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NEW GENERAL SYNTHESIS OF MEDIUM-SIZED LACTONES: A NEW ENTRY TO THE SYNTHESIS OF (±)-PHORACANTHOLIDE I [(±)-DECAN-9-OLIDE][1)]

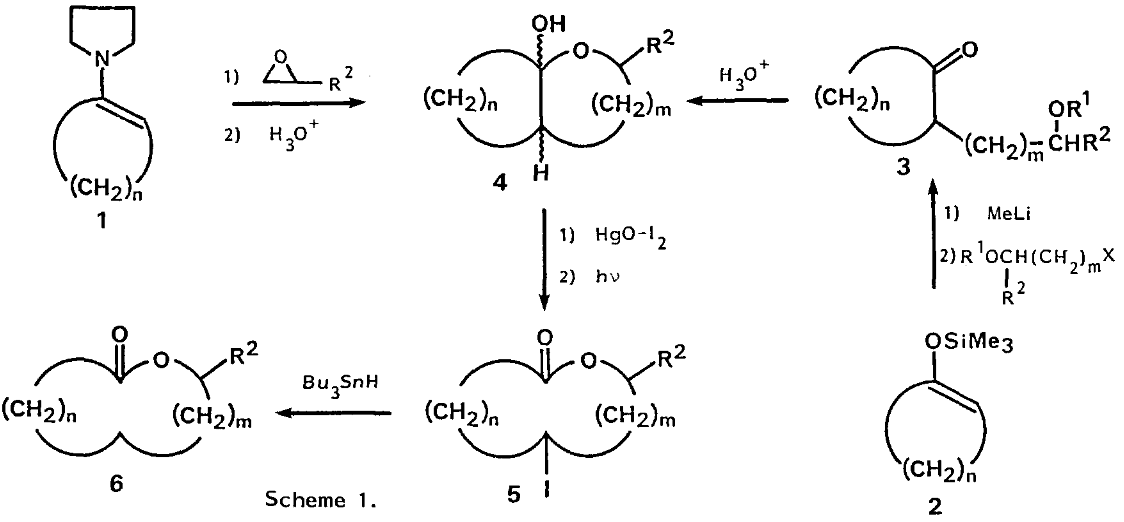
Hiroshi Suginome* and Shinji Yamada
Organic Synthesis Division, Department of Chemical
Process Engineering, Faculty of Engineering,
Hokkaido University, Sapporo 060, Japan

Abstract: We describe a new general method for the synthesis of medium-sized lactones under mild conditions involving β-scission of alkoxy radicals derived from catacondensed lactols as a key step and its application to an efficient new synthesis of a naturally occurring 10-membered lactone, phoracantholide I [(±)-decan-9-olide].

As part of our program to explore the potential of β-scission of alkoxy radicals for organic synthesis,[2] we have recently reported a new and versatile method for transforming five- and six-membered cyclic ketones as starting materials into cyclic ethers with the same ring size *via* 4 steps.[3] The method involved a regiospecific β-scission of C-C bond of the alkoxy radicals generated from the lactols derived from the cyclic ketones.

We wish to report herewith a new general method for the synthesis of medium-sized lactones under mild conditions involving a regioselective β-scission of alkoxy radicals generated from catacondensed lactols as a key step and its application to an efficient new synthesis of a naturally occurring 10-membered lactone, phoracantholide I [(±)-decan-9-olide] isolated from the metasternal secretion of the eucalypt longicorn, *Phoracantha Synonyma*.[4] Since its isolation from the beetle, phoracantholide I has been the target of several groups of synthetic organic chemists using many different approaches.[5] The synthetic sequence described in this paper, however, may perhaps be one of the simplest ones ever reported.

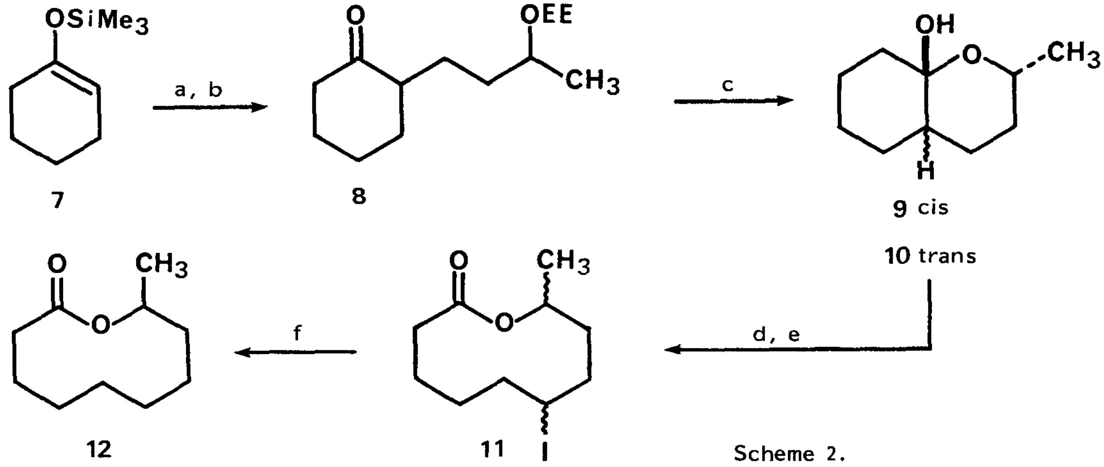
Our method uses cyclic ketones as the readily available starting materials as outlined in Scheme 1. The reaction of enamines **1** or trimethylsilyl enol ethers **2** of cyclic ketones with electrophiles such as epoxides or protected ω-hydroxyalkyl halides under appropriate conditions, followed by the removal of



Scheme 1.

the protecting group of the product with weak acids give ω-hydroxyketones **3**, most of which exist as the catacondensed lactols **4** in solution.[6] The irradiation of the hypoiodites of **4** generated in situ with an excess of mercury(II) oxide and iodine[7] in benzene containing a small amount of pyridine[3] readily leads *to a ring-expansion to give lactones* **5** *containing an iodine, by a regioselective* scission of the catacondensed bond of the intermediary alkoxy radical.[3] The smooth removal of the iodine atom of **5** with tributyltin hydride completes the synthesis of the medium-sized lactones **6**.

As the first model substrate, we chose a catacondensed lactol **4a** (n=4, m=1, $R^2=C_6H_5$) which was prepared by the reaction of 1-pyrrolidinyl-1-cyclohexene (**1**) (n=4) with styrene oxide, according to the reported procedure.[6] The lactol was treated with mercury(II) oxide-iodine-pyridine and then irradiated to give a 9-membered lactone **5a**[8] (n=4, m=1, $R^2=C_6H_5$) in 52% yield. The analogous reaction of the catacondensed lactol **4b** (n=4, m=1, $R^2=CH_3$), prepared by the reaction of **1** (n=4) with propylene oxide, gave a 9-membered lactone **5b** (n=4, m=1, $R^2=CH_3$)[9] in 53% yield. We then set out to synthesize 10-membered lactones. The trimethylsilyl enol ether of cyclohexanone (**2**) (n=4) was transformed into the lithium enolate with methyllithium in DME at -20°C.[10] The alkylation of this lithium enolate with 1-iodo-3-(1'-ethoxyethoxy)-propane [$R^1=CH(CH_3)OC_2H_5$, $R^2=H$, m=2] gave an α-alkylcyclohexanone **3** [$R^1=CH(CH_3)OC_2H_5$, $R^2=H$, n=4, m=2][11] which was hydrolyzed with aqueous acetic acid-acetone[12] to give trans cyclic lactol **4c** (n=4, m=2, $R^2=H$).[13] The lactol was transformed into a hypoiodite with an excess of mercury(II) oxide, iodine and pyridine in benzene. The irradiation of the solution with a 100-W high-pressure mercury arc through a Pyrex filter gave a 10-membered lactone, 6-iodononan-9-olide (**5c**) (n=4, m=2, $R^2=H$)[14] in 79% yield. The usefulness of the present methodology has been shown by the synthesis of phoracantholide I as outlined in Scheme 2. The lithium enolate



Scheme 2.

(a) MeLi, DME -20° (b) $ICH_2CH_2CH(CH_3)OEE$, HMPA, THF, -20°→r.t.
(c) AcOH, Acetone, H_2O (d) HgO, I_2, Py, Benzene
(e) hν (f) Bu_3SnH, Benzene, r.t.

derived from silyl enol ether **7** reacted with 1-iodo-3-(1'-ethoxyethoxy)-butane[15] to give an α-alkylcyclohexanone **8**.[16] The removal of its protecting group with aqueous acetic acid-acetone at room temperature gave a 1:1 mixture of A/B *cis*- and *trans*-1-oxa-2-methyldecalin-9-ols (**9**) and (**10**)[17] which is separable by TLC. The treatment of the *cis*, *trans* mixture with mercury(II) oxide-iodine and pyridine in benzene, followed by irradiation under the same conditions as described for lactol **4c** gave an (±)-iodophoracantholide I (**11**)[18] in 76% yield.[19] The removal of its iodine with tributyltin hydride in benzene gave (±)-phoracantholide I (**12**)[20] in 82% yield. Its various spectral data were in agreement with those published for this natural product.

The present method is applicable to a facile synthesis of medium-sized lactones using cyclic ketones as the readily available starting materials. Studies on a further extension of the scope of this method and its application to the synthesis of other naturally-occurring lactones are in progress and will be reported in due course.

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8) A 6:1 mixture of two isomers with regard to the configurations of the phenyl and the iodine substituents. M.p. 58-64°C. IR (Nujol) 1726 cm^{-1} (C=O); ^1H NMR δ 4.35-4.62 (CHI), 5.71 (dd, *J*=1.4 and 10.4 Hz, CHC_6H_5), 6.03 (dd, *J*=2.7 and 7.3 Hz, CHC_6H_5 of the isomer); Mass. *m/e* 344 (M^+, 0.7%) and 217 (M^+-I, 64.7).

9) A 1:3.5 mixture of two lactones isomeric with regard to their configurations of the methyl and the iodine substituents. An oil. IR (neat), 1728 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.25 (d, *J*=6.37, Me), 1.31 (d, *J*=5.94, Me of the isomer).

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11) An oil. IR (neat) 1708 cm^{-1} (C=O); ^1H NMR δ 1.26 (3H, d, *J*=5.94 Hz, CH_2CH_3), 1.29 (3H, d, *J*=5.27, $CHCH_3$), 3.20-3.74 (4H, m, OCH_2-), and 4.66, (1H, d, *J*=5.27, $-OCH_2-O-$); Mass. *m/e* 155 (16.2%), 139 (76.5), and 73 ($CH_3C{=}\overset{+}{O}C_2H_5$, 100).

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14) An oil. IR (neat) 1726 cm^{-1} (C=O); ^1H NMR δ 3.73-4.00 (1H, m, $-CH_2O-$), and 4.56-4.84 (2H, m, $-CH_2O-$ and CHI); Mass. *m/e* 155 (M^+-I, 100%).

15) This ester was prepared by the reaction of 1-iodo-3-butanol with ethyl vinyl ether. B.p. 49-50°C (0.4 mmHg).

16) An oil. IR (neat) 1709 cm^{-1} (C=O); ^1H NMR δ 1.08-1.32 (6H, m, Me), 3.25-3.79 (3H, m, $-CH_2O-$ and -CHO-), 4.58-4.81 (1H, m, $OC\underline{H}(CH_3)-O-$); Mass. *m/e* 153 (74%), and 73 ($C_4H_9\overset{+}{O}$, 100).

17) The two stereoisomers **9** and **10** can be separated by TLC. The *cis* form in solution was found to be in equilibrium with the ring-opened ketonic form. *Trans*-1-oxa-2α-methyldecalin-9β-ol (10). M.p. 80-82°C. IR (Nujol) 3407 cm^{-1} (OH); ^1H NMR δ 1.13 (3H, d, *J*=6.16 Hz, Me), 3.90-4.25 (1H, m, $C\underline{H}CH_3$); Mass. *m/e* 170 (M^+, 25%), 152 (M^+-H_2O, 62) and 98 (100). *Cis*-1-oxa-2α-methyldecalin-9β-ol (9). M.p. 108-110°C. IR (Nujol) 3270 cm^{-1} of the ring-opened alcohol), 3.92-4.23 (1H, m, $-O-CH-CH_3$ of the lactol form); Mass. *m/e* 170 (M^+, 8%), and 152 (M^+-H_2O, 100). The stereochemistry of **9** and **10** was assigned on the basis of their ^1H NMR spectra which indicated the signals due to their secondary methyl groups at δ 1.14 (for *cis*) and at δ 1.13 (for *trans*). A comparison of these chemical shifts excludes the possibility that the isomerism originated from the difference in the configurations of their two substituents.

18) 6-Iododecan-9-olide from the *trans*-isomer. IR (neat) 1721 cm^{-1} (C=O), ^1H NMR δ 1.29 (3H, d, *J*=6.81 Hz, Me), 4.46-4.74 (1H, m, CHI), 4.93-5.24 *cis* and *trans* iododecan-9-olide from the *cis*-isomer. IR (neat) 1725 cm^{-1} (C=O), ^1H NMR δ 1.27 and 1.28 (each d, *J*=6.37 and 6.81 Hz, Me of the *cis*- and *trans*-isomers), 4.03-4.34 and 4.43-4.75 (each m, CHI of the *cis*- and *trans*-isomers), 4.85-5.24 (1H, m, $CHCH_3$ of *cis* and *trans* isomers).

19) The photolysis of the hypoiodite generated from the *cis* isomer gave a 1:1 mixture of two isomeric iodides in a combined yield of 60% while the photolysis of the hypoiodite generated from the *trans* isomer gave a single iodide in a 90% yield. The low yield in the case of the *cis*-isomer is due to the fact that it is in equilibrium with a ring-opened form in the solution as shown by the ^1H NMR spectrum.

20) An oil. IR (neat) 1720 cm^{-1} (C=O); ^1H NMR δ 1.26 (3H, d, *J*=6.37 Hz, Me), 4.84-5.15 (1H, m, $CHCH_3$); Mass. *m/e* 170 (M^+, 1.4%), 152 (7), and 98 (100).

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