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Shaobai Li [a], Zhiwei Wang [a], Xiaoping Fang [a b] & Yulin Li [a]

[a] State Key Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou, 730000

[b] Department of Chemistry, Huizhou Normal College

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Synthesis of (*Z*)–Ligustilide

Shaobai LI * Zhiwei WANG Xiaoping FANG * * Yulin LI

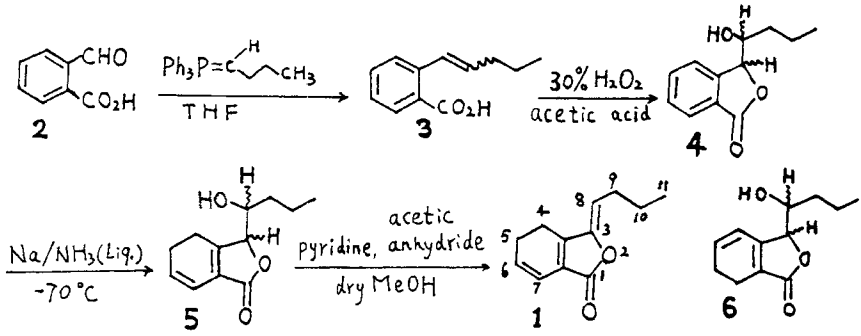
State Key Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry,Lanzhou University,Lanzhou 730000.

Abstract: The first synthesis of ligustilide (**1**) is described, starting from 2–formylbenzoic acid (**2**). The key step in synthesis is the Birch reduction of 3–hydroxybutyl–phthalide (**4**).

(*Z*)–Ligustilide(**1**) was first isolated from the roots of Hokkai–Toki,a variety of *Ligusticum acutilobum* Sieb. et Zucc in 1960[1]. Its structure was proven to be **1**[2]. Compound **1** is an important naturally 3–alkylphthalide analogue occurring in many plants belonging to the Umbelliferae[2–7] . The compound has antispasmodic, antiasthmatic and smooth muscle relaxing activities [8] . Herein we wish to describe the first synthesis of **1** starting from 2–formylbenzoic acid (**2**) .

* To whom correspondence should be addressed.

* * Visiting scholar from Department of Chemistry, Huizhou Normal College.



In our method 2–formylbenzoic acid(**2**) reacted with n–butyl–idenetriphenylphosphorane, generated in situ from n–butyltriphenyl–phosphonium bromide[9] and potassium tert–butoxide, to provide 2–pentenyl benzoic acid (**3**) in 74% yield, as mixture of *E*–and *Z*–isomers (1:1 ^{1}H NMR). The isomere mixture of **3** was dissolved in glacial acetic acid and treated with a solution of 30% hydrogen peroxide to give the desired 3–hydroxybutyl phthalide (**4**) in excellent yield. Its ^{1}H NMR spectral data indicated it to be a mixture of erythro– and threo–isomers (3:2). Birch reduction of **4** with sodium / liq. ammonia at −70℃ furnished 3–hydroxy – butyl–4,5–dihydrophthalide (**5**) in 60% yield, as mixture of erythro– and threo–isomers(1:1). Its UV[281nm (ε, 3100)] and ^{1}H NMR [δ5.92(1H, dt, J=9.7, 4.6Hz, 6–H), 6.16(1H, br, d, J=9.7Hz, 7–H] spectra were similar to those of senkyunolide–G [UV, 281nm (ε 3200). ^{1}H NMR, δ5.97(1H, dt, J=9.8, 3.0Hz, 6–H), 6.17(1H, br, d, J=9.8Hz, 7–H)][5]. Approximating calculation show that UVλ_{max} of **6** should be 297nm. These results indicate that a cross–conjugated diene is presence. The structure of 1,3–cyclohexadiene, generated from aromatic compounds using sodium / liq. ammonia, has been reported by LI Shaobai et al[10]. Dehydration of **5** with dry pyridine and acetic anhydride[11] led to the title compound **1**. The spectral data of **1** are consisent with those of the natural product[3,4,6]. The chemical shift of H–8(δ5.22ppm) is an indication for the(*Z*)– configuration (*E*–: δ5.73ppm)[3,6].

Experimental

IR spectra were recorded on a Nicolet 170SX FT–IR spectrometer. ^{1}H NMR spectra were obtained with a FT–400A spectrometer using

tetramethylsilane as internal standard. Mass spectra(70eV) were determined on a ZAB–HS spectrometer.

2–Pentenylbenzoic acid (**3**)

A solution of potassium–tert–butoxide in t–butyl alcohol (prepared from 0.65g of potassium in 20 mL t–butyl alcohol) was added to a stirred suspension of n–butyltriphenylphosphonium bromide (4.8g, 0.012 mol) in THF (30mL) under argon atomosphere over a period of 5 min. An orange coloured solution thus obtained was stirred for 20 min. and a solution of 2–formylbenzoic acid (**2**) (1.5g, 0.01 mol) in THF (20 mL) was added to it. The reaction mixture was stirred for 1 hr. at room temperature and decomposed with water (20 mL). Tetrahydrofuran and t–butyl alcohol were evaporared under reduced pressure. The residual aqueous layer was acidified to pH = 1 with 4*M* HCl aq. and extracted with ether (3 × 30 mL). The ether layer was dried (Na_2SO_4) and evaporated to give a residue. The residue was purified by flash column chromatography over silica gel(40g, 200–300 mesh) using ethyl acetate–petroleum ether (1:30) as an eluent to give a yellowish oil of **3** , a 1:1 mixture of *E*–and *Z*– isomers(1.4g, 74%). ν_{max}(cm^{-1}):3365–2872 (COOH), 3065, 1688(C = O), 1598. δ_H(ppm): 0.90, 0.99 (6H, 2t, J = 7.4, 6.8Hz, CH_3 of *E*– and *Z*–), 1.50 (4H, m, CH_2–CH_3 of *E*– and *Z*–), 2.18 (4H, m, =CH–CH_2 of *E*– and *Z*–), 5.76 (1H, dt, J = 11.6, 7.3Hz, =**CH**–CH_2 of *Z*–), 6.16 (1H, dt, J = 15.7, 6.8Hz, =**CH**–CH_2 of *E*–), 6.96 (1H, d, J = 11.6Hz,Ar–**CH**= of *Z*–), 7.15–8.15 (9H, m, Ar–H of *E*– and *Z*– plus Ar–**CH**= of *E*–). *m / z* (FAB): 191 ($[M+1]^+$, 100), 173 ($[M-19]^+$, 50), 145 ($[M-45]^+$, 55). R_f0.68(acetone: petroleum ether = 1:3).

3–Hydroxybutyl phthalide (**4**)

0.38g (2 mmol) **3** was dissolved in glacial acetic acid (7 mL) and a solution of 30% hydrogen peroxide (7mL) was added to it. The reaction mixture was stirred for 3 days at room temperature. Acetic acid was removed under reduced pressure. The residue extracted with ether (3 × 20 mL). The ether layer was washed with brine and water, respectrively, dried ($MgSO_4$) and evaporated to give a yellowish oil of **4** , a 3:2 mixture of erythro– and threo–isomers(0.40g, 97%). ν_{max}(cm^{-1}): 3389(OH), 1749 (C = O), 1615. δ_H(ppm): 0.91, 0.92 [3H, 2t(3:2), J = 7.2, 7.1Hz, CH_3 of erythro– and threo–], 1.3–1.6 (4H, m, –CH_2–CH_2– of erythro– and threo–), 2.5 (1H, br, s, OH of erythro– and threo–, D_2O exchangeable), 3.92, 4.00 [1H, 2m(3:2), **CH**–OH of erythro–

and threo–], 5.38, 5.40 [1H, 2d(3:2), J=4.9, 3.4Hz, Ar–CH of erythro– and threo–], 7.5–7.9 (4H, m, ArH of erythro– and threo–). m/z: 207([M+1]$^+$, 2), 189([M−17]$^+$, 3).R_f0.55(acetone: petroleum ether = 1:3).

3–Hydroxybutyl–4,5–dihydrophthalide (**5**)

Sodium (0.14g, 6.1 mmol) was added to a stirred solution of **4** (0.3g, 1.45 mmol) and t–butylalcohol (0.37g, 5.0 mmol) in dry ammonia (50mL). The blue reaction mixture was stirred for 3hr. at −70℃. Ammonium chloride was added, untill the blue decoloured. Ammonia was allowed to evaporate at room temperature. The residue was poured into ice–water (40mL), acidified with 10% HCl aq.to pH = 1 and extracted (3 × 20mL) with ether. The organic layer was washed with brine and water, dried ($MgSO_4$) and evaporated to give a residue. The residue was purified by flash column chromatograph over silica gel(4g,200–300 mesh) using acetone–petroleum ether(1:20) as eluent to give a colourless oil of **5**, a 1:1 mixture of erythro– and threo– isomers (180mg, 60%). UV$\lambda_{max}^{CHCl_3}$ nm(ε):281(3100).υ_{max}(cm^{-1}): 3423(OH), 1740(C=O). δ_H(ppm): 0.92, 0.94 [3H, 2t(1:1), J=7.3Hz, CH_3 of erythro– and threo–], 1.60 (2H, m, –CH_2–CH_3 of erythro– and threo–), 2.4–2.6 (6H, m, 4–H, 5–H and –CH_2–Et of erythro– and threo–), 2.27 (1H, br, s, OH of erythro– and threo–, D_2O exchangeable), 3.85 (1H, m, CH–OH of erythro– and threo–), 4.88, 4.92 [1H, 2d(1:1), J= 6.0, 1.0 Hz, 3–H of erythro– and threo–], 5.92 (1H, dt, J=9.7, 4.6Hz, 6–H of erythro– and threo–), 6.16 (1H, br, d, J=9.7Hz, 7–H of erythro– and threo–). m/z (FAB): 209([M+1]$^+$, 100). HRMS : Found : 208.1093. Calcd for $C_{12}H_{16}O_3$(M^+) = 208.1099. R_f0.54(acetone: petroleum ether = 1:3).

(Z)–Ligustilide (**1**)

To a stirred solution of **5** (85mg, 0.41 mmol) in dry pyridine (4mL) under argon at room temperature was added 1.6 mL of acetic anhydride. After 4 hr., the reaction mixture was cooled in an ice–water bath and diluted with 8mL of methanol. The resulting solution was stirred for 7hr. at room temperature. A saturated aqueous solution of sodium bicarbonate was added dropwise, till the solution was neutral. The solution was extracted with ether (3 × 15mL). The organic extracts was washed with brine and water, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatograph over silica gel(1g, 200–300 mesh) using acetone–petroleum ether (1:20) as an eluent to give a yellowish oil of **1** (40mg, 50%). υ_{max}(cm^{-1}): 3052, 1766(C=O),

1668. (The infrared spectrum of **1** was completely identical with that of the natural product.) δ_H(ppm): 0.95 (3H, t, J=7.3Hz, CH_3), 1.50 (2H, sext, J=7.3Hz, CH_2–CH_3), 2.37 (2H, dt, J=8.0, 7.3Hz, 9–H), 2.46 (2H, m, 5–H), 2.60 (2H, t, J=9.5Hz, 4–H), 5.22 (1H, t, J=8.0Hz, 8–H), 6.00 (1H, dt, J=9.6, 4.3Hz, 6–H), 6.29 (1H, dt, J=9.6, 2.0Hz, 7–H). m/z (FAB): 191([M+1]$^+$, 100). HRMS : Found : 190.1003, Calcd for $C_{12}H_{14}O_2$ (M^+) = 190.0994. R_f0.79 (acetone: petroleum ether = 1:3).

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References:

1. H. Mitsuhashi, U. Nagai, T. Muramatsu, H. Tashiro. *Chem. Pharm. Bull.* **1960, 8,** 243.
2. H. Mitsuhashi, U. Nagai, *Tetrahedron,* **1963, 19,** 1277.
3. S. K. Banerjee, B. D. Gupta, W. S. Sheldrick, G. Höfle, *Liebigs Ann. Chem.*, **1982,** 699.
4. W. Pushan, G. Xuanling, W. Yixiong, Y. Fukuyama, I. Miura, M. Sugawara, *Phytochemistry,* **1984, 23,** 2033.
5. M. Kobayashi, M. Fujita, H. Mitsuhashi, *Chem. Pharm. Bull.* **1987, 35,** 1427.
6. F. C. Fischer. M. J. M. Gijbels, *Planta medica,* **1987, 53,** 77; CA,107:217346e.
7. C. Yaozu, Z. Huidi, *Gao Deng Xue Xiao Hua Xue Xue Bao,* **1984, 5,** 515; CA, 102:3223k.
8. C. Yaozu, D. Zhixing, Z. Huidi, Lanzhou daxue xuebao, **1984, 20,** 158.
9. K. S. Mali, S. R. Patil, *Syn. Commun,* **1990, 20,** 167.
10. a). L. Shaobai, Z. Shaoming, L. Yulin, *C. N. Patent. Appl:* 92 1 11279.3
    b). L. Shaobai, W. Zhiwei, F. Xiaoping, L. Yulin, *C. N. Patent Appl:* 92 1 11278.5.
11. E. W. Yankee, U. Axen, G. L. Bundy, *J. Am. Chem. Soc.* **1974, 96,** 5865.

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