Synthesis, Conformational Analysis, and Stereoselective Reduction of 14-Membered Ring 3-Keto Lactones

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Received March 24, 1993®

The synthesis of 3-oxo-13-tetradecanolide (**5**) and its 2-methyl and 2,2-dimethyl derivatives **7** and **8** have been carried out. The keto carbonyls in **5**, **7**, and **8** have been reduced with varying degrees of stereoselectivity. The stereoselectivity of the reduction depends on the counterion with the borohydride reducing agent, but selectivities approaching 100% have been achieved for **5** and **7**. The structure of the reduced products were determined by X-ray crystallography and chemical correlation. Heavy reliance on the stereoselectivity in the Frater dianion alkylation was used. The solution conformation of the β-keto lactones was found to be based on **A** both from NMR studies and molecular mechanics calculations. However, we are not able to predict the observed stereoselectivity in the hydride reduction of the ketones using this conformation. Thus we suggest the reduction proceeds through conformation **B′** in which the two carbonyls are chelated to the counterion. The conformations of the resulting alcohols are more complex and have both inter- and intramolecular hydrogen bonding which control the conformations. The use of polar maps to illustrate similarities and differences in conformations is demonstrated. These conformations are used to rationalize the physical and chemical properties of the β-keto and β-hydroxy 14-membered lactones.

Introduction

For the past 40 years the stereochemical outcome of nucleophilic additions to carbonyl compounds has played an important role in synthetic and physical organic chemistry.[1] There has been particular interest in these reactions of cyclic ketones[2] and a great deal of effort has been devoted to understanding the principles controlling the stereochemistry of these reactions. The torsional strain model developed by Felkin and Anh[3] is the most widely accepted rationale to explain the stereochemistry of nucleophilic additions to ketones.[4] In 1976, Wipke and Gund developed an empirical molecular mechanics force field to model such nucleophilic additions to a carbonyl.[5] This model is based on steric and torsional effects in the starting ketone, and it correlated a great deal of experimental data. Perlberger and Müller extended this to an empirical molecular mechanics model for the transition structure of hydride addition to a ketone with good success.[6] More recently, Houk and co-workers have developed a molecular mechanics force field for the transition state for nucleophilic additions to carbonyls based on ab initio calculations.[7a] This model for the transition structure correlates a wealth of experimental data[7b] and emphasizes the importance of torsional effects in the addition of nucleophiles of carbonyl compounds.[7] Frontier molecular orbital methods have also been applied to this problem.[4d,8]

Following Still and Galynker's seminal work on the conformational control of reactions of medium and large rings,[9] several research groups have demonstrated the control of the stereochemistry of reactions of medium and large rings.[10,11] For example, the macrolide antibiotics have several hydroxyls on their macrocyclic skeleton. A number of syntheses of these molecules and their analogs have included a stereoselective reduction or addition to a ketone to generate these chiral centers.[12,13] A recent example of the reduction of a polyketo macrolide is shown in eq 1.[14] The tetraketo derivative **1** was synthesized from oleandomycin, presumably with the stereochemistry

® Abstract published in *Advance ACS Abstracts,* October 15, 1994.

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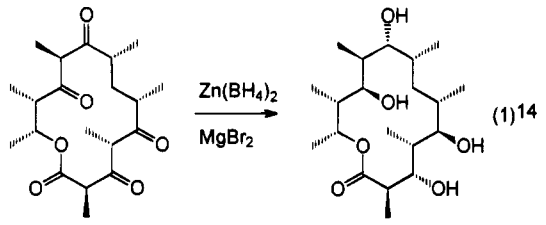
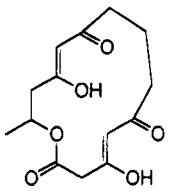
shown. Reduction of **1** with $Zn(BH_4)_2$ in the presence $MgBr_2$ remarkably gave the tetrol **2** in ca. 80% yield. The stereochemistry of **2** was determined by an X-ray crystallographic study.[14] Omission of the $MgBr_2$ in the reduction resulted in a lower yield of **2**, suggesting that metal ion chelation may be important in the reduction. The stereochemistry of all the methyl-substituted carbons in **2** is exactly the same as that of the starting oleandomycin which suggests that the β-dicarbonyls of **1** do not enolize during the reduction.



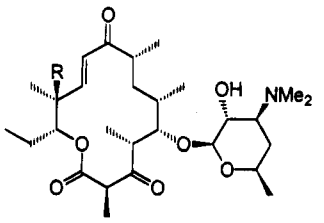
1 **2**



3

Following up on this study, Tatsuta, et al. synthesized the simple tetraketo macrolide **3**.[15] An X-ray crystallographic investigation of this compound showed that it was a bis-enol in the solid state and NMR studies confirmed that it retained this bis-enolic form in solution. Reduction of **3** with $NaBH_4$ gave a mixture of at least 8 of the possible 16 diastereomers of the corresponding tetrol. Three of the tetrols crystallized and their structures were determined by X-ray crystallography.[15] Thus the chemistry of the unsubstituted macrolide **3** was more complicated and less stereoselective than that of the complex oleandomycin derivative **1**.

This present study is devoted to the reduction of 14-membered ring β-keto lactones. Pikromycin (**4a**) and narbomycin (**4b**) are two macrolide antibiotics which contain a β-keto lactone unit.[16,17] It is interesting to note that the β-keto lactone moiety in pikromycin was finally suggested more than a decade after the first structural proposals were made for this compound.[18] Both β-keto macrolides appear to undergo stereoselective reduction. However the stereochemistry of the product was not determined. Muxfeldt et al. noted that the C-2 methine of pikromycin (**4a**) does not undergo facile exchange and they suggested this is due to the rigid conformation of the 14-membered ring.[18b] These authors also found that the NMR spectrum of **4a** was unchanged on heating to 160 °C. The C-2 hydrogen of pikromycin (**4a**) can be deprotonated in basic ethanol solution.[18a] In contrast to the NMR results, the temperature dependence CD spectra of **4a** and **4b** suggested that there may be a fast conformational equilibrium for these compounds at room temperature.[19] These results combined with the above results from Tatsuta's laboratory indicate that macrocyclic β-keto lactones have unusual chemical and physical properties that depend on the conformation of the large ring. It is also noteworthy that although there are a large number of macrolide antibiotics and their analogues which have been synthesized with a β-hydroxy lactone moiety, only one of these compounds has been prepared by stereoselective reduction of the corresponding β-keto lactone, in addition to the transformation shown in eq 1.



4a, R = OH
4b, R = H

In those cases in which a rationale for the stereochemical outcome of the macrocyclic carbonyl additions was provided, invariably the authors chose an argument based on steric-controlled approach to the more open face of the carbonyl in the lowest energy conformation. The steric approach model for small ring ketones has been the subject of some controversy.[2b,5] Therefore we were interested in exploring the stereoselectivity of the reduction of simple less substituted macrocyclic keto lactones, to determine those factors which might control reductions of the keton carbonyl.

In many of these macrocyclic systems, there are a number of conformations close in the energy to the global minimum conformation and having low barriers to interconversion. According to the Curtin–Hammett principle, it is the transition states from these conformations, not the ground states, which determines the rate of

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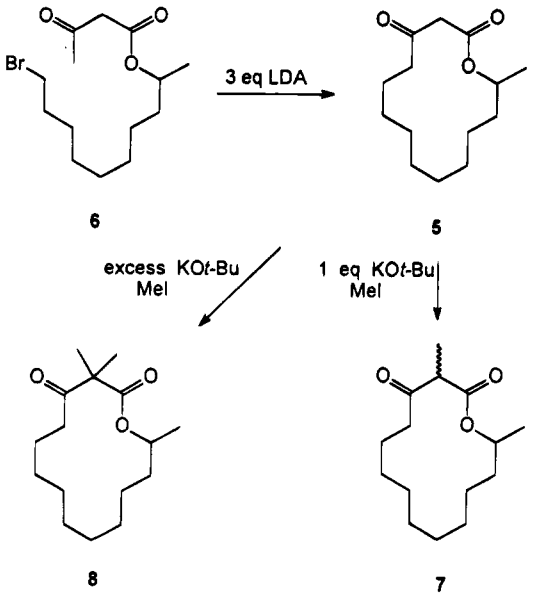
formation of products.[20] Thus the question arises, can we use ground state geometries as an approximation to the transition state in such reductions?

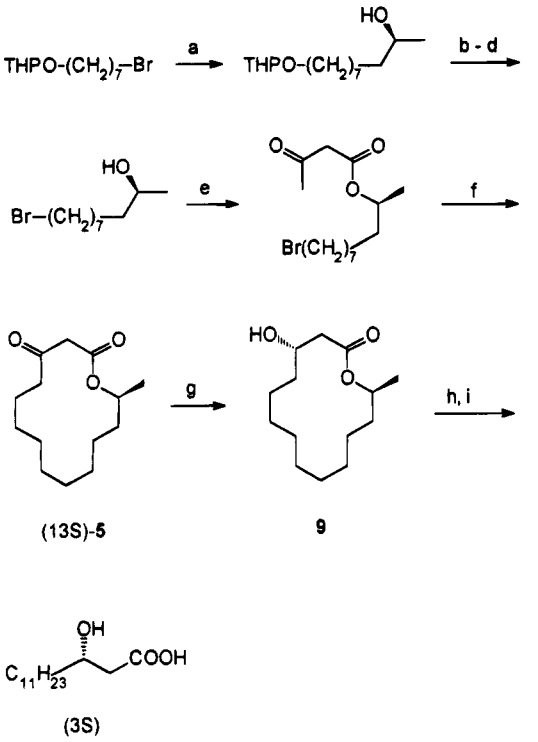
Results and Discussion

The 3-keto lactone **5** was prepared in about 50% yield by an intramolecular alkylation of the dianion from the β-keto ester **6**.[21] In addition we prepared the C-2 methylated derivatives of **5**, by treating **5** with a slight excess of potassium *tert*-butoxide and methyl iodide to give an 87% yield of the monomethylated product **7** as a 2:1 equilibrium mixture of diastereomers. We have been unable to unambiguously determine the stereochemistry of the major or minor epimer of **7** as yet. When **5** was treated with an excess of potassium *tert*-butoxide and methyl iodide the gem-dimethylated product **8** was obtained in 98% yield.



Reduction of 3-Keto Lactones and Alkylation of the Resulting Alcohols. A number of experimental conditions were investigated for the reduction of 3-oxo-13-tetradecanolide (**5**). It was found that the stereochemistry of the reduction of **5** depended on the reducing agent. With lithium tri-*sec*-butylborohydride, a single hydroxy lactone was isolated in 87% yield. No other hydroxy lactone could be detected in the crude reaction mixture by TLC or capillary column GLC. It was difficult to determine the relative stereochemistry of the substituents in this macrocyclic alcohol. We were able to assign several of the chemical shifts and coupling constants in the ^{1}H-NMR of this product. However, because of the uncertainty about its conformation at this time, we were unable to definitively determine the stereochemistry of this product from the NMR data alone. This was solved in two ways. Starting from (13*S*)-propylene oxide and 1-bromo-7-(tetrahydropyranyloxy)heptane, we prepared the (13*S*)-β-keto lactone **5** as shown in Scheme 1. This keto lactone was reduced and converted to 3-hydroxytetradecanoic acid which had the *S* configuration. Thus the major alcohol must have the 3*S*,13*S* stereochemistry as shown in **9**. This is one of the rare examples in which

Scheme 1[a]



[a] Key: (a) Mg, THF; and then (*S*)-propylene oxide; (b) AcOH–THF–H_2O, Δ; (c) TsCl, py; (d) LiBr, Me_2CO, Δ; (e) acetyl Meldrum's acid, THF, Δ; (f) 3 equiv LDA, THF, −78 °C; (g) Li(*sec*-Bu)$_3$BH, THF, −10 °C; (h) $NaSeC_6H_5$, HMPA; (i) (*n*-Bu)$_3$SnH, AIBN, C_6H_5Me, 60 °C.

the absolute stereochemistry of two asymmetric centers was determined separately in an effort to prove their relative configurations.

The structure of alcohol **9** was also unambiguously determined to be 3*S**,13*S** from an X-ray crystallographic analysis of the corresponding bromoacetate.[22] Sodium borohydride reduction of **5** gave a mixture of two alcohols in a ratio of 3:1. The major alcohol was identical to **9**. The minor alcohol was easily shown to the 3*R**,13*S** isomer **10** by oxidation back to **5** and by an X-ray crystallographic analysis of its bromoacetate derivative.[22] Both the major alcohol **9** and the minor alcohol **10** were treated with 2 equiv of lithium diisopropylamide (LDA) to generate the dianion which was alkylated with methyl iodide.[23] Alcohol **9** gave two alkylated products in a ratio of 9:1. On the basis of the chelation controlled transition state **13**[23b] for alkylation of β-hydroxy esters, the major product was predicted to have the stereochemistry shown in **11**. Alcohol **10** also gave two Frater alkylation products in a ratio of 3:1. These alcohols were different from the two products from **9**. The lower stereoselectivity in this reaction cast some doubt on using the chelated transition state model to predict the major stereoisomer on the Frater alkylation of β-hydroxy lactones. However, we were able to obtain an X-ray crystallographic analysis of the major isomer from this mixture and found that it has the relative stereochemistry shown in **12** which was consistent with transition state **14**. Thus we were confident of the assignment of the relative stereochemistry of **11** as well.

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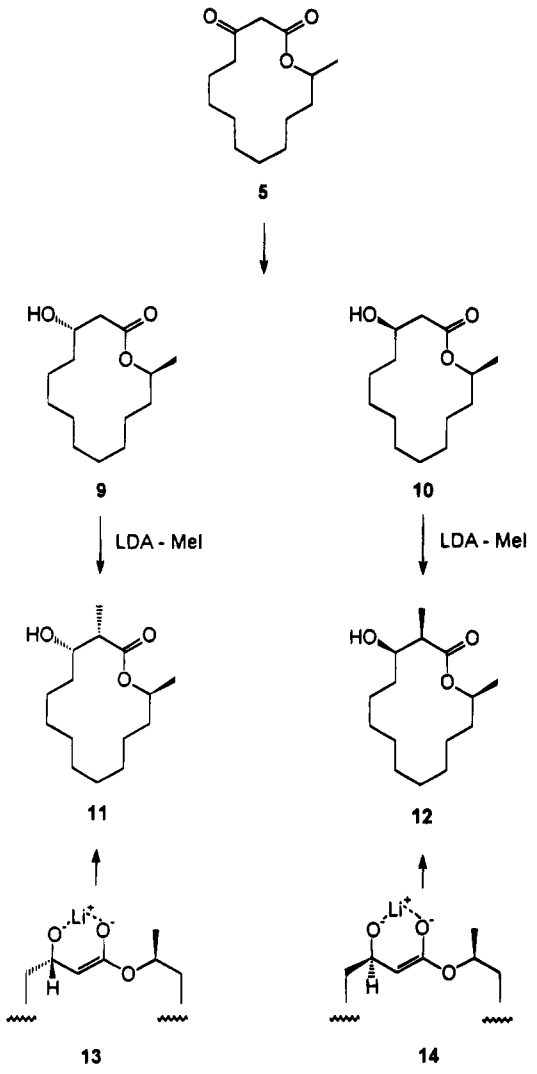

The results of these initial reduction experiments suggested that metal ion chelation of the carbonyls of **5** may be important in these reactions. In addition the change in stereochemistry using tetrabutylammonium borohydride versus the alkali metal borohydrides pointed to the importance of the counterion in the reduction (Table 1). A series of experiments in which a metal cation was added to the tetrabutylammonium borohydride reduction mixture is shown in Table 1. Addition of either LiBr or $MnCl_2$[24] led to enhanced stereoselectivity in the reduction confirming the importance of the counterion. These results are consistent with chelation control by Li^+ and Mn^{2+}, and they suggest that sodium cations may also coordinate to both carbonyls in the $NaBH_4$ reduction. It is known that sodium cations can coordinate to the carbonyl of ketones[2c] and to esters[25] separately.

The mixture of 2-methyl ketones **7** was reduced with several reducing agents to give **11**, **12**, **15**, and **16** (Table 2). The major reduction products, **11** and **15**, in the $NaBH_4$ and Li(*sec*-Bu)$_3$BH reductions have the alcohol and the C-13 methyl groups "trans" as found in the $NaBH_4$ reduction of **5**. There is a definite counterion effect on the stereoselectivity of these reductions as well.

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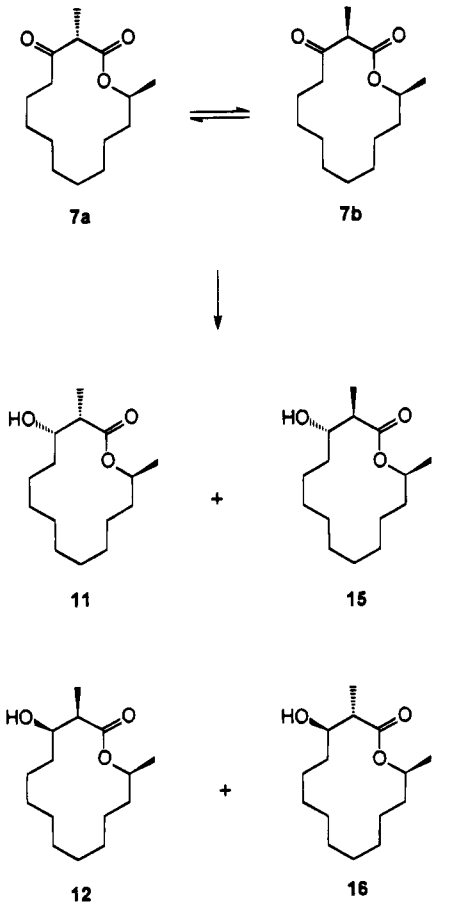
Table 1. Reduction of the β-Keto Lactone 5

	9:10
Li(*sec*-Bu)$_3$BH	>99:1
$NaBH_4$	75:25
$NaBH_4$ + $MnCl_2$	98:2
Bu_4NBH_4	40:60
Bu_4NBH_4 + LiBr	90:10
Bu_4NBH_4 + $MnCl_2$	97:3

Table 2. Reduction of Keto Lactone 7

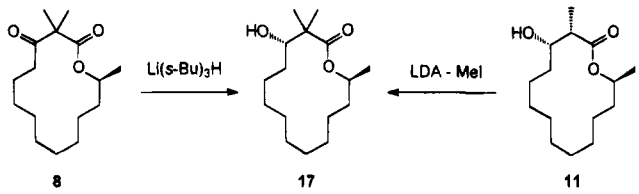
	yield, %				ratio of
	11	**15**	**12**	**16**	**(11 + 15):(12 + 16)**
$NaBH_4$	68	16	11	5	5:1
Li(*sec*-Bu)$_3$BH	90	8	2	0	49:1
Bu_4NBH_4	52	9	21	17	3:2
Bu_4NBH_4 + LiBr	56	15	14	15	7:3
Bu_4NBH_4 + $MnCl_2$	97	2	1	0	98:1

Reduction product **15** was identical to the minor isomer from the Frater alkylation of **9**; while compound **16** was identical to the minor isomer from the Frater alkylation of **10** which provides additional confirmation of their structures. The ratio of C-2 epimers in the starting ketone **7** was 2:1 by ^{1}H NMR and the yield of alcohols in the reductions was greater than 80%; thus, there must be an equilibration of the C-2 isomers during reduction, with the "trans" isomer **7a** undergoing reduction faster than the "cis" isomer **7b**. However, we are unable to say which isomer is the major one in the starting ketone **7** (see below).



Reduction of **8** with Li(*sec*-Bu)$_3$BH gave alcohol **17** in greater than 99.5% stereoselectivity (230:1). The structure of **17** was proven by subjecting **11** to the Frater alkylation to give a product identical to the product from

the reduction of **8**. In addition an X-ray crystallographic analysis of **17** confirmed that the substituents in **17** were 3*S**,13*S**.



Deuteration Exchange and Degree of Enolization of 3-Keto Lactones. The β-keto lactones **5** and **7** were treated with a trace of NaOMe in MeOH-d_4 and the exchange of the C-2 methylene or methine hydrogens was followed by ^{1}H NMR spectroscopy. In both compounds exchange occurred readily, but it was qualitatively slower than in acyclic β-keto esters. Thus the lack of exchange of the C-2 hydrogen in pikromycin (**4a**) must be associated with the stereoelectronic and/or steric effects associated with the conformation of the particular 14-membered ring in **4a** with its complex array of substituents, since the simple analog **7** undergoes exchange.

^{1}H NMR studies of β-keto lactones **5** and **7** showed that the degree of enolization in $CDCl_3$ or CD_3OD was less than 2%. This is less than the enol content of acyclic β-keto esters. For example, the starting material **6** has about 5% enol content in these solvents. However, this low degree of enolization is expected for such β-keto lactones and is in marked contrast to the high degree of enolization in **3**.[15]

Conformational Analysis of 3-Keto Lactones. The solution IR spectrum of the 3-keto lactone **5** shows three carbonyl bands at 1738, 1725, and 1709 cm^{-1} which suggests that there are at least two conformations present. ^{1}H NMR studies of **5** also suggest that at room temperature there are at least two conformations present and they are slowly interconverting on the NMR time scale. Temperature studies of the NMR spectrum of **5** suggested that a third conformation may also be present.[21b] Earlier molecular dynamics calculations using the MM2 force field[26] led to the conclusion that the global minimum energy conformation of **5** was **A** (Figure 1).[21b] Schweizer and Dunitz have found that esters of secondary alcohols usually have small torsional angles for the H–C–O–C-(=O) angle, θ.[27] It has been shown that a similar effect exists for macrocyclic lactones of secondary alcohols.[28] This effect is not included in the MM2 force field. For example, the MM2 calculated global minimum conformation of isopropyl acetate has θ = 45°, and the energy surface is very flat with other minima at 0° and 180° that are 0.65 kcal/mol above the global minimum. Whereas the MM3 calculated global minimum conformation of isopropyl acetate has θ = 25.5° and the only other stable conformation is at θ = 180° which is 1.7 kcal/mol higher energy with a calculated barrier of 2.1 kcal/mol in keeping with the solid sate structural results for such esters.

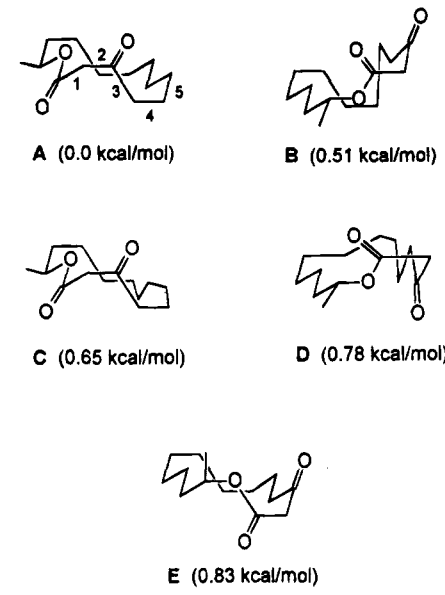
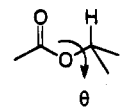


Figure 1. Conformations of the 3-keto lactone **5** with relative energies in parenthesis from a MACROMODEL conformational search.[30] The numbers on conformation **A** refer to the torsional angles used in the polar maps.

Table 3. Torsional Angles in the Lowest Energy Conformations of Lactone 5 Calculated Using MACROMODEL and the MM3 Force Field

	conformation at relative energy (kcal/mol)				
torsional angle[a]	**A**, 0.00	**B**, 0.51	**C**, 0.65	**D**, 0.78	**E**, 0.83
1	−86	105	−88	64	49
2	−69	−74	−71	52	64
3	166	160	169	−173	−174
4	−56	−176	−65	171	173
5	−52	60	−70	−60	−62
6	177	61	174	−64	−64
7	−174	−176	−60	165	169
8	56	59	−62	−73	−61
9	55	55	166	−64	−56
10	177	−177	176	−171	−176
11	64	170	51	−67	−172
12	61	−69	52	−62	56
13	−146	123	−147	152	82
14	−178	180	178	−177	179
H–C–O–C angle	−26	−1.9	−28	33	−38
conformation	[3434]	twist	[3344]	[3344]	[3434]

[a] The torsional angle 1 is between atoms O_1–C_1–C_2–C_3 within the ring.[31]



As a result we have used the MM3 force field[29] in our more recent calculations on the conformations of these macrocyclic lactones. A Monte Carlo search of conformational space of **5** using the MM3 force field in MACROMODEL[30] gave five conformations within 1 kcal/mol of the global minimum which, as for our earlier MM2 calculations, was found to be conformation **A** (Figure 1). The torsional angles of these five lowest-energy conformations are given in Table 3. These torsional angles

(26) Burkert, U.; Allinger, N. L. In *Molecular mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982.
(27) Schweizer, W. B.; Dunitz, J. D. *Helv. Chim. Acta* **1982**, *65*, 1547.
(28) (a) Keller, T. H.; Neeland, E. G.; Rettig, S.; Trotter, J.; Weiler, L. *J. Am. Chem. Soc.* **1988**, *110*, 7858. (b) Quinkert, G.; Döller, U.; Eichhorn, M.; Küber, F.; Nestler, H. P.; Becker, H.; Bats, J. W.; Zimmerman, G.; Dürner, G. *Helv. Chim. Acta* **1990**, *73*, 1999.
(29) (a) Allinger, N. L.; Yuh, Y. H.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8551. (b) Allinger, N. L.; Zhu, Z. S.; Chen, K. *J. Am. Chem. Soc.* **1992**, *114*, 6120.
(30) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

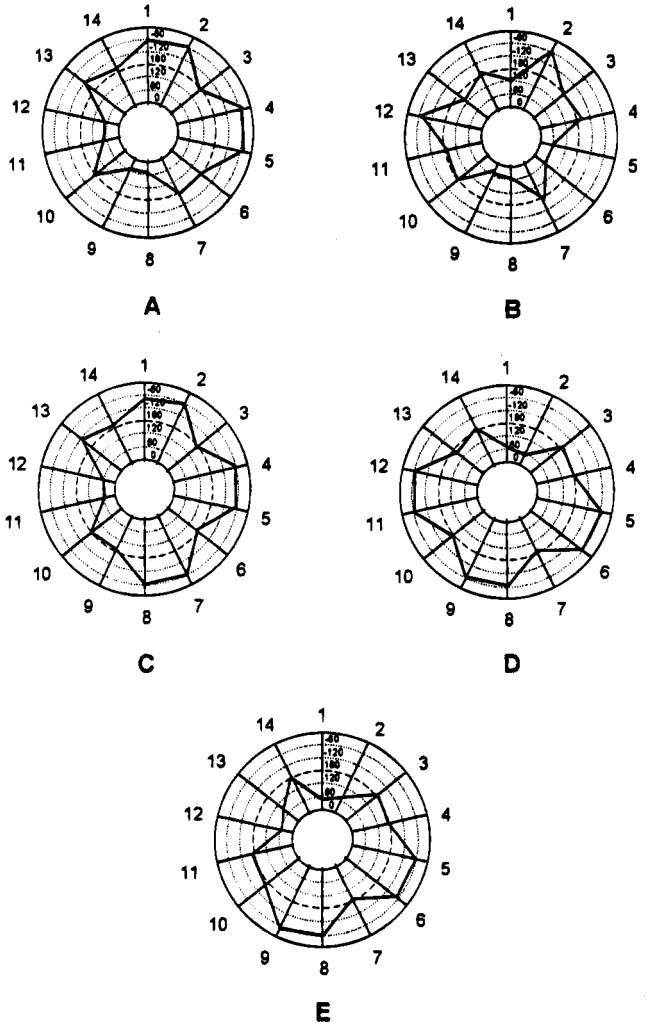
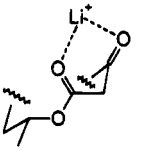


Figure 2. Polar maps[31,32] of the five lowest energy conformations of **5**. See **A** (Figure 1) for the numbering of the torsional angles.

uniquely define a conformation, but it is difficult to see the relation between these conformations from such a tabulation. This can be more readily seen from the polar maps[31,32] of these conformations which are given in Figure 2. The polar map for **A** clearly shows that this is the pattern for the [3434] conformation. These polar maps also show that **E** is a [3434] conformation with the position of the lactone and ketone exchanged. Similarly we see that **C** and **D** have the same skeletal conformation: rotate the polar map for **D** counterclockwise by 130° and it can be superimposed on the polar map for **C**. However, the functional groups are at different positions on the two [3344] conformations. All five of the conformations **A**–**E** have small H–C–O–C dihedral angles consistent with the Schweizer–Dunitz rule. The most interesting conformation for the following discussion is **B** which should be reasonably populated at room temperature. In conformation **B** the torsional angle between carbons 1–2 has opened up significantly compared to **A**, and the torsional angle between carbon-13 and oxygen-1 is eclipsed. These small changes result in the close alignment of the two carbonyls.

Hydride reduction from the more open outside face of conformations **A** or **C**–**E** will give the 3*R**,13*S** alcohol **10** which is the minor product in the reaction. However, reduction from the more open outside face of conformation **B** will yield the 3*R**,13*R** alcohol **9** which is the major product found in the reduction of **5** in the presence of metal cations. In conformation **B′** (shown below) the two carbonyls are aligned so that they can chelate a metal cation.[2c] Consistent with this model was the observation that reduction of **5** with $(n\text{-Bu})_4NBH_4$ gave a mixture of **9**:**10** in the ratio 2:3. It was also observed that addition of either LiBr or $MnCl_2$[24] in the $(n\text{-Bu})_4NBH_4$ reduction led to enhanced stereoselectivity, presumably by metal cation chelation of the two carbonyls as in **B′** which would funnel the reaction through such an intermediate. The X-ray crystallographic studies of both pikromycin (**4a**)[16d] and the *p*-bromobenzoate derivative of pikromycin[16c] show that both molecules crystallize in conformations in which the two carbonyls are aligned in a manner similar to that found in conformation **B**. If we assume that **A** and **B** undergo reduction at comparable rates, then we expect the ratio of **9**:**10** to be 1:2 in the absence of metal chelation. This is in reasonable agreement with the observed ratio of **9**:**10** = 2:3 using $(n\text{-Bu})_4NBH_4$. The calculated global minimum energy conformation **A** is the same conformation as that found in the solid state for the simple 14-membered lactone, 13-tridecanolide,[33a] and for the symmetric 14-membered dilactone from 6-hydroxyhexanoic acid.[33b] Thus we conclude that the reduction of the simple β-keto lactone **5** is controlled by metal ion chelation of the two carbonyls with reduction from the more open face of the molecule as in **B′**.



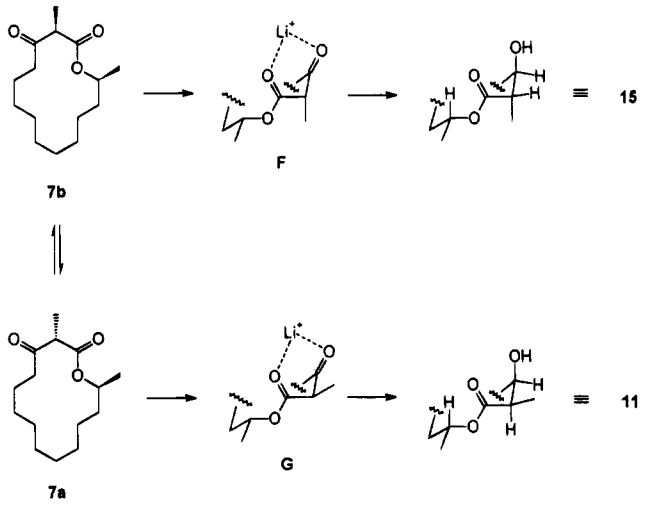
B′

The β-keto lactone **7** is a mixture of two C-2 epimers. Interestingly, they can be separated by GLC and have several differences in their NMR spectra. The distinguishing features of the NMR spectra are the signals between 2.4 and 2.8 assigned to the C-4 protons of **7**. In the major isomer the C-4 protons are multiplets at δ 2.50 and 2.68. Each of the multiplets have coupling constants of 7, 8, and 18 Hz. The C-4 protons of the minor isomer are multiplets at δ 2.37 and 2.82 with coupling constants of 6, 8, and 19 Hz. The large C-4 geminal coupling constant for each epimer suggests that these compounds exist in a conformation in which the O=O–C_4–C_5 torsional angle is small.[34] The vicinal coupling constants in both multiplets suggest a relatively rigid conformation with a large anti coupling. Similar arguments follow for the minor epimer and we suggest that each epimer has the same local conformation about the functional groups.

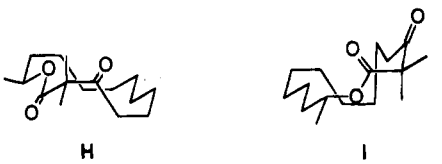
Conformational searches for the global minima for **7a** and **7b** gave the following results. The global minimum conformations for **7a** and **7b** were very similar, 19.66 kcal/mol for **7b** and 19.77 kcal/mol for **7a**, which would lead to a predicted equilibrium ratio of 55:45 based on

(31) Ounsworth, J. P.; Weiler, L. *J. Chem. Ed.* **1987**, *64*, 568.
(32) Fyles, T. M.; Gandour, R. D. *J. Incl. Phenom. Mol. Recognit. Chem.* **1992**, *12*, 313.
(33) (a) Wiberg, K. B.; Waldron, R. F.; Schulte, G.; Saunders, M. *J. Am. Chem. Soc.* **1991**, *113*, 971. (b) Groth, P. *Acta Chem. Scand.* **1985**, *A39*, 659.
(34) (a) Barfield, M.; Grant, D. M. *J. Am. Chem. Soc.* **1963**, *85*, 1899. (b) Montecalvo, D.; St-Jacques, M. *J. Org. Chem.* **1975**, *40*, 940.

the energies of the global minima compared to the observed value of 66:33. The calculations also suggest that the 3S*,13R*-isomer **7b** is the major one. There are three other conformations within 1 kcal/mol of the global minimum for **7b** and two others within 1 kcal/mol of the global minimum of **7a**. For all four conformations considered for **7b** and the three conformations for **7a**, the O=C–C_4–C_5 torsional angle is less than 16°, consistent with the large C_4 geminal coupling constants. The cation effect on the stereoselectivity of the reduction points to involvement of a metal ion-chelated transition state. The lowest energy conformation of **7a**, **G** below, and the second-lowest energy conformation of **7b**, **F**, which is 0.07 kcal/mol above the global minimum, have the two carbonyls aligned. Reduction of **G** from the more open face leads to the major observed product **11**, while reduction of **F** from the more open face leads to **15**. Thus we suggest that the reduction proceeds through the intermediate **G**. As noted above reduction must be slower than equilibration of the C-2 methyl group.



The stereoselectivity of the reduction of **8** with L-Selectride was the highest we have observed for any 14-membered keto lactone. The ^{1}H NMR spectrum of **8** suggested that this keto lactone may exist mainly in a single conformation or in conformations in which the geometry from C-12 through to C-5 must be similar. For example, one of the $J_{12,13}$ coupling constants and one of the $J_{4,5}$ coupling constants have large values which would not be expected for a compound undergoing averaging of two or more conformations with different geometries in this region. A MACROMODEL conformational search on **8** gives the global minimum conformation as **H**. The coupling constants for H_4 and H_5, and H_{12} and H_{13}, predicted from an analysis of **H** are consistent with the observed values. The C-4 geminal coupling of 18.5 Hz requires a conformation in which the C-3 ketone bisects the C-4 methylene group[34] as found in **H**. In this conformation the gem-disubstituted carbon is at a "corner" position as predicted for these large rings by Dale.[35c] Reduction of **H** from the more open exo face would give the 3*R**,13*S** isomer that was not observed. There are four other conformations within 2 kcal/mol of the global minimum. One of these conformations **I** is 0.5 kcal/mol above the global minimum. This conformation has the carbonyls aligned for metal ion chelation and the gem-disubstituted carbon again at a corner position. As above we suggest that this reduction occurs under chelation control via a transition state involving conformation **I** to give the 3*R**,13*R** isomer **17**.



We have also investigated the use of the Wu–Houk molecular mechanics parameters (in an MM2 force field) for the hydride reduction of ketones.[7a] For the reduction of **5**, **7**, and **8**, steric effects are calculated to be larger than torsional effects. This is consistent with the steric approach model which we have proposed above.

Conformational Analysis of 3-Hydroxy Lactones. The isomeric hydroxy lactones **9** and **10** have very different spectroscopic properties and these data provide some insight into their conformation. For example, alcohol **9** does not have a free OH stretch in the infrared, but does show a strong intramolecular OH stretch at 3330 cm^{-1}. In addition the CO stretch in **9** is at 1715 cm^{-1} which is consistent with an intramolecular hydrogen bond between the C-3 hydroxyl and the lactone carbonyl. This would suggest conformation such as **J** for **9**. The C-2 methylene protons of **9** exhibit an ABX pattern in the ^{1}H-NMR with couplings of 2.6 and 7.4 Hz with the proton on C-3 which is also consistent with this conformation. On the other hand **10** has a free OH stretch at 3630 cm^{-1}, a solvent dependent associated OH stretch at 3450 cm^{-1} and a CO stretch at 1725 cm^{-1} in the infrared which all are consistent with the absence of an intramolecular hydrogen bond in this compound. The C-2 methylene group of **10** also is an ABX system in the ^{1}H-NMR, but with couplings of 3.1 and 10.5 Hz to the C-3 proton. This data suggests that **10** exists in conformation such as **K**. The conformations **J** and **K** were built by putting the substituents on the appropriate carbons of the **A** conformation. We have found this to be a useful first approximation for these 14-membered lactones and it often gives the correct conformation in the vicinity of the functional groups in the molecule.

It is interesting to note that **9** runs faster on TLC than **10**, consistent with the intramolecular hydrogen bond in **9**. A similar type of intramolecular hydrogen bonding as proposed in **J** has recently been suggested in the regioselective glycosylation of erythronolide intermediates.[36] We have also used the conformational models **J** and **K** to explain the relative reactivity of the alcohols **9** and **10** in esterification and oxidation reactions.[37] The X-ray crystallographic study of the bromoacetate of **10** shows that in the solid state the bromoacetate of **10** adopts two conformations, one of which corresponds to **K** and the second conformation is the [3344] conformation in which the corner position has changed from C-6 to C-7.[22] The conformation the bromoacetate of **10** in the vicinity of the functional groups is the same in the two solid-state conformations and they are identical to **K** in the region around the functional groups. Only the

(35) (a) Dale, J. *Acta Chem. Scand.* **1973**, *27*, 1115. (b) Dale, J. *Acta Chem. Scand.* **1973**, *27*, 1131. (c) Dale, J. *Acta Chem. Scand.* **1973**, *27*, 1149.

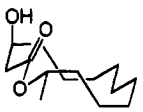
(36) Toshima, K.; Mukaiyama, S.; Yoshida, T.; Tamai, T.; Tatsuda, K. *Tetrahedron Lett.* **1991**, *32*, 6155.

(37) Ounsworth, J. P. Ph.D. Thesis, University of British Columbia, 1985.

conformation of the hydrocarbon chain varies in the two solid-state conformations.

MM3 conformational search calculations were carried out on both **9** and **10**. For **9** we found four conformations within 0.05 kcal/mol of the global minimum. This is one of the few times where we have found that the molecular mechanics calculations give a large number of conformations close to the global minimum. The two lowest-energy conformations are identical for all but one torsional angle. That is the torsional angle between $C_4-C_5-C_6-C_7$ which is $-174°$ in one and $+174°$ in the other. In fact the first three conformations are essentially the same. All four lowest-energy conformations contain an intramolecular hydrogen bond consistent with the IR data and have small H−C−O−C torsional angles. The averaged $J_{2,3}$ values for the first four conformations are 2.5 and 6.0 Hz which compares with the observed values of 2.6 and 7.4 Hz and suggests that the conformation in the area of the functional groups indeed is similar to that shown in **J**.

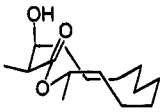
The calculations on **10** gave two conformations within 0.5 kcal/mol of the global minimum. These three conformations had similar geometries around the functional groups as seen in the calculated averaged $J_{2,2}$ values of 3.4 and 11.5 Hz which compares with the observed values of 3.1 and 10.5 Hz. These three lowest-energy conformations have the same geometry as **K** in the vicinity of the functional groups.



J

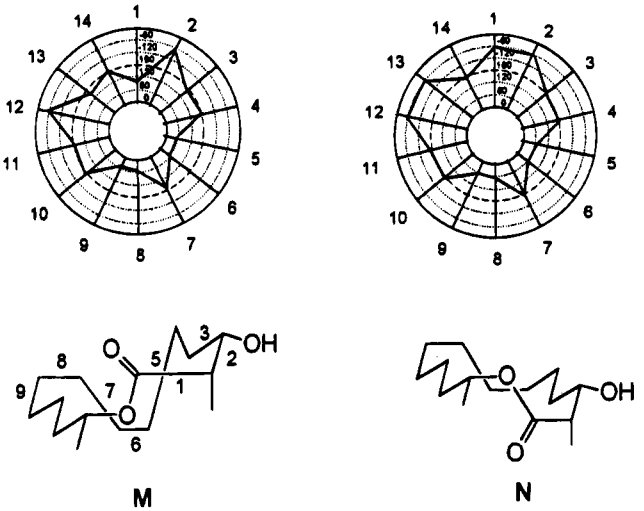
K

Spectroscopic evidence is consistent with 3-hydroxy lactone **11** existing in conformation **L**. For example, the infrared spectrum of **11** has an intramolecular hydrogen-bonded OH stretch at 3335 cm^{-1}. The proton on C-2 of **11** is a doublet of quartets with J = 2.7 and 7.6 Hz. Compound **11** has its ^{13}C carbonyl peak at 176.0 in comparison to 174.3 for its C-3 epimer **16**. This downfield shift of the carbonyl carbon peak in **11** is consistent with an intramolecular hydrogen bond in **11** as expected in **L**.



L

The hydroxy lactone **12** crystallized after purification and its structure was determined by an X-ray crystallographic analysis. The solid state structure of **12** confirmed the above chemical correlations and proved the relative stereochemistry of the substituents on the ring. The geometry about the secondary lactone was *s-trans* as expected and the C−O−C−H torsional angle of the secondary lactone was 22° consistent with the Schweizer−Dunitz rule.[27] However, the solid-state conformation of **12** was **M** (Figure 3). From the polar map of conformation **M** we see that this conformation is very similar to the [3434] conformation **N** with some differences around the lactone group. The shapes of the two polar maps are identical for **M** and **N** for all but torsional angles 1 and 13.



M N

Figure 3. Solid-state conformation **M** and a possible [3434] conformation **N** of **12**. The numbers on **M** refer to the torsional angles used in the polar maps.

Initially the solid-state conformation **M** of **12** was dismissed as a renegade arrangement. However, we and others have found additional examples of this "twist" conformation in the solid state.[28] The unit cell packing diagram of **12** revealed an intermolecular hydrogen bond between the alcohol of one molecule and the lactone carbonyl of a second molecule which may control the solid state conformation. It is interesting to note that the related [3434] conformation **N** violates the Schweizer−Dunitz rule[27] and the C-2 methyl group in **N** would effectively prevent any intermolecular hydrogen bonding to the lactone carbonyl. The NMR spectra of **12** was complex preventing us from suggesting what the solution conformation of **12** might be. Many of the geminal coupling constants were in the 3−4 Hz range suggesting that we may be dealing with several conformations in equilibrium.

The conformational search calculations on **12** gave three low energy conformations within 0.6 kcal/mol of the global minimum. The second lowest conformation which is 0.4 kcal/mol above the global minimum corresponds to the conformation found in the solid state. These three lowest energy conformations give the same values of $J_{2,3}$, $J_{3,4}$, and $J_{12,13}$. As a result we cannot say anything about the solution conformation of **12** at this time.

The conformation of **17** in the solid state was also determined by X-ray crystallography. Compound **17** consists of a 1:1 mixture of two conformations in the solid. The polar maps of these conformations clearly showed that one was the [3344] conformation **O** and the other was the [3434] conformation **P**. Neither was the expected [3434] conformation **Q** which would arise from putting the appropriate substituents on **A** and the *gem*-dimethyl carbon at the corner position. These two conformations observed in the solid state turned out not to be the lowest energy conformations from a MACROMODEL calculation (Figure 4). In both conformations **O** and **P** the lactone geometry is *s-trans* and the C−O−C−H torsional angle is small which is consistent with the Schweizer−Dunitz model.[27] These two conformations also have the *gem*-dimethyl group occupying a corner position as predicted by Dale.[35] The solution NMR data for **17** is consistent with either conformation **O** or **Q**. The $J_{3,4}$ values of 1.8 and 10.2 Hz, and the $J_{12,13}$ values of 2.5 and 9.3 Hz, are

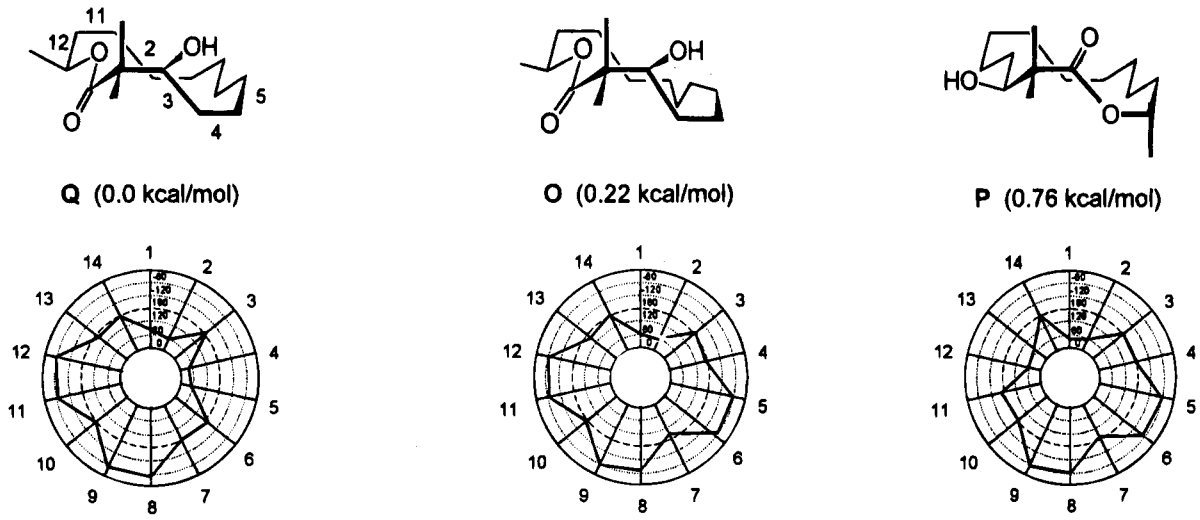


Figure 4. Solid-state conformations **O** and **P** and a possible [3434] conformation **Q** of **17**. The numbers on **Q** refer to the torsional angles used in the polar maps.

consistent with the gauche and anti relations about these bonds in **O** or **Q**, but not in **P**.

The MACROMODEL conformational search on **17** gave three conformations, **O**–**Q**, within 0.75 kcal/mol of the global minimum. The second- and third-lowest conformations correspond to the conformations found in the solid state. In solution only conformations **Q** and **O** are consistent with the observed coupling constants $J_{3,4}$ and $J_{12,13}$.

Conclusions

We can use model **A** as the starting point for the conformation of the β-hydroxy lactones. However, we must also consider the possibility of intramolecular hydrogen bonding complicating the conformational analysis of these 3-hydroxy lactones. Model **A** appears to be a useful mnemonic to assist in understanding the physical and chemical properties of 3-oxygenated 14-membered lactones. It is not without its shortcomings, but is a useful starting point in the analysis of such systems. Model **B′** with a cation chelated to the two carbonyls is the most appropriate model for the hydride reduction of these β-keto lactones. Thus in the case of these β-keto lactones, chelation by the carbonyls is the controlling feature in the stereoselectivity of the ketone reduction and it overrides torsional and steric effects.

The conformational analysis of the β-hydroxy lactones is more complex. However, using the Schweizer–Dunitz rule that the H–C–O–C torsional angle is small[27] and that gem-disubstituted carbons occupy corner positions[35] we can use the **A** conformation to predict the local conformation of these compounds in the vicinity of the functional groups. Such an analysis is consistent with the physical and chemical properties of these systems.

Experimental Section

Solvents and Reagents. Dry solvents were prepared as follows: diethyl ether (ether) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl radical under a dry nitrogen (N_2) atmosphere. Diisopropylamine was distilled from and stored over calcium hydride (CaH_2). Pyridine, *tert*-butyl alcohol and hexamethylphosphoramide (HMPA) were distilled under reduced pressure from CaH_2 and stored over molecular sieves (3 Å). Petroleum ether was of boiling range 30–60 °C. All reagents were supplied by the Aldrich Chemical Co. and unless otherwise stated were used without further purification. *n*-Butyllithium was standardized by titration against 2,2-diphenylacetic acid in THF at room temperature to the appearance of a faint yellow color.

Products. Reactions were monitored by thin layer chromatography (TLC) or gas liquid chromatography (GLC). Analytical TLC was performed on commercial aluminum backed, precoated silica (SiO_2) gel plates (E. Merck, type 5554). The plates were visualized using short wave ultraviolet light or by spraying with a 3 M solution of sulfuric acid and heating with a heat gun. Analytical GLC analyses were obtained on a Hewlett-Packard Model 5880 gas chromatograph using either a 12 m × 0.2 mm capillary Carbowax column or a 15 m × 0.2 mm capillary DB-210 column. In all cases flame ionization detection was used with a helium carrier gas. Reaction products were purified by flash chromatography[38] using 230–400 mesh ASTM silica gel supplied by E. Merck Co. Solid samples were adsorbed onto the silica gel before chromatography. Melting points were determined on a Koffler hot stage apparatus and are uncorrected.

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 710B or a Bomem Michelson 100 FT spectrophotometer as chloroform solutions. Low resolution mass spectra (MS) were determined on a Varian MAT Model CH4B or a Kratos-AEI Model MS 50 spectrometer. The parent peak as well as major ions (10% of the base peak) are reported unless lower intensity peaks were structurally diagnostic. Exact masses were obtained by high resolution mass spectroscopy (HRMS) using a Kratos-AEI model MS 50 spectrometer. All instruments were operated at 70 eV. Nuclear magnetic resonance (NMR) spectra were taken in deuteriochloroform ($CDCl_3$) solutions with signal positions given in parts per million (ppm) on the δ scale from internal tetramethylsilane. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz on a Bruker WH-400 model spectrometer and 80 MHz on a Bruker WP-80. Carbon (^{13}C) NMR spectra were recorded on a Varian 300 MHz instrument using the attached proton test (APT) program at 75.4 MHz or on the Bruker WH-400 spectrometer at 100.6 MHz. Integration ratios, signal multiplicities, and coupling constants (in hertz) are indicated in parentheses.

3-Oxo-13-tetradecanolide (5) was prepared by cyclizing the dianion from **6**.[21b]

(2*S,13*S**)- and (2*R**,13*S**)-2-Methyl-3-oxo-13-tetradecanolides (7).** Freshly sublimed potassium *tert*-butoxide (178.0 mg, 1.59 mmol) was weighed into a dry flask equipped with a N_2 inlet and septum. Freshly distilled *tert*-butanol (3.0 mL) was injected and the macrolide **5** (315.0 mg, 1.31 mmol) dissolved in 2.0 mL of *tert*-butanol was added dropwise. After

(38) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

30 min of refluxing, the reaction mixture was cooled to room temperature and MeI (0.090 mL, 1.4 mmol) was added and further refluxed for 10 min. The reaction mixture was poured into aqueous NH_4Cl and the aqueous layer extracted with ether (4 × 100 mL). The organic layers were dried and evaporated under reduced pressure. The crude oil was chromatographed using EtOAc:petroleum ether (1:19) to yield pure **7** (289.4 mg, 87%) as a yellow oil. The gem-dimethylated product **8** was isolated as a byproduct (11.4 mg, 3.2%). Compound **7** was found to exist as a 2:1 mixture of diastereomers by NMR and GLC. IR ($CHCl_3$) for major and minor isomers 1739, 1725, 1709, 1692 cm^{-1}; HRMS for major and minor isomers *m/z* calcd for $C_{15}H_{26}O_3$ 254.1882, found 254.1889.

^1H NMR (400 MHz, $CDCl_3$) for major isomer δ 5.00 (m, J = 7.2, 6.1, and 4.5 Hz, 1H), 3.55 (q, J = 7.1 Hz, 1H), 2.68 (ddd, J = 18.0, 7.8, and 7.0 Hz, 1H), 2.50 (ddd, J = 18.0, 8.0, and 6.8 Hz, 1H), 1.89–1.12 (m, 16H), 1.31 (d, J = 7.1 Hz, 3H), 1.24 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) for major isomer δ 205.5 (s), 170.3 (s), 71.9 (d), 53.4 (d), 39.0 (t), 35.4 (t), 26.1 (t), 24.8 (t), 24.4 (t), 24.2 (t), 22.9 (t), 22.8 (t), 20.7 (t), 20.4 (q), 13.1 (q).

^1H NMR (400 MHz, $CDCl_3$) for minor isomer δ 4.94 (m, J = 6.4 Hz, 1H), 3.52 (q, J = 7.1 Hz, 1H), 2.82 (ddd, J = 18.7, 7.9, and 6.8 Hz, 1H), 2.37 (ddd, J = 18.7, 7.9, and 6.0 Hz, 1H), 1.89–1.12 (m, 16H), 1.30 (d, J = 7.1 Hz, 3H), 1.21 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) for minor isomer δ 204.5 (s), 170.4 (s), 71.6 (d), 54.2 (d), 39.4 (t), 35.1 (t), 25.9 (t), 25.1 (t), 24.64 (t), 24.57 (t), 24.52 (t), 24.49 (t), 23.0 (t), 20.0 (q), 12.2 (q).

2,2-Dimethyl-3-oxo-13-tetradecanolide (8). The macrolide **5** (87.7 mg, 0.365 mmol) was dissolved in 2.0 mL of dry *tert*-butanol and added dropwise to a homogeneous solution of potassium *tert*-butoxide (164.0 mg, 1.46 mmol) in *tert*-butanol (2.0 mL). The reaction was warmed with an 85–90 °C water bath for 10 min and stirred without the bath for an additional 50 min. MeI (0.23 mL, 3.7 mmol) was added and the reaction mixture was stirred at room temperature for 14.5 h. The reaction was quenched with 1.5 mL of 1 M HCl, saturated with NaCl and extracted with ether (4 × 60 mL). Purification of the crude product through SiO_2 using EtOAc:petroleum ether (1:7) gave **8** as a yellow oil (95.8 mg, 98%): IR ($CHCl_3$) 1724, 1708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.94 (m, J = 9.0, 6.1, and 2.7 Hz, 1H), 2.51 (ddd, J = 18.5, 9.6, and 5.7 Hz, 1H), 2.41 (ddd, J = 18.5, 9.4, and 6.1 Hz, 1H), 2.74–1.12 (m, 18H), 1.33 (s, 3H), 1.30 (s, 3H), 1.17 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.4 (s), 182.9 (s), 71.5 (d), 55.8 (s), 35.9 (t), 35.4 (t), 26.1 (t), 25.8 (t), 24.1 (t), 23.9 (t), 22.7 (q), 22.6 (t), 21.7 (q), 20.2 (t), 20.1 (q); MS *m/z* (relative intensity) 268 (M^+, 1), 70 (100); HRMS *m/z* calcd for $C_{16}H_{28}O_3$ 268.2039, found 268.2047.

Reduction of 3-Oxo-13-tetradecanolide (5). (a) Using $NaBH_4$. To a solution of 689 mg (2.87 mmol) of the β-keto lactone **5** in 15 mL of ethanol at room temperature was added 109 mg (2.87 mmol) of $NaBH_4$. After stirring at room temperature for 30 min, the reaction was quenched with 1 M HCl and diluted with ether. The organic phase was washed twice with brine, dried, and concentrated under reduced pressure to yield 652 mg of a mixture of **9** and **10** as a pale orange oil. Purification by flash chromatography using petroleum ether–ethyl acetate (9:1) as eluant gave in order of elution the following:

(3*S,13*S**)-3-Hydroxy-13-tetradecanolide (9)** (449 mg, 65%) as pale yellow oil. Distillation of a small amount of this material afforded a colorless oil which very slowly crystallized to give fine while needles, mp 33–37 °C, bp 115 °C/0.1 Torr: IR ($CHCl_3$) 3330, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05–1.88 (m, 18H), 1.21 (d, J = 7 Hz, 3H), 2.61 (A part of an ABX system, J = 15 and 17 Hz, 1H), 2.67 (B part of an ABX system, J = 15 and 3 Hz, 1H), 3.01 (d, J = 9 Hz, 1H, exchangeable with D_2O), 3.76–3.89 (m, X part of an ABX system, J = 3 and 7 Hz, plus additional couplings, 1H), 4.99–5.09 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.56 (q), 21.27 (t), 22.41 (t), 23.56 (t), 23.70 (t), 24.82 (t), 25.51 (t), 26.13 (t), 34.09 (t), 40.25 (t), 68.84 (d), 70.29 (d), 172.83 (s); MS *m/z* (relative intensity) 242 (M^+, 4), 224 (11), 154 (60), 89 (100); HRMS *m/z* calcd for $C_{14}H_{26}O_3$ 242.1882, found 242.1880.

(3*R,13*S**)-3-Hydroxy-13-tetradecanolide (10)** (153 mg, 22%) as a pale yellow oil. Distillation of a small amount of this material afforded a colorless oil which slowly crystallized to give fine white needles, mp 41–45 °C, bp 115 °C/0.1 Torr: IR ($CHCl_3$) 3630, 3450, 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08–1.78 (m, 18H), 1.23 (d, J = 7 Hz, 3H), 1.78–2.00 (m, 1H, exchangeable with D_2O), 2.58 (A part of an ABX system, J = 15 and 11 Hz, 1H), 2.59 (B part of an ABX system, J = 15 and 3 Hz, 1H), 4.02–4.10 (m, X part of an ABX system, J = 3 and 11 Hz, plus additional couplings, 1H), 4.99–5.09 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.19 (q), 21.12 (t), 23.63 (t), 24.09 (t), 25.56 (t), 26.07 (t), 26.09 (t), 34.36 (t), 34.94 (t), 40.25 (t), 68.77 (d), 70.64 (d), 171.27 (s); MS *m/z* (relative intensity) 242 (M^+, 5), 224 (10), 164 (25), 154 (16), 55 (100); HRMS *m/z* calcd for $C_{14}H_{26}O_3$ 242.1882, found 242.1880.

(b) Using L-Selectride. To a solution of 24 mg (0.1 mmol) of the β-keto lactone **5** in 2 mL of dry THF at −10 °C and under a nitrogen atmosphere was added 0.2 mL (0.2 mmol) of a 1.0 M solution of lithium tri-*sec*-butylborohydride (L-Selectride) in THF and the resulting mixture was stirred at −10 °C for 1 h. The reaction was quenched with 2 drops of 1 M HCl and 2 drops of 30% H_2O_2 and the mixture was stirred for 5 min at room temperature. The mixture was then diluted with ether and the organic layer was dried and concentrated under reduced pressure to give 21 mg (87%) of **9** as a colorless oil. GLC analysis showed only the alcohol **9**. None of the diastereomeric alcohol **10** was detected.

(c) Using $(n\text{-Bu})_4NBH_4$. A solution of 35 mg (0.15 mmol) of β-keto lactone **5** in 5 mL of EtOH was treated with 52 mg (0.20 mmol) of $(n\text{-Bu})_4NBH_4$ and the solution was stirred for 1 h. The reaction was quenched with 2 mL of 1 M HCl and extracted with ether (3 × 10 mL). The extracts were washed with brine, dried, and evaporated to yield a mixture of **9** and **10** in a ratio of 2:3 by GLC.

(d) Using $NaBH_4$ and $MnCl_2$. Experiment a was repeated using 35 mg (0.15 mmol) of **5**, 5.5 mg (0.15 mmol) of $(n\text{-Bu})_4NBH_4$, and 38 mg (0.30 mmol) of $MnCl_2$ in 10 mL of EtOH. The reaction was worked up to give 32 mg (90%) of a mixture of **9** and **10** in the ratio 98:2 by GLC.

(e) Using $(n\text{-Bu})_4NBH_4$ and LiBr. Experiment c was repeated using 35 mg (0.15 mmol) of **5**, 50 mg (0.15 mmol) of $(n\text{-Bu})_4NBH_4$, and 26 mg (0.30 mmol) of LiBr in 10 mL of EtOH. The reaction was worked up to give 28 mg (80%) of a mixture of **9** and **10** in the ratio 9:1 by GLC.

(f) Using $(n\text{-Bu})_4NBH_4$ and $MnCl_2$. Experiment c was repeated using 36 mg (0.15 mmol) of **5**, 52 mg (0.16 mmol) of $(n\text{-Bu})_4NBH_4$, and 40 mg (0.32 mmol) of $MnCl_2$ in 10 mL of EtOH. The reaction was worked up to give 31 mg (86%) of a mixture of **9** and **10** in the ratio 97:3 by GLC.

1-Bromo-7-(tetrahydropyranyloxy)heptane. 7-Bromo-1-heptanol[39] (5.85 g, 30 mmol) in 20 mL of CH_2Cl_2 was treated with 3.02 g (36 mmol) of dihydropyran. The reaction mixture was stirred for 1.5 h and then diluted with 100 mL of ether. The organic solution was washed with saturated brine and dried and the solvent evaporated to give 8.8 g of a light yellow oil which was distilled to give 6.75 g (81%) of a colorless liquid, bp 132 °C/0.1 Torr: ^1H NMR (80 MHz, $CDCl_3$) δ 4.65 (bs, 1H), 3.5 (m, 6H), 1.2–2 (m, 16H).

(9*S*)-1,9-decanediol. A solution of the above bromide (3.4 g, 12 mmol) in 20 mL of THF was added to Mg turnings (354 mg, 14.7 mmol). One drop of dibromoethane was added to initiate the reaction. The reaction temperature was kept below 25 °C with a cold water bath. GLC analysis indicated that after 1 h less than 1% of the starting bromide was left. This reaction mixture was cooled with an ice-salt bath and treated with CuI (50 mg) and (*S*)-propylene oxide[40] (1.4 g, 30 mmol). The Grignard reagent was stirred at 0 °C for 80 min and quenched with saturated NH_4Cl and concd NH_4OH (3:1). The aqueous phase was extracted with ether (4 × 50 mL). The combined organic extracts were washed with saturated brine, dried, and evaporated to yield 3.1 g which contained 25% product by TLC and GLC. This product was hydrolyzed directly in the next step. The crude tetrahydropyranyl ether

(39) Mori, K. *Tetrahedron* **1974**, *30*, 3807.
(40) Seuring, B.; Seebach, D. *Helv. Chim. Acta* **1977**, *60*, 1175.

(3.1 g) was refluxed in 60 mL of HOAc:THF:H_2O (4:2:1) for 1.5 h. The product was extracted with ether (3 × 30 mL), dried, and evaporated to yield 2.8 g of product that contained some acetate that was hydrolyzed with 25 mL of 1 M NaOH and 10 mL of methanol to give on workup 1.6 g of a light yellow oil which was distilled to give 0.81 g (38% from the starting bromide) of (9*S*)-1,9-decanediol as a viscous oil, bp 130 °C/1 Torr: ^{1}H NMR (80 MHz, $CDCl_3$) δ 3.6 (m, 3H), 1.4 (m, 16H), 1.2 (d, J = 7 Hz, 3H); HRMS *m/z* calcd for $C_9H_{19}O_2$ ($M^+ - CH_3$) 159.1385, found 159.1377.

(2*S*)-10-Bromo-2-decanol. A solution of pyridine (0.43 mL, 5.4 mmol) and TsCl (1.02 g, 5.4 mmol) was prepared in 5 mL of THF. This was added to a cooled (−30 °C) solution of (9*S*)-1,9-decanediol (0.81 g, 4.7 mmol) in 5 mL of THF. This mixture was stirred at −30 °C for 1 h and allowed to warm to 0 °C and stirred at this temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), and the organic extracts were washed with dilute HCl, dilute $NaHCO_3$, and brine, dried, and evaporated to yield a crude oil which was purified by column chromatography using EtOAc:petroleum ether (1:2) to give 0.90 g (60%) of (2*S*)-10-(tosyloxy)-2-decanol: IR ($CHCl_3$) 3400−3500, 2950, 1360, 1180 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 7.8 (d, J = 8 Hz, 2H), 7.3 (d, J = 8 Hz, 2H), 4.8 (1H, exchangeable with D_2O) 4.05 (m, 1H), 4.0 (t, J = 7 Hz, 2H), 2.49 (s, 3H), 1.2−1.8 (m, 14H), 1.2 (d, J = 7 Hz, 3H); MS *m/z* (relative intensity) 328 (M^+, 1), 315 (11), 173 (100); HRMS calcd for $C_{17}H_{28}O_4S$ 328.1708, found 328.1717.

A solution of 150 mg of this tosylate (0.46 mmol) was dissolved in 2 mL of acetone and treated with 100 mg of LiBr. This mixture was refluxed for 2 h, cooled, and diluted with 20 mL of ether. The organic layer was washed with water, dried, and evaporated to give a light yellow oil which was distilled to give 120 mg of (2*S*)-10-bromo-2-decanol, bp 98−100 °C/0.15 Torr; IR ($CHCl_3$) 3630, 3480 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 3.7 (m, 1H), 3.38 (t, J = 7 Hz, 2H), 1.1−2.2 (m, 14H), 1.58 (s, 1H, exchangeable with D_2O), 1.17 (d, J = 6 Hz, 3H); MS *m/z* (relative intensity) 238 (M^+, 0.3) 236 (M^+, 0.3), 45 (100); HRMS calcd for $C_{10}H_{21}OBr$ 238.0755 and 236.0776, found 238.0739 and 236.0784.

(13*S*)-3-Oxo-13-tetradecanolide (5) was prepared via a dianion cyclization in the same way as the racemic product.[21b] The (13*S*)-ketone **5** was then reduced with $NaBH_4$ as above to give the optically active β-hydroxy lactone **9**.

(3*S*)-3-Hydroxytetradecanoic Acid. The optically active β-hydroxy lactone **9** (18 mg, 0.074 mmol) was added to a solution of $NaSeC_6H_5$ (26 mg, 0.14 mmol) in 1 mL of HMPA. This mixture was heated to 110 °C for 1 h. The reaction was cooled and diluted with 1 mL of MeOH and 10 mL of water. The aqueous phase was extracted with ether (2 × 10 mL). The extracts were washed with saturated $CuSO_4$ and brine, dried, and evaporated to give a yellow paste which was purified by preparative TLC using petroleum ether:EtOH:AcOH (60:10:1) to give 8 mg of a white solid: ^{1}H NMR (80 MHz, $CDCl_3$) δ 7.2−7.6 (m, 5H), 3.8 (m, 1H), 2.5 (m, 2H), 1.1−1.8 (m, 22H) which corresponds to the ring-opened selenide.

This selenide was dissolved in 1 mL of toluene and treated with Bu_3SnH (0.1 mL, 0.4 mmol) and 5 mg of AIBN. The mixture was heated to 60 °C for 1 h. The reaction was cooled and diluted with 20 mL of ether. The organic layer was washed with brine and aqueous KF solution, dried, and evaporated. The crude oil was purified by preparative TLC using petroleum ether:EtOH:AcOH (60:10:1) to yield 3.8 mg of a product with identical spectral properties to authentic (±)-3-hydroxytetradecanoic acid obtained by $NaBH_4$ reduction of 3-oxotetradecanoic acid. The optically active 3-hydroxytetradecanoic acid had the following properties: IR ($CHCl_3$) 2500−3600, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (m, 1H), 2.58 (dd, J = 3 and 16 Hz, 1H), 2.45 (dd, J = 8 and 16 Hz, 1H), 1.2−1.6 (m, 20H), 0.88 (t, J = 7 Hz, 3H); $[\alpha]_D$ = +11° (c = 1.3, $CHCl_3$), lit. $[\alpha]_D$ = +14° (c = 1, $CHCl_3$) for (3*S*)-3-hydroxytetradecanoic acid.[41]

Oxidation of 10. A solution of minor diastereomer **10** (20 mg, 0.08 mmol) in 1 mL of dry DMF was treated with 93 mg (0.25 mmol) of pyridinium dichromate and the resulting mixture was stirred at room temperature for 37 h. The reaction was quenched with water and extracted with ether (2 × 10 mL). The extracts were washed with brine, dried, and evaporated to yield 15 mg (78%) of a colorless oil with identical spectroscopic and chromatographic properties to the keto lactone **5**.

Reduction of 2-Methyl-3-oxo-13-tetradecanolides (7). (a) Using $NaBH_4$. The macrolides **7** (105.0 mg, 0.413 mmol) were dissolved in ethanol (2.0 mL), and $NaBH_4$ (4.3 mg, 0.46 mmol) was added and the reaction was stirred for 1.5 h. The addition of 8 drops of 1 M HCl was sufficient to quench the reaction. The reaction mixture was then saturated with NaCl and extracted with ether (4 × 100 mL) to isolate the desired products. The crude product mixture was very clean (100.3 mg, 95%). Approximately 3% of starting material was detected by GLC. The remainder of the product distribution by GLC was as follows: **11** (68.2%), **15** (16.3%), **12** (10.8%) and **16** (4.7%). Pure samples of **11**, **12**, and **15** were obtained by column chromatography using EtOAc:petroleum ether (1:7) to give the following:

(2*S,3*S**,13*S**)-2-Methyl-3-hydroxy-13-tetradecanolide (11).** IR ($CHCl_3$) 3335, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (m, J = 6.8, 6.4, and 4.2 Hz, 1H), 3.61 (m, J = 7.6 and 2.7 Hz, 1H), 2.85 (d, J = 9.5 Hz, 1H, exchangeable with D_2O), 2.67 (dq, J = 7.1 and 2.7 Hz, 1H), 1.63−1.16 (m, 18H), 1.27 (d, J = 7.1 Hz, 3H), 1.20 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.0 (s), 73.7 (d), 70.2 (d), 42.8 (d), 34.5 (t), 33.8 (t), 26.8 (t), 25.9 (t), 25.2 (t), 24.2 (t), 24.0 (t), 22.8 (t), 21.8 (t), 20.0 (q), 13.8 (q); MS *m/z* (relative intensity) 256 (M^+, 1), 154 (29), 103 (87), 74 (77), 55 (100); HRMS *m/z* calcd for $C_{15}H_{28}O_3$ 256.2039, found 256.2041.

(2*R,3*S**,13*S**)-2-Methyl-3-hydroxy-13-tetradecanolide (15).** IR ($CHCl_3$) 3650, 3550−3200, 1725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (m, J = 9.3, 6.4, and 2.7 Hz, 1H), 3.58 (m, 1H), 2.42 (m, J = 9.0 and 7.1 Hz, 1H), 1.67−1.10 (m, 18H), 1.23 (d, J = 7.1 Hz, 3H), 1.18 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 174.3 (s), 73.5 (d), 70.2 (d), 49.1 (d), 35.4 (t), 34.5 (t), 32.9 (t), 26.4 (t), 25.8 (t), 25.5 (t), 23.8 (t), 23.4 (t), 22.5 (t), 20.3 (q), 14.4 (q).

(2*R,3*R**,13*S**)-2-Methyl-3-hydroxy-13-tetradecanolide (12)**: mp 68−69 °C; IR ($CHCl_3$) 3621, 3590−3250, 1724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (m, J = 7.2, 6.3, and 3.7 Hz, 1H), 3.66 (m, J = 4.2 and 3.1 Hz, 1H), 2.65 (dq, J = 7.2 and 3.1 Hz, 1H), 2.09−1.95 (bs, 1H, exchangeable with D_2O), 1.73−1.18 (m, 18H), 1.23 (d, J = 7.2 Hz, 3H), 1.22 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.9 (s), 73.0 (d), 71.1 (d), 46.9 (d), 35.6 (t), 32.3 (t), 26.5 (t), 25.9 (t), 25.5 (t), 23.4 (t), 22.8 (t), 22.6 (t), 22.4 (t), 20.4 (q), 12.5 (q); MS *m/z* (relative intensity) 256 (M^+, 1), 164 (22), 103 (35), 74 (86), 55 (100); HRMS *m/z* calcd for $C_{15}H_{28}O_3$ 256.2039, found 256.2044.

(2*S,3*R**,13*S**)-2-Methyl-3-hydroxy-13-tetradecanolide (16).** ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.1 (s), 73.2 (d), 70.3 (d), 45.9 (d), 35.1 (t), 32.7 (t), 26.3 (t), 26.0 (t), 25.6 (t), 24.1 (t), 23.6 (t), 22.5 (t), 21.4 (t), 20.3 (q), 14.2 (q).

(b) Using L-Selectride at −78 °C. L-Selectride in THF (3.58 mmol, 3.58 mL) was added under N_2 to 2.0 mL of dry THF at −78 °C. The macrolides **7** (90.8 mg, 0.358 mmol) were added in two 0.5 mL portions in THF and stirred for 11.5 h at −78 °C. Then H_2O_2 (25 drops) and NaOH (15 mL, 1 M) were added. After 10 min, 1 M HCl was added dropwise until the reaction mixture was acidic to pH paper. The aqueous solution was saturated with NaCl and extracted three times with 100 mL of ether. Evaporation of the combined organic layers followed by passage through SiO_2 with EtOAc:petroleum ether (1:7) yielded the three alcohols, **11**, **15**, and **12**, (73.5 mg, 96% conversion, 84%) in the ratio of 90:8:2 as determined by GLC; no trace of the fourth diastereomer **16** could be detected.

(c) Using $(n\text{-}Bu)_4NBH_4$. The macrolides **7** (27.6 mg, 0.109 mmol) were dissolved in 1.5 mL of EtOH and the $(n\text{-}Bu)_4NBH_4$ (50.3 mg, 0.196 mmol) was added in one portion. After stirring for 1 h, 1 M HCl was added dropwise until H_2 evolution ceased. The reaction mixture was saturated with NaCl and extracted with ether (3 × 50 mL). Chromatography with ether gave 29.3 mg of purified products in the following ratios: **11** = 52.2%, **15** = 9.2%, **12** = 21.4%, **16** = 17.2% (by GLC).

(41) Lammek, B.; Neugebauer, W.; Kupryszewski, G. *Rocz. Chem.* **1976**, *50*, 997.

(d) Using $(n\text{-Bu})_4NBH_4$ in the presence of LiBr. The reduction procedure (c) above was repeated using the same stoichiometry, but included the addition of LiBr (80 mg, 10 equiv). A yield of 25.4 mg of products was obtained from 23.4 mg of macrolides **7**. The GLC analysis indicated **11** = 56.5%, **15** = 14.6%, **12** = 14.4%, **16** = 14.5%.

(e) Using $(n\text{-Bu})_4NBH_4$ in the presence of $MnCl_2$. The reduction procedure c above was repeated using the same stoichiometry, but included the addition of $MnCl_2$ (27 mg, 2 equiv). A yield of 26 mg of products was obtained from 28 mg of macrolides **7**. The GLC analysis indicated **11** = 97.2%, **15** = 1.9%, **12** = 0.9%.

(2*S,3*S**,13*S**)-2-Methyl-3-hydroxy-13-tetradecanolide (11) and (2*R**,3*S**,13*S**)-(15) via Dianion Methylation of (3*S**,13*S**)-3-Hydroxy-13-tetradecanolide (9).** Equimolar amounts of diisopropylamine (0.19 mL, 1.4 mmol) and *n*-BuLi (0.90 mL, 1.4 mmol) were stirred in 1.5 mL of THF at 0 °C for 0.5 h. The macrolide **9** (160.1 mg, 0.63 mmol) was dissolved in THF and added dropwise to the LDA solution. After 2 h of stirring at 0 °C, HMPA (0.44 mL, 2.5 mmol) and MeI (0.043 mL, 0.69 mmol) were added with further stirring for 15 min. The ice bath was removed and stirring of the reaction was continued for 20 min. The mixture was poured into aqueous NH_4Cl and extracted with ether (4 × 100 mL). Concentration of the crude product under reduced pressure gave a yellow oil consisting of unreacted starting material (41.3%), **11** (50.8%), **15** (6.3%), **12** and **16** (1.7%). The ratio of **11** to its C-2 epimer **15** was 89:11.

(2*R,3*R**,13*S**)-2-Methyl-3-hydroxy-13-tetradecanolide (12) and (2*S**,3*R**,13*S**)-(16) via Dianion Methylation of (3*R**,13*S**)-3-Hydroxy-13-tetradecanolide (10).** LDA (2.6 mmol) was generated at 0 °C for 1 h in 3.0 mL of THF from diisopropylamine (0.36 mL, 2.6 mmol) and *n*-BuLi (1.66 mL, 2.57 mmol). The macrolide **10** (163.0 mg, 0.64 mmol) was added dropwise in 1.5 mL of THF and stirred 4 h at 0 °C. HMPA (0.45 mL, 2.6 mmol) and MeI (0.16 mL, 2.6 mmol) were added in quick succession with continued stirring for 30 min. Workup with aqueous NH_4Cl and ether extraction (2 × 80 mL) followed by $CuSO_4$ washings (2 × 80 mL) gave a yellow oil after concentration under reduced pressure. The oil was purified by column chromatography using EtOAc:petroleum ether (1:7) to give 16.3 mg of an unidentified nonpolar fraction and 140.1 mg of diastereomeric α-methylated alcohols of which 3.4% was **11**, 1.1% was **15**, 64.8% was **12**, and 21.8% was **16** by GLC. In addition, 8.9% of starting material was detected by GLC in the reaction. The ratio of the epimers **12** and **16** was 3:1.

Reduction of 2,2-Dimethyl-3-oxo-13-tetradecanolide (8) to (3*S,13*S**)-2,2-Dimethyl-3-hydroxy-13-tetradecanolide (17).** (a) Using L-Selectride. To a 25-mL flask under N_2 at −78 °C were added 2.0 mL of THF and L-Selectride (2.02 mL, 2.02 mmol). The macrolide **8** (180.0 mg, 0.672 mmol) was added (2 × 1.0 mL portions in THF) to this mixture which was stirred for 3 h at −78 °C. The cooling bath was removed and the reaction mixture was stirred a further 2.5 h, whereupon H_2O_2 (14 drops) and NaOH (6 mL, 1 M) were added with rapid stirring. The mixture was acidified with 1 M HCl, saturated with NaCl, and extracted with ether (3 × 100 mL). GLC indicated a 231:1 ratio of **17** to its epimeric alcohol isomer. Column chromatography through SiO_2 using EtOAc:petroleum ether (1:7) gave **17** as white crystals (173.1 mg, 95%), mp = 65−66 °C: IR ($CHCl_3$) 3629, 3566−3347, 1722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.93 (m, *J* = 9.3, 6.4 and 2.5 Hz, 1H), 3.69 (m, *J* = 10.2 and 1.8 Hz, 1H), 1.68−1.13 (m, 18H), 1.22 (s, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.10 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.7 (s), 76.6 (d), 70.2 (d), 47.9 (s), 35.6 (t), 30.9 (t), 26.5 (t), 26.3 (t), 25.8 (t), 24.3 (t), 24.2 (q), 23.7 (t), 23.6 (t), 22.7 (t), 20.3 (q), 17.9 (q); MS *m/z* (relative intensity) 270 (M^+, 0.3), 117 (10), 88 (100); HRMS *m/z* calcd for $C_{16}H_{30}O_3$ 270.2195, found 270.2203.

(b) Using $(n\text{-Bu})_4NBH_4$. The macrolide **8** (26.3 mg, 0.098 mmol) was dissolved in 1.0 mL of EtOH at room temperature. The reducing agent (45.5 mg, 0.177 mmol) was added and the reaction mixture was stirred for 1 h. Further additions of $(n\text{-Bu})_4NBH_4$ (105.6 mg, 0.410 mmol) were necessary to complete the reaction in 12 h. The GLC analysis showed a 1.6:1 ratio of **17** and its epimer respectively after a 1 M HCl workup and ether extraction. The two alcohols were isolated by column chromatography as above, and the minor alcohol was characterized as the following:

(3*R,13*S**)-2,2-Dimethyl-3-hydroxy-13-tetradecanolide**: mp 64−66 °C; IR ($CHCl_3$) 3630, 3600−3450, 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.03 (m, *J* = 8.8, 6.3 and 2.9 Hz, 1H), 3.38 (dd, *J* = 10.6 and 2.0 Hz, 1H), 2.10 (bs, 1H, exchangeable with D_2O), 1.85−1.11 (m, 18H), 1.22 (s, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.16 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.4 (s), 77.2 (d), 70.6 (d), 47.8 (s), 35.6 (t), 30.6 (t), 26.7 (t), 25.7 (t), 25.2 (t), 23.6 (q), 23.0 (t), 22.6 (t), 22.5 (t), 22.4 (t), 21.0 (q), 20.4 (q); MS *m/z* (relative intensity) 270 (M^+, 1), 88 (100); HRMS *m/z* calcd for $C_{16}H_{30}O_3$ 270.2195, found 270.2199.

(c) Using $(n\text{-Bu})_4NBH_4$ in the presence of LiBr. The macrolide **8** (41.5 mg, 0.155 mmol) was dissolved in 2 mL of EtOH at room temperature and LiBr (134.5 mg, 1.55 mmol) added. $(n\text{-Bu})_4NBH_4$ (71.7 mg, 0.279 mmol) was added in one portion and stirred 8 h. Workup as above led to the isolation of **17** (11.4 mg, 27%) and its epimer (15.6 mg, 37%).

(3*S,13*S**)-2,2-Dimethyl-3-hydroxy-13-tetradecanolide (17) via Dianion Methylation of (2*S**,3*S**,13*S**)-2-Methyl-3-hydroxy-13-tetradecanolide (11).** LDA was generated from diisopropylamine (0.087 mL, 0.62 mmol) and *n*-BuLi (0.41 mL, 0.61 mmol) and stirred at 0 °C for 1 h. The macrolide **11** (62.6 mg, 0.245 mmol) was added in 2 × 0.5 mL portions in THF and the reaction mixture was stirred for 4 h at 0 °C. HMPA (0.17 mL, 0.98 mmol) and MeI (0.076 mL, 1.2 mmol) were added, and the reaction was further stirred for 15 min at 0 °C. The ice bath was removed and the reaction was stirred 10 h. The mixture was pipetted into an aqueous NH_4Cl solution and extracted with ether (4 × 20 mL). The combined ethereal layers were washed with a saturated solution of $CuSO_4$, dried over $MgSO_4$, and evaporated. The crude product was passed through SiO_2 with CH_2Cl_2 to give 44.5 mg (67%) of pure product which was identical to the major product **17** from the reduction of **8**.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council for financial support, to Professor J. Trotter and Dr. S. Rettig for X-ray crystallographic structure determinations, and to Professor W. C. Still for MACROMODEL.

Supplementary Material Available: Copies of NMR and IR spectra (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.