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TOTAL SYNTHESIS OF NAGILACTONE F , BIOLOGICALLY ACTIVE NOR-DITERPENOID DILACTONE ISOLATED FROM PODOCARPUS NAGI

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Summary : Nagilactone F was synthesized from (+)-podocarpic acid of the established structure. This work constitutes the first total synthesis of the biologically active norditerpenoid dilactones in Podocarpus plants.

Nor- and bisnor-diterpenoid dilactones[2a], isolated from various species of Podocarpus plants, constitute an important group of compounds in natural product chemistry, since a wide variety of their biological activities[3], as well as their unique structures, has attracted very much attention from physiological and pharmaceutical standpoint. However, the total synthesis of any of the members has not yet been achieved, probably because of their somewhat unusual reactivities. We herein wish to describe the first total synthesis of nagilactone F[2b] (1), one of the simplest members of the natural dilactones.

The synthesis was started from a natural resin acid, (+)-podocarpic acid, whose structure and absolute stereochemistry had already been established[4]. A tricyclic enone 3, prepared from (+)-podocarpic acid methyl ether (2) according to Spencer's procedure[5] with some modifications, was alkylated at C-14 by Michael addition [LiCu(iPr)$_2$/(CH$_3$)$_2$S/THF,-78°] and the intermediate enolate of the 14-isopropyl-12-ketone was directly quenched with PhSeCl[6]. Oxidative elimination(H_2O_2/THF) of the resulting 13-selenide gave an isopropyl enone 4 in 55% overall yield from 3. Ozonolysis of 4, followed by Jone's oxidation, produced a keto carboxylic acid 5 in 90% yield. After esterification(CH_2N_2), 5 was reduced with excess diborane in THF to give a lactone 7[7] (25%) and a hydroxy ester 6(51%). The latter can be changed by acid treatment(TsOH/benzene/80°;80%) into a lactone 8[7], which was epimeric with 7 about C-14 configuration. The saturated lactones, 7 and 8, were converted to the corresponding 9:11-unsaturated lactones, 9(71%) and 10(76%), respectively, through the usual α-selenylation(LDA/PhSeCl/THF,-78°C, 20min) and subsequent oxidative elimination (H_2O_2/THF,r.t.,1 hr); 9, mp 126-128°, $\nu_{max}^{CHCl_3}$ 1710, 1693, 1610 cm^{-1}, λ_{max}^{EtOH} 223 nm, δ $^{CDCl_3}_{ppm}$ 0.96(3H,s), 0.98(3H,d,J=7.0Hz), 1.12(3H,d,J=7.0Hz), 1.23(3H,s), 3.74(3H, s), 3.93(1H,dd,$J_{8,14}$=10.0, $J_{14,15}$=3.0Hz,H-14), 5.92(1H,d,J=2.0Hz,H-11); 10

$\nu_{max}^{CHCl_3}$ 1718, 1698, 1612 cm^{-1}, λ_{max}^{EtOH} 232 nm, $\delta_{ppm}^{CDCl_3}$ 0.98(3H,d,J=7.0Hz), 1.04(3H,s), 1.15(3H,d,J=7.0Hz), 1.20(3H,s), 3.77(3H,s), 3.87(1H,dd,$J_{8,14}$=3.5, $J_{14,15}$=10.0Hz, H-14), 5.85(1H,s,H-11). The coupling constants of H-14 in both of the C-14 epimers, 9 and 10, were well consistent with the assigned stereochemistry at C-14, where the large isopropyl group should take an equatrial conformation[8]. The enolide 10 was treated with potassium t-butoxide(3eq) in DMSO at room temperature (12 hr) gave quantitatively a diene-carboxylic acid 11, mp 145°C, $[\alpha]_D^{14}$-86.8° (MeOH,1.35mg/ml), $\nu_{max}^{CHCl_3}$ 3600-2500, 1715, 1697, 1623 cm^{-1}, $\delta_{ppm}^{CDCl_3}$ 0.81(3H,s), 0.92(3H,d,J=7.0Hz), 0.97(3H,d,J=7.0Hz), 1.20(3H,s), 3.65(3H,s,OCH_3), 5.00(1H,d, J=9.5Hz,H-14), 5.48(1H,s,H-11). The ^{13}C-nmr spectrum of 11 shows four olefinic carbon signals at 111.1(C-11), 133.6(C-8), 135.2(C-14), and 170.4(C-9) ppm($CDCl_3$), which corresponded to the assigned structure. The configuration of the 8:14-double bond in 11 must be in "E", since 11 was produced under an equilibrium condition[9]. This consideration coincides with the fact that the epimeric(C-14) enolide 9 gave the same diene-carboxylic acid as 11 under the same reaction condition. Moreover, another isomeric enolide 15(epimeric at C-8 with 10), which was derived from nagilactone F through the reductive degradation steps, also formed a dien-carboxylic acid[14]. The properties(^{1}H-nmr, ^{13}C-nmr and ir) of the last product was completely identical with those of 11, including the optical rotation; $[\alpha]_D^{14}$ = -87.2°(MeOH,9.05mg/ml). Thus, the absolute configuration of the natural nor-diterpenoid dilactone was first correlated chemically with (+)-podocarpic acid of the known stereochemistry.

Irradiation of the diene-carboxylic acid 11 with medium pressure mercury lamp in 95% ethanol(4 hrs, under N_2) produced, quantitatively and stereospecifically, a less polar single product[10], which was characterized as the 8:9-enolide 12 by the spectral analysis, $[\alpha]_D^{18}$+121.7°(MeOH,2.5mg/ml), $\nu_{max}^{CHCl_3}$ 1719 cm^{-1}, ^{1}H-nmr: $\delta_{ppm}^{CDCl_3}$ 0.84(3H,d,J=7.0Hz), 0.85(3H,s), 1.12(3H,d,J=7.0Hz), 1.25(3H,s), 2.95(2H,m,H-11), 3.67(3H,s), 4.53(1H,m,H-14), ^{13}C-nmr: $\delta_{ppm}^{CDCl_3}$ 133.8, 125.6 ppm(quaternary olefinic carbons). The stereochemistry at C-14[11] of the product 12 was to be the same as the natural dilactone (14α-isopropyl), since all of the spectral properties were again identical with those of the 8:9-enolide derived from nagilactone F[14]. On bromination(NBS/$CHCl_3$/hν) and subsequent debromination(Zn/DMF/r.t.), the enolide 12 gave a 7:8,9:11-dienolide ester 14[12], which was hydrolyzed to a dienolide acid 16 with conc.H_2SO_4 in quantitative yield. In this hydrolysis, no more satisfactory result was obtained with various basic reagents under SN_2 type ester cleavages[13]. The diene acid 16 was treated with excess $Pb(OAc)_4$ in benzene[15°C,3 days,under N_2/hν(15W fluorescent lamp)] to produce in 50% yield a γ-lactone, which was completely identical with natural nagilactone F in ir and ^{1}H-nmr comparisons.

References and Notes

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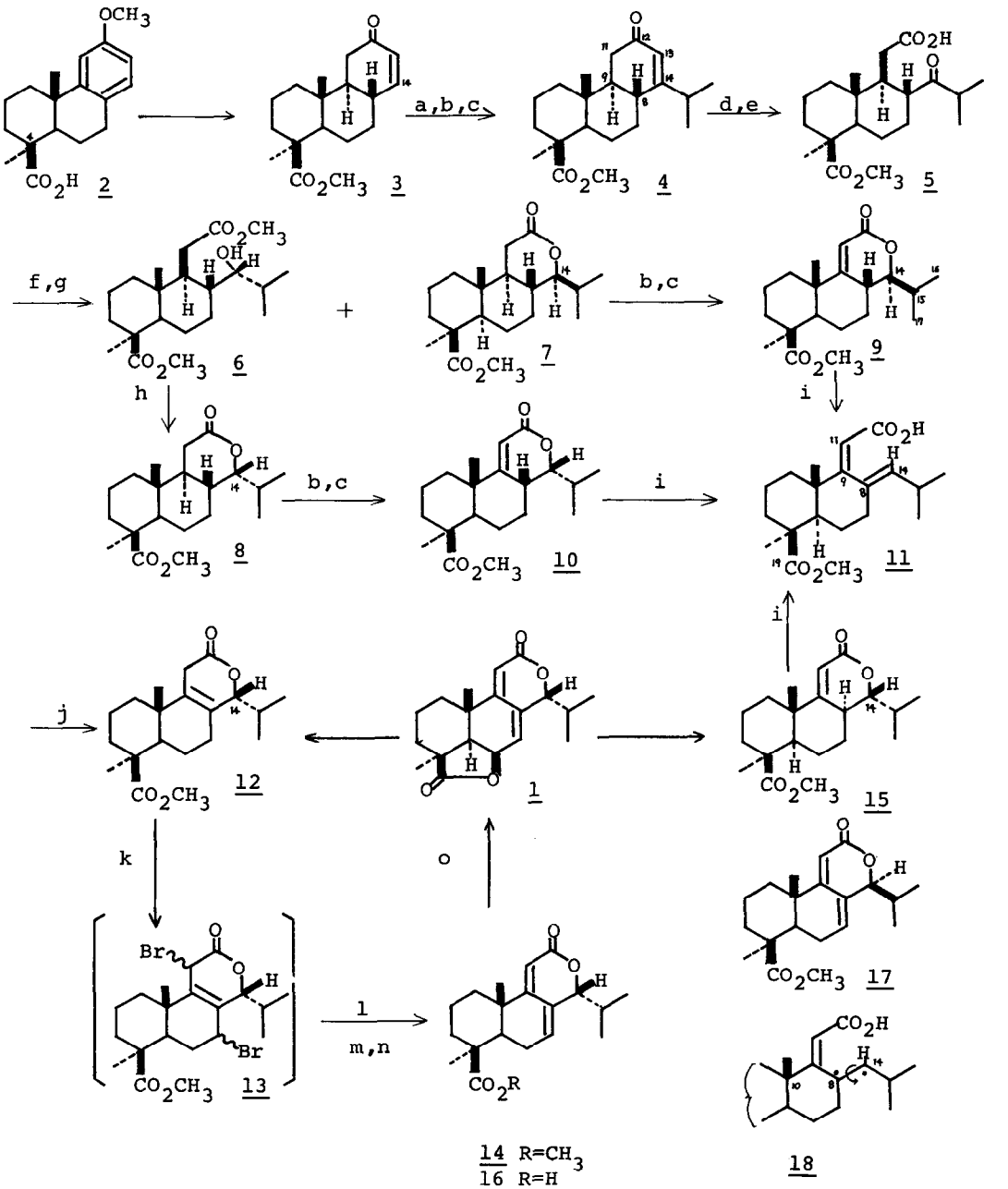
6. When this reaction sequence(Michael addition/selenylation/oxidative elimination) was performed through isolation of the intermediate saturated ketone(Michael addition product), two isomeric isopropyl enones, 4 and the corresponding 9:11-enone, were produced in 7:1 ratio.
7. Of the two epimeric lactones, 7 and 8, more easily formed isomer can be assigned as 7 with 14β(equatorial)-isopropyl group.
8. According to the moleculer model consideration, the observed dihedral angle between H-14 and H-15 is approximately 60° in 9($J_{14,15}$=∿3Hz), and 180° in 10 ($J_{14,15}$=∿10Hz), at the most probable conformation of the two methyl groups (C-16 and C-17).
9. The proton abstraction at C-8 and the double bond formation at 8:14-position by internal elimination of the carboxylate anion should proceed in an equibilium, so that the product is thermodynamically more stable 8:14[E]-isomer.
10. Pyrolysis(210°, 1 min) of 11 also gave 8:9-enolide quantitatively. However, the product was a mixture(3:5) of 12 and its 14-epimer. The identification of the components and product ratio determination in the mixture were performed by the ^{13}C-nmr comparison of pure 12 and the mixture.
11. On irradiation, photochemical excitation took place at 8:14-double bond to result in a biradical intermediate 18, in which C-14 should rotate around the 8:14-bond axis to such direction(see arrow), prior to the lactonization, that the steric interaction between the angular methyl group at C-10 and the isopropyl group at C-14 can be maximally avoided.
12. The dienolide ester 14 was formed from 12 only in poor yield. The main product was not yet characterized. When the other 8:9-enolide, isomeric to 12 at C-14, was subjected to the same bromination/debromination process, an epimeric(at C-14) dienolide ester 17 was formed in fair yield. The stereochemistry of the bromine atom in the intermediate dibromide would be different for each of the epimeric pair, depending on the configuration at C-14.

13. The SN_2 type hydrolysis of hindered esters: J.McMurry, Organic Reactions, 24, 187 (1976).
14. Details of the degradation of nagilactone F to the intermediates, 11 and 12, will be published elsewhere.



a) $(iPr)_2CuLi$, b) PhSeCl, c) H_2O_2, d) O_3, e) CrO_3, f) CH_2N_2, g) BH_3/THF, h) H^+, i) t-BuOK/DMSO, j) hν, k) NBS/$CHCl_3$, l) Zn/DMF, m) H_2SO_4, n) H_2O, o) $Pb(OAc)_4$/hν.

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