

Base-Catalyzed Intramolecular Condensations of Diligustilide.¹

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Abstract: Treatment of diligustilide (**1**) with base afforded the pentacyclic compounds **2** - **4** with novel carbon-carbon connectivities *via* lactone-ring opening, intramolecular condensations and competitive equilibrations. This reaction provides a useful entry to modified dimeric phthalides.
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Recent publications have reported the synthesis of the racemic dimeric phthalide diligustilide (**1**) from *Z*-ligustilide,^{2,3} and its conversion to wallichilide and *rel*-(3*R*)-dihydrodilgustilide,² which are bioactive natural compounds isolated from Umbelliferae species used in traditional medicine.^{4,5} During the experimentation to optimize the methanolysis of diligustilide (**1**), this compound was treated with NaOH in THF and MeOH. After 2 h a product derived from an intramolecular condensation **2** was observed. The same product was formed, although in lower yield, by refluxing **1** with MeONa in *i*-PrOH.⁶ The molecular formula of **2** (C₂₅H₃₂O₅) established the addition of methanol to **1**, and the IR region showed hydroxyl, carbonyl, and olefin absorptions. NMR experiments (COSY, DEPT, HMBC, HMQC, NOESY) of **2** established the presence of three carbonyls (two ketones and one ester), two double bonds (one tetrasubstituted and one trisubstituted), one methoxy group and a tertiary carbon linked to oxygen, one quaternary sp³ carbon, eight methylenes, five methines bearing only carbon substituents and two methyl groups linked to carbon. These data clearly indicated that the cyclohexene and the bicyclo-[2.2.2]-octene systems had remained intact in the product **2** and that the enolactone moieties of **1** had undergone transformations to form a conjugated cyclopentenone fused to a cyclohexanone, as depicted in formula **2**. The analysis of NMR data allowed the assignments of all proton and carbon signals. A NOESY crosspeak between H-8 and H-8' established the *exo*-orientation of the *n*-propyl

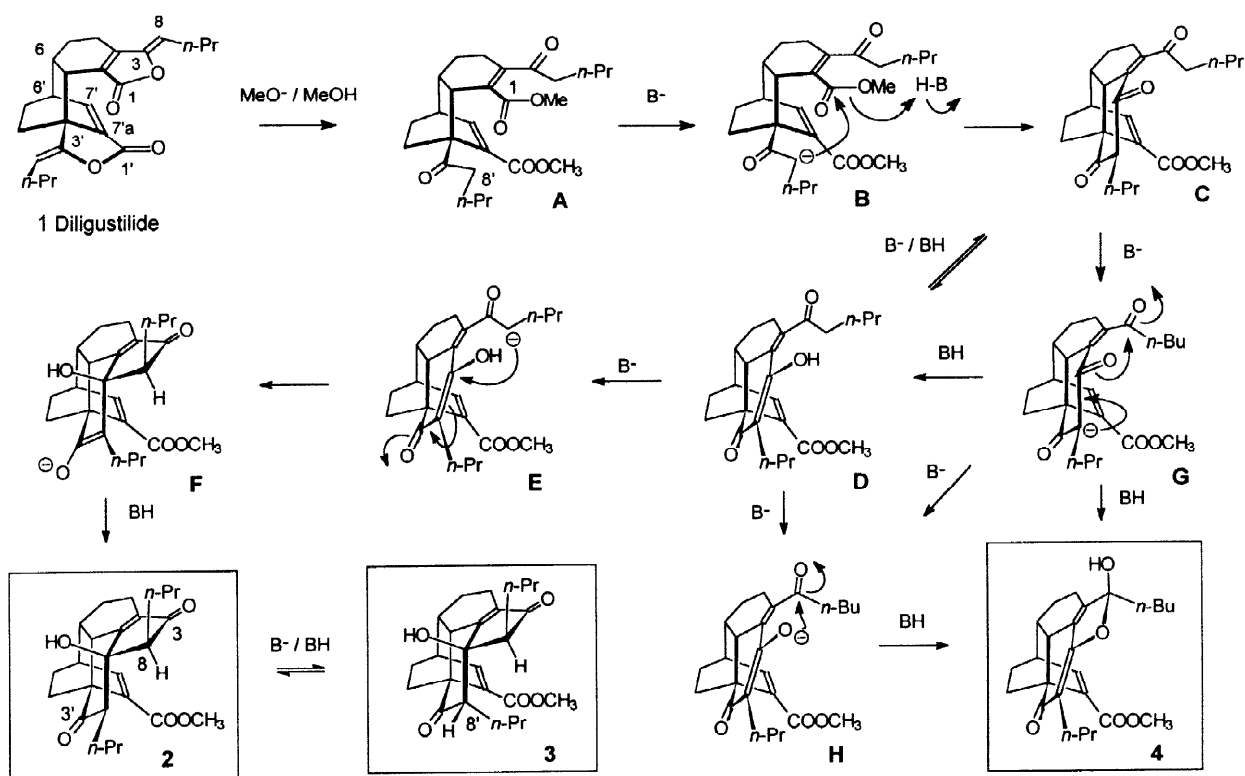
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groups in **2**. The structure **2** was confirmed by X-Ray analysis (*vide infra*).

From the mechanistic point of view, a diketo diester intermediate (**A**, formed by methanolysis of **1**, Scheme 1) undergoes intramolecular aldol reaction, by deprotonation of the acidic methylene at 8' (intermediate **B**) and addition to the carbonyl to produce tautomeric intermediates **C** and **D**, which in turn could react to give **2** via Michael-type addition of the carbanion at C-8 and equilibration (intermediates **E** and **F**, Scheme 1).

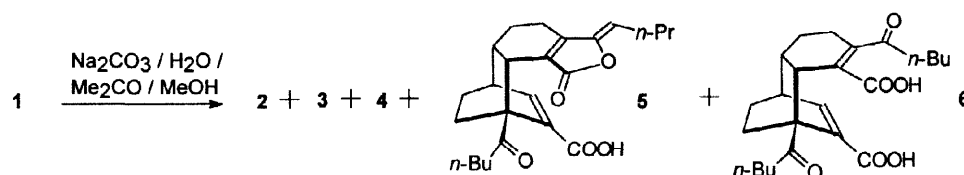
Another procedure which favours the intramolecular condensations involved reaction of **1** with Na₂CO₃ in H₂O/MeOH/Me₂CO, which afforded compounds **3** (8'-*epi*-**2**, 4%), **2** + **4** (65%), **5**² (demethylwallichilide, 9%) and **6**² (10%) (Scheme 2).⁷ From the less polar eluates of the chromatography of the reaction mixture crystallized the mixture **2** + **4**, and these crystals were suitable for X-ray analysis. Figure 1 shows the final models obtained by this study.^{7,8} The formation of the enol ether **4** can be rationalized by the *O*- alkylation of the intermediates **G** or **H** (Scheme 1). In solvents such as THF and *i*-PrOH, *C*- alkylation is preferred (to produce **2**), whereas in an aqueous system, a negative charge resides mainly on the oxygen, which allows formation of the hemiketal **4**.

Scheme 1



These transformations represent useful entries to modified polycyclic phthalide derivatives with novel carbon-carbon connectivities.

Scheme 2



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1. This paper is dedicated to Dr. Lydia Rodríguez-Hahn, Instituto de Química, UNAM, deceased on May 20, 1998.
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6. Preparation of **2**. **Method A.** To a solution of diligustilide (**1**, 66 mg, 0.17 mmol) in THF (5 mL) was added solid NaOH (18 mg, 0.46 mmol) and methanol (0.5 mL). The heterogeneous mixture was refluxed for 2 h and concentrated at reduced pressure. Methylene chloride (10 mL) was added and the organic phase was washed with diluted HCl (10%, 5x10 mL), saturated bicarbonate (2x10 mL), dried (Na₂SO₄) and concentrated in vacuum, to afford **2** (65 mg, 92%) as a pale yellow oil. **Method B.** To a solution of **1** (29 mg, 0.076 mmol) in *i*-PrOH (10 mL) was added a solution of sodium methoxide (0.2 mL, 1% of MeONa in MeOH). After the mixture had been refluxed for 10 min, it was neutralized with diluted HCl (10%, to pH 4) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated in vacuum. The residue was purified by prep. TLC (*n*-hexane-ethyl acetate 3:1) to afford **2** (26 mg, 84%). **2** Rf: 0.40 (*n*-hexane-ethyl acetate 7:3); Yellow oil; UV (MeOH) λ_{max} , nm (ϵ): 222 (3125). IR (film): 3435, 2957, 2871, 1721, 1676, 1612, 1437, 1381, 1298, 1260, 1215, 1087, 915, 741 cm⁻¹. ¹H NMR (500 MHz, CDCl₃; assignments by COSY, HMQC, HMBC and NOESY): 7.37 (1H, d, J=7.2 Hz, H-7'), 3.66 (3H, s, OCH₃), 2.92 (1H, br s, H-6'), 2.89 (1H, br s, H-7), 2.52 (1H, dd, J=10.2, 2.4 Hz, H-8), 2.40 (1H, m, H-4a), 2.40 (1H, m, H-6), 2.27 (1H, m, H-8'), 2.02 (1H, m, H-5'a), 1.85 (1H, m, H-4b), 1.84 (1H, m, H-4'a), 1.82 (2H, m, H-9), 1.80 (1H, m, H-5a), 1.70 (1H, m, H-10a), 1.51 (2H, m, H-9'), 1.43 (1H, m, H-5b), 1.25 (1H, m, H-10b), 1.25 (2H, m, H-10'), 1.24 (1H, m, H-4'b), 1.24 (1H, m, H-5'b), 0.98 (3H, t, J=7.0 Hz, H-11 or H-11'), 0.97 (3H, t, J=7.0 Hz, H-11 or H-11'). ¹³C NMR (125 MHz, CDCl₃, assignments by DEPT, HMQC, HMBC): 207.8 (C-3), 206.6 (C-3'), 169.3 (C-1'), 164.3 (C-7'a), 148.6 (C-7'), 138.4 (C-7a), 135.0 (C-3a), 81.8 (C-1), 59.2 (C-8), 54.2 (C-8'), 53.7 (C-3'a), 51.8 (OCH₃), 40.6 (C-7), 38.5 (C-6), 37.7 (C-6'), 29.9 (C-9'), 29.3 (C-5'), 26.5 (C-4'), 26.2 (C-9), 23.8 (C-5), 21.4 (C-10'), 20.7 (C-10), 17.6 (C-4), 14.5 (C-11'), 14.2 (C-11). EIMS *m/z* (rel. int.): 412 [M⁺] (62), 380 (15), 369 (22), 337 (12), 222 (100), 221 (57), 190 (66), 161 (31), 148 (23), 105 (16), 91 (14), 77 (13), 55 (22). Anal. Calcd for C₂₅H₃₂: C, 72.79; H, 7.82. Found: C, 72.62; H, 7.67.
7. Preparation of **2**, **3**, **4**, **5**, and **6** and **7**. To a stirred solution of diligustilide (**1**, 204 mg, 0.65 mmol) in acetone (12 mL) and methanol (1 mL) was added a solution of Na₂CO₃ (500 mg) in H₂O (10 mL). The reaction mixture was

refluxed for 3 h. The mixture was neutralized with diluted HCl (10% to pH 4) and then extracted with ethyl acetate (5x17 mL). The organic solution was washed with saturated NaHCO₃ and with water, dried (Na₂SO₄), and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel and eluted with *n*-hexane-ethyl acetate gradient to give a crystalline mixture of **2** + **4** (1:1, 180 mg, 65%) which was analyzed by X-Ray. Crystal data of **2** + **4**:^{8a} molecular formula: (C₂₅H₃₂O₅)₂; triclinic space group P-1, *a*=13.001(2) Å, *b*=14.190(2) Å, *c*=14.206(2) Å; α =104.53(2)°, β =114.15(2)°, γ =97.40(2)°; *V*=2234.1(5) Å³; *D*_c=1.226 g cm⁻³; *Z*=2 *F*(000)=888; μ (Cu K α)=0.678 mm⁻¹; 5763 reflections were collected in the Siemens P4 diffractometer. Final *R*=9.52% (548 parameters), *R*_w=14.24% for 3334 observed reflections with *F*≥3 σ *F* in the range 3.0° ≤ θ ≤ 110°. *T*=243 K. Intensities were corrected for background, Lorentz and polarization effects. The structure was solved by direct methods and refined by full-matrix least-squares^{8b} with anisotropic temperature factor for the non-hydrogen atoms. The hydrogen atoms were included at idealized positions. All hydrogens with a fixed temperature factor *U* = 0.08 Å². Ortep view of **2** and **4** in figure 1. **3** was isolated as an oil (10 mg, 4%); **6**² (23 mg, 9%) and **7**² (28 mg, 10%) were isolated from the polar fractions of the column chromatography. **3**: yellow oil; UV (MeOH) λ_{max} nm (ϵ): 224 (4830). IR (CHCl₃): 3589, 2962, 2935, 2873, 1774, 1711, 1464, 1439, 1368, 1277, 1254, cm⁻¹. ¹H NMR (500 MHz, CDCl₃; assignments by COSY, HMQC, HMBC and NOESY): 7.36 (1H, d, *J*=6.9 Hz, H-7'), 3.68 (3H, s, OCH₃), 2.94 (1H, m, H-6'), 2.83 (1H, dd, *J*=9.6, 2.7 Hz, H-7), 2.69 (1H, d, *J*=9.9 Hz, H-8'), 2.36 (2H, m, H-6, H-8), 2.22 (2H, m, H-9'), 2.01 (1H, m, H-4'), 1.87 (4H, m, H-9, H-5), 1.80 (1H, m, H-10'), 1.77 (1H, m, H-4'), 1.64 (1H, m, H-10), 1.51 (2H, m, H-5'), 1.27 (2H, m, H-10, H-10'), 1.00 (3H, t, *J*=7.2 Hz, H-11 or H-11'), 0.88 (3H, t, *J*=7.2 Hz, H-11 or H-11'). ¹³C NMR (125 MHz, CDCl₃, assignments by DEPT, HMBC, HMQC): 207.0 (C-3), 206.0 (C-3'), 167.2 (C-1'), 164.3 (C-7'a), 148.6 (C-7'), 139.2 (C-7a), 135.1 (C-3a), 83.5 (C-1), 57.6 (C-8), 52.9 (C-3'a), 52.88 (C-8'), 51.9 (OCH₃), 41.0 (C-7), 39.0 (C-6), 37.7 (C-6'), 31.3 (C-9'), 29.7 (C-3'), 28.9 (C-4'), 26.7 (C-9), 24.0 (C-5), 21.1 (C-10'), 19.6 (C-10), 18.0 (C-4), 14.7 (C-11 or C-11'), 14.1 (C-11 or C-11'). EIMS *m/z* (rel. int.): 412 [M⁺] (1), 370 (37), 369 (50), 337 (34), 222 (89), 221 (100), 191 (41), 190 (84), 189 (24), 164 (15), 162 (18), 161 (38), 148 (40), 134 (10), 105 (15), 83 (14), 77 (13), 61 (14), 55 (23).

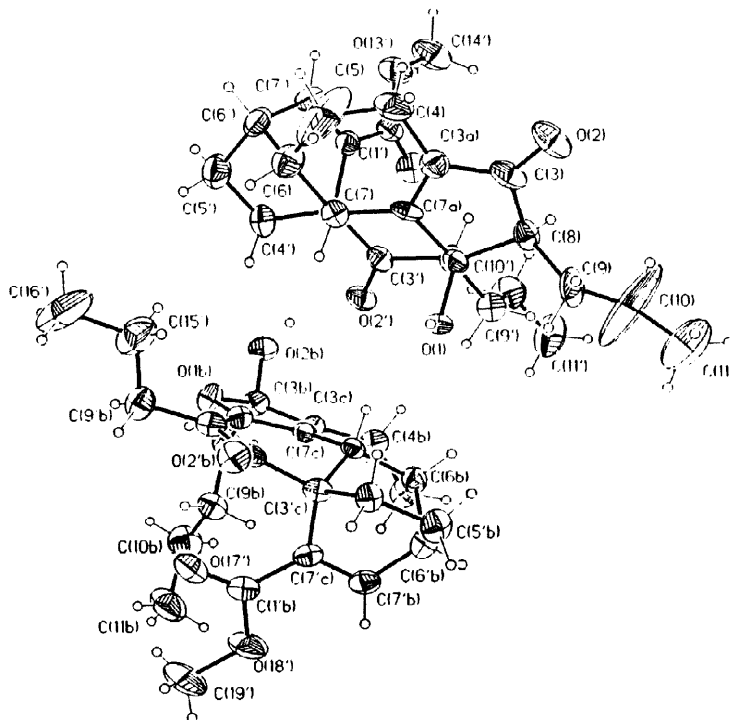


Figure 1. X-Ray Molecular Structure of **2** + **4** showing 40% probability displacement ellipsoids.

8. (a) Pertinent crystallographic data for **2** + **4** have been deposited with the Cambridge Crystallographic Data Centre. (b) Sheldrick, G. M. SHELEX/PC User's Manual Release 4.1, Siemens Analytical X-Ray Instruments Inc., Madison, Wisconsin, USA.