Synthesis of Lactones by Baeyer−Villiger Oxidation with Magnesium Monoperphthalate Hexahydrate

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Lactones and their derivatives are important natural products as well as useful intermediates in the synthesis of other natural products. For example, lactones such as 4-decanolide (**4a**), 5-decanolide (**4b**), 5-dodecanolide (**4c**), are 6-decanolide (**4e**) are widely found in flavors and fragrances, and 5-hexadecanolide (**4d**) has been isolated from the oriental hornet *Vespa orientalis*[1] in pheromone.

Lactones are usually prepared from their linear precursors such as hydroxy acids by lactonization or from cyclic substances such as ketones by Baeyer−Villiger oxidation.[2] As for Baeyer−Villiger oxidation, MCPBA has been widely used as an oxidant, but safety and cost considerations frequently discourage its use for large-scale synthesis. MCPBA in its pure form is both shock-sensitive and potentially explosive in the condensed phase. The latter is a consequence of a positive result of 30 ms upon evalution by the standard time/pressure test for products which are capable of deflagration.[3] Commercial forms of MCPBA normally contain *m*-chlorobenzoic acid as a contaminant; this leads to some reduction in the hazardous nature of the product, but it is still shock-sensitive and capable of deflagration. On the other hand, magnesium monoperphthalate hexahydrate (MMPP),[4] a recently developed peroxygen product, is non-shock-sensitive and non-deflagrating. However, to our knowledge, MMPP has not yet been applied for Baeyer−Villiger oxidation of ketones except for a few examples such as cyclohexanone, *tert*-butyl methyl ketone,[5] or benzocyclobutanone.[6] In this paper, we wish to report the synthesis of lactones **4** by regioselective Baeyer−Villiger oxidation of 2-alkylcycloalkanones **3** using MMPP and the application of this reaction to the synthesis of massoia lactone (**6**).

Ketones **3** were prepared from cycloalkanone *N*,*N*-dimethylhydrazones **2**, which were derived from cycloalkanones **1** and *N*,*N*-dimethylhydrazine using trifluoroacetic acid as a catalyst, by successive deprotonation with *n*-BuLi, alkylation with alkyl bromides, and hydrolysis (Scheme 1, Table 1). As shown in Table 2, 5-decanolide (**4b**) was obtained from 2-pentylcyclopentanone (**3b**) in good yield (94%) when treated with MMPP and $NaHCO_3$ in MeOH−H_2O at room temperature (entry 2). Other results are listed in Table 3. A variety of lactones **4** were prepared in good yields by this method.

Using this reaction, the synthesis of massoia lactone (**6**),[7] which is an important additive in butter and milk flavors, was conducted. The synthetic route to **6** is shown in Scheme 2. Lactone **4b**, easily prepared from cyclo-

Scheme 1

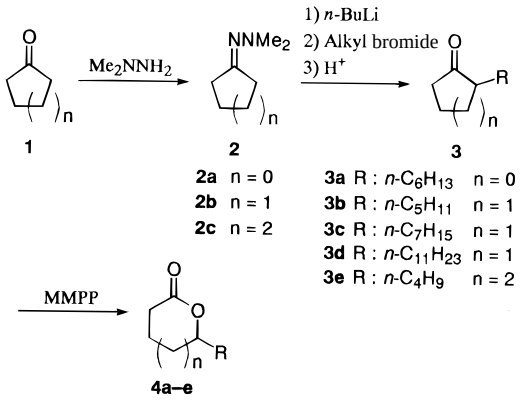

Table 1. Preparation of 2-Alkylcycloalkanones 3

entry	*n*	**2** (yield, %[a])	R	**3** (yield, %[a])
1	0	**2a** (65)	n-C_6H_{13}	**3a** (83)
2	1	**2b** (91)	n-C_5H_{11}	**3b** (86)
3	1		n-C_7H_{15}	**3c** (73)
4	1		n-$C_{11}H_{23}$	**3d** (65)
5	2	**2c** (90)	n-C_4H_9	**3e** (67)

[a] Isolated yields.

Table 2. Oxidation of 2-Pentylcyclopentanone 3b

	conditions		
entry	solvent	additive	yield, %[a]
1	MeOH	$NaHCO_3$	85
2	MeOH−H_2O	$NaHCO_3$	94
3	MeOH−H_2O		81
4	HMPA−H_2O	$NaHCO_3$	26
5	DMF−H_2O	$NaHCO_3$	68

[a] Isolated yields.

Table 3. Baeyer−Viliger Type Oxidation with MMPP

Entry	Ketone **3**	Lactone **4**	Yield / %[a]
1	**3a**	**4a**	95
2	**3b**	**4b**	94
3	**3c**	**4c**	98
4	**3d**	**4d**	60
5	**3e**	**4e**	92

[a] Isolated yields.

(1) Ikan, R.; Gottlieb, R.; Bergmann, E. D. *J. Insect Physiol.* **1969**, *15*, 1709.
(2) Ijima, A.; Takahashi, K. *Chem. Pharm. Bull.* **1973**, *21*, 215.
(3) *UN test method*, Test 2 (b) (iii) -ST/AG/AC 10/11.
(4) (a) Hignett, G. J. *European Patent Appl.* 27 693, 1981; *Chem. Abstr.* **1981**, *95*, 168 801. (b) Heaney, H. *Aldrichim. Acta* **1993**, *26*, 35.
(5) Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015.
(6) Hosoya, T.; Kuriyama, Y.; Suzuki, K. *Synlett* **1995**, 635.
(7) (a) Abe, S. *J. Chem. Soc. Jpn.* **1937**, *58*, 246. (b) Cavill, G. W. K.; Clark, D. V.; Whitfield, F. B. *Aust. J. Chem.* **1968**, *21*, 2819. (c) Hashizume, T.; Kikuchi, N.; Sasaki, Y.; Sakata, I. *Agric. Biol. Chem.* **1968**, *32*, 1306.

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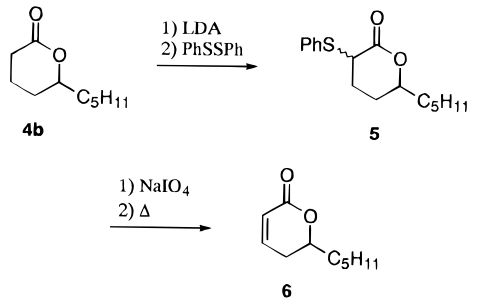
Scheme 2



pentanone *via* hydrazone method and Baeyer−Villiger oxidation with MMPP, was allowed to react with LDA in THF at −78 °C and then with diphenyl disulfide[8] to give the mixture of diastereomers of 2-(phenylthio)-5-decanolide (**5**) in 61% yield. After oxidation of **5** with $NaIO_4$, thermal elimination gave massoia lactone (**6**) in 95% yield.

In summary, MMPP was found to be an effective oxidant of 2-alkylcycloalkanones to the corresponding lactones. Using this reaction, some lactonic flavors and pheromones were prepared.

Experimental Section

General. ^{1}H NMR spectra were taken at 400 MHz in $CDCl_3$ solvent and recorded in parts per million (ppm, δ) downfield from internal tetramethylsilane (Me_4Si). Column chromatography was performed using silica gel 60 (230−400 mesh), and thin-layer chromatography (TLC) was performed on silica gel 60 plates (F_{254}). THF was dried and deoxygenated by distillation from potassium benzophenone under an argon atmosphere just before use. Benzene and toluene were purified by distillation over $CaCl_2$. Diisopropylamine was dried by distillation from potassium hydroxide. *n*-Butyllithium as a *ca.* 1.6 M hexane solution was titrated with *sec*-butyl alcohol using *o*-phenanthroline as an indicator just before use. The other organic compounds were commercial products of the highest available purity.

General Procedure for the Preparation of Cycloalkanone *N,N*-Dimethylhydrazones 2a−c. In a flask equipped with a trap to remove water, the mixture of cycloalkanone **1** (100 mmol), *N,N*-dimethylhydrazine (120 mmol, 9.12 mL), trifluoroacetic acid (0.05 mL), and benzene (40 mL) was added. The mixture was heated under reflux for 5 h and then cooled to room temperature. The reaction mixture was diluted with ether (200 mL) and water (50 mL). The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator. The residue was purified by distillation under reduced pressure.

Cyclobutanone *N,N*-dimethylhydrazone (2a): oil (65%); bp 150 °C/760 mmHg; IR (neat) 1665 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.94−2.02 (m, 2H), 2.59 (s, 6H), 2.90−3.00 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.38, 35.14, 35.31, 46.80, 160.36; MS *m/z* (rel intensity) 112 (M^+).

Cyclopentanone *N,N*-dimethylhydrazone (2b): oil (91%); bp 58 °C/17 mmHg; IR (neat) 1660 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70−1.81 (m, 4H), 2.37 (t, J = 7.2 Hz, 2H), 2.45 (t, J = 7.3 Hz, 2H), 2.53 (s, 6H); MS *m/z* (rel intensity) 126 (M^+).

Cyclohexanone *N,N*-dimethylhydrazone (2c): oil (90%); bp 75 °C/17 mmHg; IR (neat) 1655 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.63−1.71 (m, 6H), 2.24 (t, J = 6.4 Hz, 2H), 2.44 (s, 6H), 2.51 (t, J = 6.1 Hz, 2H); MS *m/z* (rel intensity) 140 (M^+).

General Procedure for the Preparation of 2-Alkylcycloalkanones 3a−e. To a solution of cycloalkanone *N,N*-dimethylhydrazone **2** (10.0 mmol) in THF (20 mL) was added *n*-BuLi in hexane (10.5 mmol, 6.8 mL) at −5 °C under an argon atmosphere. After the mixture stirred for 1 h at this temperature, alkyl bromide (10.3 mmol) was added, and stirring was continued for 20 h at room temperature. To the reaction mixture was added aqueous 2 *N* HCl (20 mL). After stirring for 1 h, the mixture was extracted with EtOAc (3 × 20 mL). The organic layer was washed with water and brine and dried over $MgSO_4$. The crude products **3a**−**e** were purified by column chromatography (hexane:EtOAc = 6−12:1).

2-Hexylcyclobutanone (3a): oil (83%); IR (neat) 1750 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.19−1.35 (br, 8H), 1.44−1.50 (m, 1H), 1.60−1.70 (m, 2H), 2.13−2.22 (m, 1H), 2.87−2.96 (m, 1H), 2.97−3.07 (m, 1H), 3.23−3.34 (m, 1H); MS *m/z* (rel intensity) 154 (M^+).

2-Pentylcyclopentanone (3b): oil (86%); IR (neat) 1740 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.19−1.36 (br, 7H), 1.47−1.57 (m, 1H), 1.71−1.83 (m, 2H), 1.96−2.06 (m, 2H), 2.08−2.15 (m, 1H), 2.17−2.34 (m, 2H); MS *m/z* (rel intensity) 154 (M^+).

2-Heptylcyclopentanone (3c): oil (73%); IR (neat) 1740 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.4 Hz, 3H), 1.19−1.36 (br, 11H), 1.47−1.57 (m, 1H), 1.73−1.83 (m, 2H), 1.97−2.06 (m, 2H), 2.08−2.15 (m, 1H), 2.21−2.34 (m, 2H); MS *m/z* (rel intensity) 182 (M^+).

2-Undecylcyclopentanone (3d): solid (65%); mp 24 °C; IR (Nujol) 1745 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.19−1.36 (br, 19H), 1.47−1.57 (m, 1H), 1.71−1.83 (m, 2H), 1.96−2.06 (m, 2H), 2.07−2.18 (m, 1H), 2.20−2.33 (m, 2H); MS *m/z* (rel intensity) 239 ($M^+ + 1$).

2-Butylcyclohexanone (3e): oil (67%); IR (neat) 1715 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.7 Hz, 3H), 1.17−1.44 (m, 6H), 1.61−1.89 (br, 4H), 2.00−2.13 (m, 2H), 2.24−2.32 (m, 2H), 2.36−2.41 (m, 1H); MS *m/z* (rel intensity) 154 (M^+).

General Procedure for the Baeyer−Villiger Oxidation of 2-Alkylcycloalkanones 3 Using MMPP. A typical procedure is described for the synthesis of 5-decanolide (**4b**): To a solution of 2-pentylcyclopentanone (**3b**) (0.5 mmol, 0.077 g) in MeOH (2.0 mL)−H_2O (2.0 mL) were added MMPP (1.0 mmol, 0.49 g) and $NaHCO_3$ (1.0 mmol, 0.084 g) at room temperature. After stirring for 24 h, the reaction mixture was diluted with water (10 mL) and ethyl acetate (50 mL). The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvents and bulb-to-bulb distillation (145 °C/9 mmHg) gave 5-decanolide (**4b**) (0.47 mmol, 0.0797 g, 94%). **4b** was characterized by ^{1}H NMR, MS, IR, and GC comparsion with an authentic sample.

4-Decanolide (4a): oil (95%); bp 150 °C/10 mmHg; IR (neat) 1785 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3H), 1.29−1.46 (br, 8H), 1.56−1.63 (m, 1H), 1.70−1.75 (m, 1H), 1.81−1.91 (m, 1H), 2.29−2.37 (m, 1H), 2.51−2.55 (m, 1H), 4.46−4.53 (m, 1H); MS *m/z* (rel intensity) 171 ($M^+ + 1$).

5-Decanolide (4b): oil (94%); bp 145 °C/9 mmHg; IR (neat) 1740 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.7 Hz, 3H), 1.29−1.93 (m, 12H), 2.40−2.48 (m, 1H), 2.55−2.61 (m, 1H), 4.27−4.30 (m, 1H); MS *m/z* (rel intensity) 171 ($M^+ + 1$).

5-Dodecanolide (4c): oil (98%); bp 130 °C/2 mmHg; IR (neat) 1740 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.28−1.93 (br, 16H), 2.40−4.49 (m, 1H), 2.55−2.61 (m, 1H), 4.26−4.27 (m, 1H); MS *m/z* (rel intensity) 199 ($M^+ + 1$).

5-Hexadecanolide (4d): solid (60%); mp 38 °C; IR (Nujol) 1745 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.19−1.29 (br, 17H), 1.49−1.60 (m, 3H), 1.66−1.74 (m, 1H), 1.81−1.92 (m, 3H), 2.40−2.48 (m, 1H), 2.55−2.63 (m, 1H), 4.26−4.29 (m, 1H); MS *m/z* (rel intensity) 255 ($M^+ + 1$).

6-Decanolide (4e): oil (92%); bp 150 °C/10 mmHg; IR (neat) 1735 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3H), 1.23−1.42 (br, 7H), 1.47−1.62 (m, 2H), 1.67−1.94 (m, 3H), 2.40−2.48 (m, 1H), 2.55−2.61 (m, 1H), 4.26−4.30 (m, 1H); MS *m/z* (rel intensity) 170 (M^+).

2-(Phenylthio)-5-decanolide (5). To a THF (5 mL) solution of diisopropylamine (5.5 mmol, 0.78 mL) in a dried reaction flask was added *n*-BuLi in hexane (6.0 mmol, 3.8 mL) at −5 °C under an argon atmosphere. After 0.5 h, lactone **4b** (5 mmol, 0.77 g) was added at −78 °C. After 1 h, diphenyl disulfide (7.0 mmol, 0.76 g) in THF (2 mL) was added at −78 °C, and stirring was continued for 20 h at room temperature. The reaction was quenched with water, and the mixture was diluted with ether (50 mL). The organic layer was washed with aqueous 0.1*N* HCl, aqueous saturated $NaHCO_3$, and brine and dried over $MgSO_4$. The crude product **5** was purified by column chromatography (hexane:EtOAc = 4:1) (3.03 mmol, 0.84 g, 61%): solid; mp 48 °C; IR (Nujol) 1715 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87−0.98

(8) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

(m, 3H), 1.28−1.70 (br, 9H), 1.91−2.14 (m, 2H), 2.28−2.34 (m, 1H), 3.81−3.86 (m, 1H), 4.43−4.46 (m, 1H), 7.31−7.54 (m, 5H); MS *m*/*z* (rel intensity) 278 (M^+). Anal. Calcd for $C_{16}H_{22}O_2S$: C, 69.03; H, 7.96. Found: C, 69.12; H, 8.19.

Massoia Lactone (6). To a MeOH (6 mL) solution of 2-(phenylthio)-5-decanolide (**5**) (1.72 mmol, 0.48 g) in a reaction flask was added dropwise $NaIO_4$ (2.1 mmol, 0.44 g) in H_2O (2 mL) at −5 °C. After 20 h, the reaction mixture was filtered, and the precipitate was washed several times with MeOH. After the combined filtrate and washings were concentrated in vacuo, the residue was added to the solution of $CaCO_3$ (1.0 g) in toluene (5 mL) at room temperature, and the solution was refluxed for 20 h. After toluene was evaporated, the reaction was quenched with water, and the mixture was diluted with ethyl acetate (50 mL), washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane:EtOAc = 4:1) to give the lactone **6** (1.64 mmol, 0.275 g, 95%): oil; IR (neat) 1760 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7.0 Hz, 3H), 1.19−1.81 (br, 8H), 2.31−2.35 (m, 2H), 4.39−4.46 (m, 1H), 6.02 (dd, J = 1.5, 9.8 Hz, 1H), 6.87−6.91 (m, 1H); MS *m*/*z* (rel intensity) 168 (M^+).

Registry numbers provided by the author: 2b, 14090-60-9; **2c**, 10424-93-8; **3a**, 35493-43-7; **3b**, 116877-29-3; **3c**, 137-03-1; **3d**, 83019-13-0; **3e**, 1126-18-7; **4a**, 706-14-9; **4b**, 705-86-2; **4c**, 713-95-1; **4d**, 7370-44-7; **4e**, 5579-78-2; **6**, 501-23-5.

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