The Stereoselective Reduction and Conformational Analysis of 11-Oxo-13-tetradecanolide

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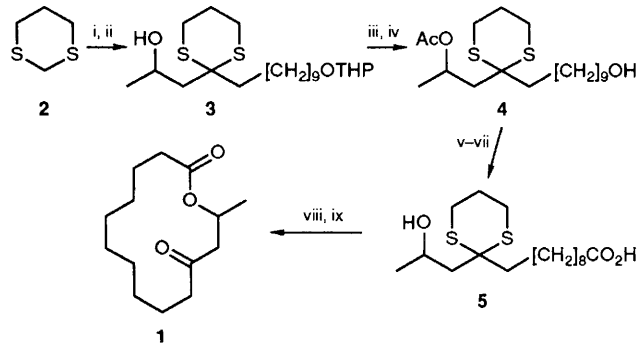
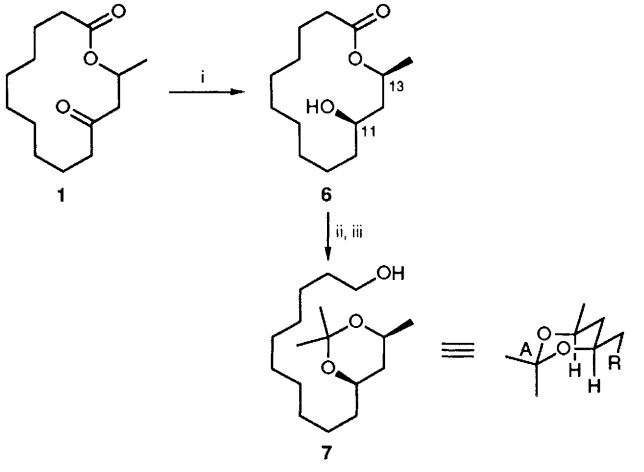
11-Oxo-13-tetradecanolide was synthesized by the lactonization of the corresponding thioketal of 11-oxo-13-hydroxytetradecanoic acid; after hydrolysis of the thioketal, the resulting ketone was reduced in 62% yield with >99.8% stereoselectivity.

Interest in the chemistry of macrocyclic compounds dates from 1926,[1] while the first macrolide antibiotic was isolated in 1950.[2] Macrocyclic compounds continue to attract the attention of chemists today, in terms of both their isolation–structural elucidation and their synthesis. A variety of synthetic strategies have been successfully applied to these compounds.[3] Clearly, any successful approach must address the problem of construction of the large ring itself, as well as control of the stereochemistry of the numerous substituents on the ring. One solution to this latter problem is to exploit the conformation of the ring to introduce the various substituents with stereochemical control. However, there are only a few successful examples of this approach to these compounds.[4]

We have been interested in this area, specifically in the chemistry of 14- and 16-membered lactones and lactams,[5] and now we report our findings on the diastereoselective reduction



Scheme 1 *Reagents and conditions*:† i, Bu^{n}Li, THF, −20 °C; (ii) Br[CH$_2$]$_{10}$OTHP, 78%; ii, Bu^{n}Li, THF, −20 °C; (ii) propylene oxide, 85%; iii, Et$_3$N, DMAP, Ac$_2$O, CH$_2$Cl$_2$, 91%; iv, TsOH, MeOH, 84%; v, DMSO, py, CF$_3$CO$_2$H, DCC, C$_6$H$_6$; vi, AgNO$_3$, NaOH, THF–H$_2$O (1 : 1), 50% for two steps; vii, NaOH, MeOH–H$_2$O (3 : 1), 53%; viii, 2,4,6-trichlorobenzoyl chloride, Et$_3$N, DMAP, PhMe, reflux, 47%; ix, NBS, acetone–H$_2$O (9 : 1), 42%



Scheme 2 *Reagents and conditions*:† i, LiBu$^s_3$BH, THF, −78 °C, 62%; ii, LiAlH$_4$, THF, 0 °C; iii, acetone, CuSO$_4$, TsOH, 48% for two steps

of 11-oxo-13-tetradecanolide **1**. The synthesis of compound **1** is shown in Scheme 1. Difficulties in the synthesis, which we highlight, were encountered in the oxidation of alcohol **4** to acid **5**. We could not find a one-step method to achieve this transformation without affecting the dithiane ring, but the route shown was successful. In the alkylation of **2**, reversing the order of steps i and ii was unsuccessful. The cyclization (step viii) was carried out with Yamaguchi's reagent,[6] which gave a significantly higher yield than another cyclization method, previously used in our laboratory with some success.[7]

The reduction of ketone **1** and conversion to the acetonide **7** is shown in Scheme 2. The relative stereochemistry of the C-11 and C-13 substituents in alcohol **6** was determined by two independent NMR methods: (*i*) NOE analysis of **6**, and (*ii*) ^{13}C NMR analysis of acetonide **7**. The NOE experiment showed an enhancement of 11-H upon irradiation of 13-H in **6**. This suggested a configuration and conformation of **6** in which these two protons are in close proximity. This can occur in the (11*R**,13*S**)-diastereoisomer. The ^{13}C NMR spectrum of **7** showed resonances for the acetonide axial and equatorial methyl carbons at δ 19 and 30 respectively, as well as a signal for the quaternary C$_A$ at δ 98. This is consistent with the *syn*

† THF = tetrahydrofuran; THP = tetrahydropyran-2-yl; DMAP = 4-dimethylaminopyridine; Ts = *p*-MeC$_6$H$_4$SO$_2$; DMSO = dimethyl sulfoxide; py = pyridine; DCC = dicyclohexylcarbodiimide; NBS = *N*-bromosuccinimide.

Table 1 Calculated local conformations of **1**

Conformation	Dihedral angle/°					$J_{12,13}$/	
E/kcal mol^{-1} [a]	10	11	12	13	14	Hz	$d_{O\cdots O}$/Å
a 0.00	171	−162	67	−142	−179	1.6 & 11	3.8
b 0.23	164	−156	66	−154	−175	1.6 & 11	4.2
c 0.24	165	−150	68	−162	−173	1.5 & 11	4.4
e 0.48	63	−162	65	−152	−178	1.7 & 11	4.1

[a] 1 cal = 4.184 J.

orientation of 1,3-diols.[8] There was no evidence for formation of the other diastereoisomer of alcohol **6** in the reduction step i by either NMR or GLC.

The conformational analysis of the ketone **1** is complex. For example, a MACROMODEL calculation[9] on **1** using the MM2 force field[10] gave several conformations of oxo lactone **1** within 2 kcal mol^{-1} of the global minimum. Four of the five lowest energy conformations follow the Schweizer–Dunitz rule[11] and have the same local conformation **8**; *cf.* Table 1 which gives dihedral angles (conformation **d** violates the Schweizer–Dunitz rule). In these conformations the two carbonyl groups have similar orientations and the methyl group occupies a pseudo-equatorial position. The two carbonyl groups are within 4.4 Å and provide an opportunity for the lithium cation to coordinate to the carbonyl groups during the reduction.[5f] These four conformations are not regular [3434] conformations, but are much closer to the twist [3434] conformation.[5d] The observed $J_{12,13}$ coupling constants in **1** and **2** are 10 Hz which is consistent with any one or a mixture of these conformations in solution. Reduction of each of these conformations from the more open face will give the observed (11*R**,13*S**)-isomer **6**.

The conformation of **6** also was interesting. The IR spectrum of **6** showed a single carbonyl peak at 1720 cm^{-1}. This frequency was slightly lower than we usually find in these 14-membered lactones and we attribute this to an intramolecular hydrogen bond. MACROMODEL calculations show that the global minimum energy conformation of **6** has this internal hydrogen bond between the hydroxy and the lactone carbonyl groups. However, this conformation violates the Schweizer–Dunitz rule[11] and thus we did not consider it any further. The second lowest energy conformation, which is 0.52 kcal mol^{-1} above the global minimum, also has an intramolecular hydrogen bond. The local conformation for this conformation is illustrated in **9**. The next lowest energy conformation is 1.00 kcal mol^{-1} above the calculated global minimum. It is unusual to have such large energy separations between the conformations of these macrocyclic systems. We believe that **6** exists mainly or completely in conformation **9** which is a [3344] conformation. Several ^{1}H NMR experiments yield $J_{11,12}$ = 4 and 8 Hz, and $J_{12,13}$ = 2 and 10 Hz. The calculated values for conformation **9** are $J_{11,12}$ = 2.0 and 11.6 Hz, and $J_{12,13}$ = 1.0 and 9.3 Hz in reasonable agreement with the observed data. In conformation **9**, the calculated intramolecular distance between the methine hydrogen atoms on C-11 and C-13 is 2.54 Å which agrees with the NOE observed between these two atoms.

In summary, we have reported the diastereoselective reduction of 11-oxo-13-tetradecanolide **1** to **6**, and suggested a conformation through which the reaction may proceed to give the observed results. These results are an extension of the

model we have developed for other reactions of 14-membered ring ketones and suggest that there may be some generality to these observations.

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