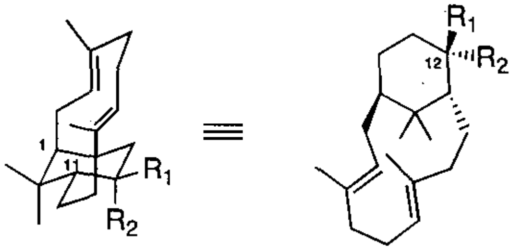
AN ALTERNATIVE METHOD FOR LACTONIZATION OF β, γ-ENOIC ACIDS AND ITS APPLICATION TO VERTICILLENE-10-CARBOXYLIC ACID[1]

Yoshihiro Yaguchi, Mitsuhiro Akiba, Makoto Harada, and Tadahiro Kato*

Department of Chemistry, Faculty of Science, Science University of Tokyo. Kagurazaka 1-3, Shinjuku-ku, Tokyo 162, Japan

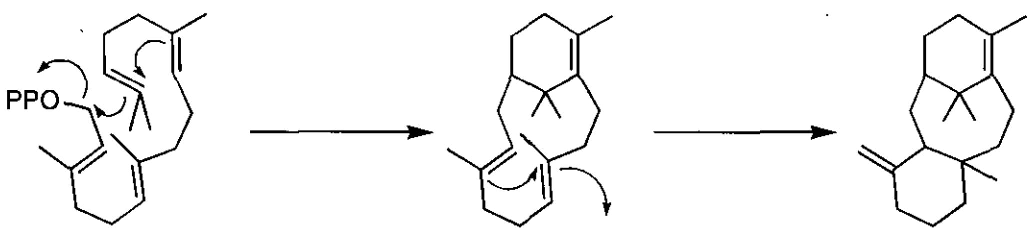
Abstract-The reaction with iodine in refluxing acetic acid was found to be an alternative method for the lactonization of β, γ-enoic acids. Application of the method to verticillene-10-carboxylic acid (**6**) resulted in the formation of three γ-lactones (**7**, **12**, and **13**), **12** being an unexpected product.

The diterpene alcohols, verticillol (**1**)[2] and 12-epiverticillol (**2**),[3] are the constituent of an evergreen wood of conifer Sciadopitys vertilillata and a moss, Jackiella javanica, respectively. Inspite of the early discovery of verticillols, there had been no report on the synthesis of the natural products excepting the construction of the hydrocarbon, verticillene.[4] The bicyclic verticillene is biogenetically related to tricyclic taxane nucleus[5] and is the putative biogenetic intermediate from the geranylgeranyl pyrophosphate (Scheme 1). The novel IN OUT structure of verticillols as well as their biogenetical relation with tricyclic taxane skeleton prompted us to elaborate the synthetic route of **1** and **2**, in which 10-cyanoverticillene (**3**) was settled as a key intermediate. Furthermore, Lewis acid promoted cyclization of the bicyclic intermediate (**3**) and its derivatives to a taxane skeleton is much interested from biogenetical viewpoints.[6]



verticillol (**1**) : R_1=OH, R_2=Me
12-epi-verticillol (**2**) : R_1=Me, R_2=OH

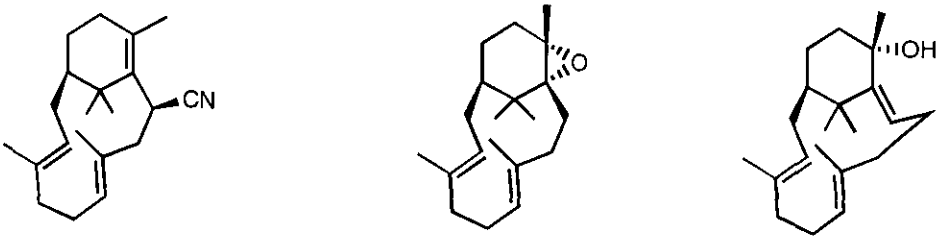
Figure 1. Structure of Verticillols



geranylgeranyl-pyrophosphate verticillene taxane skeleton

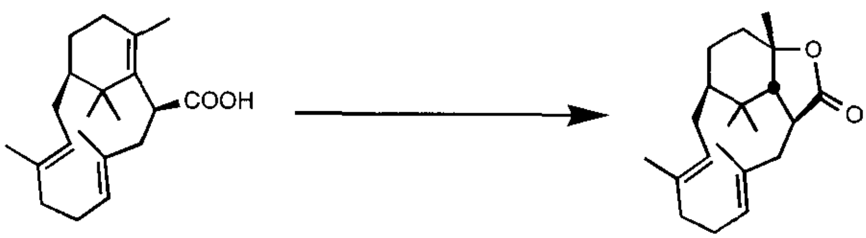
Scheme 1

Thus, we have explored the synthetic route and reactivity of the intermediate (**3**), from which epoxide (**4**) and allyl alcohol (**5**) were derived (Chart 1).[7] Since our trials to convert **4** or **5** to the epiverticillol (**2**) were all unsuccessful, we were compelled to adopt an alternative route, being the lactonization of verticillene-10-carboxylic acid (**6**) to γ-lactone (**7**) (Figure 2). The γ-lactone (**7**) is expected a promising intermediate, from which **2** may be synthesized by decarbonylation. For this purpose, lactonization of acid (**6**) derived from **3** was tried under several typical conditions including reactions with Lewis acid such as H_2SO_4[8] and $SnCl_4$[9] and also oxymercuration and iodo-lactonization. Since all attempts led to unsuccessful results,[10] we have, therefore, searched an alternative lactonization conditions using homogeranic acids as model compounds. This paper concerns with our results of exploration of lactonization conditions and their application to the verticillene-10-carboxylic acid (**6**), leading to the formation of three lactonic products (**7**, **12** and **13**).



3 **4** **5**

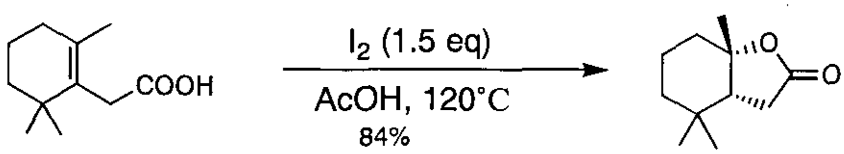
Chart 1



6 **7**

Figure 2

Lactonization of Homogeranic Acids (8 and 9). After considerable experimentations, we have ultimately found that monocyclohomogeranic acid (**8**) was effectively converted to the corresponding γ-lactone (**10**) when treated with iodine (1.5 mol equiv) in refluxing acetic acid. No iodine atom was introduced in the lactone (**10**), differing from the product obtainable by the usual iodolactonization conditions (K_2CO_3 and iodine). Both iodine and acetic acid are substantial for the lactonization. Although exact mechanism is unclear, iodine or some active species derived therefrom in acetic acid may activate the double bond to make the lactone ring. In order to get insight into the mechanism, the reaction of acyclic homogeranic acid (**9**) was examined under several conditions, the result being summarized in Table 1. It was found that cyclization followed by lactonization occurred in high yield under the same conditions (run 1). In the meanwhile, reaction at room temperature for 1 h resulted in the formation of complex



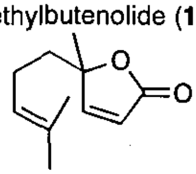
8 **10**

9 **10**

Table 1. Conditions of Lactonization Reactions of **9**

run	reagent (equiv.)	solv.	temp. (℃)	time	result
1	I_2 (1.5)	AcOH	120	1 h	84%
2	I_2 (1.5) + NaOAc (3.2)	AcOH	120	1 h	5%[a]
3	I_2 (1.5)	^{t}BuCOOH	120	1 h	68%
4	I_2 (1.5)	AcOH	80	1 h	70%
5	I_2 (1.5)	AcOH	room temperature	1 h	mixture
6	I_2 (1.5)	AcOH	room temperature	1 day	58%
7	I_2 (0.03)	AcOH	120	1 h	40%
8	ICH_2COOH (1.5)	AcOH	120	1 h	no reaction
9	$ClCH_2COOH$ (1.5)	AcOH	120	1 h	no reaction
10	54% aq HI (1.5)	AcOH	room temperature	1 h	mixture
11	54% aq HI (1.5)	AcOH	80	1 h	mixture

a; 5-(4-Methyl-3-pentenyl)-5-methylbutenolide (**11**) was isolated in 40% yield.



11

mixture, probably being composed of double bond isomers (run 5). After one day treatment at room temperature, the final product (**10**) was yielded in moderate yield (run 6). The result in run 7 indicated iodine acted catalytically. When sodium acetate was added (run 2), the lactone (**10**) was isolated in only 5% yield and the major product obtained in 40% yield was 5-(4-methyl-3-pentenyl)-5-methylbutenolide (**11**), probably formed by normal iodolactonization followed by dehydroiodination. By the action of halogenated acetic acids (runs 8 and 9) or hydroiodic acid (runs 10 and 11), the lactone (**10**) was not isolated from the reaction mixture. The results in Table 1 demonstrate clearly that I_2-AcOH system promotes cyclization as well as lactonization reactions of acyclic homogeranic acid (**9**).

Application of I_2-AcOH to Verticillene-10-carboxylic Acid (6). In our model experiments, we have revealed that the double bond of homogeranic acid is activated and cyclization followed by lactonization occurs easily and efficiently by the action of iodine in refluxing acetic acid. Since verticillene skeleton is considered as a putative biogenetic progenitor of tricyclic taxane skeleton (Scheme 1), it seems,therefore, intriguing to examine the reactivity of **6** with iodine in refluxing acetic acid from view points of both achievement of verticillol synthesis and also examination of cyclization to the taxane skeleton.

By treatment of **6** with iodine in refluxing acetic acid, three γ lactonic products (**7**, **12** and **13**) were isolated in 20, 28 and 8% yields, respectively (Chart 2). The product (**12**) possesses tetracyclic ring system with γ lactone ring (1770 cm^{-1}). At the outset of our study, **12** could not be differentiated from the expected taxane skeleton (**14**) by usual means of ^1H and ^{13}C nmr spectra. Ultimately, the structure (**12**) was unequivocally determined by X-ray crystallographic analysis. The structures (**7** and **13**) were deduced from physical evidence.

Although formation mechanism of **12** is still unclear, protonization at C11 double bond

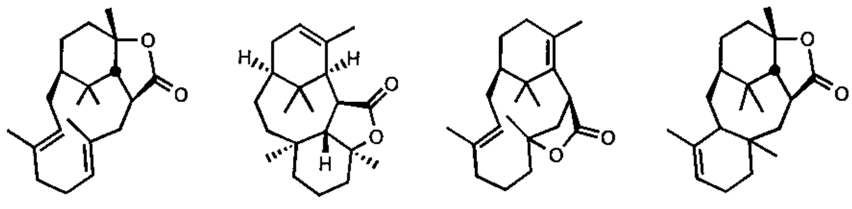
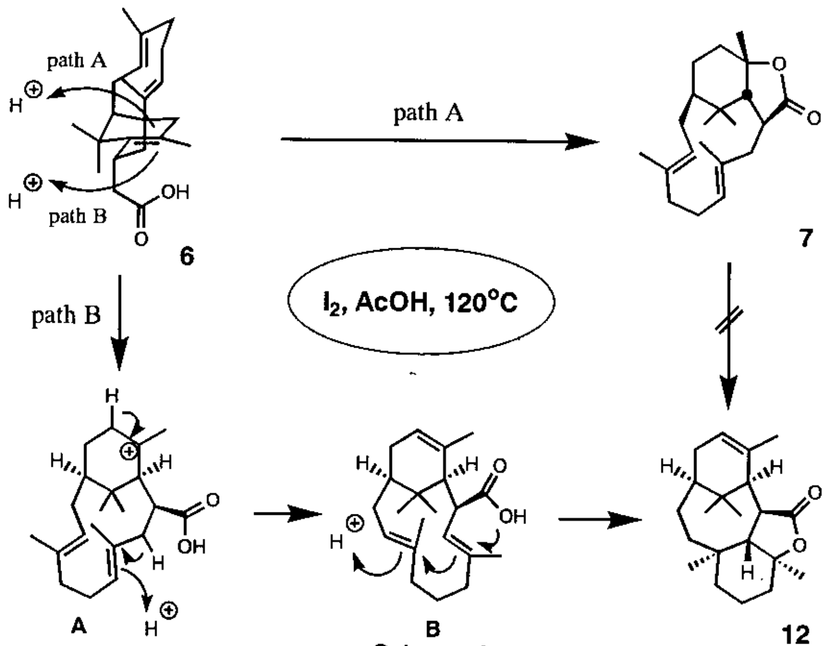
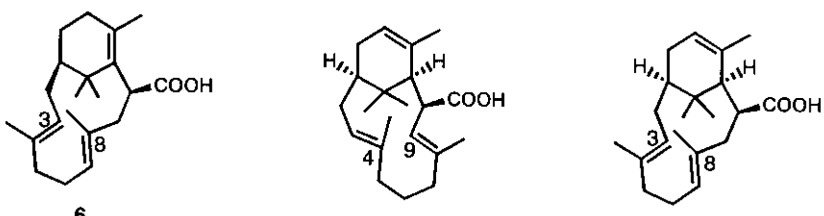


Chart 2



Scheme 2



	6	B	A*
ΔE	+6.3 kcal/mol	0 kcal/mol	+5.5 kcal/mol
Bond distance	C3-C8 4.03 Å	C4-C9 3.23 Å	C3-C8 3.52 Å

Figure 3. Molecular mechanics minimization and bond distances

from β face of **6** with concomitant lactonization (path A) leads to lactone (**7**). Protonization from α face followed by isomerization of double bond would transform to a plausible intermediate (**B**) (path B), from which the tetracyclic product (**12**) may be formed by cyclization-lactonization as demonstrated in Scheme 2. Our preliminary MM2 calculation[11] allows us to estimate that the intermediate (**B**) is energitically more stable, having distance between C4 and C9 enough for ring closure, as compared with those of starting material (**6**) and hypothetical intermediate (**A***), derived by deprotonization from an intermediate (**A**) (Figure 3). The lactone (**7**) remained unchanged when subjected to the conditions of iodine in refluxing acetic acid, indicating the path A is irreversible. Thus, we have demonstrated *that iodine in acetic acid is an alternative lactonization* conditions of β,γ-enoic acids. Application of the present method to verticillene-10-carboxylic acid furnished the expected lactone (**7**) although the yield is not satisfactory. Transformation of the lactone (**7**) to the natural product, verticillol (**2**) is now in progress.

EXPERIMENTAL

Melting points (measured on Yanaco-MP) are uncorrected. Unless otherwise noted, ^{1}H nmr and ^{13}C nmr spectra were recorded on solutions in $CDCl_3$ with $SiMe_4$ as internal standard with JEOL spectrometers. Chemical shifts are reported in δ-units with δ_H (^{1}H nmr) and δ_C (^{13}C nmr), and J-values are in Hz. The mass spectra were measured with Hitachi M-80 and M-80A spectrometers. The infrared spectra were measured with Hitachi 270-30 spectrophotometer in solution. The characteristic absorption bands were reported with ν_{max}, the solvent being indicated in parentheses. The usual work-up involved dilution of the reaction mixture with water, extraction with ether, washing of the organic extracts with water and brine, followed by drying over Na_2SO_4, and evaporation at aspirator pressure. Column chromatographic purification was carried out on Kiesel gel 60, Art 7734 (70-230 mesh), the elution solvents being indicated.

Lactonization of Monocyclohomogeranic Acid (8). A mixture of homogeranic acid (**8**) (56.6 mg, 0.31 mmol) and iodine (119 mg, 0.47 mmol, 1.5 eq) in acetic acid (4 ml) was refluxed for 1 h under argon atmosphere. After cooling, the reaction mixture was diluted with ether, washed successively with aq saturated $NaHCO_3$, aq saturated $Na_2S_2O_3$ and brine. The ether was removed and the residue was chromatographed with hexane-AcOEt 50:1 and then 1:1 to afford γ-lactone (**10**) (48 mg, 84%) as colorless oil. ν_{max} (CCl_4) 1784 cm^{-1}. δ_H (90 MHz) 0.96 (3H, s), 1.06 (3H, s), 1.53 (3H, s), 2.41 (1H, s), 2.54 (1H, d, J=4.8 Hz). δ_C (23 MHz) 175.5, 85.8, 51.8, 34.6, 33.5, 33.1, 32.1, 29.9, 28.3, 26.8, and 18.9. HRms Found: m/z 182.1301. Calcd for $C_{11}H_{18}O_2$: M, 182.1307.

General Procedure of Reaction of Homogeranic Acid (9) in Table 1. Homogeranic acid (**9**) (30 mg) in acetic acid (6 ml) was treated under the conditions listed in Table 1. The reaction mixture was treated as in the case of **8**.

9. ν_{max} (CCl_4) 1712 cm^{-1}. δ_H (90 MHz) 1.61 (3H, s), 1.66 (3H, s), 1.69 (3H, s), 2.05 (4H, s), 3.10 (2H, d, J=7.2 Hz), 5.10 (1H, br s), and 5.33 (1H, br t, J=7.2 Hz).

Reaction of Homogeranic Acid (9) with Iodine and Sodium Acetate. A mixture of homogeranic acid (**9**) (43.4 mg, 0.24 mmol), I_2 (90.7 mg, 0.36 mmol, 1.5 eq) and NaOAc (62.5 mg, 0.76 mmol, 3.2 eq) in AcOH (7 ml) was refluxed for 1 h under argon atmosphere and the reaction mixture was treated as in the case of **8**. Column chromatography afforded butenolide (**11**) (17.1 mg, 40%), cis-lactone (**10**) (2.5 mg, 6%) and trans-lactone (1.8 mg, 4%).

11. ν_{max} (CCl_4) 1768 cm^{-1}. δ_H (90 MHz) 1.48 (3H, s), 1.57 (3H, s), 1.68 (3H, s), 5.04 (1H, m), 6.03 (1H, d, J=5.7 Hz), and 7.35 (1H, d, J=5.7 Hz). HRms Found: m/z 180.1154. Calcd for $C_{11}H_{16}O_2$: M, 180.1150.

Lactonization of Verticillene-10-carboxylic Acid (6). A mixture of verticillene-10-carboxylic acid (**6**) (110 mg, 0.348 mmol) and iodine (132 mg, 0.532 mmol, 1.5 eq) in acetic acid (20 ml) was refluxed for 1 h under argon atmosphere. After cooling, the reaction mixture was diluted with ether, washed successively with aq saturated $NaHCO_3$, aq saturated $Na_2S_2O_3$ and brine. The ether was removed and the residue was chromatographed with hexane-AcOEt 50:1 and then 1:1 to afford **7** (22.4 mg, 20%), **12** (30.4 mg, 28%) and **13** (9.3 mg, 8%). **7** colorless powder, mp 169-170℃ (hexane). ν_{max} (CCl_4) 1766 cm^{-1}. δ_H (200 MHz) 0.62 (3H, s), 0.93 (3H, s), 1.53 (6H, s), 1.56 (3H, s), 4.96 (1H, br d, J=10.0 Hz), and 5.32 (1H, br d, J=12.3 Hz). δ_C (50 MHz) 180.6 (s), 134.7 (s), 132.7 (d), 132.2 (s), 123.7 (d), 86.1 (s), 46.9 (d), 41.9 (t), 41.5 (t), 40.2 (d), 40.1 (d), 34.5 (s), 32.8 (t), 31.5 (t), 29.4 (q), 28.4 (q), 26.6 (t), 25.7 (q), 23.4 (t), 16.3 (q), and 16.0 (q). HRms Found: m/z 316.2400. Calcd for $C_{21}H_{32}O_2$: M, 316.2402. **12** colorless prisms, mp 118-120℃ (hexane). Crystal System: orthorhombic. Cell Constant: a=13.120 (4), b=16.479 (1), c=16.413 (2) Å. V=3648.5 (1.7) $Å^3$. Dcolc: 1.184 g/cm^3. Z: 8. ν_{max} (CCl_4) 1770 cm^{-1}. δ_H (500 MHz) 0.96 (3H, s), 1.06 (6H, s), 1.33 (3H, s), 1.53 (3H, s), 2.55 (1H, br s), 2.70 (1H, dd, J=1, 13 Hz), and 5.54 (1H, m). δ_C (50 MHz) 181.4 (s), 132.8 (s), 125.5 (d), 84.5 (s), 57.9 (d), 46.9 (d), 42.9 (t), 40.8 (d), 39.8 (t), 38.8 (d), 37.6 (t), 35.6 (s), 34.5 (s), 33.3 (q), 28.3 (t), 26.9 (q), 24.8 (q), 24.3 (t), 22.4 (q), 20.6 (t), and 19.3 (q). HRms Found: m/z 316.2421. Calcd for $C_{21}H_{32}O_2$: M, 316.2402. **13** colorless needles, mp 173-175℃ (hexane). δ_H (200 MHz) 0.99 (3H, s), 1.11 (3H, s), 1.33 (3H, s), 1.63 (3H, s), 1.65 (3H, s), 2.74 (1H, m), 3.28 (1H, br d, J=10.3 Hz), 5.18 (1H, br d, J=12.0 Hz). δ_C

(50 MHz) 180.5 (s), 133.7 (s), 130.9 (s), 129.0 (s), 127.6 (d), 87.3 (s), 44.1 (d), 43.0 (d), 41.1 (t), 38.1 (t), 37.7 (s), 36.6 (t), 34.0 (t), 32.5 (t), 31.8 (q), 26.7 (q), 26.1 (q), 25.5 (t), 22.2 (q), 20.2 (t), and 15.5 (q). HRms Found: m/z 316.2400. Calcd for $C_{21}H_{32}O_2$: M, 316.2402.

REFERENCES

1. This constitutes Part 53 of the series Cyclization of Polyenes. For Part 52, *Bull. Chem. Soc. Jpn.*, in press. For Part 51, see *J. Chem. Soc., Chem. Commun.*,1994, 311 .

2 a). M. Sumimoto, Y. Ito, and H. Yokoi, 6th Symposium on the Chemistry of Natural Products, Symposium Papers 125, 1962.

b). H. Erdtman, T. Norin, M. Sumimoto, and A. Morrison, *Tetrahedron Lett.*, 1964, 3879.

c). B. Karlsson, A. Pilotti, A. Soderholm, T. Norin, S. Sundin, and M. Sumimoto, *Tetrahedron*, 1978, **34**, 2349.

3. L. J. Harrison, M. Tori, Z. Hirayosi, and Y. Asakawa, 28th Symposium on the Chemistry of Perfume, Terpenes and Essential Oil, Symposium Papers 285, 1984.

4. C. B. Jackson and G. Pattenden, *Tetrahedron Lett.*, 1985, **26**, 3393.

5. J. W. Harrison, R. M. Scrowston, and B. Lythgoe, *J. Chem. Soc. (C)*,1966, 1933. See also C. S. Swindell, *Org. Prep. and Proc. Int.*, 1991, **23**, 465.

6. S. A. Hitchcock and G. Pattenden, *Tetrahedron Lett.*, 1992, **33**, 4843.

7. T. Kato, T. Hirano, M. Hoshikawa, and T. Uyehara, *Bull Chem. Soc. Jpn.*, in Press.

8. For an example, Y. Kitahara, T. Kato, T. Suzuki, S. Kanno, and M. Tanemura, *J. Chem. Soc., Chem. Commun.*, 1969, 342.

9. For an example, T. Kato, S. Kumazawa, and Y, Kitahara, *Synthesis*, 1972, 573.

10. Unpublished results in our laboratory.

11. N. L. Allinger, *J. Amer. Chem.Soc.*, 1977, **99**, 8127. The calculation was carried out using Chem 3D program.

Received, 11th October, 1995