Macrolide Fundamental Chemistry: Sequential Conversion of the 14-Membered Ring Macrolide Antibiotic Oleandomycin to 12- and 10-Membered Ring Macrocyclic Lactone Systems

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The phosphate salt of the 14-membered ring lactone antibiotic oleandomycin (1) undergoes translactonization in refluxing acetone to the 12-membered ring lactone **2**. This reaction is not reversible under a variety of acidic conditions; only degradation of the aglycon is observed. The 12-membered ring lactone **2** undergoes further rearrangement to the 10-membered ring lactone **3** in the presence of tetramethylguanidine. Carboxylic acid **4** was shown to be an intermediate in the conversion of the 12-membered ring lactone **2** to the 10-membered ring lactone **3**.

This paper[1] describes two interesting transformations that sequentially convert the 14-membered ring macrolide antibiotic oleandomycin (1) to 12- and 10-membered ring lactone systems. The first rearrangement proceeds via a translactonization, while the second rearrangement presumably involves ring opening of an epoxide functionality by a carboxylic acid anion.

Oleandomycin (1) (Figure 1), one of ca. 20 known naturally occurring 14-membered ring macrolide antibiotics,[2] was first isolated in the early 1950s.[3] The absolute configuration was established in 1965[4] and confirmed by X-ray analysis in 1978.[5] The basic β-D-desosamine sugar attached to C5 of the aglycon conveniently allows oleandomycin to be precipitated from fermentation broth extracts as the phosphate salt. The phosphate salt of oleandomycin is stable as an aqueous solution at room temperature; heating the solution causes concurrent hydrolysis of the C8 epoxide and cleavage of the C3 neutral sugar α-L-oleandrose. While the stability of oleandomycin phosphate in nonaqueous systems was being studied, the first of two interesting rearrangements was observed.

As the phosphate salt of **1** is refluxed in acetone, the initial suspension gradually dissolves and a new precipitate slowly separates from the solution. After ca. 18 h of reflux, the new precipitate is collected by filtration, suspended in aqueous base (pH 9), and reisolated to provide new crystalline solid **2**. Examination of the filtrate (HPLC) reveals that this solution contains only the starting oleandomycin phosphate; continued refluxing yields additional amounts of **2**, thereby increasing the yield of derivative **2** to 50%.

Spectral analysis (HPLC, ^{1}H NMR, ^{13}C NMR) indicated that crystalline **2** exists as a single diastereomer and is isomeric with oleandomycin (1) (C, H, N; MS). The ^{13}C NMR (Table I) indicated the presence of a lactone (173.4 ppm) and a third anomeric carbon (96.5 ppm) and the disappearance of the original C9 ketone. Primarily on the basis of this evidence, **2** was assigned the 12-membered ring lactone structure indicated (Figure 1).

The ^{1}H NMR spectrum of compound **2** (Table II) revealed a large (J = 9.5 Hz) coupling constant between the protons attached to positions C12 and C13, which, under the assumption of a chair conformation of the six-membered hemiketal ring, would imply an inversion of configuration at position C13. An X-ray crystal structure determination was therefore undertaken, which showed

Table I. ^{13}C NMR Chemical Shifts of Oleandomycin (1), Lactones 2 and 3, Carboxylic Acid 4[a]

atom	1[b]	2	3	4
C1	177.1	173.4	173.8	182.4
C2	45.1	47.0	47.0	42.1
C3	81.3	82.2	79.1	78.3
C4	32.3	41.7	41.7	38.9
C5	84.2	83.9	84.4	83.6
C6	31.8	31.4	29.4	33.3
C7	42.1	34.4	42.5	38.3
C8	63.1	59.9	81.3	62.2
C9	208.7	96.5	203.3	198.9
C10	45.1	39.0	134.6	134.8
C11	69.6	79.5	147.5	147.4
C12	44.2	29.0	40.9	40.5
C13	70.8	67.5	70.9	70.4
C2-CH_3	18.4 (b)[c]	15.5	14.8 (a)	11.1 br[d]
C4-CH_3	7.7	9.7	10.9 (a)	10.6
C_6-CH_3	14.7 (b, c)	18.6	21.4	16.6
C8-CH_2	49.4	49.3	70.0	50.4
C10-CH_3	10.0 (c)	13.6 (a)	12.9	11.9
C12-CH_3	9.3	13.5 (a)	14.5	14.2
C13-CH_3	20.1 (a)	18.2	21.1	20.7
C1′	105.1	104.0	104.2	103.2
C2′	70.8	70.7	70.6	70.1
C3′	65.8	65.6	65.6	64.8
C4′	29.3	28.6	28.6	33.1 br
C5′	69.6	69.1	69.3	68.3
C6′	21.6 (a)	21.1	21.1	20.9
C3′-$N(CH_3)_2$	40.6	40.3	40.3	40.2 br
C1″	95.0	100.7	99.7	96.1 br
C2″	34.4	34.2	33.9	34.2
C3″	78.2	78.1	78.0	78.3
C4″	76.3	76.3	76.1	76.2
C5″	69.6	68.6	68.6	68.3
C6″	18.7 (b)	17.5	17.4	17.7
C3″-OCH_3	56.2	56.6	56.5	56.5

[a] $CDCl_3$ solutions in parts per million from Me_4Si. [b] Nourse, J. G.; Roberts, J. D. *J. Am. Chem. Soc.* **1975**, *97*, 4854. [c] Letters in parentheses indicate interchangeable carbons. [d] Line-broadened signals are designated by br.

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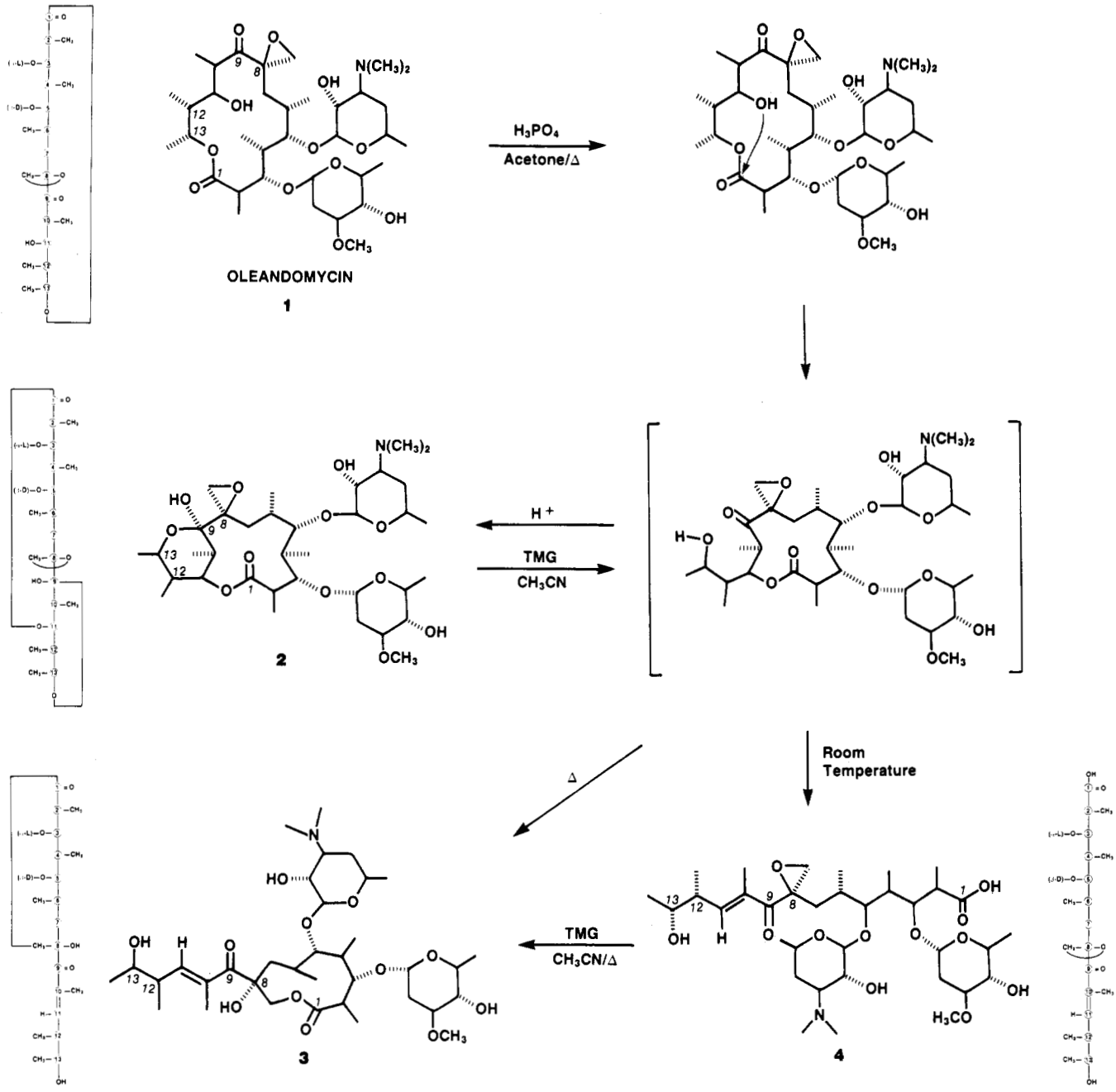

Figure 1.

that the 6-membered ring conformation in **2** is in fact a boat (Figure 2) and that the rearrangement proceeds with complete retention of configuration. The X-ray analysis also determined the configuration of the new asymmetric center at C9.

The mechanism involved in the formation of **2** is postulated to involve initial protonation of the lactone in oleandomycin, followed by translactonization via the C11 alcohol (Figure 1). The rigidity of the newly formed 12-membered ring lactone accounts for the formation of only one of the two possible hemiketal diastereomers and locks the 6-membered ring into a boat conformation.

Translactonizations involving equal or larger member ring lactone systems have been observed previously during both the chemical modification and total synthesis of related macrolide antibiotics. For example, Tanaka et al.[6] observed a translactonization in which a 16-membered ring mycaminosyltylonolide derivative was transesterified via a C23 alcohol to produce a new 16-membered ring system. Also, Corey and co-workers[7] observed a 6- to 10-membered ring translactonization of a synthetic intermediate in the synthesis of erythromycin B. In fact, translactonizations of this type have formed the basis of synthesis of large membered ring systems.[8]

The above translactonization does not appear to be reversible under a variety of acidic conditions; only degradation (epoxide opening and/or neutral sugar cleavage) of the 12-membered ring lactone **2** is observed. However, attempted regeneration of oleandomycin from 12-membered ring lactone **2** under basic conditions leads instead

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Table II. ^{1}H NMR Chemical Shifts[a]

atom	1[b]	2	3	4
H2	2.85	2.81	2.71	2.52
H3	3.75	3.73	3.78	4.20
H4		1.60	1.92	1.77
H5	3.48	3.29	3.32	3.40
H6		2.83	2.32	1.73
H7a	2.36	2.36	2.20	2.90
H7b		1.09	1.55	1.10
H10	3.03	2.28		
H11	3.84	4.40	7.12	7.20
H12		2.50	2.64	2.60
H13	5.56	4.18	3.80	3.80
2-CH_3		1.26	1.27	1.00
4-CH_3		1.12	1.14	0.97
6-CH_3		1.17	0.91	0.94
10-CH_3		0.92	1.06	1.01
13-CH_3		1.29	1.19	1.18
8-CH_2	2.92	2.72	4.39	2.77
	2.81	2.31	4.02	2.77
H1″	4.95	4.88	4.88	5.00
H2″a	2.3	2.36	2.30	2.26
H2″b		1.52	1.48	1.37
H3″	3.48	3.44	3.43	3.43
H4″	3.13	3.15	3.13	3.03
H5″	3.74	3.78	3.78	3.65
5″-CH_3		1.31	1.25	1.17
3″-OCH_3		3.40	3.40	3.35
H1′	4.21	4.16	4.21	4.70
H2′	3.19	3.15	3.18	3.44
H3′	2.50	2.49	2.48	3.17
H4′a		1.60	1.63	1.94
H4′b		1.22	1.27	1.40
H5′	3.4	3.45	3.47	3.48
5′-CH_3		1.19	1.17	1.10
3′-$H(CH_3)_2$	2.22	2.25	2.67	

[a] Measured indirectly from residual $CHCl_3$ at 7.27 ppm. In most cases, shifts were measured from 2D correlation peaks. [b] Egan, R. S. Ph.D. Thesis, University of Illinois, Medical Center, 1971.

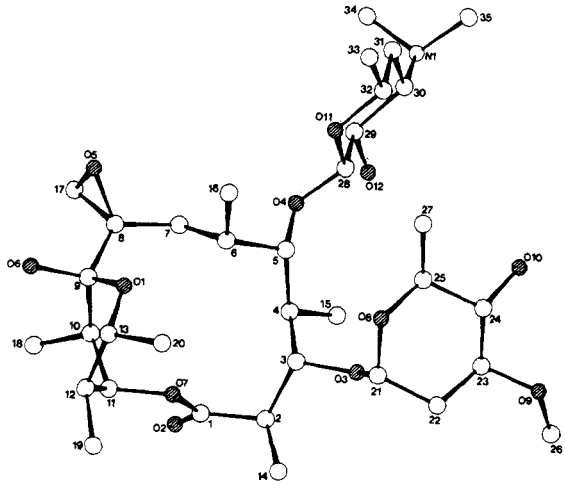

Figure 2.

to another interesting rearrangement.

Addition of excess tetramethylguanidine (TMG) to a suspension of the 12-membered ring lactone **2** in refluxing acetonitrile or tetrahydrofuran induces further rearrangement to a new crystalline solid **3** in 50% isolated yield. Both the mass spectrum (*m/e* 688 (P + 1)) and elemental analysis indicated that **3** was also isomeric with oleandomycin (**1**) and 12-membered ring lactone **2**. ^{13}C NMR, ^{1}H NMR, and IR spectral analyses indicated the absence of an epoxide linkage and the presence of both a lactone and an α,β-unsaturated ketone. On the basis of this information, the 10-membered ring lactone structure (Figure 1) was assigned to structure **3**. The stereochemistry about the double bond was deduced from (i) small nuclear Overhauser enhancements of H12 from saturation of the C10-methyl proton signal, and negative results from all other possibilities, and (ii) an 8.1-Hz coupling between the methyl carbon attached to C10 and the H11 vinyl proton.

It is interesting to note that the reduction of the 12-membered ring lactone **2** with TMG in refluxing solvent proceeds first to a polar intermediate, which, on continued refluxing, is gradually converted to 10-membered ring lactone **3**. Isolation of the polar intermediate can be accomplished by running the reaction at room temperature. Subsequent evaporation of solvent followed by silica gel chromatography affords the zwitterionic carboxylic acid derivative **4** (Figure 1) as a white amorphous solid. Structural identification of acid **4** was based on the mass spectrum (*m/e* 688 (P + 1)) and ^{13}C NMR and ^{1}H NMR analyses (Tables I and II).

The mechanism for the conversion of 12-membered ring lactone **2** to 10-membered ring lactone **3** is postulated to proceed via hemiketal ring opening to the C9 ketone, β-elimination of the C12 lactone to form acid intermediate **4**, and subsequent lactonization through the epoxide functionality. As expected, acid **4** can be converted to lactone **3** with TMG in refluxing acetonitrile.

In summary, a two-step sequential conversion of the 14-membered ring macrolide antibiotic oleandomycin (**1**) to 12- and 10-membered lactone ring systems is described. Structural assignments are based primarily on ^{1}H NMR, ^{13}C NMR, and mass spectral analyses, with the absolute configuration of lactone **2** derived by X-ray. When compared with oleandomycin (**1**), compounds **2**–**4** were biologically less active antibacterial agents.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Bruker (^{1}H NMR, 250 MHz; ^{13}C NMR, 62.8 MHz) or a Varian (^{1}H NMR, 300 MHz; ^{13}C NMR, 75 MHz) spectrometer, and chemical shifts are reported in parts per million downfield from internal tetramethylsilane (Tables I and II). Mass spectra were recorded on an AEI MS-30 spectrometer equipped with a D5-50 data system. X-ray data processing was done at Yale University on a departmental NMRVAX 11/750 (Digital Equipment Corp.) using the Enraf-Nonius SDP-PLUS programs and MULTAN 80, a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data: Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; and Woolfson, M. M. The programs URANUS and SKK–PUB, programs to generate plots and tables, respectively, were written by Simon Kay Kearsley, Yale University, 1985. TLC and column chromatography were carried out on silica gel. HPLC studies were carried out with use of a Waters C18 Microbondapak column using a mobile-phase mixture of 65% (0.1 N sodium acetate, 0.1 N acetic acid) buffer and 35% acetonitrile.

5-[(2,6-Dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)oxy]-11-hydroxy-4,6,8,13,14-pentamethyl-7-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-[1*S*-(1*R,4*S**,6*S**,7*R**,8*R**,10*S**,11*S**,13*S**,14*S**,15*S**)]-spiro[2,12-dioxabicyclo[9.3.1]pentadecane-10,2′-oxiran]-3-one (2).** A suspension of 400 g (0.509 mol) of the off-white crystalline solid oleandomycin (**1**) phosphate salt was refluxed in 2 L of acetone for 18 h. During this time, the suspension gradually solubilized, after which a white solid then precipitated from the solution. The reaction mixture was cooled to room temperature and filtered. The precipitate was dissolved in 2 L of a $CHCl_3/H_2O$ mixture (1:1) and the pH adjusted to 8.8. The layers were separated, and the aqueous phase was extracted with additional $CHCl_3$. The $CHCl_3$ extracts were combined, dried (Na_2SO_4), and evaporated. The white residue was crystallized from hot hexane to yield 160 g (40%) of 12-membered ring lactone **2**. Further refluxing of the original acetone filtrate and repetition of the above procedure yielded an additional 40 g of lactone **2**.

Combination of the two crystalline fractions yielded 200 g (50%) of 12-membered ring lactone free base **2**: mp 186–187 °C; mass spectrum *m/e* 688 (P + 1), 546.3274 (P – 141), 369.2265 (P – 318), 351.2135 (P – 336), 158.1182 (P – 529, base peak), 145.0087 (P – 542). Anal. Calcd for $C_{35}H_{61}O_{12}N$: C, 61.11; H, 8.94; N, 2.03. Found: C, 60.93; H, 8.89; N, 2.08.

X-ray Data. A hexagonal prism of dimensions 0.37 × 0.25 × 0.25 mm suitable for X-ray diffraction studies was mounted on a glass fiber. Diffraction measurements were made on an Enraf-Nonius CAD-4 fully automated diffractometer using graphite-monochromated Cu Kα radiation. Preliminary indications of unit cell based on 25 randomly selected reflections revealed orthorhombic symmetry with the following lattice parameters: a = 37.038 (12) Å, b = 11.685 (2) Å, and c = 8.861 (3) Å, with $\alpha = \beta = \gamma = 90$. On the basis of observed systematic extinctions, the space group could be assigned as $P2_12_12$ (No. 18), $Z = 4$ with one molecule of composition $C_{35}H_{61}O_{12}N$ forming the asymmetric unit. The calculated density was 1.191 g/cm^3. There were 2980 reflections collected with $2\theta \leq 114°$; of those reflections, 2137 (72%) with $I \geq 3\sigma(\mathbf{I})$ were adjudged observed.

The structure was solved by using MULTAN 80. The phasing of 248 E values ≥ 1.648 resulted in an electron density map that revealed 45 out of the 48 non-hydrogen atoms. The complete structure was revealed by using the WFO option in Normal. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were calculated by using SDP and HYDRO and were added to the structure calculations. The following full-matrix refinement of the non-hydrogen atoms and addition of the hydrogen atoms to the structure factor calculations, without refinement of their positions, resulted in convergence to a standard crystallographic unweighted residual of 0.044 and a weighted residual of 0.044. All intramolecular bond distances and angles are with normal ranges.

4-[(2,6-Dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)oxy]-9-hydroxy-9-(5-hydroxy-2,4-dimethyl-1-oxo-2-hexenyl)-3,5,7-trimethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-[3*R*-[3*R,4*S**,5*R**,6*S**,7*S**,9*R**(2*E*,4*R**,5*R**)]]-2-oxecanone (3).** A suspension of 8.0 g (0.116 mol) of the 12-membered ring lactone **2** and 8.0 g (0.0696 mol) of TMG in 100 mL of acetonitrile was refluxed for 12 h. The initial suspension gradually solubilized, followed by the precipitation of a white solid. The reaction mixture was cooled to room temperature and filtered. The precipitate was crystallized from ethyl acetate to yield 3.9 g (49%) of 10-membered ring lactone **3**: mp 208–210 °C; mass spectrum *m/e* 688 (P + 1), 546 (P – 141), 402 (P – 285), 158 (P – 529, base peak), 145 (P – 542). Anal. Calcd for $C_{35}H_{61}O_{12}N$: C, 61.11; H, 8.94; N, 2.03. Found: C, 60.97; H, 8.80; N, 1.97.

β-[(2,6-Dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)oxy]-2-(5-hydroxy-2,4-dimethyl-1-oxo-2-hexenyl)-α,γ,ε-trimethyl-δ-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-[2*R*-[2*R(2*E*,4*R**,5*R**),2-(α*R**,β*S**,γ*R**,δ*S**,ε*S**)]]-oxiraneheptanoic Acid (4).** A solution of 1.7 g (2.47 mmol) of the 12-membered ring lactone **2** and 1.7 g (14.8 mmol) of TMG in 50 mL of THF was stirred at room temperature for 48 h. TLC (9:3:0.3 $CHCl_3/CH_3OH/NH_4OH$) of the reaction mixture indicated disappearance of starting lactone **2** (R_f 0.45) and appearance of a new polar product (R_f 0.12). Evaporation of the THF and chromatography of the residue (silica gel; 3:1 $CHCl_3/CH_3OH$) yielded 0.62 g (37%) of carboxylic acid **4** as a white amorphous solid: mass spectrum, *m/e* 688.1 (P + 1), 614 (P – 73), 544 (P – 143), 514 (P – 173), 496 (P – 191), 470 (P – 217), 369 (P – 318), 158 (P – 529), 145 (P – 742); TLC (9:3:0.3 $CHCl_3/CH_3OH/NH_4OH$) R_f 0.12.

Conversion of Carboxylic Acid 4 to 10-Membered Ring Lactone 3. A solution of 0.15 g (0.218 mmol) of the carboxylic acid **4** and 0.15 g of TMG was refluxed in 5 mL of acetonitrile for 24 h. The reaction mixture was cooled to room temperature and the solvent evaporated. The residue was suspended in water and extracted with ethyl acetate. The ethyl acetate extracts were dried (Na_2SO_4) and evaporated to yield 0.11 g (73%) of lactone **3**: mp 184–186 °C. ^{1}H NMR, ^{13}C NMR, and mass spectral data were the same as those reported for the 10-membered ring lactone **3** synthesized from the 12-membered ring lactone **2**.

Supplementary Material Available: Tables containing fractional coordinates, isotropic temperature parameters, bond distances, bond angles, torsion angles, and anisotropic temperature factors for compound **2** (9 pages). Ordering information is given on any current masthead page.

1,3-Dimethyl-2-phenylbenzimidazoline as a Novel and Efficient Reagent for Mild Reductive Dehalogenation of α-Halo Carbonyl Compounds and Acid Chlorides

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1,3-Dimethyl-2-phenylbenzimidazoline (DMBI) has been found to be a powerful, chemoselective, and useful reducing agent for mild reductive dehalogenation of a variety of α-halo carbonyl compounds (halo = Br, Cl, F) and acid chlorides. The reduction of α-halo ketones, aldehydes, esters, lactones, and carboxylic acids with this new reagent in ether is quite selective and clean and generally proceeds in almost quantitative yields at moderate temperatures with no additives. The order of relative reactivities in a series of α-halo carbonyl compounds was Br > Cl > F (for halides), primary > secondary > tertiary (for substitution at the halogenated carbon), and cyclohexyl > cyclododecyl (for ring size). The reduction of α-bromocamphor with DMBI-2-*d* led stereospecifically to the formation of camphor-3-*exo*-*d*. Based on these results together with experiments with para-substituted DMBIs, the mechanism of the present dehalogenation reaction of α-halo carbonyl compounds is postulated to proceed via a simple linear transition state (direct S_N2 displacement) featuring an attack on the halogenated carbon center by hydrogen at the C-2 position of DMBI as a hydride. Reductive dechlorination of acid chlorides to the corresponding aldehydes or aldehyde-*d* with DMBI or DMBI-2-*d* has also been achieved most effectively in the presence of an acetic acid catalyst.

Selective reduction of organic functional groups is an important and frequently encountered synthetic operation in organic synthesis. Many methods have been developed toward this goal and many types of "selective reduction" have been accepted as synthetically useful. Despite much work, however, in the reduction field, there are only a few

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