Tetrahedron Vol. 35, pp. 941 to 945
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TOTAL SYNTHESIS OF VERNOLEPIN—I
SYNTHESIS OF THE KEY INTERMEDIATE

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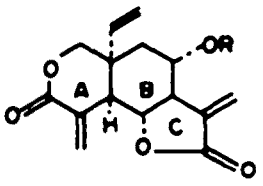
(*Received in Japan 12 September 1978*)

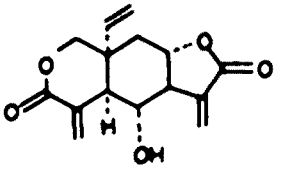
Abstract—The key intermediate (9) for the total synthesis of antitumor sesquiterpene vernolepin (1) was prepared in seventeen steps from 2,5-dihydroxanisyl alcohol. Intramolecular Michael addition (7→8) afforded the *cis*-2-oxadecalone system, which was stereospecifically converted to 9 by using the enolization character of 8.

During the continuing search for tumor inhibitors from plant sources, vernolepin (1) was isolated by Kupchan *et al.* as the major active principle in an alcoholic extract of Ethiopian Compositae, *Vernonia hymenolepis* A. Rich.[1] Vernolepin is responsible for significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB) in tissue culture and *in vivo* tumor inhibitory activity against Walker intramuscular carcinosarcoma in rats. The structure and stereochemistry of 1 were established by X-ray crystallographic examination of its *p*-bromobenzenesulfonate (2). Closely related dilactones, vernomenin (3), vernodalin (4)[2,3] and 5 (isolated as bitter substance)[4] were also reported. Compound 3 and 4 were chemically co-related to the methanol adduct of vernolepin (1), which is 5.

Conformational analysis on the cyclohexane ring in 5 suggests that conformer I should exist largely as the more stable one since five of the six substituents are located in equatorial, whereas conformer II should have very little chance to exist by itself. The latter conformer II, however, is of interest in synthetic utility, since it contains promising axial bondings to be introduced into a



1: R = H
2: R = $SO_2C_6H_4Br$
4: R = $COC(=CH_2)CH_2OH$



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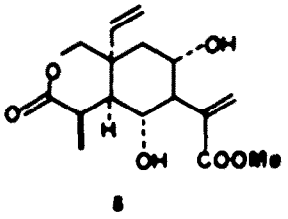
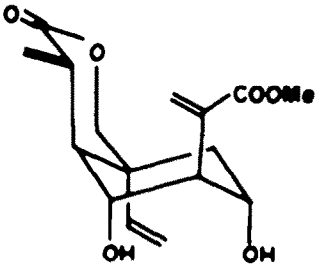
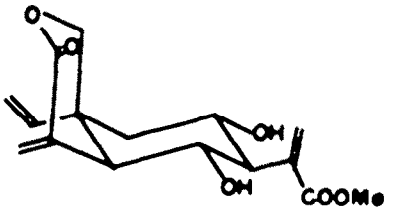


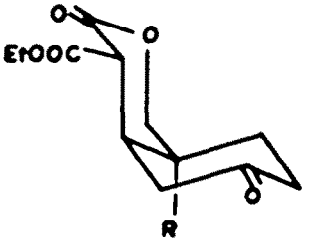
8



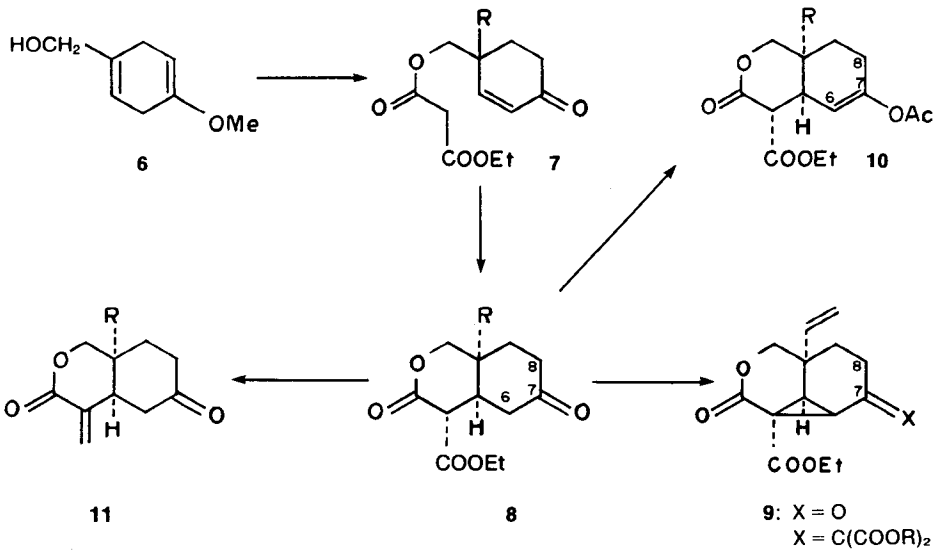
II



I



8a



Scheme 1.

simple cyclohexane derivative as the starting material for the total synthesis. Based on these conformational analyses our synthetic route was planed starting from **6** as shown Scheme 1, which involves complete stereospecific elaboration of the *cis*-valerolactone system in **1** as one of the key steps.[5] The intramolecular Michael addition reaction of **7** should be stereoelectronically controlled to form axial C-4, C-5 bonding for a direct construction of the *cis* fused oxadecalin system (**8**) which is convertible into α-methylene-δ-valerolactone **11**, the A-ring of **1**. For further stereospecific functionalization on the B-ring of the *cis*-oxadecalin-dione system as **8**, the conformationally flexible *cis*-system should be fixed into a rigid cyclopropyl derivative as **9**. This fixation also ensures the opposite enolization on the C-7 CO group (directing to the C-8 position) to the general enolization-character of *cis*-decalone (directing to the C-6 position as **10**). Thus the initial synthetic scheme calls for the preparation of compound **8** and its conversion to the cyclopropane key intermediate **9**. Here we describe the study directed toward the preparation of this key compound for the total synthesis of **1**.

RESULTS AND DISCUSSION

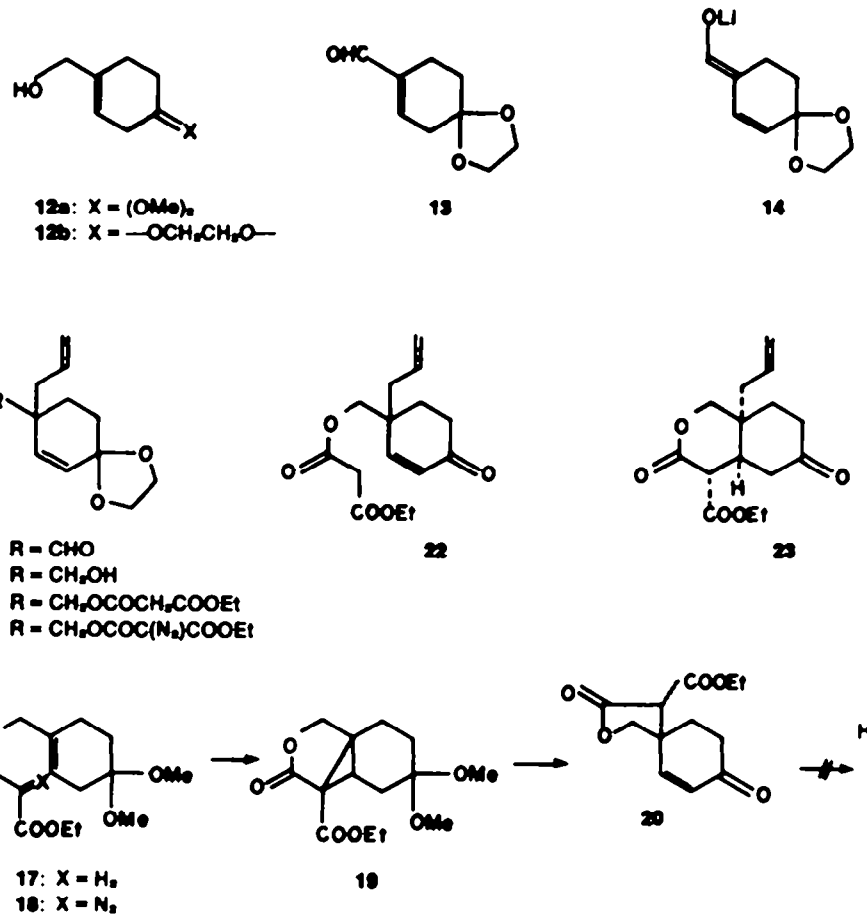
Preparation of the cyclohexenone malonate (**22**). Birch reported that the aromatic ring of *p*-anisyl alcohol was reduced by sodium in liquid ammonia in the presence of a proton source to give a 4:3 mixture of 2,5-dihydroanisyl alcohol (**6**) and 2,5-dihydroanisidine in 73% yield.[6] We found that this Birch reduction, when carried out in a mixture of liquid ammonia tetrahydrofuran(THF)-ethanol [5:1:3], converted *p*-anisyl alcohol to these mixture in improved ratio, 4:1 and that the desired **6** was readily isolable by vacuum distillation to afford in 61% pure yield. This compound was ketalized either to dimethyl ketal **12a** or to ethylene ketal **12b** by treatment with methyl orthoformate and DL-camphorsulfonic acid (CSA) in methanol or with ethylene glycol and BF_3-etherate in THF, respectively. The ethylene ketal (**12b**) was oxidized into the corresponding aldehyde (**13**) by pyridinium chlorochromate and anhydrous sodium acetate in methylene chloride.[7]

As has been reported previously, the general alkylation of the ambident dienolate derived from unsaturated carbonyl compound took place largely at the α-position to the CO group (deconjugative alkylation).[8] The lithium dienolate **14** of the aldehyde **13** was generated by lithium diisopropylamide in a mixture of THF and hexamethylphosphoramide (HMPA) at −40°. This enolate was treated with a variety of electrophiles which were likely to be convertible into the vinyl group. For example, *p*-chlorophenyl vinyl sulfoxide,[9] allyl bromide, acetaldehyde, formaldehyde, etc. were tested to show that the reaction occurred in low yield at the α-position to the aldehyde carbonyl. Only allyl iodide by treatment for 3 hr at 0° with the enolate **14** afforded in high yield the quaternary product **15**, the allyl group of which could be transformed to the vinyl one in a later stage. Reduction of the alkylated aldehyde **15** with sodium borohydride produced quantitatively the ketal alcohol **16**.

Another approach via carbene addition for quaternarization at C-10 position was examined as shown in Scheme 2. The dimethyl ketal alcohol **12a** was esterified into its malonate **17**, which was further treated with tosyl azide in acetonitrile in the presence of triethylamine[10] to give the diazomalonyl ester **18** in 92% yield. Refluxing toluene solution of **18** with cuprous iodide and trimethyl phosphite afforded the carbene adduct **19**, which was successively hydrolyzed with 1N HCl at 50° for 30 min giving the spiro enone **20** [δ 6.82 and 6.12 each 1H, d, J = 11 Hz] in 32% yield. after chromatographic separation. Clevage of the γ-lactone in **20**, however, was unsuccessful for conversion into any usable product.

The ketal alchol **16** was, then, esterified by ethyl malonyl chloride and 1.4 eq. of pyridine in ether at 0° to give the ketal ester **21**, which was subsequently treated with 0.1N HCl affording ester enone **22**. Hydrolysis of **16** followed by esterification also afforded **22**.

Elaboration of δ-valerolactone via intramolecular Michael addition. The enone malonate **22** was made into its Na salt by sodium hydride at 0° in THF, and the solution was stirred for 3 hr at room temp. to produce quantitatively a single lactone **23** [m.p. 83–84°; crystal yield 89%; *m/e* 280 (M+)]. NMR data of **23** suggested its conformation as **23a** since the methine proton at the C-4 position coupled with the juncture C-5-H in 9.5 Hz. Stereochemistry of this valerolactone **23** was chemically proven by a further conversion to cyclopropane deriva-

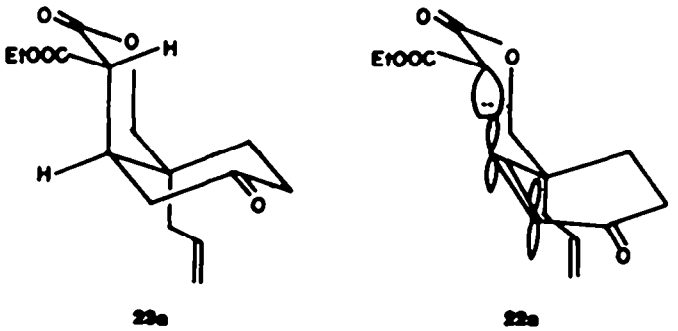


Scheme 2.

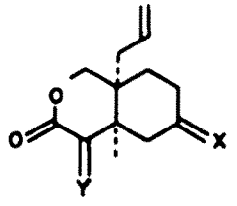
tive 29 (*vide* following section). The transition state 22a of this cyclization is likely in a similar conformation as the product 23a; namely, the carbanion of the malonyl residue approaches to the β-carbon of the enone in stereo-electronically more feasible axial manner.

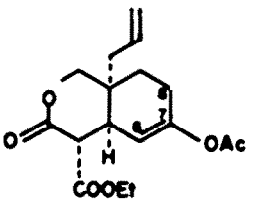
The facile *cis*-ring fusion in this intramolecular Michael addition[11] could be mechanistically interpreted as (1) active methylene (pKa = 13) of the malonate readily forms the corresponding carbanion, (2) it adds to the enone to generate another enolate at C-6 which is highly basic (pKa = 20) and could instantaneously be protonated by the more acidic active methine proton at C-4 and (3) final carbanion at C-4 has pKa at about 14 and is stable under the reaction condition. The carbethoxyl group is indispensable not only for the role controlling the acidity of those protons concerned in this reaction but also for the contribution making the methylenation easier. Thus, α-methylene-δ-valerolactone ring formation in 1 was readily achieved via Mannich reaction on the corresponding ketal carboxylic acid 24 to afford 25 [m.p. 91°]; the corresponding ketone (26) was also crystalline [m.p. 77°].

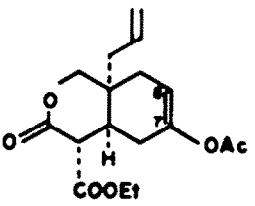
Generally, the CO in angularly substituted *cis*-3-decalone system enolizes largely to the C-4 position; incidentally, *trans*-3-decalone system does exclusively to the C-2 position.[12] In our *cis*-oxadecalone system, was found that 23 also enolized predominantly to the C-6 direction (27) and not to the C-8 direction (28) by treatment with acetic anhydride in the presence of catalytic amount of perchloric acid. Proportion of the generated



22a 22a







24: X =  Y = 

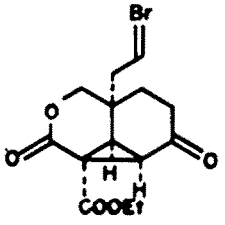
25: X = , Y =

26: X = O, Y = CH_2

30: X = O, Y = —COOEt

27

28



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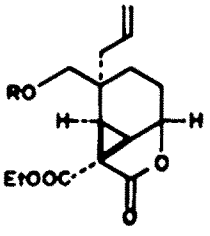

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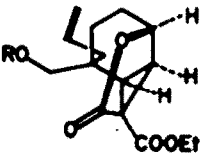
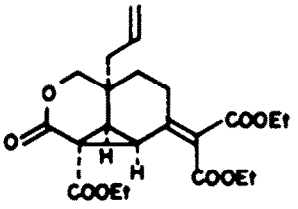
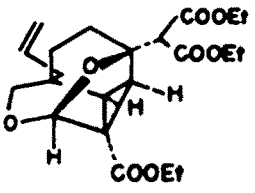


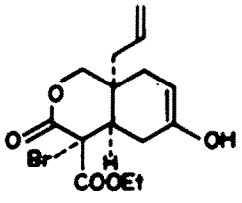
31a

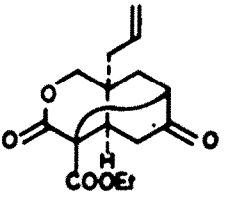


A



B





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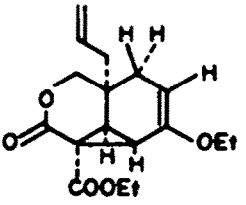


33

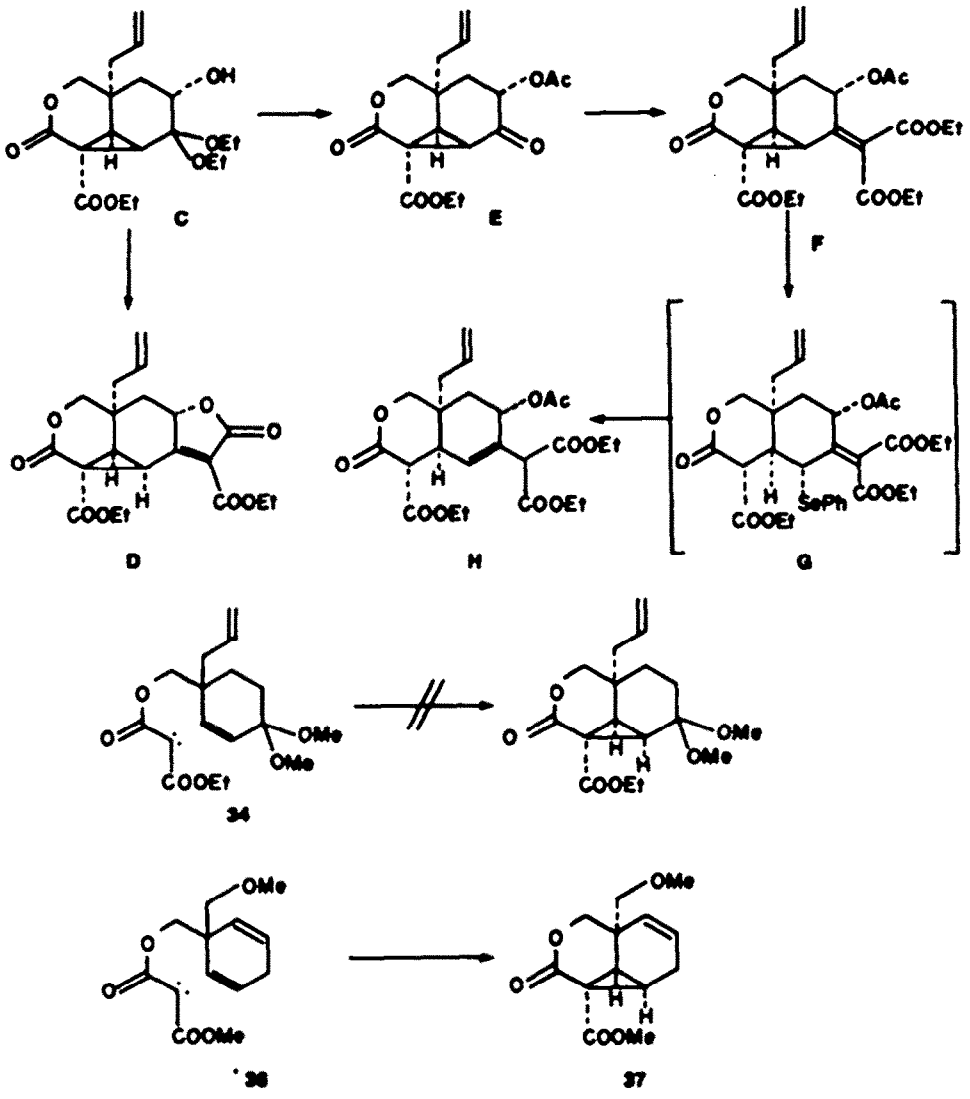
enol acetates 27/28 was examined by NMR and the ratios were 2 (25°, 1.5 hr), 4.5(0°, 6.5 hr), 6(−20°, 9 hr) and 9(−40°, 4 days). The NMR data of the major enol acetate (27) confirmed its structure, thus the olefinic proton [δ 5.38 ppm] coupled with angular proton [δ 2.8 (dd, J = 3 & 10 Hz]; the latter further coupled with the active methine proton [δ 3.36 (d, J = 10 Hz)].

Elaboration of the cyclopropane ring. Predominantly directed-enolization character in 23 prompted its conversion to our key intermediate, the cyclopropane ketone 29. Namely, 23 was carefully mono-brominated at the C-4 position [1.0 eq. of N-Bromosuccinimide in THF at 0°] to afford mainly α-bromide 30 [*m/e* 358, 360 (M+); CMR signal of C-4 (52.1 ppm) in 23 shifted to lower field (63.0 ppm) in 30] together with small amount (less than 10%) of its β-epimer. This mixture, without isolation, was successively treated with diazabicycloundecene in isopropyl alcohol to obtain, in 85% isolable yield from 23, the cyclopropane ketone 29 [m.p. 66.5–67°; *m/e* 278; ν 1742, 1735, 1698, 1640 cm^{-1}; δ 4.12 (2H, ABq) 2.84 (1H, d, J = 8 Hz); 35% equivalent of Eu-DPM, showed an isolated AX system (J = 8) assigned to protons at the C-5 and C-6 positions].

The cyclopropyl moiety in 29 could be reduced back with zinc power in acetic acid at 80° to afford in 99% yield the product whose TLC and spectral data were identical with those of 23. However, reduction of 29 by sodium borohydride afforded a γ-lactone [*m/e* 280; ν 1772 cm^{-1}; δ 4.95 (1H, m), 3.55 (2H, brs)] with the same molecular weight as 23. Acetylation of this product revealed down field shift of the two acetoxy methylene protons [δ 4.03 (2H, ABq, J = 11 Hz)] whereas the signal at δ 4.95 ppm moved only slightly to δ 4.90; thus the structure was determined to be 31. Thus, trans-lactonization occurred between the primary alcohol and the C-7 β-hydroxyl group, which formed by the hydride attack to C-7 CO carbon from less hindered convex face.†

Functionalization of the B-ring. The preferential enolization should lead the stereoselective formation of the

†Similar tetrahydrofuran-ring formation took place in the reduction of compound A [derived from 29 in 89% yield by treatment with diethyl malonate and $TiCl_4$ in THF and pyridine][5] by $NaBH_4$ (in ethanol) which converted to B [CMR δ 99.0 ppm, C-3; *m/e* 422 (M+)] in 60% yield.



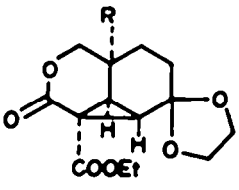
cyclopropane ring in 29 rather than another plausible cyclopentane structure 32, which could only form via C-8 enol form. In order to eliminate any ambiguity, the product 29 was further ketalized to its diethyl ketal followed by pyrolysis at 180° affording the enol ethyl ether 33 in 92.7% overall yield. The fact that the olefinic proton in the enol ether 33 [δ 4.75 (dd, $J = 2$ & 7)] coupled with each of the geminal methylene protons at C-9 [δ 2.56 (dd, $J = 2$ & 18) and 2.02 (dd, $J = 7$ & 18 Hz)] confirmed the structure of 33.† This fact also confirmed the formation of the cyclopropane structure 29 and thus proved the stereochemistry of 23 as the *cis* fused lactone structure in the internal Michael reaction.

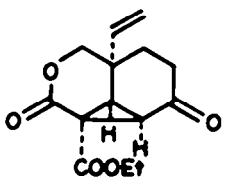
†This enolethyl ether (33) is of synthetic interest in the introduction of an OH group at the C-8 position. Namely, treatments of 33 with mCPBA in ethanol-methylene chloride followed by triethyl orthoformate plus CSA provided 8-α-hydroxyl ketal (C) in 66% yield. Esterification of C with ethyl malonyl chloride and subsequent ketal-hydrolysis followed by internal condensation afforded D which has the carbon skeleton required for vernomenin synthesis. Acetylation of C, on the other hand, followed by intermolecular Knoevenagel condensation (diethyl malonate, $TiCl_4$ and pyridine)[13] gave F which further converted into H. H was obtained by treatment of F with sodium phenylselenide via disproportionation reduction as shown in G.

A similar intramolecular Michael addition was reported by Torii *et al.* under heating in methanol with potassium flouride obtained in 66% yield the cytized product, which, they disclosed, was identical with the *cis*-product obtained by using sodium hydride in THF.[14] Incidentally, we had examined another approach aimed at direct formation of the key cyclopropyl intermediate, although failed under our restricted experiments that the carbene 34 generated by heating the azide 35 (prepared from dimethyl ketal of 22 by treatment with tosyl azide and triethylamine in acetonitrile) in refluxing toluene, hexane or cyclohexane in the presence of copper salts afforded no double bond adduct, although very similar reaction from 18 to 19 had worked as described previously in this paper. On the other hand, Zutterman *et al.* described a similar carbene addition approach in the diene system 36 and obtained in 71% yield a tricyclic compound 37.[15]

Preparation of the key synthetic intermediate. The allyl side chain in the compounds described should be converted into a vinyl group at a stage when most of the reactive sites were blocked. Since the tricyclic skeleton of 38 was considered to have little reactivity against oxidation and reduction, 29 was ketalized and then the terminal carbon in its allyl group was lessened by ozonolysis (methylene chloride, −78°). The ozonide, which could

not be reduced by dimethyl sulfide, was successfully converted by triethylamine to the corresponding aldehyde 39 in an almost quantitative yield. Reduction ($NaBH_4$) of the aldehyde 39 followed by mesylation and then phenylselenylation afforded selenide 41, which was oxidized by ozone at −20° and then heated to 50° to produce the vinyl ketal 42. Acid hydrolysis of the ketal group in 42 gave our key synthetic intermediate 9 in 75% overall yield (6.61 g crystal) from the allyl ketone 29 (9.26 g).





9

38: R = —CH_2CH=CH_2
39: R = —CHCHO
40: R = —CH_2CH_2OH
41: R = —CH_2CH_2SePh
42: R = —CH=CH_2

We have recently succeeded in the total synthesis of 1 via this key synthetic intermediate 9.[36] Further chemistry toward 1 will be described in details in our following paper.

EXPERIMENTAL

Notes. M.ps were determined on a hot stage apparatus (uncorrected). IR spectra were recorded on JASCO IR-G. PMR spectra were measured with JEOL MH-100 or FX-100 spectrometer, reporting chemical shifts in δ (ppm) using TMS as an internal standard. Low resolution electron impact (EI) mass spectra were recorded on JEOL D-100 instrument using direct probe insertion. High resolution and field desorption (FD) mass spectra were determined on JEOL 01SG2 instrument. Microanalyses were performed by Analytical Laboratories of this Faculty or of Meijo University. Tlc was performed on 0.25 mm pre-coated silica gel PF_{254} plates supplied by E. Merck (Art No. 5715). Preparative tlc separation were made on plates prepared with a 2 mm layer of silica gel PF_{254} obtained from E. Merck (Art No. 7747). Column chromatography were conducted on silica gel supplied by also E. Merck (Art No. 7734).

2,5-Dihydroanisylalcohol (6). *p*-Anisylalcohol (110 g, 0.796 mole) was dissolved in THF (300 ml) and added into a mixture of liquid ammonia (1.5 l) and EtOH (1.0 l). To this mixture was added Na (80 g, 3.48 gatom) in portions and then NH_4Cl (150 g). After removal of the solvents the pale yellow residue was extracted with CH_2Cl_2 and the extracts were washed with H_2O, dried (Na_2SO_4) and evaporated to give 90 g of crude product. Shortpass distillation afforded 17 g (17%) of 2,5-dihydroanisidine (60°/0.1 mmHg) and 68 g (61%, 120°/0.1 mmHg) of 6: δ 5.56 (1H, brs), 4.56 (1H, brs), 3.90 (2H, s), 3.48 (3H, s), 3.08 (1H, brs, D_2O exchangeable), 2.68 (4H, s).

Katalization of 6. To a solution of 2,5-dihydroanisyl alcohol (45 g, 0.321 mole) in THF (200 ml) and ethylene glycol (70 ml) was added BF_3-Et_2O (7 ml) with cooling in ice bath under N_2. After stirring for 20 min, the mixture was poured into cold $NaHCO_3$aq (150 ml) and extracted with six portions CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4 and then evaporated to give an colorless oil, which by distillation (105°/0.15 mmHg) afforded 52.2 g (95.5%) of 12b: PMR($CDCl_3$) δ 5.46 (1H, m), 3.90 (6H, s), 2.76 (1H, brs), 2.10 (4H, m), 1.75 (2H, m); CMR($CDCl_3$) δ 137.2, 119.4, 108.1, 66.2, 64.3(2C), 35.3, 30.7, 24.8; ν 3420, 2880, 1113, 1056, 958, 857 cm^{-1}; *m/e* 170.0924 (req. 170.0943 for $C_9H_{14}O_3$).

Oxidation of 12b. To a suspension of pyridinium chlorochromate (100 g, 0.46 mole) and anhyd NaOAc (25 g, 0.30 mole) in CH_2Cl_2 (500 ml) was added a soln of 12b (50 g, 0.29 mole) over 10 min with cooling in an ice bath with mechanical stirring. After stirring for an additional 1 hr at room temp., the mixture was diluted by ether (500 ml) and then decanted. The residual gum was washed with ether. The combined organic solvents were filtered through 50 g of silica gel column. The eluate was concentrated and the residual oil distilled (90°/0.05 mm Hg) to obtain 42 g (85%) of 13; PMR($CDCl_3$) δ 9.50 (1H, s), 6.70 (1H, m), 4.00 (4H, s), 2.55 (2H, m), 2.40 (2H, m), 1.75 (2H, t, J = 6); CMR($CDCl_3$) δ 192.9, 147.3, 140.4, 107.3, 64.5(2C), 36.8, 30.0, 20.3; ν 1680, 1644 cm^{-1}; *m/e* 168.0802 (req. 168.0786 for $C_9H_{12}O_3$).

Preparation of 14. To a cold soln (−40°) of lithium diisopropylamide (0.256 mole) in THF (600 ml) containing 1 mg of triphenylmethane in HMPA (50 ml) was added dropwise a soln of 13 (33.6 g, 0.20 mole) in THF (75 ml) over 2 hr at −40° and the mixture was stirred for additional 40 min. Allyl iodide (50 g, 0.30 mole) was added to the mixture and the temp. was allowed to rise to 0°. After the mixture had been stirred for 3 hr at 0°, it was poured into a cold NH_4Cl aq and then extracted with ether. The extract was washed with water and brine, dried over Na_2SO_4 and then evaporated to give a light yellow oil (38.7 g) which was used for the next reaction without further purification. The crude aldehyde 15 [when partially purified gave PMR(CCl_4) δ 9.42 (1H, s), 6.0–5.5 (1H, m), 5.7 (2H, brs), 5.2–5.0 (2H, m), 3.90 (4H, s), 2.30 (2H, d, J = 7), 2.0–1.6 (4H, m); ν 1725, 1642 cm^{-1}; *m/e* 180 (M^+-28)] was reduced in EtOH (200 ml) with $NaBH_4$ (2.1 g, 0.053 mole) with cooling in an ice bath. After neutralization with AcOH, the mixture was washed with water, dried over Na_2SO_4 and then evaporated. The residual oil was distilled (135°/0.05 mmHg) to afford 30.4 g (72.4% overall yield) of 16: PMR($CDCl_3$) δ 6.04–4.94 (3H, m), 5.68 (2H, s), 3.96 (4H, s), 3.42 (2H, s), 2.15 (2H, d, J = 7), 1.76 (4H, m); ν 3450, 1640 cm^{-1}; *m/e* 210.1279 (req. 210.1256 for $C_{13}H_{18}O_3$).

Preparation of 22. To a soln of 16 (30.4 g, 0.145 mole) in ether (300 ml) was added dropwise two solns of pyridine (15.6 g, 0.198 mole in 40 ml of ether) and ethyl malonyl chloride (24.0 g, 0.160 mole in 80 ml of ether) at 0° over 1 hr so as each addition ended simultaneously. After stirring for additional 1 hr, the resulting ppt was removed by filtration. The filtrate was extracted with ether, and the extract was washed with water, dried over Na_2SO_4, evaporated to give the crude 21 (45.5 g). Crude 21 (0.140 mole) was dissolved in EtOH (200 ml) and 0.1 N NCl (200 ml). After standing at room temp. for 30 min, the mixture was concentrated to one half volume and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and then evaporated. The residual oil was distilled (140°/0.05 mmHg) to afford 22 (32.2 g, 79.4% from 16): PMR($CDCl_3$) δ 6.68 (1H, d, J = 11), 6.00 (1H, d, J = 11), 6.80–5.80 (3H, m), 4.20 (2H, q, J = 7), 4.12 (2H, ABq), 3.40 (2H, s), 2.49 (2H, t, J = 6), 2.31 (2H, d, J = 7), 1.96 (2H, t, J = 6), 1.28 (3H, t, J = 7); ν 1750(sh), 1735, 1680 cm^{-1}; *m/e* 280.1305 (req. 280.1311 for $C_{15}H_{20}O_5$).

Preparation of the spirolactone 28. To a soln of 12a (1.23 g, 7.15 mmole) in ether (40 ml) was added pyridine (0.60 g, 7.6 mmole) and ethyl malonyl chloride (1.2 g, 7.2 mmole) at 0°. After stirring for 30 min, the ppt was removed by filtration. The filtrate, washed with water, dried over Na_2SO_4, was evaporated to give an oil which was chromatographed on Al_2O_3 (5% AcOEt-hexane) to afford 1.8 g (88%) of 17. This product (1.5 g, 5.24 mmole) was dissolved in acetonitrile and mixed with triethylamine (0.69 g, 6.8 mmole) and tosyl azide (1.34 g, 6.8 mmole) for 12 hr at room temp. Evaporating the solvent, the mixture was suspended in ether (50 ml) and the insoluble material was removed by filtration. The filtrate was washed with 1 N NaOH, water and brine, and dried (Na_2SO_4) and then evaporated to produce an oil, which on separation (Al_2O_3/CH_2Cl_2) afforded 1.5 g (92%) of 18. A soln of 18 (1.8 g, 3.2 mmole) in toluene (40 ml) was refluxed for 5 hr with trimethyl phosphite-copper iodide complex. After cooling, the mixture was filtered and evaporated to give oil, which on passing Al_2O_3 (CH_2Cl_2) afforded 0.9 g of the crude 19. It was dissolved in 30 ml EtOH and 1 N HCl (2 ml) and stirred at 50° for 30 min. The mixture was extracted (CH_2Cl_2) and the extracts were washed (H_2O), dried (Na_2SO_4) and evaporated. The residual oil was chromatographed on SiO_2 (1.5% MeOH/CH_2Cl_2) to afford epi-

meric mixture of **20** (0.24 g, 32%): PMR($CDCl_3$) δ 6.82 (1*H, d*, J = 11), 6.12 (1H, d, J = 11), 4.3 (4H, m), 3.59 (1H, s), 2.58 (2H, m), 2.24 (2H, m), 1.32 (3H, t, J = 7).

Preparation of **23** *by internal Michael addition of* **22**. The enone **22** (225 mg, 0.804 mmole) in THF (3 ml) was added to sodium hydride slurry (60% in mineral oil, 35 mg, 0.875 mmole, washed with pet. ether) in THF (5 ml) at 0° under N_2. After the evolution of H_2 ceased, the cooling bath was removed and the mixture was stirred for 2.5 hr at room temp. The mixture was poured into cold 0.1 N HCl and then extracted with CH_2Cl_2. The extracts were washed ($NaHCO_3$, H_2O), dried (Na_2SO_4) and evaporated to give a homogeneous product **23** (crude crystal 229 mg, 100%), which was recrystallized from ether to give 197 mg of pure **23** (m.p. 83–84°, 87.6% yield): PMR($CDCl_2$) δ 6.10–5.08 (3H, m), 4.30 (2H, q, J = 7), 4.12 (2H, ABq, J = 12), 3.28 (1H, d, J = 9.5), 2.70–2.20 (7H, m), 1.85 (2H, t, J = 6), 1.30 (3H, t, J = 7); CMR δ 209.2(s), 168.2(s), 131.4(d), 120.6(t), 71.8(t), 62.0(t), 51.0(d), 41.5(t), 40.7(t), 38.2(d), 35.6(s), 34.6(t), 25.7(t), 14.0(q); ν (KBr) 1740(sh), 1728, 1720, 1640 cm^{-1}; *m/e* 280; Found; C, 64.38; H, 7.18. Calc. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19.

Cyclopropanation of **23**. N-Bromosuccinimide (8.9 g, 50 mmole) was added to a soln of **23** (14 g, 50 mmole) in THF (100 ml) at 0° with stirring. After 15 min, the mixture was diluted with isopropyl alcohol (100 ml). To this mixture diazabicycloundecene (15.2 g, 100 mmole in 30 ml of isopropyl alcohol) was added dropwise over 15 min at 0°. After stirring for additional 1 hr at room temp., the mixture was poured into cold dil HCl and then extracted with ether. The extract was washed with $NaHCO_3$aq, water and brine, dried over Na_2SO_4 and then evaporated. The residual oil was crystallized from ether to afford 6.31 g of **29** (m.p. 66.5–67.0°). The mother liquor was concentrated and then chromatographed on silica gel column (ether–hexane 3:1) to give 2.87 g of crystalline **29** and 3.0 g of the recovered crystalline **23**. The combined yield **29** based on the consumed ketone **23** was 85.0%. **29**: PMR($CDCl_3$) δ 6.08–5.10 (3H, m), 4.12 (2H, ABq), 4.15 (2H, q, J = 7), 2.84 (1H, d, J = 8), 2.60–2.20 (5H, m), 2.04 (2H, m), 1.30 (3H, t, J = 7); CMR δ 201.8, 167.1, 163.9, 131.1, 121.0, 79.3, 63.0, 43.3, 37.1, 36.8, 35.6, 35.1, 32.6, 30.7, 14.0; ν (KBr) 1742, 1735, 1698, 1640 cm^{-1}; *m/e* 278 (M^+); Found: C, 64.67; H, 6.48. Calc. for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52.

Zinc reduction of **29**. The ketone **29** (12 mg, 0.043 mmole) was treated with Zn powder (50 mg) in AcOH (0.2 ml) at 80° for 2 hr. After cooling, the inorganic material was removed by filtration and the filtrate was extracted with CH_2Cl_2. The extract was washed (H_2O), dried (Na_2SO_4) and evaporated to give **23** (12 mg, 99%) which was identical with authentic sample by comparison of PMR, IR and tlc.

Sodium borohydride reduction of **29**. The cyclopropane **29** (24 mg, 0.086 mmole) was treated with $NaBH_4$ (5 mg, 0.13 mmole) in MeOH (1 ml) at 0° for 30 min. The mixture was poured into cold 0.1 N HCl and extracted with CH_2Cl_2. The extract was washed with $NaHCO_3$ and water, dried and then evaporated to produce **31** (24 mg, 99% yield): PMR($CDCl_3$) δ 6.16–5.04 (3H, m), 4.95 (1H, m), 4.16 (2H, q, J = 7), 3.55 (2H, brs), 3.00 (1H, dd, J = 6.5 & 8), 2.40 (2H, d, J = 7), 2.22 (1H, d, J = 8), 2.1–1.5 (4H, m), 1.32 (3H, t, J = 7); ν ($CHCl_3$) 3500, 1772, 1725 cm^{-1}; *m/e* (FI) 281 ($M^+ + 1$). **31** (12 mg) was acetylated with 0.3 ml Ac_2O and pyridine (0.3 ml) at room temp. for 3 hr. The mixture was dried *in vacuo* to obtain **31b** (13.8 mg, 100%): PMR($CDCl_3$) δ 6.10–5.05 (3H, m), 4.90 (1H, m), 4.28 (2H, d, J = 7), 4.03 (2H, ABq), 2.98 (1H, dd, J = 6.5 & 8), 2.35 (1H, d, J = 7), 2.16 (1H, d, J = 8), 2.11 (3H, s), 2.0–1.4 (4H, m), 1.31 (3H, t, J = 7); ν (neat) 1775, 1737, 1725 cm^{-1}; *m/e* 322 (M^+).

Preparation of the enol ethyl ether **33**. The ketone **29** (100 mg, 0.36 mmole) was dissolved in EtOH (5 ml) and ethyl orthoformate (1 ml) and then stirred with DL-10-camphorsulfonic acid (30 mg, 0.18 mmole) for 6 hr at room temp. The mixture was poured into cold $NaHCO_3$aq and then extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4 and evaporated to give 125 mg of **29**. This ketal (125 mg) was heated at 200° in *o*-dichlorobenzene, large amount of which was distilled off while the conversion completed. After cooling, the residual solvent was removed *in vacuo* to give an oil. The oil was dissolved in ether and passed through Al_2O_3 (2 g, ether) to give 102 mg (92.7%) of **33**: PMR($CDCl_3$) δ 6.1–5.1 (3H, m), 4.75 (1H, dd, J = 2 & 7), 4.28 (2H, q, J = 7), 4.10 (2H, ABq), 3.73 (2H, q, J = 7), 2.63 (1H, d, J = 9), 2.56 (1H, dd, J = 2 & 18), 2.31 (2H, d, J = 7), 2.24 (1H, d, J = 9), 2.02 (1H, dd, J = 7 & 18), 1.32 (3H, t, J = 7), 1.28 (3H, t, J = 7).

Introduction of hydroxyl group at the C-8 *position*. A soln of **33** (80 mg, 0.26 mmole) in $CHCl_3$ (4 ml) and EtOH (0.4 ml) was treated with *m*-chloroperbenzoic acid (85%, 80 mg, 0.39 mmole) for 20 min at room temp. To this mixture was added a soln of DL-10-camphorsulfonic acid (20 mg, 0.09 mmole) in triethyl orthoformate (0.4 ml) and stirred for additional 20 min. The mixture was poured into a mixed soln of Na_2SO_3 (0.5%, 10 ml), and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and then evaporated to give crude product (96 mg), which was chromatographed on SiO_2 to afford 64 mg (66%) of **C**: PMR($CDCl_3$) δ 6.1–5.1 (3H, m), 4.14 (2H, q, J = 7), 4.04 (2H, ABq), 3.96 (1H, dd, J = 5 and 7), 3.73 (2H, q, J = 7), 3.59 (2H, q, J = 7), 3.05 (1H, brs, D_2O exchangeable), 2.57 (1H, d, J = 9.5), 2.36 (2H, d, J = 7), 1.92 (1H, d, J = 9.5), 1.76 (2H, m), 1.28 (3H, t, J = 7), 1.24 (3H, t, J = 7), 1.13 (3H, t, J = 7); *m/e* 368 (M^+).

α-Methylene-δ-valerolactone **26** *via Mannich reaction*. The ethylene ketal of **23** (780 mg, 2.40 mmole) was dissolved in EtOH (15 ml) and 1 N NaOH (15 ml), and the mixture was stirred at room temp. for 5 hr. Acidification of this mixture to pH2 by 1 N HCl followed by extraction with EtOAc afforded crude hydrolysate (685 mg), which was successively treated with diethylamine (1.35 ml) and aqueous formalin (35%, 2.55 ml) at room temp. for 1 hr. To this mixture was added water (10 ml), and extracted with ether. The extracts were dried (Na_2SO_4), evaporated and then crystallized to give **25** (312 mg; m.p. 87–91°). **25** (340 mg, 1.29 mmole) was mixed with aqueous trifluoroacetic acid (2 ml, TFA:H_2O = 1:5) at room temp. After 30 min, the mixture was neutralized with 5% $NaHCO_3$aq and then extracted with ether. The extracts were dried (Na_2SO_4) filtered through SiO_2 and then evaporated to give crude oil of **26** (290 mg), which was crystallized from ether–hexane and afforded **26**: [200 mg, m.p. 74–77°]: PMR($CDCl_3$) 6.48 (1H, s), 5.62 (1H, s), 6.0–5.3 (1H, m), 5.3–4.8 (2H, m), 4.29 (2H, AB, J = 12 Hz), 3.0–2.0 (7H, m), 2.0–1.4 (2H, m); *m/e* 220.1122 (req. 220.1100). Found: C, 71.00; H, 7.31. Calc. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32.

Transformation of the allyl group into the vinyl group [from **29** *to* **9**]. The ketone **29** (9.26 g, 33.3 mmole) was dissolved in benzene (100 ml) and ethylene glycol (5.5 g, 99.6 mmole) and was heated to reflux for 30 min in the presence of CSA (1.0 g, 4.3 mmole) with Dean Stark water separator. After cooling, the mixture was poured into cold $NaHCO_3$aq and extracted with ether. The extract was washed (H_2O, brine) dried (Na_2SO_4) and evaporated to give 10.8 g (crude yield 100%) of **38** [PMR δ 6.1–5.1 (3H, m), 4.26 (2H, q, J = 7), 4.08 (6H, m), 2.36 (1H, d, J = 9), 2.23 (2H, d, J = 7), 2.02 (1H, d, J = 9), 1.75 (4H, m), 1.27 (3H, t, J = 7); ν ($CHCl_3$) 1742, 1640 cm^{-1}; *m/e* 322.1443 (req. 322.1416 for $C_{17}H_{22}O_6$)], which was used for the following reaction without further purification.

To a soln of **38** (10.8 g, 33.5 mmole) in CH_2Cl_2 (400 ml), O_3 was passed at −78° until the soln turned light purple. After purging nitrogen, the mixture was treated with triethylamine (30 ml in 20 ml of CH_2Cl_2) for 3 hr at −78°. Filtration and subsequent evaporation of the filtrate afforded **39** [partial purification gave PMR($CDCl_3$) δ 9.82 (1H, brs), 4.28 (2H, ABq, J = 11), 4.21 (2H, q, J = 7), 4.02 (4H, m), 2.64 (2H, brs), 2.40 (1H, d, J = 9.5), 2.13 (1H, d, J = 9.5), 1.84 (4H, m), 1.30 (3H, t, J = 7); ν ($CHCl_3$) 1746, 1726 cm^{-1}; *m/e* (EI) 295, 266, 250, 233, 222, (FD) 324 (M^+), 295].

Compound **39** was dissolved in EtOH (200 ml) and reduced with $NaBH_4$ (1.5 g, 39.6 mmole) in ice bath. After neutralization with AcOH, the mixture was extracted with CH_2Cl_2. The extract was washed with water, dried and evaporated to give 10.6 g (96.8% crude yield) of **40** [partial purification gave PMR($CDCl_3$) δ 4.40–3.70 (10H, m), 2.47 (brs, OH), 2.38 (1H, d, J = 9.5), 2.10 (1H, d, J = 9.5), 1.76 (6H, m), 1.28 (3H, t, J = 7; ν ($CHCl_3$) 3470, 1740 cm^{-1}; *m/e* 326.1374 (req. 326.1365 for $C_{16}H_{22}O_7$)].

The alcohol **40** was further treated at 0° in CH_2Cl_2 (200 ml) with methanesulfonyl chloride (7.4 g, 64.6 mmole) and triethylamine (7.0 g, 69.3 mmole). After stirring for 2 hr, the mixture was

washed with $NaHCO_3$aq and water. Organic layer was dried and evaporated to afford the mesylate of **40** (12.4 g, 94% crude yield) [partial purification gave PMR($CDCl_3$) δ 4.50–3.80 (10H, m), 3.04 (3H, s), 2.36 (1H, d, J = 9.5), 2.03 (1H, d, J = 9.5), 1.96 (2H, t, J = 6.5), 1.77 (4H, m), 1.28 (3H, t, J = 7); ν ($CHCl_3$) 1745, 1730(sh) cm^{-1}; *m/e* 404.1117 (req. 404.1141 for $C_{17}H_{24}O_9S_1$)].

To a soln of the mesylate (12.4 g, 31.3 mmole) in THF (200 ml), a soln of Na salt of phenyl selenide [prepared from diphenyl diselenide (5.2 g, 16.7 mmole) in EtOH (200 ml) and $NaBH_4$ (1.3 g, 34.3 mmole)] was added dropwise over 1 hr and stirred for additional 15 hr at room temp. under argon. The mixture was poured into cold $NaHCO_3$aq and extracted with CH_2Cl_2. The extract was washed with water, dried and evaporated to afford the crude **41** (5.9 g, 98% crude yield) [partial purification gave PMR($CDCl_3$) δ 7.60–7.20 (5H, m), 3.80–4.35 (8H, m), 3.90 (2H, m), 2.35 (1H, d, J = 9.5), 1.93 (1H, d, J = 9.5), 1.70 (6H, m), 1.26 (3H, t, J = 7); ν ($CHCl_3$) 1746, 1730(sh), 1580 cm^{-1}; m.p. 87–88°; *m/e* 466.0921 (req. 466.0895); Found: C, 56.61; H, 5.65. Calc. for $C_{22}H_{26}O_6Se_1$: C, 56.78; H, 5.63].

The crude selenide (5.9 g) in $CHCl_3$ (200 ml) was treated with O_3 at −20° until the yellow soln became colorless. After purging excess O_3 with N_2 for 30 min, the soln was heated at 50° for 3 hr. Evaporation of the solvent left a yellow oil, which was chromatographed on SiO_2 (120 g, ether–hexane 2:1) to give 7.87 g of **42**: PMR($CDCl_3$) δ 5.98 (1H, dd, J = 11 & 17.5), 5.24 (1H, d, J = 11), 5.09 (1H, d, J = 17.5), 3.90–4.20 (8H, m), 2.41 (1H, d, J = 9.5), 2.20 (1H, d, J = 9.5), 1.84 (4H, m), 1.29 (3H, t, J = 7); ν ($CHCl_3$) 1745, 1730(sh), 1640 cm^{-1}; m.p. 77–78°; *m/e* 308.1247 (req. 308.1260); Found: C, 61.87; H, 6.45. Calc. for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. The overall yield of **42** was 76.7% from **29**.

The vinyl ketal (7.87 g, 25.6 mmol) in CH_2Cl_2 (60 ml) was treated with 10 ml of aq. trifluroacetic acid (TFA:H_2O = 5:1) at room temp. for 5 hr. The mixture was neutralized with $NaHCO_3$aq and extracted with CH_2Cl_2. The extract was washed with water, dried and evaporated to produce 6.61 g (98% cryst. yield) of **9**, overall yield of which from **29** was 75%. **9**: PMR($CDCl_3$) δ 5.92 (1H, dd, J = 11 & 17.5), 5.34 (1H, d, J = 11), 5.25 (1H, d, J = 17.5), 4.34 (2H, ABq, J = 12), 4.25 (2H, q, J = 7), 2.85 (1H, d, J = 8.5), 2.61 (1H, d, J = 8.5), 2.40 (2H, m), 2.10 (2H, m), 1.33 (3H, t, J = 7); m.p. 65.5–66.0°; *m/e* 264.0994 (req. 264.0998); Found: C, 63.37; H, 6.22. Calc. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10.

Acknowledgements—Authors are grateful to Science Foundation of Japan Ministry of Education and to Kudo Science Foundation for financial support of this work. Authors are also indebted to Mr. S. Kitamura of this Department and to Analytical Laboratory of Meijo University for elemental analyses.

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