Scheme 20. Synthesis of 11-((1,3-dithian-2-yl)-13-tetradecanolate (71).
Scheme 20. Synthesis of 11-(1,3-dithian-2-yl)-13-tetradecanolide (71).
2.1.3 CYCLIZATION TO FORM 11-(1,3-DITHIAN-2-YL)-13-TETRADECANOLIDE (71)

The cyclization was achieved using a modification of Corey's double activation method. This procedure, which activates the carboxyl group with 1-phenyl-1H-tetrazole-5-thiol and tert-butyl isocyanide had been used in our laboratory to successfully prepare 14-membered lactones with consistently good yields (80%), however, attempts to cyclize compound 70 by this method gave very poor results (20%). The mechanism for this reaction is outlined in Scheme 21.
Ignoring for a moment, the conformation of the alkyl chain, the transition state for cyclization is shown below.

From this model, it follows that substitution near the reaction center would impede cyclization and this has in fact been observed previously. Secondary alcohols as in 70 lactonize slower than the corresponding primary alcohols. Interestingly, many reports of new cyclization procedures have only been tested on the primary hydroxy-acids.

If we now consider the conformation of the alkyl chain, it is predicted that the seco-acid will have some of the conformational rigidity of the cyclized macrolide. Only one of the low energy conformations (the [3335] conformation) possible for compound 71 is shown below. A detailed conformational analysis for this compound is presented in section 2.2.1.
The strain energy of the 11-substituted-13-tetradecanolide 71 in this conformation is calculated to be 4.3 kcal/mol higher than its unsubstituted analogue 71a. If the transition states to cyclization of the seco-acids reflect some of this strain energy, then it is not surprising that compound 71 does not cyclize as readily as its unsubstituted analogue.

The dithiane in compound 71 was then hydrolyzed using N-bromosuccinimide in aqueous acetone (42% yield), to give the keto lactone 44 (Scheme 20).

2.1.4 ALKYLATION OF 11-(1,3-DITHIAN-2-YL)-13-TETRADECANOLIDE (71)

Deprotonation of compound 71 under kinetic conditions, followed by alkylation with iodomethane gave a 6:1 mixture of 72 and 73 as determined by GLC (Scheme 22). The stereochemistry at C-2 could not be determined directly, so 72 and 73 were converted to 74 and 75, whose structures had been unambiguously determined. It was shown that the major isomer from the alkylation of 71 was (2R*, 13S*)-11-(1,3-dithian-2-yl)-2-methyl-13-tetradecanolide (72).
Scheme 22. Alkylation of 71 and desulfurization of products.
2.2 CONFORMATIONAL STUDIES

2.2.1 MM2 CALCULATIONS

It would seem that the conformational mobility of the macrolides would enable them to exist in a variety of conformations. Indeed, Saunders\textsuperscript{52} has used a computer program to generate thirteen diamond lattice conformations for cyclotetradecane. If one also considers the low-energy non-diamond lattice [3335] and [3344] conformations, then each macrolide could exist in 15 possible conformations, making the analysis very tedious and time consuming. Studies in our laboratory\textsuperscript{51} have used MM2 calculations to determine the strain energy for all these conformations (Figure 3) and as expected, many of them have prohibitively large strain energies which makes them irrelevant to the conformational analysis of 14-membered rings. For compound 71, we arbitrarily chose to examine the three lowest energy conformations, i.e., the [3434], [3344], and [3335] conformations.
Figure 3. Possible conformations and relative strain energies for cyclotetradeane (in kcal/mol).
With the carbon framework of the macrocyclic ring set, it remained to substitute the functional groups of compound \(7_1\), namely the lactone and the dithiane ring at the appropriate positions. Once again, upon first inspection, it seems that there would be a large number of possibilities to consider. However, some experimental and empirical results have simplified this task.

Substituents which point into the middle of the macrocyclic ring experience severe transannular interactions\(^53\) - the degree of this interaction varies for different positions around the ring. For example, in the [3434] conformation, the steric interaction decreases in order of \(H_1>H_2>H_3\) (Figure 4). Therefore, we only need consider conformations where the substituents point away from the ring.

![Figure 4. Internal hydrogen atoms experiencing transannular interactions (* corner position).](image)

From the preceding discussion, it follows that geminal substituents must both point away from the ring to minimize repulsive interactions. The only position in the macrolides which can accommodate geminal substitution is the so-called "corner" position\(^54\) in Figure 4 - (see Appendix I for a definition of corner positions). Therefore, only conformations which possess a geminally substituted atom in a corner position were considered in our analysis.
A further simplification of the analysis results from consideration of the lactone functionality. The s-trans geometry of esters (Figure 5) is more stable than the s-cis form by an estimated 3 kcal/mol,\textsuperscript{55} hence any conformations with the s-cis geometry were eliminated.

![Figure 5. The possible geometries for the ester moiety.](image)

In addition, it has been observed\textsuperscript{56} that esters of secondary alcohols contain a C-O-C-H dihedral angle in the range of 0-60° (Figure 6). This is based on an analysis of over 1750 compounds containing the C-C(O)-O-C functionality.

![Figure 6. The C-O-C-H dihedral angle of secondary esters.](image)
In summary, the following restrictions were applied to simplify our conformational analysis:

1. Ring substituents must not be directed into the interior of the ring.
2. Geminally substituted atoms must occupy a corner position.
3. The lactone must adopt the s-trans geometry.
4. The lactone C-O-C-H dihedral angle must be in the range of 0-60°.

From the preceding restrictions, there is only one conformation which can meet all the criteria: the [3335] conformation shown below.

\[
\text{[3335] conformation}
\]

However, another question came to mind concerning the C-S bond length. It occurred to us that with the longer C-S bond (1.81 Å vs. 1.54 Å for C-C), the sulfur atoms of the dithiane ring may be far enough away from the rest of the macrocycle to relieve any transannular interactions and thus they might occupy non-corner positions. Therefore, we calculated the strain energies of all possible conformations, irrespective of whether the dithiane occupied a corner position or not, and which still met criteria 1, 3, and 4 as outlined above.

The possible [3434] conformations, none of which can accommodate the dithiane in a corner position, are shown in Figure 7 with the strain energies relative to the
corresponding unsubstituted 13-tetradecanolide in this conformation. The known trends of preferred substitution (Figure 4) are confirmed by these calculations.

The results of substitution on the [3344] conformation were surprising (Figure 8). One of the possible [3344] conformations (A) (with geminal substitution at a non-corner position) gives a strain energy comparable to the [3335] conformation (with geminal substitution at a corner position). This would indicate that the C-S bond distance is sufficiently long that the transannular interactions are relieved in some conformations. If this is so, it means that the dithiane ring is not as useful a device to lock the ring conformation as we had hoped, because it is not restricted to the corner positions.

To support our MM2 calculations, we examined the $^1$H NMR of compound 71. The methine signal ($\delta$ 5.1 ppm), which is well resolved from any other signals in the spectrum, is coupled to the neighbouring protons of the methyl and methylene groups. A conformationally rigid system is expected to exhibit a sharp eleven line pattern for this signal, while a conformationally mobile system exhibits a broadened six line pattern. Compound 71 shows a broadened multiplet for this signal, indicative of the multiple conformations predicted by our calculations.
Figure 7. The possible [3434] conformations of compound 71 and the strain energies relative to the unsubstituted 13-tetradecanolide in this conformation.

Figure 8. The possible [3344] conformations of compound 71 and the strain energies relative to the unsubstituted 13-tetradecanolide in this conformation.
2.2.2 APPLICATIONS OF MM2 CALCULATIONS

According to the Hammond postulate,\textsuperscript{50} if we consider the alkylation to be an exothermic reaction,\textsuperscript{58} the transition state is "reactant-like" and the low energy conformations of the starting enolate are relevant (as opposed to the conformations of the product for an endothermic reaction). Consider both the [3335] and [3344] conformations of the enolate from 71. If the electrophile attacks the enolate of the ring from the exterior face,\textsuperscript{58} then we would expect the "R" configuration at C-2 as observed (Figure 9). This peripheral attack is expected because the transannular hydrogen interactions of the ring make electrophilic attack from the interior of the ring impossible.

![Figure 9. Electrophilic attack on the low energy conformations of the enolate from 71 with the olefin aligned perpendicular to the plane of the ring.](image)

However, there is a complication in that C-2 is a corner position in both these conformations. The corner position is unique because its attached atoms experience the least steric interaction and thus it is the only atom that can easily accommodate...
geminal substitution. The enolate from 71 may align such that the olefinic bond is parallel to the plane of the ring and therefore, the electrophile could attack from either side, which would decrease the selectivity. There is in fact a slight preference for pseudo-equatorial attack\textsuperscript{51} which would give rise to the observed products in both cases (Figure 10).

Figure 10. Electrophilic attack on the low energy conformations of the enolate from 71 with the olefin aligned parallel to the plane of the ring.

2.3 CONCLUSION

The problems encountered in the synthesis of compound 71 illustrate the advantage of the macrocyclic approach to these compounds. If the cyclization is poor yielding, then in a multi-step synthesis, it is beneficial to have this step at the beginning of the sequence when the materials are more readily available and less expensive.

The effect of the dithiane ring on the macrocyclic conformation was not as pronounced as we had postulated originally. Unexpectedly, we found low energy
conformations with the dithiane ring in non-corner positions. This limits the use of this group in setting up any bias in the conformation of the 14-membered ring.

Future studies are needed to more thoroughly examine the effect of this group on the conformation of the macrocycles. Substitution of the dithiane ring on the macrocycle at positions other than C-11 may show more pronounced effects on the ring conformation. In addition, the effect of the dithiane group on a more substituted ring system may be more significant, which would make it a useful device to employ in the later stages of the synthesis of complex macrolides.
3.1 GENERAL

Unless otherwise stated, all reactions were performed under nitrogen using oven-dried glassware. Cold temperature baths were maintained as follows: -78 °C (dry ice-acetone), -23 °C (dry ice-carbon tetrachloride), and 0 °C (ice-water).

Anhydrous reagents and solvents were prepared according to the procedures reported in the literature.59

Preparative flash column chromatography was performed using silica gel 60, 230-240 mesh, supplied by E. Merck Co.

Melting points were performed on a Gallenkamp apparatus, and are uncorrected. Reported boiling points are also uncorrected.

Infrared spectra were recorded on a Bomem FT-IR Michelson-100 connected to an IBM compatible microcomputer. IR spectra were recorded either neat, or in a chloroform solution using NaCl cells of 0.2 mm thickness. Proton nuclear magnetic resonance spectra were recorded in a deuteriochloroform solution on a Varian XL-300 (300 MHz) or a Bruker WH-400 (400 MHz) spectrometer. Chemical shifts are given in parts per million (ppm) on the δ scale versus tetramethylsilane (δ 0) as internal standard. Signal multiplicities, coupling constants, and integration ratios are indicated in parentheses.

Low resolution mass spectra were recorded on either a Kratos-AEI model MS 50 or MS 9 spectrometer. Only peaks with greater than 20% relative intensity or those which were analytically useful are reported. High resolution mass spectra were carried out on a Kratos-AEI model MS 50 instrument. An ionization voltage of 70 eV was used in all measurements.
3.2 SYNTHESIS AND REACTIONS OF 11-SUBSTITUTED-13-TETRADECANOLIDES

10-Bromo-1-decanol (56)

A suspension of 1,10-decanediol (20 g, 0.11 mol) in 48% hydrobromic acid (8.9 M, 32 mL, 0.29 mol) was prepared in a liquid-liquid extractor. The suspension was heated to 90 °C, while being continuously extracted with n-heptane for 24 h. The layers were separated and the aqueous layer was further extracted with n-heptane. The combined organic layers were washed successively with water, saturated NaHCO₃, saturated NaCl and then dried (MgSO₄). Rotary evaporation to remove the solvent and distillation (135-138 °C/2.5 torr) yield 56 as a clear, colourless liquid (20 g, 75%).

IR (neat, cm⁻¹): 3600-3200, 2930, 2856, 1460, 1272, 1050.

¹H NMR (CDCl₃, 300 MHz) δ: 3.65 (t, J = 6 Hz, 2H), 3.42 (t, J = 6 Hz, 2H), 1.86 (m, J = 7.5 Hz, 2H), 1.57 (m, J = 6 Hz, 2H), 1.50-1.24 (m, 13H, 1H D₂O exchangeable) ppm.

LRMS (m/z) from CI: 256 (⁸¹Br, M⁺+18, 96), 254 (⁷⁹Br, M⁺+18, 100).
LRMS (m/z) from EI ionization: 150 (25), 148 (26), 97 (26), 83 (43), 69 (83), 68 (24), 56 (21), 55 (100), 43 (35), 42 (23), 41 (90), 39 (22), 31 (27), 29 (33), 27 (25).

10-Bromo-1-(2-tetrahydropyranyloxy)-decane (63)

3,4-Dihydro-2H-pyran (12 mL, 0.13 mol) and a catalytic amount of p-toluenesulfonic acid monohydrate were added to a solution of 10-bromo-1-decanol (56) (20 g, 0.085 mol) in THF (200 mL). The resulting mixture was stirred overnight at room temperature. The solution was then washed successively with saturated NaHCO₃ and saturated NaCl and then dried (MgSO₄). Removal of the solvent and distillation (132-135 °C/0.2 torr) yielded the bromo-tetrahydropyranyl ether 63 as a clear, colourless liquid (22 g, 80%).

IR (neat, cm⁻¹): 2929, 2857, 1456, 1356, 1126, 1073, 1030.

¹H NMR (CDCl₃, 400 MHz) δ: 4.57 (t, J = 8 Hz, 1H), 3.87-3.40 (m, 6H), 1.85-1.25 (m, 22H) ppm.

LRMS (m/z): 322 (⁸¹Br, M⁺, 0.1), 320 (⁷⁹Br, M⁺, 0.2), 85 (100), 56 (22), 55 (22).
Exact mass calcd for C\textsubscript{15}H\textsubscript{29}\textsuperscript{79}Br\textsubscript{2}: 320.1351; found: 320.1350.

calcd for C\textsubscript{15}H\textsubscript{29}\textsuperscript{81}Br\textsubscript{2}: 322.1330; found: 322.1297.

1-(1,3-Dithian-2-yl)-11-(2-tetrahydropyranloxy)-undecane (64)

![Chemical structure](image)

1,3-Dithiane (6.6 g, 0.055 mol) was dissolved in THF (250 mL) and the solution cooled to -20 °C. A solution of n-butyllithium in hexanes (1.6 M, 35 mL, 0.056 mol) was added dropwise via syringe and the resulting yellow solution was stirred at low temperature (-20 °C) for 4 h. A solution of 10-bromo-1-(2-tetrahydropyranloxy)-decane (63) (19 g, 0.059 mol) in THF (60 mL) was then added dropwise and the solution was stirred at low temperature (-20 °C) for a further 4 h. It was then allowed to warm to room temperature and stirred overnight. The solution was poured into water and the layers separated. The aqueous layer was acidified with 1 M HCl and extracted with EtOAc. The combined organic layers were washed with saturated NaHCO\textsubscript{3}, saturated NaCl and then dried (MgSO\textsubscript{4}). Rotary evaporation, followed by column chromatography with ethyl acetate-hexanes (1:7) as eluant, gave 64 as a clear, colourless liquid (15 g, 78%).

IR (neat, cm\textsuperscript{-1}): 2923, 2856, 1459, 1356, 1276, 1126, 1074, 1029, 980, 904, 867.
**1H NMR** (CDCl₃, 400 MHz) δ: 4.58 (t, J = 8 Hz, 1H), 4.04 (t, J = 7 Hz, 1H), 4.87-4.38 (m, 4H), 3.86 (m, 4H), 1.92-1.25 (m, 26H) ppm.

**LRMS (m/z):** 360 (M⁺, 3.4), 275 (62), 119 (85), 55 (22), 41 (28).

**Exact mass calcd for C₁₉H₃₆O₂S₂:** 360.2157; found: 360.2158.

4-(1,3-Dithian-2-yl)-14-(2-tetrahydropyranloxy)-tetradecan-2-ol (65)

![Chemical structure of 4-(1,3-Dithian-2-yl)-14-(2-tetrahydropyranloxy)-tetradecan-2-ol (65)](image)

1-(1,3-Dithian-2-yl)-11-(2-tetrahydropyranloxy)-undecane (64) (7.0 g, 0.019 mol) was dissolved in THF (100 mL) and cooled to -20 °C. A solution of n-butyllithium in hexanes (1.6 M, 13 mL, 0.021 mol) was added dropwise and the solution stirred at low temperature (-20 °C) for 3.5 h. Propylene oxide (2.7 mL, 0.038 mol) was added and the mixture was stirred at -20 °C for an additional hour. The mixture was then poured into water and the layers separated. The aqueous layer was acidified with 1 M HCl and extracted with EtOAc. The combined organic layers were washed with saturated NaHCO₃, saturated NaCl and then dried (MgSO₄). Evaporation of the solvent and subsequent column chromatography with ethyl acetate-hexanes (1:3) as eluant, yielded 65 as a clear, colourless liquid (7.0 g, 85%).
IR (neat, cm⁻¹): 3850-3200, 2929, 2855, 1454, 1365, 1278, 1126, 1071, 1029, 905, 867.

¹H NMR (CDCl₃, 400 MHz) δ: 4.58 (t, J = 8 Hz, 1H), 4.13 (m, 1H), 3.92-3.35 (m, 4H), 3.58 (s, 1H, D₂O exchangeable), 3.10-2.74 (m, 4H), 2.00-1.24 (m, 28H), 1.20 (d, J = 4 Hz, 3H) ppm.

LRMS (m/z): 418 (M⁺, 6.8), 177 (33), 133 (16), 101 (10), 85 (100), 67 (13), 55 (18), 45 (10), 43 (13), 41 (23).

Exact mass calcd for C₂₂H₄₂O₃S₂: 418.2576; found: 418.2571.

2-Acetoxy-4-(1,3-dithian-2-yl)-14-(2-tetrahydropyranoxy)-tetradecane (66)

4-(1,3-Dithian-2-yl)-14-(2-tetrahydropyranoxy)-tetradecan-2-ol (65) (7.0 g, 0.017 mol) was dissolved in methylene chloride (100 mL). Triethylamine (3.5 mL, 0.025 mol) and a catalytic amount of 4-dimethylaminopyridine (DMAP) were added to the solution which was then stirred for 10 minutes. Acetic anhydride (2.4 mL, 0.025 mol) was added and the resulting solution was stirred overnight at room temperature. It was then diluted with Et₂O, washed with 1 M HCl, saturated NaCl and dried
Evaporation of the solvent yielded 66 as a clear, colourless liquid (7.0 g, 91%).

**IR** (neat, cm⁻¹): 2929, 2855, 1735, 1454, 1365, 1240, 1126, 1071, 1029, 905, 867.

**¹H NMR** (CDCl₃, 300 MHz) δ: 5.20 (m, 1H), 4.58 (t, J = 8 Hz, 1H), 3.92-3.55 (m, 4H), 2.78 (m, 4H), 2.04 (s, 3H), 1.98-1.20 (m, 31H) ppm.

**LRMS** (m/z): 460 (M⁺, 3.3), 159 (37), 101 (19), 85 (100), 81 (15), 79 (15), 67 (24), 55 (28), 45 (18), 44 (16), 43 (57), 41 (42), 39 (28).

Exact mass calcd for C₂₄H₄₄O₄S₂: 460.2681; found: 460.2673.

13-Acetoxy-11-(1,3-dithian-2-yl)-tetradecanol (67)

2-Acetoxy-4-(1,3-dithian-2-yl)-14-(2-tetrahydropyranloxy)-tetradecane (66) (7.0 g, 0.015 mol) was dissolved in methanol (75 mL). A catalytic amount of p-toluenesulfonic acid monohydrate was added and the resulting solution was stirred overnight. After evaporation of the methanol, the residue was dissolved in Et₂O,
washed with saturated NaCl and then dried (MgSO₄). Removal of the solvent and column chromatography with ethyl acetate-hexanes (1.1) as eluant yielded 67 as a clear, colourless liquid (4.8 g, 84%).

**IR (neat, cm⁻¹):** 3620-3200, 2929, 2855, 1740, 1454, 1365, 1210, 1126, 1029, 905, 867.

**¹H NMR (CDCl₃, 300 MHz)** δ: 5.20 (m, 1H), 3.64 (t, J = 6 Hz, 2H), 2.80 (m, 5H), 2.05 (s, 3H), 2.00-1.80 (m, 4H), 1.60-1.20 (m, 21H) ppm.

**LRMS (m/z):** 376 (M⁺, 16), 275 (23), 241 (16), 159 (100), 107 (19), 100 (31), 95 (19), 85 (18), 81 (27), 67 (27), 55 (30), 43 (86), 41 (38).

Exact mass calcd for C₁₉H₃₆O₃S₂: 376.2106; found: 376.2098.

**13-Acetoxy-11-(1,3-dithian-2-yl)-tetradecanal (68)**

A solution of 13-acetoxy-11-(1,3-dithian-2-yl)-tetradecanol (67) (3.1 g, 8.2 mmol) in benzene (30 mL) was prepared and the following were added successively: dimethyl sulfoxide (DMSO) (13 mL, 180 mmol), pyridine (0.68 mL, 8.4 mmol), trifluoroacetic acid (0.32 mL, 4.2 mmol) and 1,3-dicyclohexylcarbodiimide (DCC) (5.2
g, 25 mmol). The resulting mixture was stirred at room temperature for 7 h, after which time it was diluted with ethyl acetate. Oxalic acid (3.2 g, 25 mmol) was added to destroy excess DCC and the mixture was poured into saturated NaCl and filtered to remove the urea precipitate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with saturated NaCl and dried (MgSO₄). Evaporation of the solvent afforded a yellow oil containing a small amount of dicyclohexylurea as a white precipitate (3.9 g). The aldehyde 68, which was unstable to column chromatography, was used directly in the next step without further purification.

**IR** (neat, cm⁻¹): 2930, 2856, 2718, 1739, 1730, 1454, 1365, 1210, 1126, 1071, 1029, 905, 867.

**¹H NMR** (CDCl₃, 300 MHz) δ: 9.76 (t, J = 2 Hz, 1H), 5.20 (m, 1H), 2.90-2.70 (m, 4H), 2.43 (td, J = 8, 4 Hz, 2H), 2.05-1.80 (m, 8H), 1.73 (t, J = 8 Hz, 2H), 1.53-1.20 (m, 16H) ppm.

**LRMS** (m/z): 374 (M⁺, 34), 273 (36), 239 (20), 211 (23), 159 (100), 100 (31), 99 (20), 56 (20), 43 (32).

**Exact mass** calcd for C₁₉H₃₄O₃S₂: 374.1949; found: 374.1949.
13-Acetoxy-11-(1,3-dithian-2-yl)-tetradecanal (68) (3.2 g) was dissolved in THF (10 mL). Water (10 mL), silver nitrate (16 g, 94 mmol) and sodium hydroxide (10 g, 250 mmol) were added and the resulting mixture was stirred for 4 h. The precipitate was filtered and washed with ethyl acetate and water. The layers of the filtrate were separated and the aqueous layer acidified with 1 M HCl. This was extracted with ethyl acetate, then the combined organic layers were washed with saturated NaCl and dried (MgSO₄). Evaporation of the solvent yielded a yellow-brown liquid which was dissolved in ethyl acetate. After extraction with 1 M NaOH, re-acidification of the aqueous extract with 1 M HCl and extraction with ethyl acetate, this organic layer was washed with saturated NaCl and dried (MgSO₄). Evaporation of the solvent yielded the acid 69 as a yellow oil (1.6 g, 50% for two steps).

IR (neat, cm⁻¹): 3600-2400, 1740, 1720, 1454, 1365, 1210, 1126, 1071, 1029.

¹H NMR (CDCl₃, 300 MHz) δ: 5.20 (m, 1H), 2.86-2.76 (m, 4H), 2.35 (t, J = 7.5 Hz, 2H), 2.05-1.80 (m, 9H), 1.62 (t, J = 7.5 Hz, 2H), 1.40-1.23 (m, 16H) ppm.

LRMS (m/z): 390 (M⁺, 15), 348 (21), 289 (50), 256 (23), 255 (20), 223 (47), 177 (65), 161 (20), 159 (100), 133 (53), 107 (34), 106 (30), 100 (39), 98 (33), 95 (35), 84 (97), 79 (26), 74 (28), 73 (38), 67 (42), 56 (39), 55 (62), 45 (23), 43 (71), 41 (82).
Exact mass calcd for C_{19}H_{34}O_{4}S_{2}: 390.1897; found: 390.1906.

11-(1,3-Dithian-2-yl)-13-hydroxy-tetradecanoic acid (70)

13-Acetoxy-11-(1,3-dithian-2-yl)-tetradecanoic acid (69) (0.32 g, 0.82 mmol) was dissolved in a methanol-water (3:1) mixture (10 mL). Sodium hydroxide was added until the solution was basic and then the solution was heated at reflux for 40 h. The solvent was reduced to ~5 mL and the solution extracted with ethyl acetate. The aqueous layer was acidified with 1 M HCl and then extracted with ethyl acetate. This organic layer was washed with saturated NaCl and dried (MgSO₄). After removal of the solvent and column chromatography with ethyl acetate-hexanes (1:1) as eluant, the acid 70 was left as a yellow oil (0.15 g, 53%).

IR (neat, cm⁻¹): 3600-2400, 1720, 1454, 1365, 1210, 1126, 1071, 1029.

¹H NMR (CDCl₃, 300 MHz) δ: 4.13 (m, 1H), 3.10-2.70 (m, 4H), 2.35 (t, J = 8.4 Hz, 2H) 2.10-1.80 (m, 6H), 1.60 (t, J = 8.4 Hz, 2H), 1.45-1.23 (m, 14H), 1.20 (d, J = 6 Hz, 3H) ppm.
**LRMS (m/z):** 348 (M⁺, 40), 223 (42), 177 (100), 133 (58), 107 (34), 95 (25), 83 (21), 71 (31), 74 (29), 69 (39), 67 (27), 55 (60), 45 (39), 43 (52), 41 (67).

**Exact mass** calcd for C₁₇H₃₂O₃S₂: 348.1793; found: 348.1787.

**11-(1,3-dithian-2-yl)-13-tetradecanolide (71)**

1-Phenyl-1H-tetrazole-5-thiol (62 mg, 0.35 mmol) was dissolved in toluene (5 mL). *Tert*-butyl isocyanide (39 µL, 0.34 mmol) was added to the resulting solution and the mixture stirred at room temperature until homogeneous. The hydroxy acid **70** (95 mg, 0.27 mmol) was then added, the solution was diluted with toluene (50 mL) and then heated at reflux for 2 h. The solvent was evaporated to ~5 mL and the residue chromatographed with toluene as eluant. Column chromatography of the resulting yellow oil, with ethyl acetate-hexanes (1:8) as eluant, yielded the macrolide **71** as a pale yellow oil (18 mg, 20%).
IR (CHCl₃, cm⁻¹): 2931, 2860, 1721, 1488, 1460, 1371, 1258, 1109, 1048, 1018.

**¹H NMR** (CDCl₃, 400 MHz) δ: 5.18 (m, 1H), 2.95-2.68 (m, 4H), 2.40-2.20 (m, 4H), 2.05 (m, 1H), 1.95-1.83 (m, 2H), 1.80-1.65 (m, 2H), 1.45-1.32 (m, 13H), 1.30 (d, J = 6 Hz, 3H) ppm.

**LRMS** (m/z): 330 (M⁺, 73), 256 (38), 223 (25), 159 (100), 149 (22), 106 (28), 100 (46), 85 (22), 81 (23), 69 (26), 55 (46).

**Exact mass** calcd for C₁₇H₃₀O₂S₂: 330.1687; found: 330.1685

**11-(1,3-Dithian-2-yl)-2-methyl-13-tetradecanolide (72, 73)**

Diisopropylamine (154 µL, 1.10 mmol) was dissolved in THF (2 mL), the solution cooled to 0 °C and n-butyllithium in hexanes (1.4 M, 0.75 mL, 1.0 mmol) was added. The mixture was stirred at 0 °C for 0.5 h. At this time, the solution was cooled to -78 °C, and 11-(1,3-dithian-2-yl)-13-tetradecanolide (71) (0.19 g, 0.57
mmol) was added as a solution in THF (3 mL). The resulting mixture was stirred at -78 °C for 4.5 h. Methyl iodide (71 µL, 1.10 mmol) was added and the solution stirred at -78 °C for an additional 1 h, after which time the solution was warmed to room temperature and stirred overnight. The reaction was quenched with 1 M HCl, diluted with Et2O and the layers separated. The organic layer was washed with saturated NaHCO3, saturated NaCl and dried (MgSO4). Rotary evaporation to remove the solvent, followed by column chromatography with ethyl acetate-petroleum ether (1:6) as eluant, yielded a light brown oil (0.15 g, 76%), which was a 6:1 (GLC) mixture of 72 and 73 (DB-210 column, 140 °C isothermal).

**1H NMR** (CDCl3: 400 MHz) δ: 5.10 (m, 1H), 2.93-2.68 (m, 4H), 2.40-2.20 (m,3H), 2.00-1.70 (m, 4H), 1.50-1.20 (m, 17H), 1.10 (d, J = 6 Hz, 3H) ppm.

2-Methyl-13-tetradecanolide (74, 75)

11-(1,3-Dithian-2-yl)-2-methyl-13-tetradecanolide (72, 73) (0.15 g, 0.44 mmol) was dissolved in THF (5 mL). An aqueous suspension of Raney nickel (in pH 10 H2O, 1 g, 80-100 m2·g⁻¹) was added and the mixture heated at reflux for 4 h, after
which time the catalyst was removed by filtration. The filtrate was extracted with 
Et₂O, washed with saturated NaCl and dried (MgSO₄). Rotary evaporation to 
remove the solvent yielded a 6:1 mixture (GLC) of 74 and 75 (5.4 mg, 51%) (DB-210 
column, 140 °C isothermal).

**IR** (CHCl₃, cm⁻¹): 2928, 2857, 1709, 1460, 1378, 1278, 1082.

**¹H NMR** (CDCl₃, 300 MHz) δ: 4.93 (m, 1H), 2.42 (m, 1H), 1.70-1.10 (m, 26H) ppm.

**LRMS** (m/z): 240 (M⁺, 2.3), 111 (21), 97 (38), 85 (22), 83 (47), 74 (80), 70 (40), 67 
(20), 57 (38), 56 (53), 55 (100), 43 (44) 41 (63).

**Exact mass** calcd for C₁₅H₂₈O₂: 240.2089; found: 240.2095.

11-Oxo-13-tetradecanolide (44)

![Diagram of 11-Oxo-13-tetradecanolide (44)]

11-(1,3-Dithian-2-yl)-13-tetradecanolide (71) (0.22 g, 0.67 mmol) was 
dissolved in 90% acetone (25 mL), the resulting solution was cooled to 0 °C and N-
bromosuccinimide (0.80 g, 4.5 mmol) was added. This mixture was stirred at 0 °C for
2 h. Aqueous sodium sulphite was then added, the layers were separated and the organic layer was washed with saturated NaCl and dried (MgSO₄). Rotary evaporation to remove the solvent yielded yellow crystals. Column chromatography with petroleum ether-acetone (8:1) as eluant yielded white crystals of **44** (67 mg, 42%).

**MP** 37.5-39 °C

**IR** (CHCl₃, cm⁻¹): 2933, 2862, 1725, 1714, 1455, 1376, 1256, 1130, 1092.

**¹H NMR** (CDCl₃, 400 MHz) δ: 5.45 (m, 1H), 2.85 (m, 1H), 2.55-2.40 (m, 3H), 2.40-2.20 (m, 2H), 1.75-1.60 (m, 2H), 1.40-1.20 (m, 15H) ppm.

**LRMS** (m/z): 240 (M⁺, 2.6), 98 (38), 97 (25), 85 (28), 84 (97), 83 (20), 69 (100), 56 (26), 55 (72), 43 (34), 42 (24), 41 (49).

**Exact mass** calcd for C₁₄H₂₄O₃: 240.1725; found: 240.1722.
REFERENCES


47. in reference 8(b), p 597.

48. in reference 8(b), p 591.

49. in reference 18, p 3214.


APPENDIX I

NOMENCLATURE, CORNER POSITIONS AND POLAR MAPS

Dale\textsuperscript{22} recognized that when the lowest energy conformation of cyclotetradecane is viewed from the top, there are four atoms whose substituents point away from the ring. These atoms, known as the corner atoms, are shown below.

By definition, a corner position has two contiguous gauche dihedral angles of the same sign flanked on either side by an anti dihedral angle.\textsuperscript{61}
It was also Dale who devised a nomenclature system using the corner atom concept.61 The sides of the ring are named by the number of bonds between corner positions, with the direction around the ring chosen such that the smallest side is followed by the next smallest side. For example, the [3335] conformation is shown below.

To help identify corner atoms, as well as to distinguish between similar conformations, the concept of polar maps is useful.62 These are circular plots of the magnitude and sign of the endocyclic dihedral angles of a cyclic molecule versus the bond number (Figure 11). The atoms and bonds are arbitrarily labelled as in Figure 11, and the torsional angle between the planes of atoms 14'-1'-2' and 1'-2'-3' is defined as angle 1. The magnitude and sign of this angle is determined by looking at a Newman projection along the bond, with the lower numbered atom closest to the observer. An example is shown in Figure 12. The angle is positive if the direction of rotation from the front plane to the rear plane is clockwise. For angles of 180°, ambiguity arises as to the sign of the angle (Figure 13). By convention, we consider the remaining atoms of the ring and define the sign of the anti angle as the angle formed within the ring.
Figure 11. The atom (a) and bond (b) numbering used for the construction of a polar map (below).
Figure 12. An example of the definition of dihedral angles used in the construction of polar maps (angle 6 is shown).

Figure 13. Rule for determining the sign of the anti dihedral angle.
The polar maps for the three lowest energy conformations of cyclotetradecane are shown in Figure 14.

Figure 14. Polar maps for the three lowest energy conformations of cyclotetradecane.
APPENDIX II

THE MM2 PROGRAM

The strain energies of all compounds were calculated using Allinger's computer program. The equations of the program are derived from classical mechanics, and contain adjustable parameters that had been optimized to obtain the best fit consistent with the calculated and experimental properties of a large number of molecules. The advantage of the MM2 program over quantum mechanical calculations is in its speed for complex molecules, while still giving accurate results.

To minimize the energy of a molecule, the MM2 program uses the steepest descent method. The energy is first calculated for the input coordinates, and then every atom in the molecule is simultaneously moved to new coordinates and the energy recalculated. If the new energy is lower, the atom(s) are further moved in this direction until the energy difference is less than some preset value. The final strain energy quoted is the sum of the following contributions: bond stretching, angle bending, torsional strain, van der Waals interactions, and electrostatic effects.

For the calculations in this thesis, the input parameters used were from the 1982 MM2 force field. In addition, the dithiane ring was approximated simply with the two sulfur atoms and the methylene carbons were omitted as they were not expected to affect the macrocyclic conformation.
APPENDIX III

IR AND $^1$H NMR SPECTRA