[Chem. Pharm. Bull.
28(7)2166—2171(1980)]

Large Scale Syntheses of (±)-Isodrimenin and (±)-Confertifolin[1]

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(Received February 19, 1980)

Large scale syntheses of (±)-isodrimenin (**4**) and (±)-confertifolin (**5**) were achieved starting from β-ionone *via* the tricyclic furan derivative (**16**). Oxidation of this intermediate (**16**) with lead tetraacetate followed by pyrolysis afforded (±)-confertifolin (**5**) as a main product. Conversion of the lead tetraacetate oxidation product (**17**) into (±)-winterin (**19**) followed by $NaBH_4$ reduction produced (±)-isodrimenin (**4**) as a main product.

Keywords——oxidation of furan; pyrolysis; $NaBH_4$ reduction; acid-induced cyclization; acetal formation

We have already reported[3] the conversion of the phenols **2** and **3** derived from dehydroabietic acid (**1**) into (+)-isodrimenin (**4**)[4] and (+)-confertifolin (**5**),[4] respectively, based on cleavage of the phenolic C-rings of **2** and **3** by ozonolysis.

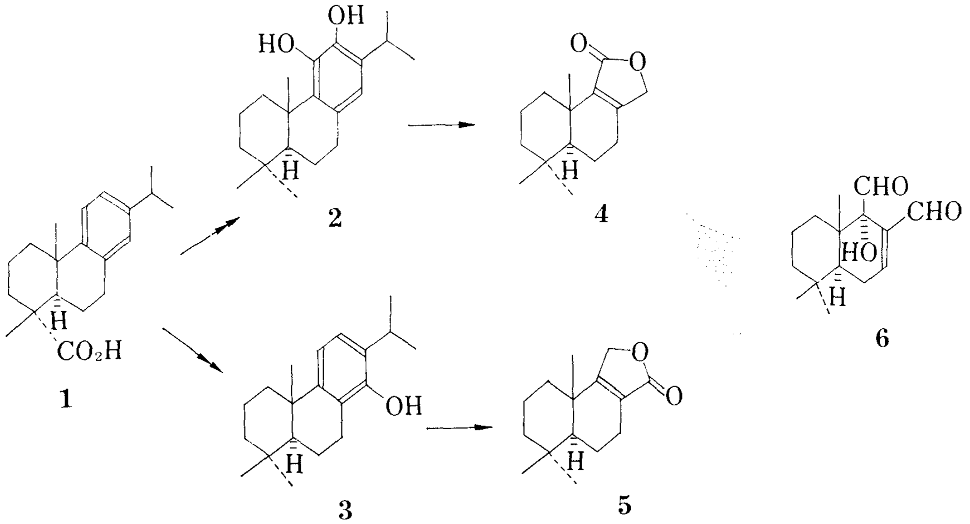

Chart 1

Meanwhile, warburganal (**6**) was isolated by Kubo, Nakanishi, and co-workers from the bark of the East African medicinal trees *Warburgia ugandensis* and *W. stuhlmannii* (Canellaceae), and was reported to have remarkable bio-activity.[5] Although the oxidation stage of **6** is different from those of **4** and **5**, the carbon skeleton of these compounds is the same. Therefore, possible transformations of **4** and **5** into optically active warburganal **6**

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[1] A portion of this work was published as a preliminary communication. H. Akita, T. Naito, and T. Oishi, *Chemistry Lett.*, **1979**, 1365.

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[4] H.H. Appel, J.D. Connolly, K.H. Overton, and R.P.M. Bond, *J. Chem. Soc.*, **1960**, 4685.

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were examined. However, since the preparation of sufficient amounts of optically active **4** and **5** from **1** for further synthetic work is rather difficult, we first tried to find a route to **6** using (±)-**4** and (±)-**5** prepared in quantity by synthesis.[6] In this report, a new route satisfying this requirement will be described.

Dihydro-β-ionone (**7**), which can be obtained from β-ionone by partial reduction with Raney Ni, was used as a starting material. Formylation[7] of **7** with trimethyl orthoformate in the presence of 70% $HClO_4$ gave a mixture of the β-methoxyenal derivative (**8**) and the tetramethoxy derivative (**9**) in yields of 14% and 25%, respectively. When **8** was treated with pyridine hydrobromide at 50° in MeOH–THF (2: 3), the desired β-keto acetal (**10**) was obtained as an oil in 69% yield. Conversion of **9** into **10** proceeded (72%) in the same way as above, but in this case the presence of one molar equivalent of water was necessary. However, since the overall yield of **10** from **7** was unsatisfactory, formylation with ethyl formate in the presence of alkoxide anion was then investigated.[8] In this case, the reaction proceeded cleanly and afforded the β-formyl ketone (**11**) which, without purification. was refluxed

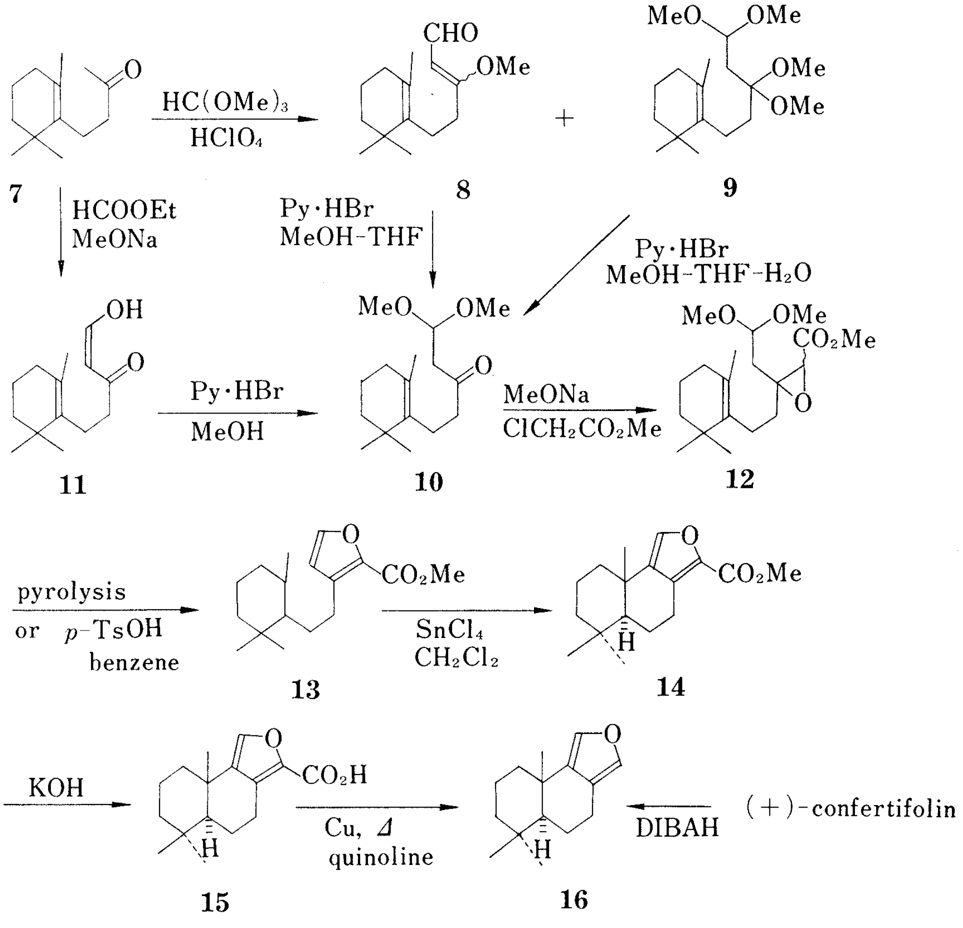

Chart 2

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6) *a*) E. Wenkert and D.P. Strike, *J. Am. Chem. Soc.*, **86**, 2044 (1964); *b*) Y. Kitahara, T. Kato, T. Suzuki, S. Kanno, and M. Tanemura, *J. Chem. Soc. Chem. Commun.*, **1969**, 342; *c*) H. Yanagawa, T. Kato, and Y. Kitahara, *Synthesis*, **1970**, 257; *d*) A. Matsukawa, H. Shintani, and A. Ohsuka, The 22nd Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics, Yokohama, 1978, Abstracts of Papers, p. 231.

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in MeOH in the presence of a catalytic amount of pyridine hydrobromide to produce the β-keto acetal (**10**) in 82% yield from **7**. The spectral data for **10** were all consistent with the assigned structure (see the experimental section). Conversion of **10** with methyl chloroacetate (3 eq) using NaOMe (3 eq) as a base in ether produced the epoxy ester (**12**) in 84% yield.[9] The appearance of the signal at δ: 3.76 (3H, s) in the nuclear magnetic resonance (NMR) spectrum of **12** shows that the methyl ester moiety was introduced into **10**. Refluxing of **12** in benzene for 2 hr in the presence of a catalytic amount of p-toluenesulfonic acid (p-TsOH·H_2O) produced the methoxycarbonyl furan (**13**) in 90% yield. Here, the by-product methanol was continuously removed by distillation to drive the reaction to completion. On heating **12**,[9] **13** was also obtained in good yield, but when a large amount of **12** was subjected to the reaction, the yield was appreciably decreased and the product was mostly a tarry material. Cyclization of **13** with $SnCl_4$ (2 eq) in CH_2Cl_2 produced the crystalline tricyclic compound (**14**), mp 96—97°, in 77% yield. The progress of the reaction was monitored by gas chromatography (GC) and the reaction was continued until all of **13** was consumed, because the separation of **13** from **14** was very difficult. No stereoisomer of **14** was detected in this cyclization. Hydrolysis of the ester group of **14** with potassium hydroxide in methanol–water (10:1) afforded the carboxylic acid (**15**), mp 185—187°, in 92% yield. Decarboxylation was then effected by heating **15** for 1 hr at 220—230° (bath temp.) in quinoline in the presence of copper powder under nitrogen[10] to produce the furan (**16**) in 97% yield as an oil, which solidified on storage in a refrigerator. This compound (**16**) was found to be identical with an authentic sample prepared by the reduction of (+)-confertifolin (**5**) with diisobutylaluminum hydride (DIBAH)–tetrahydrofuran (THF); this showed that **16** possessed the same *trans*-decaline configuration as (+)-confertifolin. Treatment of **16** with one equiv. of lead tetraacetate[11a] in benzene at room temperature afforded the diacetoxy derivative (**17**), mp 124—126°, in 90% yield.

On heating **17** for 1 hr at 170° (bath temp.)[11b] and subsequent repeated recrystallization of the resulting solid from CH_2Cl_2–hexane, (±)-confertifolin (**5**), mp 116—117°, was obtained in 68% yield. The combined filtrate was subjected to chromatography using a Lobar column to afford (±)-isodrimenin (**4**), mp 89—90°, in 17% yield together with a small amount of **5**

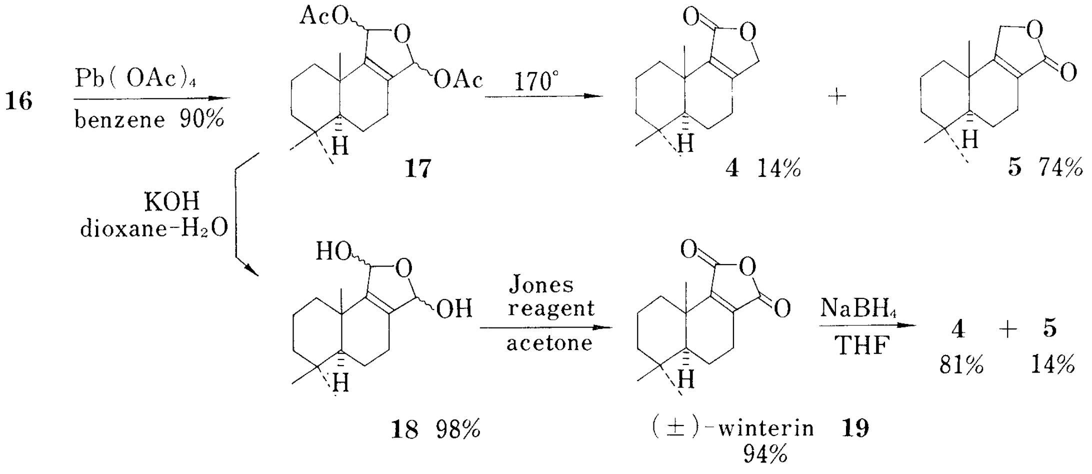

Chart 3

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[9] D.M. Burness, "Organic Syntheses," Coll. Vol. IV, ed. by N. Rabjohn, John Wiley and Sons, Inc., New York, 1963, p. 649.

[10] D.M. Burness, "Organic Syntheses," Coll. Vol. IV, ed. by N. Rabjohn, John Wiley and Sons, Inc., New York, 1963, p. 628.

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(total yield, 74%). Spectral data (NMR, IR, GC–MS) for **4** and **5** were identical with those for authentic (+)-isodrimenin[3,4] and (+)-confertifolin,[3,4] respectively.

In order to obtain isodrimenin (**4**) in quantity, another route was sought. Hydrolysis of **17** with 10% KOH–dioxane (4: 7) at room temperature yielded **18**, mp 134—137°, in 98% yield. Jones oxidation of **18** in acetone gave (±)-winterin (**19**),[3,12] mp 144—145°, in 88% yield. Sodium borohydride reduction of **19** proceeded selectively in THF, affording (±)-isodrimenin (**4**) in 81% yield together with a much smaller amount of **5** (14%).

Every step in the above synthesis can be carried out on a large scale by a standard procedure. The methods for the syntheses of (±)-isodrimenin and (±)-confertifolin were thus established, and the total synthesis of (±)-warburganal was accomplished using (±)-isodrimenin thus prepared as a starting materials; this will be described in the accompanying paper.[13]

Experimental

Melting points were measured with a Kofler micro melting point apparatus, and are uncorrected. IR spectra were measured on a JASCO A-3 spectrophotometer, NMR spectra on Varian HA-100 and JEOL MH-60 instruments, and MS spectra on a Hitachi RMU-6M mass spectrometer.

Dihydro-β-ionone (7)——A mixture of β-ionone [bp 126° (10 mmHg), 19.23 g (0.1 mol)] and Raney Ni (prepared from 8.0 g of Ni-Aloe according to Poul's procedure[14]) was stirred at 65° (bath temp.) under a hydrogen atmosphere. The hydrogenation was stopped when just one molar equivalent of hydrogen had been absorbed. The catalyst was filtered off with the aid of Celite and washed well with ether. The filtrate was dried (Na_2SO_4) and concentrated to give an oil (19.75 g), which was distilled under reduced pressure to afford 17.15 g (88%) of dihydro-β-ionone (7)[15] [bp 112—114° (8 mmHg)].

3-Methoxy-5-(2,6,6-trimethylcyclohex-1-en-1-yl)pent-2-enal (8) **and 3,3-Dimethoxy-5-(2,6,6-trimethylcyclohex-1-en-1-yl)pentanal Dimethyl Acetal** (9)——$HClO_4$ (70%, 10 g) was added to a solution of dihydro-β-ionone (7) (9.46 g) in trimethyl orthoformate (150 ml) under ice-cooling within 8 min, and the mixture was stirred for 10 min at room temperature. After addition of pyridine (25 ml) under ice-cooling, a sat. $NaHCO_3$ solution was added and the mixture was extracted with $CHCl_3$. The extract was washed with sat. NaCl solution, dried over Na_2SO_4, and concentrated to give 11.54 g of an oil, which was subjected to silica gel chromatography. The fraction eluted with hexane-ethyl acetate (20: 1) afforded 3.88 g (25%) of **9**, a colorless oil. NMR ($CDCl_3$, 60 MHz) δ: 3.69 (3H, s, OMe), 5.36 (1H, d, $J=8.4$ Hz, $=C\underline{H}$–CHO), 9.84 (1H, d, $J=8.4$ Hz, $=CH$–$C\underline{H}O$). IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1660, 1610. MS *m/e*: 236 (M^+-MeOH). The next fraction, eluted with hexane–ethyl acetate (1: 4—1: 9), gave 1.58 g (14%) of **8**, a colorless oil. NMR ($CDCl_3$, 60 MHz) δ: 1.97 [2H, d, $J=4.8$ Hz, $C\underline{H}_2CH(OMe)_2$], 3.20 (6H, s, $2\times OMe$), 3.32 (6H s, $2\times OMe$), 4.51 [1H, $J=4.8$ Hz, $CH_2C\underline{H}(OMe)_2$]. MS *m/e*: 250 ($M^+-2\times MeOH$), 218 ($M^+-3\times MeOH$).

3-Oxo-5-(2,6,6-trimethylcyclohex-1-en-1-yl)pentanal Dimethyl Acetal (10)——a) Preparation from **8**: A solution of **8** (3.6 g) in THF (90 ml)–MeOH (60 ml) and pyridine hydrobromide (2.4 g) was stirred for 30 min at 50° and, after addition of sat. $NaHCO_3$, was extracted with CH_2Cl_2. The extract was washed with sat. NaCl solution, dried over Na_2SO_4 and concentrated to dryness to afford 4.14 g of an oil, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (30: 1—10: 1) afforded 2.81 g (69%) of pure **10** as an oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1715. NMR ($CDCl_3$, 60 MHz) δ: 2.69 [2H, d, $J=6$ Hz, $C\underline{H}_2CH(OMe)_2$] 3.36 (6H, s, $2\times OMe$), 4.77 [1H, t, $J=6$ Hz, $CH_2C\underline{H}(OMe)_2$]. MS *m/e*: 268 ($M^+$).

b) Preparation from **9**: Water (18 μl) and pyridine hydrobromide (160 mg) were added to a solution of **9** (314 mg) in THF (6 ml)–MeOH (4 ml), and the solution was kept for 1 hr at 50° then poured into sat. $NaHCO_3$ solution. The mixture was extracted with ether. The extract was dried over Na_2SO_4 and concentrated to give an oil, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (10: 1) afforded 192 mg (72%) of an oil, which was identical with **10**.

c) Preparation from **7** without isolating **8** and **9**: A solution of **7** (22.8 g), trimethyl orthoformate (352 ml) and 70% $HClO_4$ (26 ml) was treated in the manner described for the preparation of **8** and **9**, and the resulting oil was dissolved in THF (232 ml)–MeOH (174 ml). After addition of pyridine hydrobromide (6 g), the mixture was stirred at 70° for 50 min. Water (5 ml) was then added and the solution was kept for 30 min at 50°. After usual work-up and silica gel chromatography, 12.2 g (39%) of **10** was obtained.

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[13] T. Nakata, H. Akita, T. Naito, and T. Oishi, *Chem. Pharm. Bull.*, **28**, 2172 (1980).

[14] R. Poul and G. Hilly, *Bull. Soc. Chem. Fr.*, 3, 2330 (1936).

[15] *a*) J. Kandel, *Compt. Rend. Acad. Sci.*, **205**, 994 (1937); *b*) J. Kandel, *Ann. Chem.*, **11**, 73 (1939).

d) Preparation *via* **11**: Ethyl formate (3 ml) and sodium methoxide (1.35 g) were added to a solution of **7** (977 mg) in ether (20 ml) under ice-cooling, and the mixture was stirred for 30 min at room temperature, then again cooled with ice-water. Acetic acid (1.43 ml) in 5 ml of ether and ice-water was then added and the ether layer was washed with sat. NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent afforded 1.58 g of **11** as an oil. This crude **11** was dissolved in MeOH without purification and pyridine hydrobromide (160 mg) was added. After the mixture had been stirred for 2 hr at 80° (bath temp.), most of the MeOH was evaporated off. The residue was dissolved in ether and the ether solution was washed with sat. $NaHCO_3$ solution then with sat. NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent afforded 1.30 g of an oil, which was subjected to silica gel chromatography. Elution with hexane–ethyl acetate (10: 1) afforded 1.1 g (82% from **7**) of **10**, which was identical with an authentic sample of **10**.

Methyl 3-(2,2-Dimethoxyethyl)-5-[2-(2,6,6-trimethylcyclohex-1-en-1-yl)]-2,3-epoxypentanoate (12)——Methyl chloroacetate (16.6 g, 51×3 mmol) and sodium methoxide (8.26 g, 51×3 mmol) were added to a solution of the β-ketoacetal (**10**) (13.77 g, 51 mmol) in ether (150 ml) with ice-cooling under a nitrogen atmosphere, and the solution was stirred for 2 hr at the same temperature. After the addition of dilute acetic acid (20 ml, AcOH: $H_2O=1:15$), ether was added. The ether extract was washed with sat. $NaHCO_3$ solution and then with sat. NaCl solution, dried over Na_2SO_4 and concentrated to afford an oil, which was subjected to silica gel chromatography. Elution with hexane–ethyl acetate (20: 1—10: 1) afforded 14.68 g (84%) of **12** as an oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ $\mathrm{cm^{-1}}$: 1760, 1735. NMR ($CDCl_3$, 60 MHz) δ: 3.76 (3H, s, COOMe). GC-MS *m/e*: 308 (M^+-MeOH), 276 (M^+-2 MeOH).

Methyl 3-[2-(2,6,6-Trimethylcyclohex-1-en-1-yl)ethyl]-2-furoate (13)——a) The epoxide (**12**) was kept at 200° for 45 min while distilling off liberated methanol, and the resulting oil was chromatographed on silica gel. Elution with hexane–ethyl acetate (20: 1) gave 2.36 g (80%) of the furan (**13**). IR $\nu_{\max}^{\mathrm{CCl_4}}$ $\mathrm{cm^{-1}}$: 1730, 1715, 890. NMR ($CDCl_3$, 60 MHz) δ: 3.86 (3H, s, COOMe), 6.39 (1H, d, $J=2$ Hz, β-H of furan ring), 7.40 (1H, d, $J=2$ Hz, α-H of furan ring). GC-MS *m/e*: 276 (M^+).

b) *p*-TsOH·H_2O (100 mg) was added to a solution of **12** (2.38 g) in benzene (20 ml) and the mixture was heated for 2 hr. During that time benzene was allowed to distill off slowly, while the same solvent was continuously added so as to keep the total volume constant. The whole solution was poured into 5% Na_2CO_3 solution and the organic layer was washed with sat. NaCl solution, dried over Na_2SO_4 and concentrated to leave an oil, which was chromatographed on silica gel. Elution with hexane-ethyl acetate (40: 1—30: 1) afforded 1.74 g (90%) of the furan (**13**).

Methyl 4,5,5a,6,7,8,9,9a-Octahydro-6,6,9a-trimethyl-3-naphto[1,2-*c*]-2-furoate (14)——Anhydrous $SnCl_4$ (25 g) in 50 ml of CH_2Cl_2 was added to a solution of **13** (13.2 g) in CH_2Cl_2 (200 ml) under ice-cooling and the resulting solution was stirred for 8 hr at room temperature. The mixture was poured into ice-water and the organic fraction was washed successively with water, sat. $NaHCO_3$ solution, and sat. NaCl solution, dried over Na_2SO_4 and concentrated to give 12.7 g of an oil, which solidified on standing. Recrystallization from MeOH provided 7.39 g of the furan (**14**), mp 96—97°. The filtrate was subjected to silica gel chromatography. Elution with hexane–ethyl acetate (50: 1) afforded 2.27 g of **14** (total yield of **14** from **13**, 77%). IR $\nu_{\max}^{\mathrm{CCl_4}}$ $\mathrm{cm^{-1}}$: 1708. NMR ($CDCl_3$, 60 MHz) δ: 3.85 (3H, s, CO_2Me), 7.20 (1H, s, α-H of furan ring). GC-MS *m/e*: 276 (M^+). *Anal.* Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.91; H, 8.71. Further elution with the same solvent system produced 0.49 g of the dihydro compound (**13**), which presumably originated from the tetrahydro-β-ionone.

4,5,5a,6,7,8,9,9a-Octahydro-6,6,9a-trimethyl-3-naphto[1,2-*c*]-2-furoic Acid (15)——The furan (**14**) (19.85 g) was dissolved in MeOH (500 ml) containing KOH (50 g) and the solution was refluxed for 2 hr. When the mixture was allowed to cool, the potassium salt of **15** precipitated. The solid was collected by filtration and the filtrate was concentrated *in vacuo* to leave a residue, which, after addition of water, was shaken with ether to remove any neutral material. The water layer was combined with the potassium salt and made acidic by the addition of 10% HCl. The liberated carboxylic acid (**15**) was extracted with ether and the extract was washed with sat. NaCl solution, dried over Na_2SO_4 and concentrated to afford a solid, which was recrystallized from ethyl acetate to give 17.33 g (92%) of colorless prisms of **15**, mp 185—187°. IR $\nu_{\max}^{\mathrm{CCl_4}}$ $\mathrm{cm^{-1}}$: 1670. *Anal.* Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.40; H, 8.47.

4,5,5a,6,7,8,9,9a-Octahydro-6,6,9a-trimethylnaphto[1,2-*c*]furan (16)——The carboxylic acid (**15**) (11.75 g) was heated for 1 hr in quinoline (20 ml) containing copper powder (1 g) at 220—230° (bath temp.) under nitrogen. Evolution of carbon dioxide was observed. The product was subjected to silica gel chromatography and the fraction eluted with hexane afforded 9.50 g (97%) of the furan (**16**) as an oil. NMR ($CDCl_3$, 60 MHz) δ: 7.02 (2H, s, α-H of furan ring). The spectral data for compound (**16**) were identical with those for a sample prepared from (+)-confertifolin (**5**).

Preparation of 16 from (+)-Confertifolin (5)——A solution of (+)-confertifolin (323 mg) in THF (4 ml) was treated with a 20% hexane solution of diisobutylaluminum hydride (4.13 ml). After 2 hr, 10% H_2SO_4 (2 ml), water, and ether were successively added to this solution. The ether layer was washed with sat. $NaHCO_3$ solution then with sat. NaCl solution, dried over Na_2SO_4 and concentrated to give an oil, which was chromatographed on silica gel. Elution with hexane afforded 196 mg (65%) of **16**.

1,3-Diacetoxy-1,3,4,5,5a,6,7,8,9,9a-decahydro-6,6,9a-trimethylnaphto[1,2-*c*]furan (17)——A solution of **16** (0.86 g) in benzene (20 ml) was treated with lead tetraacetate (1.73 g) and the mixture was stirred for

3 hr at room temperature. After usual work-up, the product was subjected to silica gel chromatography. Elution with hexane–ethyl acetate (5: 1) afforded 1.19 g (90%) of crude **17**, which was recrystallized from ether–hexane to give **17**, colorless plates, mp 124—126°. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1760, 1220. NMR ($CDCl_3$, 60 MHz) δ: 2.10 (6H, s, 2 × OAc), 6.47 (1H, s, C$\underline{H}$OAc), 6.71 (1H, s, C$\underline{H}$OAc). *Anal.* Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.99; H, 8.39.

1,3-Dihydroxy-1,3,4,5,5a,6,7,8,9,9a-decahydro-6,6,9a-trimethylnaphtho[1,2-*c*]furan (18)——A solution of the diacetate derivative (**17**) (9.08 g) in dioxane (70 ml) was mixed with 10% KOH solution (40 ml) under ice-cooling. The mixture was stirred for 40 min and, after the addition of water, was extracted with ether. The extract was washed with sat. NaCl solution, dried over Na_2SO_4 and concentrated *in vacuo* to give a solid, which was recrystallized from ether to give 6.61 g (98%) of the dihydroxy derivative (**18**), mp 134—137°. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 3350, 3250. NMR[$(CD_3)_2SO$, 100 MHz] δ: 5.91 (1H, d, J=8 Hz, C$\underline{H}$OH), 5.98 (1H, d, J= 8 Hz, C$\underline{H}$OH). *Anal.* Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.41; H, 9.56.

(±)-Winterin (19)——Jones reagent (2.5 ml) was added to a suspension of **18** (674 mg) in acetone (40 ml) under ice-cooling. The mixture was stirred for 2 hr and, after the addition of water, was extracted with ether. The extract was washed with sat. NaCl solution, dried over Na_2SO_4, and concentrated to give a solid, which was recrystallized from ether–hexane to afford 533 mg of **19**. The filtrate was chromatographed on silica gel and the fraction eluted with hexane–ethyl acetate (10: 1) gave 53 mg of **19** (total yield, 88%), mp 144—145°, the spectra data for which were identical with those for (+)-winterin.

(±)-Isodrimenin (4) and (±)-Confertifolin (5)——a) The diacetate (**17**) (16.86 g) was heated for 1 hr at 170° (bath temp.) and the product was recrystallized from hexane to give 7.92 g of (±)-confertifolin (**5**), mp 116—117°. The filtrate was subjected to silica gel chromatography repeatedly using a Lobar column with hexane–ethyl acetate (4: 1) as a solvent system, yielding 0.75 g of **5** (total yield, 74%) and 1.98 g (17%) of **4**, mp 89—90°. The spectral data for **4** and **5** were identical with those for the corresponding natural products.

b) A solution of (±)-winterin (497 mg, 2 mmol) in THF (20 ml) was treated with $NaBH_4$ (400 mg) under ice-cooling and the mixture was stirred for 1 hr. After addition of further $NaBH_4$ (400 mg), the whole was stirred for 3 hr, cooled again in an ice bath, made acidic by the addition of 10% HCl and water, and extracted with ether. The extract was washed with sat. $NaHCO_3$ solution and sat. NaCl solution, dried over Na_2SO_4, and concentrated to give a solid, which was subjected to chromatography using a Lobar column as above. The yields of **4** and **5** were 81% and 14%, respectively.

Acknowledgement We thank Messrs. K. Nagano and M. Hatozaki for their technical assistance. This work was supported in part by a grant for "Biosciences" to this Institute from the Science and Technology Agency of Japan, which is gratefully acknowledged.