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Chemical Reactivity of Phthalides. Relay Synthesis of Diligustilide, *Rel*-(3'*R*)-3',8'-Dihydrodiligustilide and Wallichilide.[1]

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Abstract. Diels Alder reaction using *Z*-ligustilide (**3**) both as diene and dienophile afforded the natural product diligustilide (**1**). The relay synthesis of **5** from **1** (*via* situ-selective lactone ring opening, reduction with $NaBH_4$/MeOH and lactonization with $SOCl_2$/THF) was achieved and confirmed the revised structure of **5**, a secondary constituent of *Ligusticum wallichii*. The natural substance wallichilide (**8**) was also obtained directly from **1**.

Introduction

Phthalides are secondary metabolites of umbelliferous plants, which are widely used in traditional medicine in Europe, North America, and Asia.[2] Some of these constituents are dimeric compounds that exist as racemic mixture, and they can formally be considered to arise by [π4s + π2s] (as diligustilide **1**[3]) or [π2s + π2s] (as riligustilide **2**[4]) cycloadditions of the monomeric phthalides or derivatives (for **1** and **2**: *Z*-ligustilide **3**). These plant metabolites are interesting not only because they are pharmacologically important natural products, but also because they have unique molecular architectures. Although several reports have been devoted to isolation of phthalide derivatives,[5] and some synthetic[6] and chemical studies[7] have been performed on the monomeric phthalides, a chemical overview of the dimeric derivatives is still lacking.

Several years ago, we proposed that the structure of 3,8-dihydrodiligustilide (**4**, unknown stereochemistry at C-3), a dimeric phthalide isolated from the Chinese medicinal plant *Ligusticum wallichi*[8] should be revised to **5**. This revision was based on a reassignment of the NMR spectroscopic data, and in particular by comparison with the NMR spectroscopic data of **6**, a reduction product of diligustilide (**1**), a

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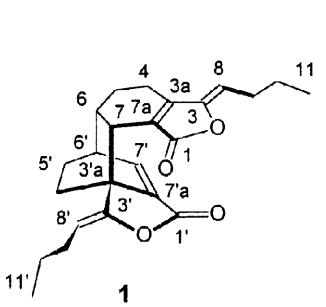
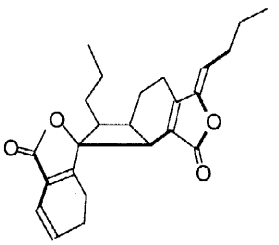
compound isolated from *L. porteri*.[9,10] Herein we describe that the [π4s + π2s] reaction of *Z*-ligustilide (**3**) affords **1**, which is converted to **5** and **7**, confirming the revised structure of **5**. In addition, wallichilide (**8**), also a constituent of *L. wallichii*,[11] was obtained by selective methanolysis of diligustilide (**1**).



1



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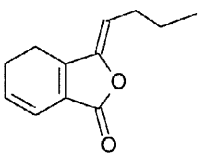

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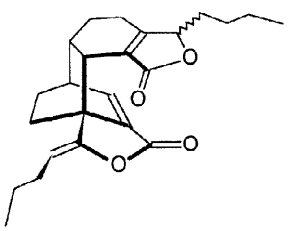

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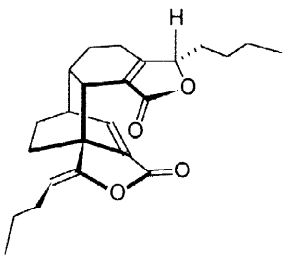

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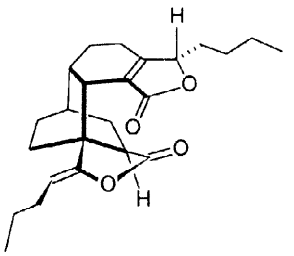

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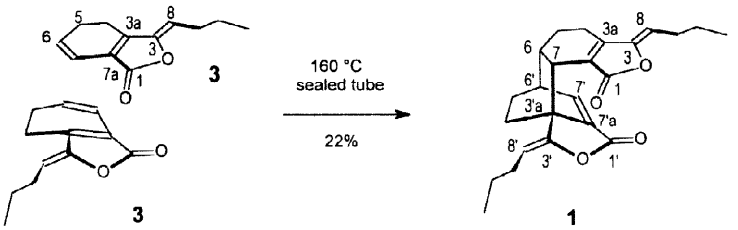
Results and discussion

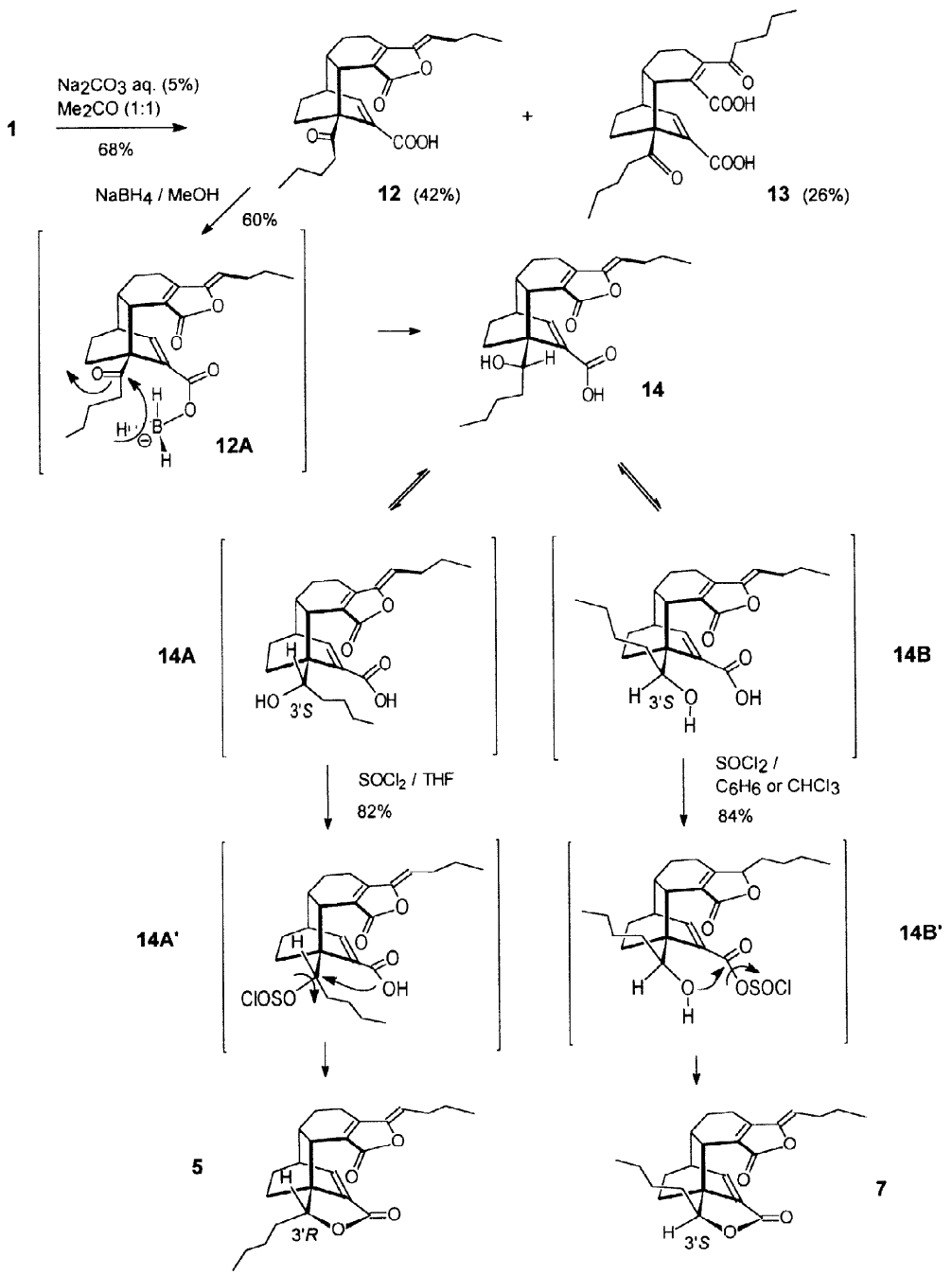
An appropriate starting material for the synthesis appeared to be (*Z*)-ligustilide (**3**), a natural product isolated in our laboratory from *L. porteri*,[9] and the biogenetic precursor of **1**. *Z*-ligustilide (**3**) reacts with maleic anhydride to afford the Diels-Alder adduct,[12] and therefore, a reduced reactivity would be expected using **3** both as diene and dienophile. Lewis acid catalysis ($TiCl_4$, BF_3 or $SnCl_4$) did not provide cycloaddition products, and some polymeric material invariably formed. Using water as solvent also failed to perform the Diels Alder reaction.[13] However, thermal reaction of **3** for 40 h at 160 °C in sealed tubes allowed conversion into diligustilide (**1**), demonstrating the regio- and stereo- preference of the reaction (Scheme 1). The identity of **1** was confirmed by direct comparison with an authentic sample from our laboratory, and natural **1** was used for subsequent conversions to **5**, **7** and **8**. An independent report on the thermal dimerization of *Z*-ligustilide (**3**) was recently published.[14]

Attempts to selectively reduce the 3',8' double bond of **1** proved unsuccessful. Direct catalytic hydrogenation of **1** afforded **6** and **9**,[9] and treatment of **1** with diborane under a variety of conditions resulted in the isolation of starting material. In view of these results, it was envisaged that an effective synthesis of **5** from **1** would then require stereoselective lactone ring opening to afford the ketone at C-3', stereoselective reduction of the ketone, and relactonization, as outlined in Scheme 2.

Scheme 1

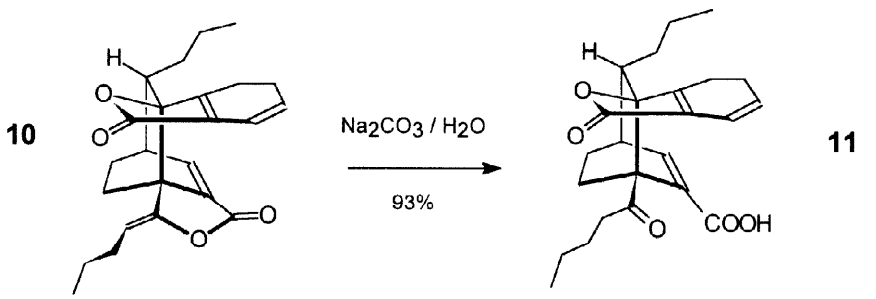


Scheme 2



It was anticipated that the lactone moiety fused to the bicyclic system of **1** would be more reactive due to torsional strain. This assumption was in accord with the hydrolysis of angeolide (**10**), which afforded the keto acid **11** (Scheme 3).[15]

Scheme 3

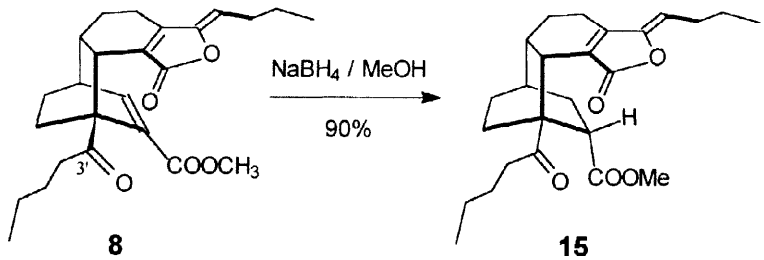


Treatment of diligustilide **1** under these reaction conditions led to a mixture of **12** and **13** (Scheme 2), presumably due to comparable rates of nucleophilic attack on both carbonyl groups. A 1.6:1 mixture of demethylwallichilide (**12**) and **13** was obtained after chromatography. The structure of **12** was confirmed by X-Ray analysis.[16] Treatment of demethylwallichilide (**12**) with $NaBH_4$ in methanol at room temperature gave the desired hydroxy acid **14** (Scheme 2). The chemical shift of H-3' in **14** (δ 4.49) is in agreement with the *rel*-3'*S* configuration, as previously discussed.[9] Diastereofacial selectivity in the reduction of **12** appears to be a consequence of borohydride complexation with the carboxylic acid, and the ketonic carbonyl (oriented *exo*- in the preferred conformation in methanol, **12A**) is reduced at the *re*- face to produce the *rel*-(3'*S*)-hydroxy acid **14** (Scheme 2). Evidence supporting this proposal was obtained by the observation that the C-3' carbonyl of wallichilide **8** (obtained as described below) was not reduced with sodium borohydride under these conditions. In fact, keto ester **15** was obtained (Scheme 4) in this reaction. The unreactivity of the C-3' carbonyl of **8** toward reduction is likely related to increased steric hindrance of the ketone and presumably to the lack of complexation of the reducing reagent. Using the $NaBH_4/CeCl_3$ complex[17] to avoid the 1,4-reduction under different conditions failed to reduce the ketone of **8**, yielding only recovered starting material.

Lactonization of the hydroxy acid **14** was accomplished in nearly quantitative yield using thionyl chloride, tosyl chloride or mesyl chloride. The stereochemistry of the product was found to be solvent dependent (Scheme 2). When THF was used as the solvent, the product was *rel*-(3'*R*)-3',8'-dihydrodiligustilide (**5**),[10] but when the reaction was carried out using chloroform or benzene as solvent, the product was *rel*-(3'*S*)-3',8'-dihydrodiligustilide (**7**). The stereochemistry of **5** and **7** was rigorously established by COSY and NOESY experiments. In particular the observed NOE between H-3' and H-7, and the chemical shift for H-3' (δ 5.11, deshielded by the carbonyl at C-1)[7] in **5** supported the assigned relative configuration. In contrast, the upfield chemical shift of H-3' (at δ 4.38, due to the lack of deshielding effect),

supports the stereochemistry *rel*-3'*S* in **7**. The spectroscopic data of **5** were found to be indistinguishable to those reported for the natural product,[8-10] confirming the revised structure **5**[9] for the secondary metabolite of *L. wallichii*[8] and *L. chuangxiong*.[10]

Scheme 4



8 **15**

The results of the lactonization reaction might be explained by assuming two reaction mechanisms that reflect easier approach of the electrophile to the active site-oxygen. Presumably in THF the preferred conformation is **14A**, where the secondary alcohol is exposed to the solvent (the hydroxyl *exo*- and *anti*- to the C(3'a)-C(7'a) σ bond) and then the electrophile activates the alcohol for an S_N2-type displacement mechanism, with inversion at C-3' (**14A'**, Scheme 2). In contrast, in non polar solvents (chloroform and benzene), **14** presumably exists in the conformation **14B** (the *n*-butyl *exo*- and *anti*- to the C(3'a)-C(7'a) σ bond), and the electrophile ($SOCl_2$) activates the acid for an addition-elimination reaction (**14B'**, Scheme 2), since the secondary alcohol is hindered (Scheme 2). These results provide stereoselective entries for the two epimers at C-3' of 3',8'-dihydrodiligustilide (**5** and **7**).

Wallichilide (**8**) was quantitatively obtained by methylation of **12**, and its structure was confirmed by X-ray analysis[16] as shown in Figure 1. Compound **8** was also prepared directly from **1** by treatment with Li_2CO_3 in MeOH at 0 °C. Using different bases and higher temperatures for the methanolysis did not improve the yield of **8**. An alternative procedure for the synthesis of wallichilide (**8**) involved the treatment of **1** with $NaBH_4$ in MeOH at room temperature to give **8** (75%), **15** (4%) and an inseparable mixture of minor reduction products. Interestingly, the reaction of **1** with $NaBH_4$ in THF afforded **16**, the product of conjugate addition of hydride to C(7'), in 94% yield (Scheme 5). These results demonstrate the relative reactivities of the unsaturations toward different reducing conditions.

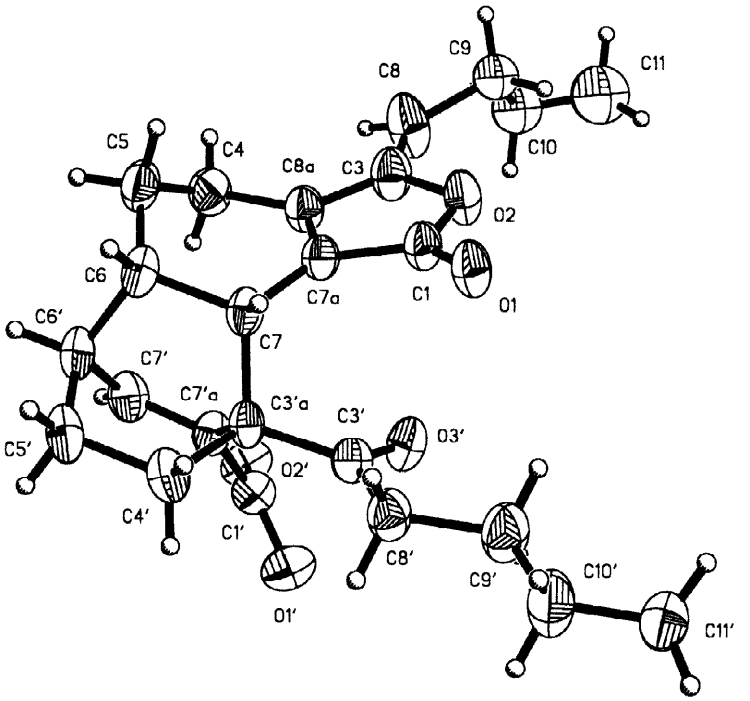
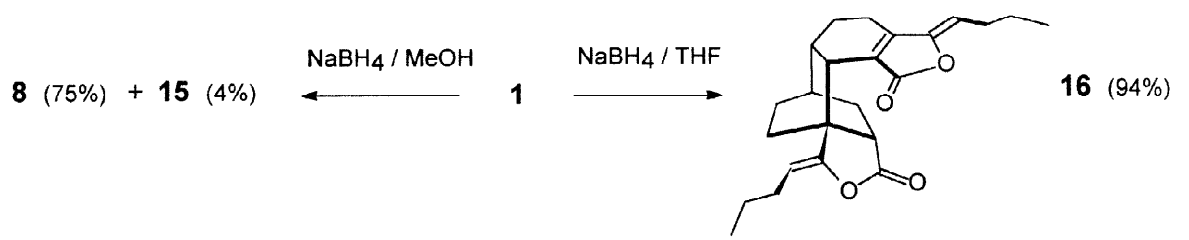


Figure 1. ORTEP view of the molecular structure of Wallichilide (**8**). Thermal ellipsoids are drawn at the 30% probability level.

Scheme 5



Conclusions

We have shown that diligustilide (**1**), the two epimers of 3',8'-dihydrodiligustilide **5** and **7**, and wallichilide (**8**) can be prepared from *Z*-ligustilide (**3**). The results show that dimerization of *Z*-ligustilide (**3**) produced diligustilide (**1**), establishing the *regio-* and *stereo-* preferences of the Diels Alder reaction. Sodium borohydride reduction of demethylwallichilide **12** was stereoselective, and the stereochemistry of the products derived from the lactonization of **14** was found to be solvent dependent. The synthesis of **5** confirmed the revised structure of the natural product from *L. wallichii*. Studies intended to synthesize novel analogs of natural phthalides continue to be of interest in our laboratories.

Experimental Section

Melting points were determined on a Fisher Johns apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200, Varian VXR-300 and Varian Unity Plus-500 instruments, and the chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane. Samples for NOE experiments were degassed (freeze, pump, thaw, 3x) and sealed under Argon. Infrared spectra were recorded with a Nicolet Magna IR TM 750 and Perkin Elmer 283B instruments. MS data were recorded with a JEOL JMS-AX 505 HA mass spectrometer. Electron impact mass spectra were obtained at 70 eV ionization energy. Vaccuum chromatography[18] was performed on Merck Kieselgel 60 (0.040-0.863 mm). The eluent is specified in each experiment. All separations were carried out by using distilled solvents. TLC analyses were performed on ALUGRAM® SIL G/UV_{254} silica gel plates. TLC visualization was accomplished with either a UV lamp or a charring solution (12 g of ceric ammonium sulfate dihydrate, 22.2 mL of concentrated H_2SO_4 and 350 g of ice). System used for the X-ray analysis: Siemens SHELXTL PLUS (PC version); solution by direct methods, refinement by full-matrix least squares, quantity minimized: $\sum w(F_o-F_c)^2$. *Z*-Ligustilide (**3**) and diligustilide (**1**) were isolated from the organic extracts of the roots of *Ligusticum porteri* by succesive column chromatographies, as described previously.[9] All reactions were carried out under an atmosphere of nitrogen.

Thermal Treatment of 3. *Z*-Ligustilide (**3**, 60 mg) in a sealed tube was heated for 40 h at 160 °C. The reaction gave an oily residue, and TLC and ^1H NMR analysis (500 MHz) indicated the presence of *Z*-ligustilide (**3**) as the major constituent and diligustilide (**1**) in 22% yield. Column chromatography of this residue using *n*-hexane-EtOAc (20:1) as eluent gave diligustilide (**1**), the identity of which was confirmed by direct comparison with an authentic sample.

Hydrolysis of Diligustilide (1). Preparation of Demethylwallichilide (12) and Diketodiacid (13). To a solution of diligustilide (**1**) (250 mg, 0.65 mmol) in acetone (12 mL) was added a solution of Na_2CO_3 (250 mg) in H_2O (13 mL), and the mixture was stirred under nitrogen at reflux for 3.5 h. The mixture was acidified with diluted HCl (10%, to pH 4) and extracted with ethyl acetate (3x9 mL). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography using mixtures of *n*-hexane-ethyl acetate to obtain diligustilide **1**, (79 mg, 32%), demethylwallichilide (**12**, 105 mg, 42%), and the diketodiacid **13** (65 mg, 26%). **12**: colorless needles (ethyl acetate-*n*-hexane); mp: 184-187 °C, Rf 0.44 (*n*-hexane-ethyl acetate 1:1); UV (MeOH) λ_{max} nm (ε): 273 (28855); IR ($CHCl_3$): 3502, 3005, 2958, 2936, 2872, 2661, 1754, 1707, 1450, 1433, 1408, 1380, 1278 cm^{-1}; ^1H NMR (300 Mz, $CDCl_3$): δ 6.98 (1H, d, J=7.0 Hz, H-7'), 5.09 (1H, t, J=7.8 Hz, H-8), 3.24 (1H, d, J=9.0 Hz, H-7),), 2.97 (1H, ddd, J=8.4, 6.3, 6.0 Hz, H-8'), 2.66 (1H, ddd, J=7.0, 2.4, 2.0 Hz, H-6'), 2.59 (1H, dd, J=8.4, 6.3 Hz, H-8'), 2.53 (1H, dd, J=7.5, 7.5 Hz, H-6), 2.28 (2H, ddd, J=7.7, 7.7, 2.0 Hz, H-4), 2.17 (2H, m, H-9), 1.88 (2H, m, H-5), 1.62 (4H, m, H-4', H-5'), 1.40 (2H, q, J=7,0 Hz, H-10), 1.35 (2H, q, J=7.0 Hz, H-10'), 1.28 (2H, dd, J=7.0, 7.0 Hz, H-9'), 0.93 (3H, t, J=7.0 Hz, H-11), 0.92 (3H. t, J=7.0 Hz, H-11'); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): 209.0 (C-3'), 171.2 (C-1'), 169.3 (C-1), 153.5 (C-3a), 148.4 (C-3), 19.0 (C-4), 142.5 (C-7'), 136.8 (C-7'a), 126.8 (C-7a), 111.4 (C-8), 57.1 (C-3'a), 39.2 (C-7), 38.8 (C-8'), 38.2 (C-6'), 37.7 (C-6), 29.2 (C-4'), 28.5 (C-5), 27.8 (C-9), 27.7 (C-9'), 25.3

(C-5'), 22.2 (C-10, C-10'), 14.0 (C-11), 13.8 (C-11'); EIMS *m/z* 398 [M^+] (1.3 %), 396 [M^+-2H] (1), 380 [M^+-H_2O] (3.1), 351 [M^+-C_2H_5] (1), 257 (11), 192 (28), 191 (68), 190 (86), 161 (51), 148 (100), 105 (33), 79 (18), 77 (25), 57 (17), 55 (22). Crystal data:[16] crystal system: triclinic; space group: P-1; crystal size (mm): 0.40 x 0.30 x 0.10; unit cell dimensions (a, b, c) Å: 8.943(3), 8.991(3), 14.833(4); α = 72.57(2)°, β = 76.21(1)°, γ = 88.95(2)°; volume (A^3): 1103.3(7); *Z*: 2; density (cal. Mg/m^3): 1.199; F(000): 428; diffractometer used: Nicolet P3/F; radiation (λ, Å): CuKα (1.54178 Å); 2θ range: 3 to 105°; scan range (ω):1.40°; standard reflections: 3 measured every 47 reflections; reflections collected: 2721; observed reflections: 1757 ($F > 4.0\sigma(F)$); final R indices (obs. data): R = 8.79%, wR = 13.40%; goodness on fit: 1.65. Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.33; H, 7.59. Found: C, 72.18; H, 7.66. **13** colorless needles (ethyl acetate-*n*-hexane); Rf 0.35 (*n*-hexane-ethyl acetate 1:1); mp: 168-170 °C; UV_{MeOH} λ_{max} nm (ε): 300 (32640), 212 (28533); IR ($CHCl_3$): 3572, 2961, 2936, 2874, 2638, 1697, 1631, 1425, 1352, cm^{-1}; ^1H NMR (300 MHz, CD_3OD): 7.29 (1H, d, J=7.0 Hz, H-7'), 2.87 (1H, m, H-6'), 2.69 (1H, d, J=9.9 Hz, H-7), 2.44 (1H, m, H-6), 2.22 (4H, dd, J=7.8, 7.8 Hz, H-8, H-8'), 2.10 (1H, m, H-4), 1.98 (2H, m, H-5), 1.88-1.72 (2H, m, H-10), 1.66 (2H, m, H-9, H-9'), 1.51 (4H, m, H-9, H-9', H-10), 1.24 (2H, m, H-10'), 1.1 (1H, m, H-4), 0.90 (3H, t, J=7.0 Hz, H-11 or H-11'), 0.89 (3H, t, J=7.0 Hz, H-11 or H-11'); ^{13}C NMR (75 MHz, CD_3OD, DEPT): 203. 7 (C-3, C-3'), 168.3 (C-1), 166.4 (C-1'), 147.9 (C-7'), 144.9 (C-3a), 138.5 (C-7'a), 134.3 (C-7a), 50.9 (C-3'a), 39.7 (C-6), 37.7 (C-7, C-6'), 37.1 (C-8'), 30.5 (C-5), 29.2 (C-9'), 27.0 (C-4', C-9), 26.6 (C-8), 24.9 (C-5'), 23.6 (C-10), 22.5 (C-10'), 21.2 (C-4), 14.7 (C-11 or C-11'), 14.3 (C-11 or C-11'); EIMS *m/z*: 398 [M^+-H_2O] (9), 380 [M^+-$2H_2O$] (67), 351 [M^+-$2H_2O$ - C_2H_5] (100), 323 [M^+-$2H_2O$ - *n*-Bu] (22), 309 (13), 257 (7), 229 (8), 191 (4), 171 (8), 151 (10), 129 (10), 97 (14), 57 (30), 43 (26).

***Rel*-(3'*S*)-(3',8')-dihydrodemethylwallichilide (14).** To a stirred solution of $NaBH_4$ (190 mg, 10 mmol) in methanol (10 mL) was added dropwise a solution of **12** (232 mg, 0.59 mmol) in methanol (10 mL). The resultant mixture was stirred for 2 h at room temperature, decomposed with diluted HCl (10%, to pH 4), and extracted with ethyl acetate (3x25 mL). The combined organic layer was washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the resultant material was purified by column chromatography (*n*-hexane-ethyl acetate gradient) to give recovered **12** (118 mg, 50%) and **14** (84 mg, 36%). The recovered starting material **12** was treated again under the same reaction conditions (twice), improving the total yield of **14** to 60%. **14**: colorless oil; Rf: 0.56 (*n*-hexane-ethyl acetate 3:2); UV (MeOH) λ nm (ε): 275 (5775), 204 (5875); IR ($CHCl_3$): 3401, 2959, 2934, 2872, 1732, 1628, 1458, 1428, 1226, 1209, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.37 (1H, d, J=6.9 Hz, H-7'), 5.16 (1H, t, J=7.8 Hz, H-8), 4.49 (1H, d, J=8.4 Hz, H-3'), 3.34 (1H, d, J=9.3 Hz, H-7), 2.64 (1H, m, H-6'), 2.50 (1H, dd, J=7.8, 7.6 Hz, H-6), 2.32 (2H, m, H-4), 2.15-1.96 (2H, m, H-9), 1.96-1.80 (4H, m, H-4', H-5), 1.70-1.20 (12H, m, H-5', H-8', H-9', H-10', H-9, H-10), 0.92 (3H, t, J=7.3 Hz, H-11 or H-11'), 0.84 (3H, t, J=9.0 Hz, H-11 or H-11'). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ 172.5 (C-1), 169.9 (C-1'), 155.1 (C-3a), 149.0 (C-7'), 148.6 (C-3), 136.8 (C-7'a), 128.1 (C-7a), 112.6 (C-8), 70.3 (C-3'), 49.6 (C-3'a), 39.5 (C-6), 39.3 (C-6'), 38.5 (C-7), 34.4 (C-8'), 29.8 (C-4'), 29.6 (C-5), 27.9 (C-9), 26.0 (C-5'), 22.7 (C-10), 22.3 (C-9', C-10'), 19.6 (C-4), 14.1 (C-11 or C-11'), 13.7 (C-11 or C-11'). EIMS *m/z*: 282 [M^+-16] (1.8), 193 (100), 192 (94), 191 (97), 190 (73), 175 (11), 161 (32), 149 (38), 148 (90), 135 (16), 107 (92), 105 (32), 91 (38), 85 (23), 79 (48), 77 (55), 71 (19), 69 (19), 57 (20), 55 (35), 43 (30), 41 (27).

***Rel*-(3'*R*)-3',8'-dihydrodiligustilide (5).** To a stirred solution of **14** (100 mg, 0.25 mmol) in THF (5 mL) at room temperature was added $SOCl_2$ (0.3 mL). After 15 min water was added and the mixture was extracted with ethyl acetate (3x20 mL), and the combined organic layer was washed with $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. Column chromatography (*n*-hexane-ethyl acetate gradient) of the residue gave dilactone **5** (79 mg, 82%) as a pale yellow oil. **5:** Rf: 0.50 (*n*-hexane-ethyl acetate, 3:2); UV (MeOH) λ_{max} nm (ε): 282 (7818), 220 (9808); IR ($CHCl_3$): 2961, 2936, 2876, 1770, 1750, 1466, 1267, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.31 (1H, d, J=6.3 Hz, H-7'), 5.18 (1H, t, J=7.8 Hz, H-8), 5.11 (1H, dd, J=9.6, 2.7 Hz, H-3'), 3.02 (1H, d, J=8.4 Hz, H-7), 2.95 (1H, ddd, J=6.6, 5.1, 2.4 Hz, H-6'), 2.47 (1H, m. H-6), 2.33 (2H, dd, J=15.0, 8.1 Hz, H-9), 2.22-2.12 (2H, m, H-4), 1.92.1.82 (3H, m, H-4', H-5, H-8'), 1.82-1.70 (2H, m, H-5', H-8'), 1.66-1.52 (3H, m, H-4, H-5, H-4'), 1.52-1.34 (7H, m, H-5', H-9', H-10, H-10'). 0.94 (3H, t J=7.2 Hz, H-11 or H-11'), 0.93 (3H, t, J=6.9 Hz, H-11 or H-11'). NOESY experiments indicated correlation between H-7 (δ 3.02) and H-3'(δ 5.11). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): 170.5 (C-1), 167.6 (C-1'), 156.1 (C-3), 148.3 (C-3a), 141.8 (C-7'), 135.9 (C-7'a), 126.0 (C-7a), 113.2 (C-8), 84.3 (C-3'), 48.3 (C-3'a), 40.6 (C-6'), 39.8 (C-7), 39.0 (C-6), 32.0 (C-8'), 28.7 (C-5), 28.7 (C-9'), 28.0 (C-9), 25.8 (C-5' y C-4'), 22.5 (C-10'), 22.3 (C-10), 19.7 (C-4), 14.0 (C-11'), 13.8 (C-11). EIMS *m/z*: 382 [M^+] (3.8), 366 [M^+-16] (2), 193 (100), 192 (56), 191 (32), 190 (83), 161 (25), 148 (52), 137 (8), 107 (41), 105 (11), 91 (12), 85 (13), 79 (14), 77 (12), 57 (17), 55 (16), 43 (13), 41 (12). Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.09; H, 7.79.

***Rel*-(3'*S*)-3',8'-dihydrodiligustilide (7). Method A**. To a stirred solution of **14** (103 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) maintained at 0°C was added pyridine (0.3 mL) and mesylchloride (0.3 mL, 3.8 mmol). The reaction was quenched after 15 min with the addition of diluted HCl (10%) and the organic layer was washed with saturated $NaHCO_3$, brine and dried (Na_2SO_4). Evaporation of the organic residue yielded **7** (83 mg, 84%). The same product was obtained using tosyl chloride instead of mesyl chloride affording the same yield. **Method B**. To a stirred solution of **14** (110 mg, 0.277 mmol) in benzene (5 mL) at room temperature was added dropwise $SOCl_2$ (0.3 mL). The solution was stirred for 15 min and water was added to decompose excess reagent. The mixture was extracted with ethyl acetate (3x20 mL), and the organic phase was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. Column chromatography of the product (*n*-hexane-ethyl acetate, 7:3) yielded of dilactone **7** (90 mg, 86%) as a pale yellow oil; Rf: 0.50 (*n*-hexane-ethyl acetate 3:2); UV (MeOH) λ_{max} nm (ε): 281 (8323), 245 (4552). IR ($CHCl_3$): 2959, 2934, 2874, 1869, 1466, 1261 cm^{-1}; ^1H NMR (500 Mz, $CDCl_3$, COSY): δ 7.35 (1H, d, J=6.5 Hz, H-7'), 5.14 (1H, t, J=8.0 Hz, H-8), 4.38 (1H, dd, J=10.5, 4.2 Hz, H-3'), 3.25 (1H, d, J=8.0 Hz, H-7), 2.99 (1H, m, H-6'), 2.52 (1H, dd, J=7.5 Hz, H-6), 2.31 (2H, dd, J=15.5, 8.0 Hz, H-9), 2.27-1.12 (1H, m, H-9'), 2.08-1.94 (3H, m, H-5' y H-9'), 1.94-1.84 (2H, m, H-4, H-5'), 1-60-1.50 (1H, m, H-4), 1.50-1.20 (8H, m, H-4', H-5, H-10', H-10), 0.94 (3H, t, J=7.2 Hz, H-11 or H-11'), 0.93 (3H, t, J=7.2 Hz, H-11 or H-11'). ^{13}C NMR (125 MHz, $CDCl_3$, DEPT,): δ 169.3 (C-1), 167.8 (C-1'), 156.9 (C-3a), 148.0 (C-3), 142.9 (C-7'), 136.7 (C-7a), 127.0 (C-7'a), 112.5 (C-8), 90.0 (C-3'), 49.7 (C-3'a), 41.3 (C-6'), 39.6 (C-6), 39.5 (C-7), 31.6 (C-8'), 29.8 (C-4 y C-5'), 29.0 (C-5), 27.9 (C-9), 26.6 (C-4'), 22.3 (C-10), 22.2 (C-10'), 20.5 (C-9'), 13.8 (C-11 or C-11'), 13.7 (C-11 or C-11'). Assignments were confirmed by the correlations observed in the HMQC and HMBC experiments. EIMS *m/z*: 382 [M^+] (1.5%), 339 [M^+-

C_3H_7] (1.0), 193 (66), 192 (54), 190 (67), 161 (23), 148 (68), 124 (22), 107 (100), 105 (27), 91 (19), 79 (26), 77 (34), 57 (22), 55 (28). Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.22; H, 8.07.

Methanolysis of 1 with Li_2CO_3. Preparation of Wallichilide (8). To a stirred solution of **1** (50 mg, 0.132 mmol) in methanol (7 mL) at 0°C, was added a mixture of the base (Li_2CO_3, 100 mg) in methanol (3 mL). The reaction was maintained for 15 min at 0°C, filtered, and the filtrate was diluted with water and neutralized with diluted HCl (10%). This mixture was extracted with ethyl acetate (4x20 mL), and the organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (*n*-hexane-ethyl acetate gradient) to afford diligustilide (**1,** 4 mg 8%), wallichilide (**8,** 32 mg, 60%), and a mixture of minor products. Using K_2CO_3 or Cs_2CO_3 instead of Li_2CO_3 did not improve the yield of **8**. **8:** Mp: 163 - 164.5°C,[8] Rf: 0.47 (*n*-hexane-ethyl acetate 7:3); UV (MeOH) λ_{max} nm (ε): 272 (4236), 203 (7882); IR ($CHCl_3$): 2958, 2900, 2873, 1757, 1723, 1632, 1454, 1435, 1367, 1275, 1171 cm^{-1}; ^1H and ^{13}C NMR data were identical with those reported in the literature.[8,10] Crystal data (see also Figure 1 and supplementary material):[16] crystal system: triclinic; crystal size (mm): 0.48 x 0.36 x 0.20; space group: p-1; unit cell dimensions (a, b, c)Å: 8.875(1), 8.991(1), 13.764(2); $\alpha = 91.84(0)^\circ$, $\beta = 93.80(0)^\circ$, $\gamma = 91.21(0)^\circ$; volume (A^3): 1095.1(2); *Z*: 2; density (cal. Mg/m^3): 1.251; F(000): 444; diffractometer used: Siements P4/PC; radiation (λ, Å): MoKα (0.71073); 2θ range: 3 to 50°; scan range: 0.80°; reflections collected: 4133; observed reflections: 2270 $F > 4.0\sigma(F)$); final R indices (obs. Data): R = 6.06%, wR = 7.14%.

Preparation of 15. To a stirred solution of sodium borohydride (11 mg, 0.29 mmol) in methanol (10 mL) was added solution of **8** (11 mg, 0.026 mmol) in methanol (10 mL). The mixture was stirred for 15 min at room temperature and the reaction was neutralized with diluted HCl (10%, to pH 4), and extracted with ethyl acetate (x 4, 30 ml), to obtain **15** (10.8 mg, 90%). **15** Rf: 0.4 (n-hexane-ethyl acetate 7:3); IR ($CHCl_3$): 2960, 2886, 2874, 1755, 1728, 1721, 1610, 1362, 1461. 1125, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, COSY): 5.07 (1H, t, J=7.8 Hz, H-8), 3.55 (3H, s, OCH_3), 3.40 (1H, d, J=9.0 Hz, H-7), 3.05 (2H, ddd, J=18.0, 8.4, 6.3 Hz, H-8'), 2.72 (1H, t, J=10.2 Hz, H-6'), 2.51-2.24 (5H, m, H-9, H-6, H-4), 1.90 (2H, m, H-5), 1.66-1.2 (10H, m, H-10', H-9',H-5', H -4', H-10), 0.94 (3H, t, J=7.2 Hz, H-11), 0.91 (3H, t, J=7.0 Hz, H-11'); EIMS *m/z*: 414 [M^+] (1.0%), 399 [M^+-15] (3.0), 386 (6), 385 (7), 382 (6), 288 (41), 148 (100), 105 (28), 148 (63), 124 (12), 107 (75), 105 (11), 91 (12), 79 (16), 55 (22).

Attempted Reduction of 8 with $NaBH_4/CeCl_3.7H_2O$. To a stirred solution of wallichilide (**8**, 92.3 mg, 0.22 mmol) in THF (45 mL) at 0°C was added a solution of $CeCl_3 7H_2O$ (270 mg, 0.72 mmol) in methanol (7 mL). The mixture was stirred at 0°C for 5 h, and no change was observed. Heating of the solution to room temperature for 8 h also resulted in no observable change. After subsequent addition of $NaBH_4$ (10 mg, 0.27 mmol) to the reaction mixture, this was allowed to stand at room temperature for 2 h, then diluted with water (30 mL), concentrated at reduced pressure and extracted with ethyl acetate (3x25 mL). The organic layer was washed, dried, evaporated and examined by ^1H NMR. This showed **8** as the only product. The same results were obtained using *p*-dioxane instead of THF as solvent.

***Rel*-(7a'*S*)-7',7a'dihydrodiligustilide (16).** To a stirred solution of sodium borohydride (4 mg, 0.12 mmol) in THF (5 ml) was added dropwise a solution of diligustilide (**1**, 20 mg, 0.54 mmol) in THF (10 ml). The mixture was stirred at room temperature for 40 min and diluted with water (15 mL). The mixture was extracted with ethyl acetate (3x20 ml) and the combined organic layer was washed with brine, dried (Na_2SO_4) and evaporated at reduced pressure, to afford **16** (19 mg, 94%) as a pale yellow oil. Rf: 0.56 (*n*-hexane-ethyl acetate 4:1); UV (MeOH) $\lambda_{max.}$ nm (ε): 287 (1892), 241 (5966), 222 (16007). IR (film): 2958, 2929, 2873, 1801, 1773, 1728, 1463, 1273, 1124 cm^{-1}. IR ($CHCl_3$): 2962, 2933, 2874, 1774, 1720, 1464, 1279, 1128 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 5.15 (1H, t, J=7.8 Hz, H-8), 4.72 (1H, t, J=7.5 Hz, H-8'), 2.93 (1H, d, J=9.6 Hz, H-7), 2.57 (1H, ddd, J=12.6, 5.4, 2.5 Hz, H-6'), 2.48 (1H, m, H-6), 2.33 (1H, dd, J=15.3,8.1 Hz, H-7'a), 2.22 (1H, m, H-4'), 2.13 (2H, m), 2.0-1.94 (m), 1.94-1.90 (m), 1.88-1.80 (m), 1.70-1.32 (m), 0.94 (3H, t, J=7.2 Hz, H-11 or H-11'), 0.92 (3H, t, J=7.2 Hz, H-11 or H-11'). EIMS *m/z*: 382 [M^+] (14), 380 [M^+-2H] (28), 354 [M^+-CO] (10), 343 (27), 342 (52), 314 (90), 313 (47), 285 (33), 279 (18), 270 (30), 258 (29), 228 (20), 214 (9), 191 (22), 167 (42), 163 (89), 149 (100), 129 (15), 107 (58), 91 (25), 83 (38), 79 (37), 77 (24), 61 (40), 57 (38), 55 (83), 43 (38), 41 (31).

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