

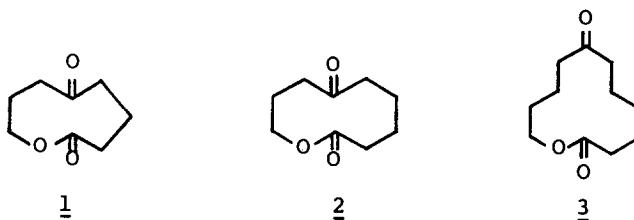
THE SYNTHESIS OF OXOALKANOLIDES OF THE MEDIUM RING SIZE

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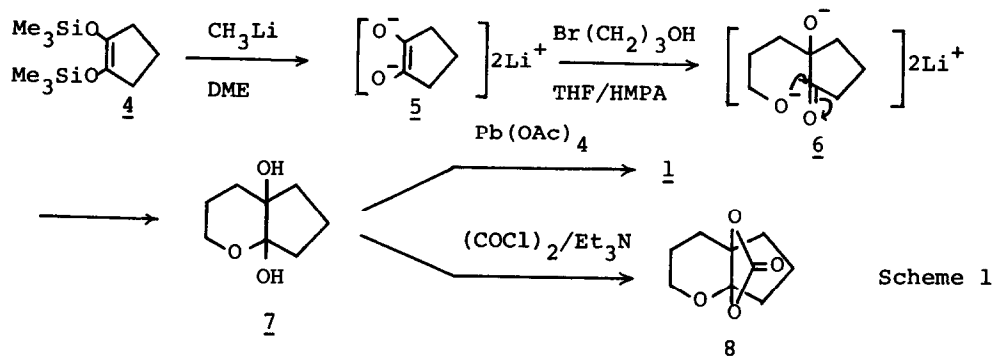
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A simplified alkylation of the acyclic or alicyclic lithium 1,2-enediolates has been recently developed in our laboratory to provide a convenient synthetic method of ketones and oxoalkanenitriles,^{1a,c} which has been extended to a new synthesis of cis-jasmone.^{1b} We present herein that the method has been applied with success to a facile synthesis of the oxoalkanolides (1 2 3),^{2a-e} which constitute the parent ring system of biologically active substances such as diploidalides or methymycin and so on.

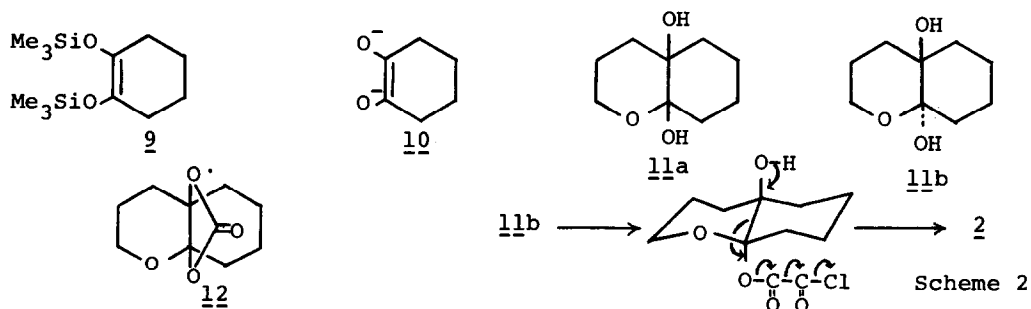


The readily available 1,2-enediolate 5^{1a-c} from 4 with 2 equiv. of methyl-lithium in monoglyme at -20° was subjected to alkylation with 3-bromo-1-propanol (THF/HMPA 1:4, rt, 21hr) to give the cis-fused bicyclic glycol 7³ [mp 86-87°, ir max (nujol) 3300cm⁻¹] in 46% yield. Oxidation of 7 (Pb(OAc)₄/benzene, rt, 2hr) afforded 5-ketooctanolide 1 [ir max(neat) 1720, 1700cm⁻¹, ms 156(M⁺)] as a colorless oil in a nearly quantitative yield. The stereochemistry of the cis-glycol 7 was confirmed by conversion to the carbonate 8³ [mp 29-30°, ir max(neat) 1795cm⁻¹] ((COCl)₂/Et₃N/CH₂Cl₂, rt, 1hr). The reaction processes involved are demonstrated in Scheme 1.



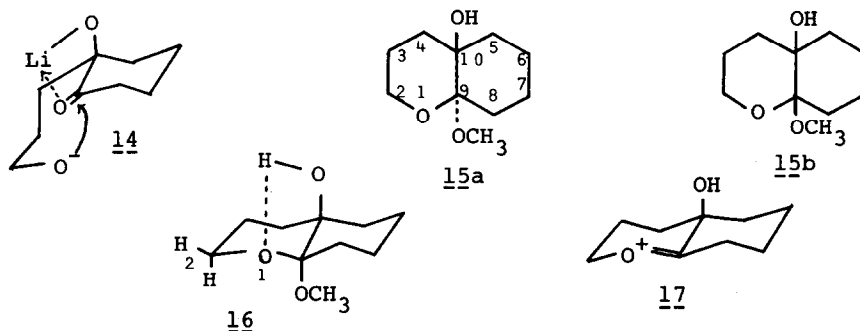
When the reaction sequence described above was carried out using 9 as the starting material, the cis-glycol 11a³ [mp 126-127°, ir max(nujol) 3450, 3250cm⁻¹] was obtained in 68% yield, which upon oxidation (Pb(OAc)₄/benzene, rt, 2hr) was converted to the corresponding 6-ketononolide 2 [mp 70-72° (lit.^{2a} 68-69°), ir max (nujol) 1720, 1700cm⁻¹, ms 170 (M⁺)] in 80% yield. Isomerization of 11a (10% HCl/CH₂Cl₂, rt, 30min) to the trans-glycol 11b [mp 128-130°, (lit.^{2c} 125-127°), ir max (nujol) 3450, 3250cm⁻¹] smoothly occurred. The trans-glycol 11b was also oxidized in a similar manner to give 2 in high yield.

The structural assignment of 11a and 11b was established by the following chemical evidences. The carbonate 12³ [mp 90-92°, ir max(nujol) 1800cm⁻¹, ms 198 (M⁺)] was obtained only from 11a ((COCl)₂/Et₃N/CH₂Cl₂, rt, 30min), while 11b gave 2 in a similar manner, for which a pathway can be visualized in Scheme 2.

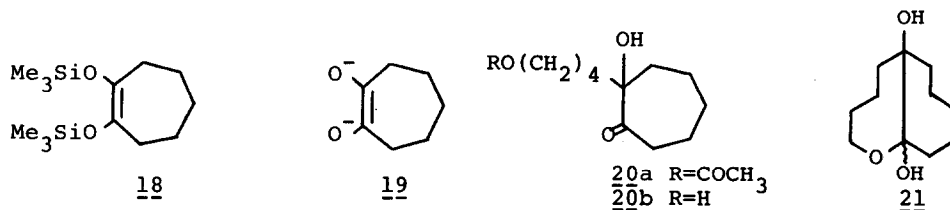


The stereochemical course of the cyclization leading to the cis-glycol 11a is the result of the stereospecific process initiated by the backside attack of alkoxy anion to the lithiated side as is shown in formula (14). Treatment 11a (10% HCl/CH₃OH/CH₂Cl₂, rt, 30min) furnished 15a³ [mp 43°, ir max(CCl₄, 1M) 3570, 3500cm⁻¹ (CCl₄, 0.1M) 3570cm⁻¹, nmr δ(CDCl₃) 2.26 (1H, d, J=2Hz), 3.22 (3H, s), ms 186 (M⁺), 155

($M^+ - OCH_3$), 154 ($M^+ - CH_3OH$) and $\underline{15b}^3$ [mp 87° (lit.^{2c} $86.5-87^\circ$), ir max(CCl_4 , 1M) 3580 , 3470cm^{-1} , (CCl_4 , 0.1M) 3580cm^{-1} , nmr δ ($CDCl_3$) 2.27 (1H, s), 3.20 (3H, s), ms 186 (M^+), 155 ($M^+ - OCH_3$), 154 ($M^+ - CH_3OH$)] in a ratio of 3:1.



The structures of $\underline{15a}$ and $\underline{15b}$ were proved by their elemental compositions and spectral properties. In particular, the nmr spectrum of $\underline{15a}$ demonstrated a signal as a doublet ($J=2\text{Hz}$) at 2.26 ppm due to the hydroxy proton at C-10, which should be ascribed to the long range coupling with the protons at C-2 through a hydrogen bonding as is indicated in formula ($\underline{16}$), but this kind of coupling was not observed with $\underline{15b}$. Since the mass spectra of $\underline{15a}$ and $\underline{15b}$ were similar in the fragmentation pattern, the common intermediate might be represented by a fragment ($\underline{17}$).⁴



Alkylation of $\underline{19}$ derived from $\underline{18}$ with 4-iodobutyl acetate gave the α -hydroxy ketone $\underline{20a}$ [ir max(neat) 3450 , 1730 , 1700cm^{-1}] in 80% yield after purification on silica gel chromatography. Hydrolysis of $\underline{20a}$ (2% KOH/ CH_3OH , rt, 5hr) followed by cyclization of $\underline{20b}$ (2 equiv. $n\text{-BuLi}/\text{THF}/-78^\circ$, then rt, 15hr) afforded the desired glycol $\underline{21}^3$ [mp $132-133^\circ$, ir max(nujol) 3300 , 3200cm^{-1} , ms 182 ($M^+ - H_2O$)] in 90% yield. Oxidation of $\underline{21}$ ($Pb(OAc)_4/\text{DMSO}$, rt, 15hr) gave poor yield of 7-ketoundecanolide $\underline{3}$ [mp $37-38^\circ$ (lit.^{2b} $42-43^\circ$), ir max(CCl_4) 1735 , 1710cm^{-1} , ms 198 (M^+)]. Fortunately, the ketolactone $\underline{3}$ was obtained directly from $\underline{20b}$ ($(NH_4)_2Ce(NO_2)_6/\text{THF}-\text{AcOH}-H_2O$,

50°, 20hr) in 40% yield.

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REFERENCES AND NOTES

1. a) T. Wakamatsu, K. Akasaka, and Y. Ban, Tetrahedron Letters, 3879 (1974).
b) T. Wakamatsu, K. Akasaka, and Y. Ban, ibid., 3883 (1974).
c) T. Wakamatsu, M. Fukui, and Y. Ban, Synthesis, 341 (1976).
2. Borowitz and co-workers discovered that the ketolactones (2 3), including 7-ketoundecanolide (3), the parent system present in methymycin, can be synthesized by the oxidation of bicyclic enol ethers derived from the acid-catalyzed closure of 2-(ω -hydroxyalkyl)cycloalkanones.
 - a) I. J. Borowitz, G. Gonis, R. Kelsey, R. D. Rapp, and G. J. Williams, J. Org. Chem., 31, 3032 (1966).
 - b) I. J. Borowitz, G. J. Williams, L. Gross, and R. D. Rapp, ibid., 33, 2013 (1968).
 - c) I. J. Borowitz and R. D. Rapp, ibid., 34, 1370 (1969); I. J. Borowitz and R. D. Rapp, J. Chem. Soc., Chem. Commun., 1202 (1969).
 - d) I. J. Borowitz, G. J. Williams, L. Gross, H. Beller, D. Kurland, N. Suciu, V. Bandurco, and R. D. G. Rigby, J. Org. Chem., 37, 581 (1972).
 - e) I. J. Borowitz and N. Suciu, ibid., 38, 1061 (1973); I. J. Borowitz, V. Bandurco, M. Heyman, R. D. G. Rigby, and S. N. Ueng, ibid., 38, 1234 (1973).
3. Satisfactory elemental analysis has been obtained for these compounds.
4. The methoxy group of 15a and 15b is in antiparallel with one of lone pairs of the ring oxygen, resulting in a similar fragmentation pattern.