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TOTAL SYNTHESIS OF (±)-JOLKINOLIDE A, B, AND E UTILIZING A NEW MILD ESTERIFICATION FOLLOWED BY INTRAMOLECULAR WITTIG-HORNER REACTION†

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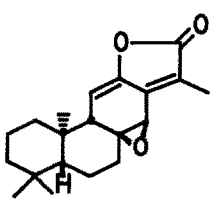
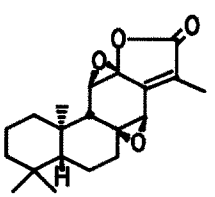
Abstract; Jolkinolide A, B, and E were efficiently synthesized from 9-methoxycarbonyl-4,4,10-trimethyl-Δ^5-8-octalone 8 through $\Delta^{8(14)}$-podocalpen-13-one 12. A new synthetic method of γ-ylidenbutenolide consisting of mild esterification and the succeeding intramolecular Wittig-Horner reaction of α-diketone was developed.

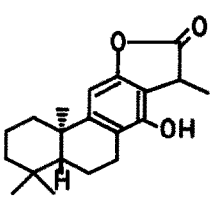
Jolkinolide A(1), B(2), C, D, and E(3) were isolated from the roots of Euphorbia Jolkini Boiss by Uemura and Hirata in 1972. The structure of jolkinolide B(2) which has a novel epoxylactone function was first elucidated by the spectroscopy and chemical evidence,[1] and later its relative stereochemistry was confirmed by X-ray crystallography.[2] The absolute structures of A(1) and B(2) were determined by the transformation to ferruginol possessing an abietane-type skeleton. Jolkinolide A(1) having γ-ylidenbutenolide function was converted into B(2) by MCPBA oxidation and to C by acid treatment. The structure of C, D, and E(3) were elucidated by the correlation with A(1) except the stereochemistry at C-12 of D and E(3).[3] It has also been reported that jolkinolide B inhibits the growth of cultured Hela cells.[2] Herein we report in detail the first and efficient syntheses of jolkinolide A, B and E, and the determination of the relative stereochemistry at C-12 of jolkinolide E. In these syntheses, we developed a new synthetic method of γ-ylidenbutenolide by the intramolecular Wittig-Horner reaction of α-diketone enolester, and a mild esterification method using a mixed anhydride of trichloroacetic acid catalyzed by 4-dimethylaminopyridine(DMAP).[4]



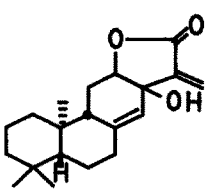
Jolkinolide A(1)



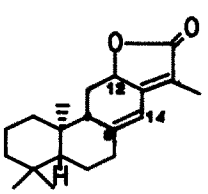
B(2)



C



D

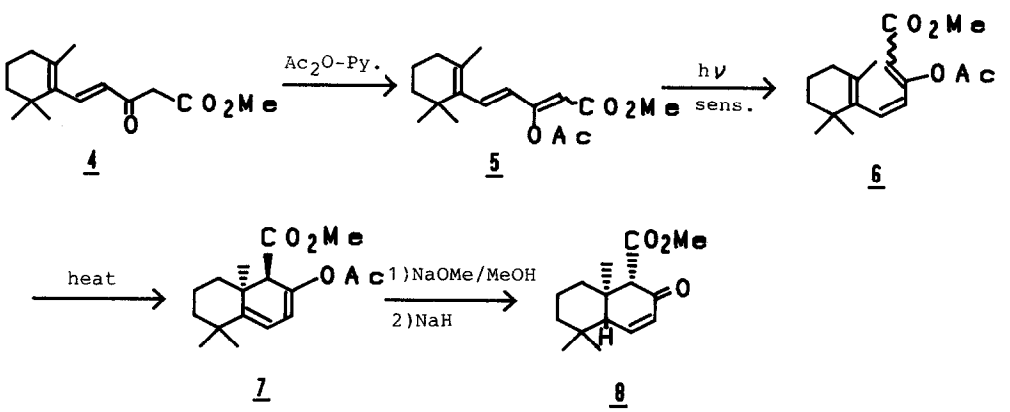


E(3)

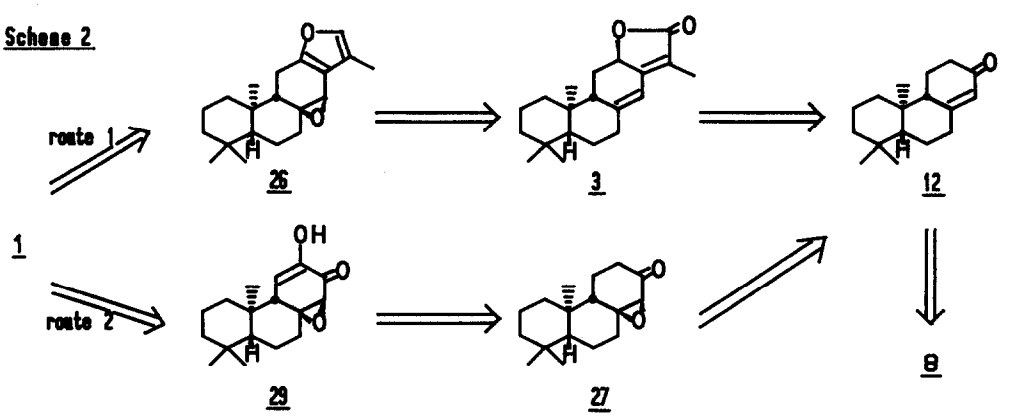
For the synthesis of jolkinolides, we used 9-methoxycarbonyl-4,4,10-trimethyl-Δ^6-8-octalone (8) as a building block. The efficient synthesis of this versatile building block has been established by us starting from β-ionone.[5] Thus, 10-methoxycarbonyl-β-ionone(4) obtained by the reaction of β-ionone with dimethylcarbonate in the presence of NaH in dioxane was converted into its enolacetate 5 in 85% yield from β-ionone. The enolacetate 5 was irradiated with high-pressure mercury lamp through pyrex filter in the presence of benzanthrone as a sensitizer in THF under N_2 at 0°C[6] to give 7,8-cis-enolacetate 6 (90% yield), which was followed by thermal electrocyclization at 190-200°C to afford a bicyclic enolacetate 7 quantitatively. Treatment of 7 with NaOMe in methanol followed by completion of epimerization at C-9 with NaH gave a trans-decalone derivative 8 as a major product. The solvolytic conditions used here was considerably critical to obtain 8 with the desired stereochemistry and the yield varied depending on the reaction scale (Scheme 1). The simpleness of the above procedure leading to 8 has made total syntheses of various sesqui-[5] and di-terpenoids readily.[7]

The outline of our synthetic plan for jolkinolide A and B from 8 was shown in Scheme 2. We envisioned two routes. An epoxyfuran derivative 26 which was expected to be derivable from jolkinolide E (3) would be a good precursor for A(1), because singlet oxygen or MCPBA oxidation of 26 followed by mild dehydration would afford A(1). Jolkinolide E would be synthesized from $\Delta^{8(14)}$-podocarpen-13-one(12)[9] through an α-hydroxyenone derivative by intramolecular Wittig-Horner

Scheme 1



Scheme 2

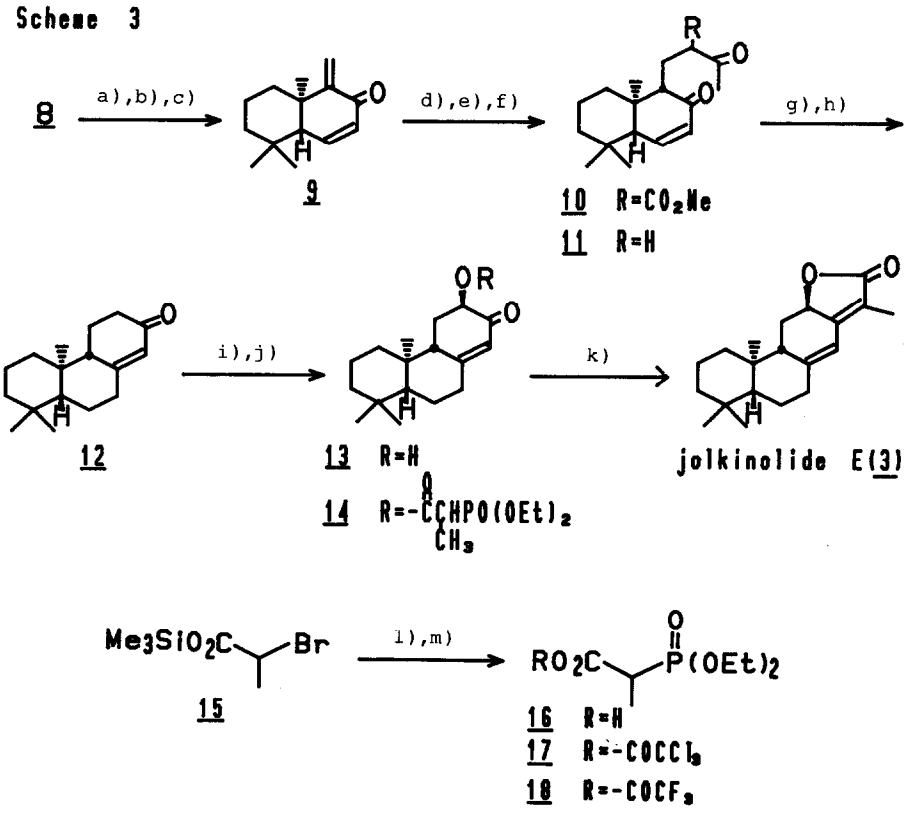


reaction efficiently (route 1). Another route which includs the construction of γ-ylidenebutenolide moiety from a diosphenol 29 by intramolecular Wittig-Horner reaction seemed to be more straightforward for the synthesis of 8. The diosphenol 29 would be prepared from 12 through an epoxide 27(route 2). The latter route was quite attractive because of its efficiency, although the synthetic method of 4-yliden-2,3-disubstituted butenolide by the intramolecular Wittig-Horner reaction from diosphenol has not been reported yet.

In both approaches, the common intermediate was the tricyclic enone 12 which was synthesized from 8 as follows(Scheme 3). Reduction of 8 with LAH gave the corresponding diol which was subjected to selective oxidation with MnO_2 followed by dehydration with acid to give an exomethylene enone 9 in 88% overall yield. The Michael addition of methyl acetoacetate to 9 was effected with 0.5 equivalent of NaOMe in methanol to afford 10, which was submitted to hydrolysis with 1% aqueous NaOH under mild conditions (1.3 equivalent, MeOH, room temperature) followed by decarboxylation (pH 3, 35°C under reduced pressure) to give 11. Hydrogenation of 11 on Pd-C yielded a saturated diketone, which was treated with 1% aqueous NaOH in methanol at 100°C to afford 12[9] in 71% yield for five steps.

Synthesis of jolkinolide E (Scheme 3). For the synthesis of jolkinolide E(3), the next subject was to find an efficient construction method of the α,β,γ-trisubstituted butenolide moiety. Intramolecular Wittig-Horner reaction is the general synthetic method of β-substituted butenolides from α-hydroxyketones in

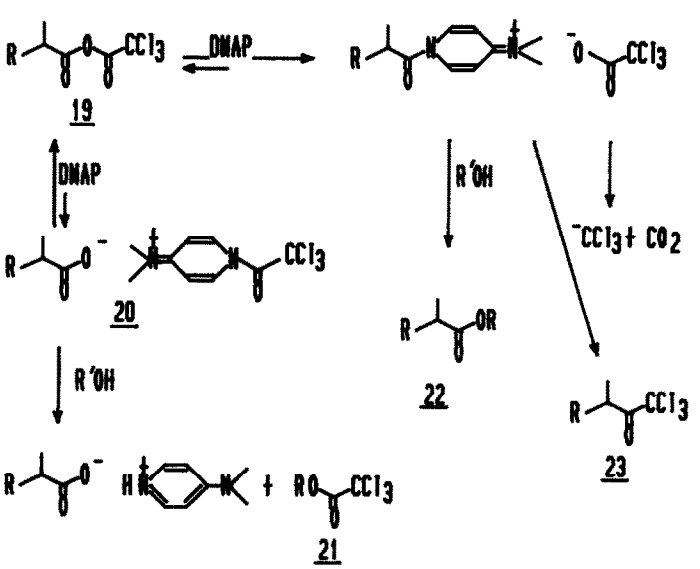
Scheme 3



a)LAH; b)MnO_2; c)H_3O^+; d)$CH_3COCH_2CO_2CH_3$/NaOMe/MeOH; e)aq.NaOH/MeOH; f)H_3O^+ g)Pd-C/H_2; h)aq.NaOH/MeOH; i)(1)LDA/TMSCl (2)MCPBA/hexane (3)Bu_4NF $3H_2O$; j)17/DMAP; k)NaH/DME; l)(1)$P(OEt)_3$ (2)H_3O^+; m)$ClCOCX_3/Et_3N$

open chain systems.[10] We applied this method to a cyclic α-hydroxyenone 13 which was prepared as follows. The tricyclic enone 12 was converted to its silyl enol ether(LDA, Me_3SiCl) which was then epoxidized with 1 equivalent of MCPBA in hexane at -15°C, and treatment of the product with $Bu_4NF \cdot 3H_2O$ in CH_2Cl_2 gave 13 in 71% yield for three steps.[11] No stereoisomer of 13 was recognized in its nmr spectrum. In the intermediary silyl enol ether derived from 12, MCPBA must attack the β face exclusively to give the β hydroxyl group, owing to the α face of the C-ring extremely crowded with the α oriented methyl group at C-10. This assignment was also supported by the nmr spectra of both 13 and its ester 14 which was obtained by the following steps. α-(Diethylphosphono)propionic acid (16)[12] of a Wittg reagent was prepared from α-bromopropionic acid trimethylsilylester (15) and triethylphosphite by Arbusov reaction (160°C, 6h.) followed by acid treatment in 60% overall yield.[13] Esterification of the hydroxyenone 13 with 16 was achieved by the following mixed anhydride method. The Wittig reagent 16 was treated with trichloroacetyl chloride in the presence of triethylamine in THF to give a mixed anhydride 17, and excess 17 was submitted to reaction with 13 *in situ* witn the aid of DMAP.[14] The reaction proceeded very smoothly (benzene, room temperature, 10 min.) and the desired ester 14 was obtained in 92% yield. On the other hand, trifluoroacetyl derivative 18[10c] gave 14 in only 54% yield, and 20% of the starting material 13 which was generated on the preparative TLC from by-product, the trifluoroacetate of 13, was recovered. The above results indicated that in the mixed anhydride 18, the attack of the hydroxyl group of 13 to the anhydride was less regio-selective due to the steric hindrance of the methyl group in propionic acid than the general high regio-selectivity reported in the mixed anhydride of phosphonoacetic acid.[10c] The results obtained above also indicated that the larger steric hindrance of the trichloromethyl group enhanced the selective attack of DMAP to the propionyl carbonyl rather than the trichloroacetyl carbonyl. Finally the synthesis of jolkinolide E was achieved by treatment of 14 with 1.1 equivalent of NaH in DME (room temperature, 30 min) in 70% yield. The synthesized compound was identical with the natural one (ir, nmr, uv, and mass specrta, and TLC behavior). Thus the stereochemistry at C-12 of jolkinolide E is depicted in formula 3.

Scheme 4



We could not find any precedent of the rapid and mild esterification method using trichloroacetyl group as a counterpart of mixed anhydride in combination with DMAP in the literature.[15] Therefore, we studied this reaction in more detail using simple carboxylic acids and alcohols.[16] As shown in Scheme 4, both trichloroacetate 21 and trichloromethyl ketone 23 were only isolable by-products in this reaction. It was concluded, therefore, that use of a small excess of the starting carboxylic acid based on trichloroacetyl chloride was neccessary to obtain the objective ester 22 in more than 95% yield by the following reasons. 1) An excess of the carboxylic acid should displace the equilibrium between 19 and 20 toward starting 19. 2) The excess carboxylic acid also acts as a proton source to quench trichloromethyl anion[17] generated thermally from trichloroacetyl anion resulting to the depression of formation of 23.[18]

Synthesis of jolkinolide A and B (Scheme 5). The first synthetic approach to jolkinolide A was the transformation of E(3) (route 1). Unfortunately attempted epoxidation of jolkinolide E with various oxidizing agents were unsuccessful. A furan derivative 24 obtained from E(3) (DIBAL, H_3O^+, 80% yield) did also not afford the desired epoxidized γ-hydroxybutenolide 25 by oxidation with 3 equivalents of MCPBA under various conditions.[19] In the cases of both hydroxyenone 13 and its t-butyldimethylsilyl ether, attempted epoxydation with H_2O_2-NaOH or Triton B resulted in recovery of the starting material. It was difficult to epoxidize the double bond at C-8,14 after introduction of a β-hydroxyl group to C-12.

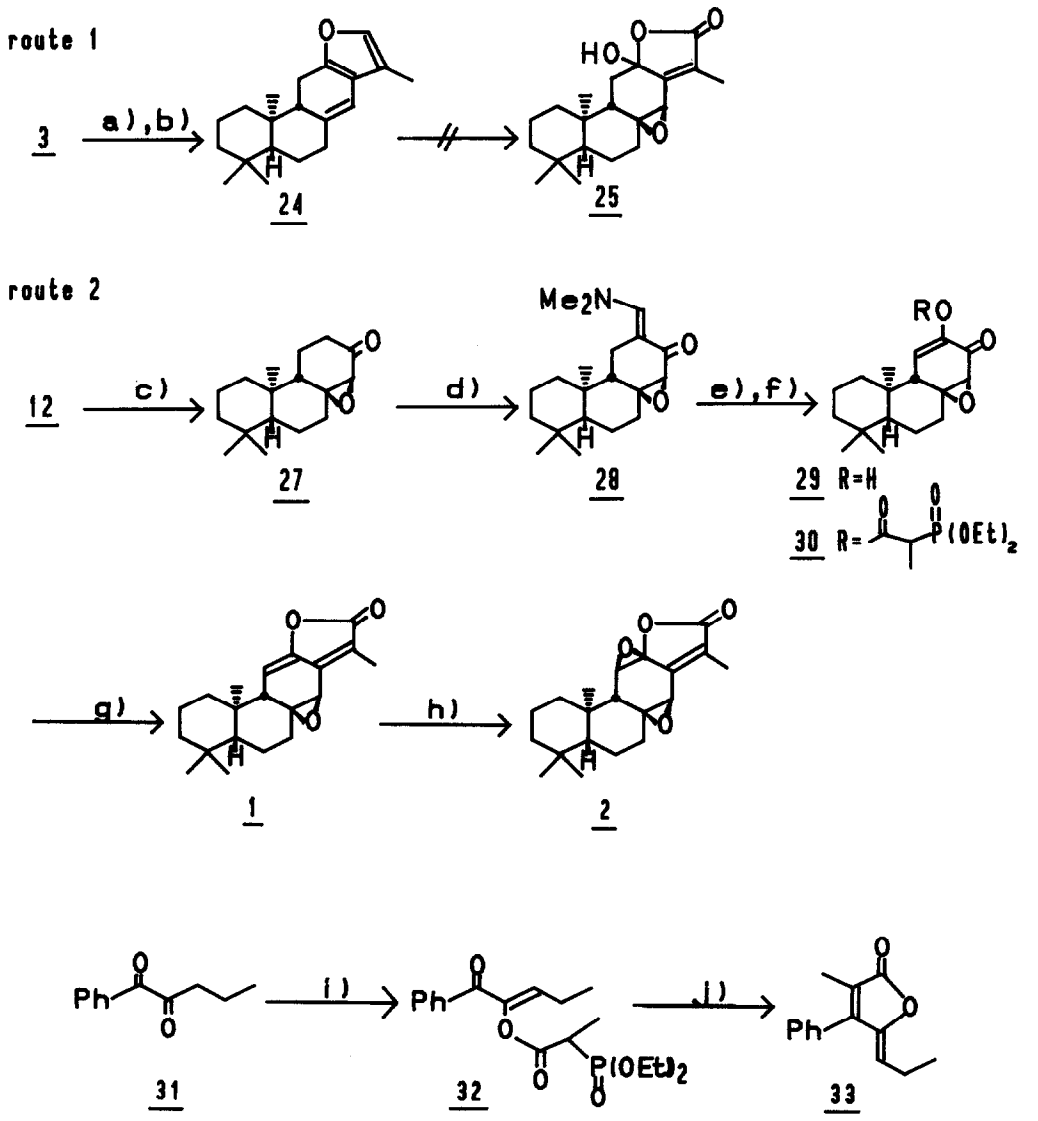
The second and successful approach to jolkinolide A was the construction of γ-ylidenbutenolide moiety by intramolecular Wittig-Horner reaction of the diosphenol prepared from 12 which gave an epoxyketone 27 with H_2O_2-NaOH quantitatively. Since the synthetic method of γ-ylidenbutenolide from α-diketone through α-diketone enolester by intramolecular Wittig-Horner reaction had not been reported yet, simpler α-diketone 31 was used as a model in preference to 29. Treatment of 1-phenylpentane-1,2-dione (31)[20] with the mixed anhydride of trichloroacetate 17 in the same manner as the preparation of 14 afforded a α-diketone enolester 32 in 74% conversion yield. The intramolecular Wittig-Horner reaction of 32 was carried out by treatment with NaH in DME to give an unstable γ-yliden-α,β-substituted butenolide 33 (65.4% yield). This was the first example of the γ-ylidenbutenolide synthesis by intramolecular Wittig-Horner reaction of α-diketone[21](Scheme 5). It was interesting that 33 showed an antimicrobial activity toward Candida utilis(MIC, 25μg/ml) and Trichophyton mentagrophytes(MIC, 12.5μg/ml).

Obtaining the successful result, the above sequences were applied to the epoxyketone 27. The introduction of a hydroxyl group to C-12 of the epoxyketone 27 was unsuccessful in the same procedure as that applied to the conversion of 12 to 13. According to Wasserman,[22] treatment of 27 with t-butoxybis(dimethylamino)-methane gave an enaminoketone 28 (87% yield), which was successively oxidized with singlet oxygen to afford a stable α-diketone in 60% yield. The ^1H nmr spectrum of this α-diketone in $CDCl_3$ showed that more than 70% existed as diosphenol 29. The esterification of 29 was achieved by our mixed anhydride method again. The mixed anhydride 17 reacted with 29 with the aid of DMAP to yield a α-diketone enolester 30, after workup, which was used to the next step without purification, since 30 was gradually hydrolyzed to 29 by SiO_2 chromatography. The final step was the clean intramolecular Wittig-Horner reaction. The synthesis of jolkinolide A(1) was completed by treatment of crude 30 with NaH (1.2 equivalent, DME) in 82% yield from 29. The synthesized jolkinolide A(1), mp 202-203°C, was converted into jolkinolide B (2), mp 221-222°C, with MCPBA, and the both compounds were identical

with the natural ones(ir, nmr, uv, and mass spectra). The synthesized jolkinolide B showed the specific antimicrobiral activity toward Trichophyton mentagraphytes(MIC,12.5μg/ml).

The intramolecular Wittig-Horner rection of α-diketone enolester described here is promissing as a useful methodology in the synthesis of 4-yliden-2,3-disubstituted butenolides.[23]

Scheme 5



a)DIBAL; b)H_3O^+; c)H_2O_2/NaOH; d)t-BuOCH$(NCH_3)_2$; e)$^1O_2$; f)17/DMAP; g)NaH/DME; h)MCPBA; i)17/DMAP; j)NaH/DME

Experimental

Melting points were determined on a Kofler hot plate. All m.ps and b.ps were uncorrected. IR spectra were recorded on a Jasco IRA-102 spectrometer. NMR spectra were recorded with TMS as an internal standard at 100 MHz on a JEOL PS-100 spectrometer or at 100 MHz on a JEOL JNM FX-100 spectrometer. UV spectra were recorded on a Hitachi EPS-2 spectrometer. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. E. Merck Silica Gel 60, 70-230 mesh was used for SiO_2 column chromatography. E. Merck Silica Gel GF 254 was used for preparative TLC. The anhydrous reactions were performed under N_2 or Ar atmosphere.

10-Methoxycarbonyl-β-ionone (4). A mixture of NaH (83.3 g, 60 % dispersion in mineral oil, 2.08 mol) and dimethyl carbonate (190 g, 2.11 mol) in dry dioxane (700 ml) was stirred and heated under reflux in N_2 atmosphere. To this suspension was added dropwise a solution of β-ionone (100 g, 0.52 mol) in dry dioxane (150 ml) over 2 h. The mixture was stirred and heated under reflux for 2 h. It was then cooled in an ice-bath, quenched and neutralized with 4N-aq. HCl, and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled under reduced pressure to give 110 g (85 %) of 4 as an oil, bp 127-130°C/1.5 torr; νmax(oil) 1738, 1635, 1585, 1235 cm^{-1}; λmax (EtOH) 308(ε 11800)nm ; nmr(CCl_4) δ 1.04 (3H, s), 1.07(3H,s), 1.77 (3H, s), 3.44 (2H, s), 3.66 (3H, s), 6.67 (1H, d, J=16Hz), 7.20 (1H, d, J=16Hz).

10-Methoxycarbonyl-β-ionone-9-enolacetate (5). To a solution of 4 (100 g, 0.4 mol) in dry pyridine (150 g, 1.9 mol) was added Ac_2O (200 g, 1.96 mol) dropwise. After the mixture had been stirred at room temperature overnight, it was neutralized with 4N-aq. HCl under ice-cooling and then extracted with ether. The extract was washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo to give 117 g (quantitative) of 5 as an unstable, oily mixture of the stereoisomers at C-10 (E:Z/2:3), νmax(oil) 1780, 1720, 1232, 1200, 1133 cm^{-1}; λmax(EtOH) 254(ε 12300), 314(ε 16100)nm; nmr(CCl_4) δ of E-isomer 1.06(6H,s), 1.76(3H,s), 3.69(3H,s), 5.52(1H, s), 5.92(1H,d,J=16Hz), 6.58(1H,d,J=16Hz), δ of Z-isomer 1.11(6H,s), 1.82(3H,s), 2.26(3H,s), 3.74(3H, s), 5.48(1H,s), 6.53(1H,d, J=16Hz), 7.34(1H,d,J=16 Hz).

10-Methoxycarbonyl-7-cis-β-ionone-9-enolacetate (6a,b). A solution of 5(50 g, 0.17 mol) and benzanthrone(5.3 g, 0.023 mol) in THF (1l) was irradiated with a 450-W, high-pressure, mercury-vapor lamp through a Pyrex filter under N_2 for 6 h under ice-cooling. After the reaction mixture had been concentrated in vacuo, a small amount of hexane was added and then benzanthrone was filtered off. The filtrate was concentrated in vacuo to give 45g (90 %) of crude 6 as an unstable, oily mixture of stereoisomers at C-10, νmax(oil)1770, 1720, 1200, 1135 cm^{-1}; λmax(EtOH) 262nm; nmr(CCl_4) δ of 6a 1.04(6H,s), 1.60(3H,s), 2.13(3H,s), 3.66(3H, s), 5.68(1H,s), 5.91(1H,d,J=13Hz), 6.26(1H,d,J=13Hz), δ of 6b 1.05(6H,s), 1.55(s), 2.06(3H,s), 3.72(3H,s), 5.52(1H,s), 6.27(1H,d,J=13Hz), 7.21(1H,d, J=13Hz).

4-Methoxycarbonyl-3-acetoxy-4a,8,8-trimethyl-4,4a,5,6,7,8-hexahydronaphthalene(7). The compound 6a, b was heated at 190~200°C for 1 h in a Claisen flask and the residue was distilled to give 87 g (97 %) of 7 as an oil, bp 130~135°C/1 torr, νmax(CCl_4) 1765, 1743, 1217, 1150, 1130 cm^{-1}; λmax(EtOH) 279(ε 7300)nm; nmr(CCl_4) δ 1.16(6H,s), 1.30(3H,s), 2.08(3H,s), 2.70(1H,s), 3.53(3H,s), 5.61(1H,d,J=6Hz), 5.67(1H,d,J=6Hz). (Found: C,69.93; H,8.13. Calc. for $C_{17}H_{26}O_4$: C,69.83; H,8.27).

9-Methoxycarbonyl-4,4,10-trimethyl-Δ⁶-8-octalone (8). To a solution of 7 (10 g, 34 mmol) in anhydrous MeOH (300 ml) was added NaOMe (2.2 g, 41 mmol) in one portion under reflux under N_2 atmosphere. After the mixture had been refluxed for 10 minutes, it was acidified with 10 % aqueous phosphoric acid to pH 6 under ice-cooling. MeOH was evaporated in vacuo, and the residue was extracted with ether. The extract was washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil which was used to the next step without purification. To suspension of NaH (2.0 g, 60 % in oil, 51 mmol) in benzene(50 ml) was added the oil obtained above in benzene (50 ml) dropwise over 30 minutes under reflux under N_2 atmosphere. After the mixture had been refluxed for 30 minutes, it was acidified with 10 % aqueous phosphoric acid to pH 6 under ice-cooling and then extracted with ether. The extract was washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo to give semi-crystals which were crystallized from hexane to give 2.8 g of 8 as needles. The filtrate was chromatographed over SiO_2. Elution with hexane-ether(4:1) gave 0.6g of 8 as crystals(total 3.6g, 40%), m.p.121-123°C; νmax($CHCl_3$) 1740, 1675, 1600, 1143 cm-1; λmax(EtOH) 235nm(ε 8250); nmr(CCl_4) δ 0.94(3H,s), 1.02(3H,s), 1.13(3H,s), 2.12 (1H,t,J=3,J=2Hz), 3.06(1H,s), 3.63(3H,s), 5.99(1H,q,J=10.5,J=2Hz). (Found: C,71.69 ; H,8.89. Calc.for $C_{15}H_{22}O_3$: C,72.00; H,8.88 %).

4,4,10-trimethyl-9-Methylidene-Δ⁶-8-octalone 9. To a solution of 8(11 g, 44 mmol) in absolute ether (400 ml) was added LAH (4 g, 110 mmol) portionwise under ice-cooling. After the mixture had been stirred for 4 h at the same temperature, the excess of LAH was decomposed by addition of ice-water. The resulting suspension was filtered through Celite and the residue was washed with ether several times. The filtrate was washed with brine, dried ($MgSO_4$), and

concentrated in vacuo to give a diol. A mixture of the diol obtained and activated MnO_2 (70 g) in CH_2Cl_2 (300 ml) was stirred vigorously at room temperature for 3 h and filtered through Celite. The filtrate was concentrated in vacuo. The residue was stirred with p-TsOH (200 mg) in benzene (200 ml) overnight under Ar, and followed by azeotropic dehydration using a Dean-Stark apparatus for 10 minutes. The solution was diluted with sat. $NaHCO_3$ solution and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 to give 7.85g(88%) of 9 as an oil, νmax(CCl_4) 1670, 1610, 845 cm-1; nmr(CCl_4) δ 1.00(3H,s), 1.03(3H,s), 1.12(3H,s), 2.18(1H,t,J=3,J=2Hz), 4.99(1H,d,J=2Hz), 5.72 (1H,d, J=2Hz), 6.06(1H, dd,J=10,J=3Hz), 6.85(1H,dd,J=10,J=2Hz). (Found: C, 82.15; H, 9.95. Calc.for $C_{14}H_{20}O$: C, 82.30; H, 9.87%).

4,4,10-trimethyl-9-(3-Oxobutyl)-Δ^6-8-octalone (11). To a solution of Na (244 mg, 10.6mmol) in MeOH (200 ml) was added methyl acetoacetate (22.4 g, 193 mmol) in MeOH (50 ml) and then 9 (4.9 g, 24.1 mmole) in MeOH (30 ml) under ice-cooling. After stirring for 40 h at room temperature under N_2, the mixture was neutralized with 4N HCl under ice-cooling . MeOH was evaporated in vacuo, and the residue was extracted with ether. The extract was washed with sat $NaHCO_3$ solution and brine, dried($MgSO_4$), and concentrated to give an oil. The methyl acetoacetate remained in the oil was removed by distillation at 35∿40°C/1 torr to give crude β-ketoester (7.5 g) which was dissolved in MeOH (220 ml). To this solution was added 1 % aqueous NaOH solution (128 ml; 1.3 equivalent) dropwise under ice-cooling. After stirring 15 h at 15°C under N_2, the mixture was acidified to pH 3 with 4N HCl under ice-cooling and MeOH was evaporated in vacuo. The residue was extracted with benzene and the extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give a crude acid. The obtained acid was refluxed in benzene(180ml) for 1 h under N_2 and the solvent was removed in vacuo. The residue was chromatographed over SiO_2 to give 5.1 g (81 %) of 11 as an oil, νmax(CCl_4) 1720, 1675 cm-1; nmr(CCl_4) δ 0.80(3H,s), 0.91(3H,s), 1.03(3H,s), 2.03(3H,s), 2.18(1H,t,J=3,J=2Hz), 5.86(1H,dd, J=10,J=3Hz), 6.76(1H,dd, J=10,J=2Hz).

$\Delta^{8(14)}$-Podocarpen-13-one (12)[9]. A mixture of 11 (5 g, 19.1mmol) and 10% Pd-C (500 mg) in DME (150 ml) was stirred vigorously under H_2 at 28°C for 1.5 h, and was filtered through Celite. The filtrate was concentrated in vacuo to give the crude saturated diketone (5g) which was used for the next step without purification. A mixture of the diketone obtained above (2 g, 7.58 mmol) in MeOH (226 ml) and 1 % aqueous NaOH (136 ml) was refluxed for 30 minutes, and was neutralized with dil. HCl under ice-cooling. MeOH was evaporated in vacuo and the residue was extracted with ether. The extract was washed with sat $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give crystals which were collected from n-hexane by a filtration to give 1.55 g of 12. The filtrate was chromatographed over SiO_2 to give an additional 12 (0.07g) (total yield, 1.62g, 87%), mp 91-92°C; νmax($CHCl_3$) 1655, 1620 cm-1; nmr($CDCl_3$) δ 0.80(3H,s), 0.87(3H,s), 0.92(3H,s), 5.85(1H,s). (Found: C,82.83; H,10.66. Calc. for $C_{17}H_{26}O$: C,82.87; H,10.64).

12-Hydroxy-$\Delta^{8(14)}$-podocarpen-13-one (13). To a solution of LDA prepared from diisopropylamine (392 mg, 3.9 mmol) and n-BuLi (2.4 ml of 1.58 N in hexane, 3.8 mmol) in DME (3.5 ml) was added 12 (795 mg, 3.23 mmol) in DME (3.5 ml) at -15°C for 10 minutes. After the mixture was stirred for 10 minutes at the same temperature, TMSCl (0.79 ml, 6.2 mmol) was added rapidly. The mixture was warmed gradually to room temperature (1.5 h), and the solvent was evaporated in vacuo. The crude enolsilyl ether was obtained by extraction of the residue with dry pentane followed by centrifugal separation of the pentane layer, which was concentrated in vacuo. To a prestirred suspension (20 minutes at room temperature) of MCPBA (653 mg of 94 % purity, 3.55 mmol) in hexane (45 ml) at -15°C was added enolsilyl ether obtained above in hexane (3 ml). After stirring for 40 minutes at room temperature, the mixture was filtered under an Ar pressure, and the hexane was evaporated in vacuo. The residual MCPBA was removed by filtration with the aid of pentane (5 ml), and the filtrate was concentrated in vacuo. The residue and tetrabutylammonium fluoride trihydrate (1.2 g, 3.8 mmol) were dissolved in CH_2Cl_2 (100 ml). After stirring over night at room temperature, the mixture was washed successively with sat. $NaHCO_3$, 1.5 N HCl, sat. $NaHCO_3$ solution , and brine, dried ($MgSO_4$), and then concentrated in vacuo to give a pale yellow oil which was chromatographed over SiO_2 to give 597mg(70.5%) of 13 as crystals, mp 133-134°C; νmax(Nujol) 3500, 1670, 1620 cm-1; nmr($CDCl_3$) δ 0.87(3H, s), 0.92(3H,s), 1.02(3H,s), 3.42(1H,OH), 4.2(1H, dd,J=7,J=12Hz), 5.83(1H, s). (Found: C,77.72; H,10.07. Calc.for $C_{17}H_{26}O_2$: C,77.81; H,10.00).

12-(2-diethylphosphonopropionyloxy)-$\Delta^{8(14)}$-podocarpen-13-one (14). To a solution of 2-diethylphosphonopropionic acid (630 mg, 3 mmol) and triethylamine (304 mg, 3 mmol) in THF (15 ml) was added trichloroacetyl chloride (546 mg, 3 mmol), and the mixture was stirred for 30 minutes at room temperature. After removal of triethylamine hydrochloride and the solvent, a mixture of 13 (524 mg, 2 mmol) and dimethylaminopyridine (733 mg, 6 mmol) in benzene(5 ml) was added to the mixed anhydride obtained above in benzene (5 ml). After stirring at room temperature for 10 minutes, the mixture was poured onto 3 % HCl solution under ice-cooling and was extracted with CH_2Cl_2. The extract was washed with cold 5 % $NaHCO_3$ solution

and brine, dried ($MgSO_4$), and concentrated in vacuo to give an oil which was chromatographed over SiO_2 to give 14 (833mg, 92%) as an oil besides 13(38mg). 14, λmax(oil) 1740, 1685, 1620 cm-1; nmr(CCl_4) δ 0.87(3H,s), 0.93(6H,s), 1.27(3H,t,J= 7Hz), 1.32(6H,t,J=7Hz), 4.1(4H,m,J=4Hz), 5.17(1H,br.t,J=7Hz), 5.80(1H,s).

Jolkinolide E (3). To a solution of 14 (118 mg, 0.26 mmol) in DME (2 ml) was added NaH (12 mg of 60 % in oil, 0.3 mmol) under ice-cooling. The mixture was stirred for 30 minutes at room temperature and poured onto cold sat NH_4Cl solution, and was extracted with ether. The extract was washed with sat $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was separated by preparative TLC (SiO_2, developed with n-hexane:ether/1:1) yielding 54 mg (69.5 %) of 3 as crystals which were recrystallized from n-hexane-ether, mp 154-155°C; νmax(Nujol) 1750, 1665, 1605 cm-1; λmax(MeOH) 278nm; nmr($CDCl_3$) δ 0.85(3H,s), 0.93(6H,s), 1.82(3H,d,J=1.5Hz), 4.87(1H,dd,J=6,J=12Hz), 6.23(1H,br.s); m/e 300(M^+). The spectra were identical with those of natural compounds. (Found: C,79.85; H,9.39. Calc. for $C_{20}H_{28}O_2$: C,79.95; H,9.39).

2-Diethylphosphonopropionic acid (16).[12] Trimethylsilyl 2-bromopropionate (2.4 g, 10.7mmol) prepared from 2-bromopropionic acid (11.46g, 74.9mmol) and hexamethyldisilazane (14g, 87mmol) was heated with diethylphosphite (1.95g, 11.73mmol) at 130-140°C for 6 h under slightly reduced pressure. The mixture was distilled to give 2.0 g (67 %) of trimethylsilyl 2-diethylphosphonopropionate, b.p. 92-94°C/0.8 torr, which was treated with 2 N HCl solution (2 ml) to give 1.25 g (84 %) of 16 as an oil, νmax(oil) 3350, 1710, 1170, 1010, 960 cm-1; nmr(CCl_4) δ 1.15-1.58(9H, m) 2.75(0.5H,m,J=7Hz), 3.14(0.5H,m,J=7Hz), 4.17(4H,m,J= 7Hz), 10.6(1H,br.).

A typical procedure of the esterification by a mixed anhydride of trichloroacetic acid catalyzed by DMAP. To a solution of carboxylic acid (2mmol) and triethylamine(0.21ml, 1.5mmol) in THF(2ml) was added trichloroacetyl chloride(0.17ml, 1.5mmol) dropwise and the mixture was stirred for 30 minutes at 0°C. After the removal of triethylamine hydrochloride by filtration , THF was replaced with benzene(2ml). A solution of alcohol(1mmol) and DMAP(428mg, 3.5mmol) in benzene was added to the mixed anhydride solution obtained above over 7 minutes under ice-cooling. After stirring 30 minutes at room temperature, the mixture was poured onto ice-cold brine and was extracted with ether. The extract was washed with 3% aqueous HCl, sat. $NaHCO_3$ solution, and brine, dried($MgSO_4$), and concentrated in vacuo to give ester. The yield of the ester was determined by isolation or GLPC by the addition of the appropriate internal standard.

8,14-Epoxy-13-podocarpanone (27). To a mixture of 12(400 mg, 1.63 mmol) and 30 % H_2O_2 (0.5 ml, 4.4 mmol) in MeOH (3.7 ml) was added 6 N NaOH (0.08 ml, 0.48 mmol) at 15°C. After stirring 3.5 h at 25-30°C, the mixture was diluted with ice-water and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 405 mg (95 %) of 27 as crystals which were recrystallized from n-hexane-ether, mp 98-99°C; νmax(Nujol) 1700, 980, 965, 840, 800 cm^{-1}; nmr($CDCl_3$) δ 0.92(3H,s), 0.85(6H,s), 3.15(1H,s). (Found: C,77.69; H,10.04. Calc. for $C_{17}H_{26}O_2$: C,77.81; H,9.98).

8,14-Epoxy-12-(dimethylaminomethylene)-13-podocarpanone (28). A mixture of 27 (650 mg, 2.48 mmol) and t-butoxybis(dimethylamino)methane (1.65 g, 7.78 mmol) was stirred at 60-65°C for 14 h under Ar. After volatility was evaporated in vacuo, the mixture was diluted with ice-water and extracted with CH_2Cl_2. The extract was washed with brine, dried($MgSO_4$), and concentrated in vacuo. The residue was washed with hexane to give 700 mg (89 %) of 28 as crystals, mp 133.5-135°C, which were used for the next step without further purification, νmax(Nujol) 1650, 1550, 1135, 855 cm^{-1}; nmr(CCl_4) δ 0.85(6H,s), 0.92(3H,s), 2.93(1H,s), 3.05(6H,s), 7.05(1H,s).

8,14-Epoxy-12-hydroxy-Δ^{11}-podocarpen-13-one (29). A mixture of 28 (100 mg, 0.32 mmol) and tetraphenylporphine(1.5 mg) in CH_2Cl_2(30 ml) was irradiated with a 300 W iodo-halogen lamp while oxygen was bubbling at -78°C and then concentrated in vacuo. The residue was separated by preparative TLC (SiO_2) to give 53 mg(60.9 %) of 29 as crystals which were recrystallized from n-hexene-ether, mp 185-186.5° C; νmax(Nujol) 3500, 1680, 1660, 1235, 1210, 1160, 865, 815, 770, 760 cm-1; nmr($CDCl_3$) δ 0.73(3H,s), 0.86(3H,s), 0.94(3H,s), 2.59(d,J=6Hz), 3.32(1H,d,J=1.5 Hz), 5.67(1H,br.OH), 5.68(1H,d,J=6Hz); m/e 276(M^+). (Found: C,73.82; H,8.75. Calc.for $C_{17}H_{24}O_3$: C,73.88; H,8.75).

Jolkinolide A (1). In the same manner as described for the preparation of 14 and 3 except that 5% H_3PO_4 solution was used instead of 3% HCl solution, 29 (76mg, 0.025 mmol) gave 30 which was successively treated with NaH (1.2 equivalent) in DME (2 ml) yielding 71 mg (82%) of 1 as crystals which were recrystallized from ether-MeOH, mp 202-203°C; νmax($CHCl_3$) 1770, 1670, 1660 Cm-1; λmax(MeOH) 288nm; nmr ($CDCl_3$) δ 0.73(3H,s), 0.88(3H,s), 0.97(3H,s), 2.08(3H,s), 2.66(1H,d,J=6Hz), 3.74,(1H,s), 5.46(1H,d,J=6Hz); m/e 314(M^+). The spectra were identical with those of natural compounds. (Found: C,76.32; H,8.35. Calc. for $C_{20}H_{26}O_3$: C,76,40; H,8.34).

Jolkinolide B (2). To a solution of 1 (50 mg, 0.159 mmol) in CH_2Cl_2 (1.5 ml) was added MCPBA (37 mg of 94% purity, 0.20 mmol) under ice-cooling. After stirring over night at room temperature, the mixture was poured onto cold sat. $NaHCO_3$

solution and extracted with CH_2Cl_2. The extract was washed with brine, dried($MgSO_4$), and concentrated in vacuo. The residue was separated by preparative TLC (SiO_2, developed with n-hexane: ether: $CHCl_3$/ 2:1:10) yielding 49 mg (76.2 %) of 2 as crystals which were recrystallized from ether-MeOH, mp 221-222°; νmax($CHCl_3$) 1790, 1690 cm-1; λmax(MeOH) 240nm; nmr($CDCl_3$) δ 0.83(3H,s), 0.86(3H,s), 0.96(3H,s), 2.12 (3H,s), 2.32(1H,br.s), 3.72(1H,s), 4.07(1H,d,J=1.5Hz); m/e 330.1829(M^+) (330.1831 Calc. for $C_{20}H_{26}O_4$). The above spectra were identical with those of natural ones.

2-Methyl-3-phenyl-4-propylidene-Δ^2-dihydrofuranone-1 (33). In the same manner described for the preparation of 30, 200 mg of 31[20] gave 205 mg (47%) of 32 besides 106 mg of 31 after preparative TLC (SiO_2). 134 mg (0.38 mmole) of crude 32 gave 53mg (65.4%) of 33 in the same manner described for the preparation of 1. Crude 33 gradually decomposed on standing after workup. The nmr spectrum demonstrated that the purified 33 was the single z-isomer in the ylidene moiety,[23] ν_{max}(oil) 3050, 1775, 1760, 1660, 1630, 1595, 1570 cm^{-1}; nmr(CCl_4) δ 1.08(3H,t, J=7.5Hz), 1.95(3H,s), 2.42(2H,m,J=7.5Hz), 5.05(1H,t,J=7.5 Hz), 7.4(5H,m); m/e 214.1006(M^+) (214.1084 Calc. for $C_{14}H_{14}O_2$).

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