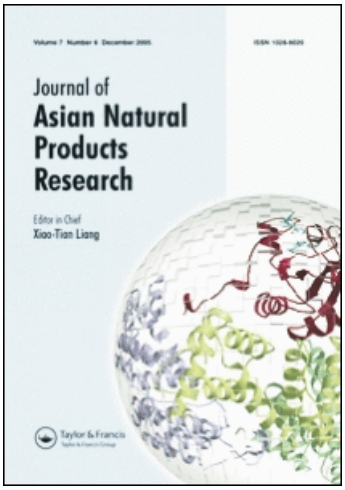

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STUDY OF STEREOSELECTIVE SYNTHESIS OF (±)-NEOCNIDILIDE

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Neocnidilide **1**, isolated from *Apium graveleues L* (Umbelliferae), has shown activity to inhibit the growth of mycotoxin-producing fungi. An efficient method for the synthesis of the racemic neocnidilide by the stereoselective reaction of hemiacetal **6** with *n*-BuMgBr has been developed.

Keywords: Neocnidilide; Stereoselective; Racemic

INTRODUCTION

Neocnidilide **1** (Fig. 1) is one major constituent of the volatile oil of *Apium graveleues L* (Umbelliferae) and has been found to inhibit the growth and toxin production of mycotoxin-producing fungi [1]. Although the synthesis of lactone **8**, which is a stereoisomer of cnidilide, and lactone **1** has been reported by others [2,3], we would like to report the highly stereoselective synthesis of the racemic form of **1**.

RESULTS AND DISCUSSION

(±)-Neocnidilide **1** was stereoselectively synthesized *via* malonic acid as a starting material in seven steps (Scheme 1).

According to the literature [4], compound **3** was prepared from malonic acid by treatment with acrolein in pyridine at 75–80°C. Reduction of **3** with $LiAlH_4$ gave compound **4**, and the subsequent Diels–Alder reaction of **4** and methyl acrylate in refluxing toluene over one week gave 1(3*H*)-isobenzofuranone **5** in 45% yield [5].

Reduction of **5** with diisobutylaluminium hydride (DIBAH) in THF at −78°C under nitrogen gave hemiacetal **6** in 80% yield [6]. The hemiacetal **6** with *n*-BuMgBr in dry ether under nitrogen at room temperature yielded diol **7** stereoselectively in 90% yield. The highly

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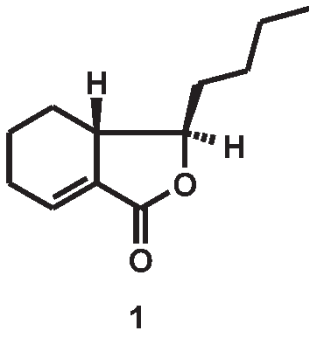
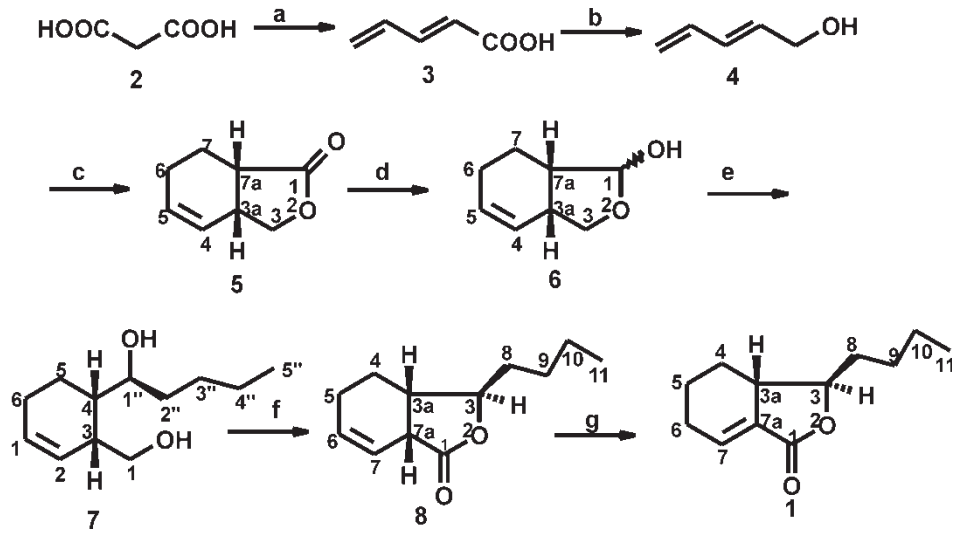


FIGURE 1 Configuration of compound **1**.

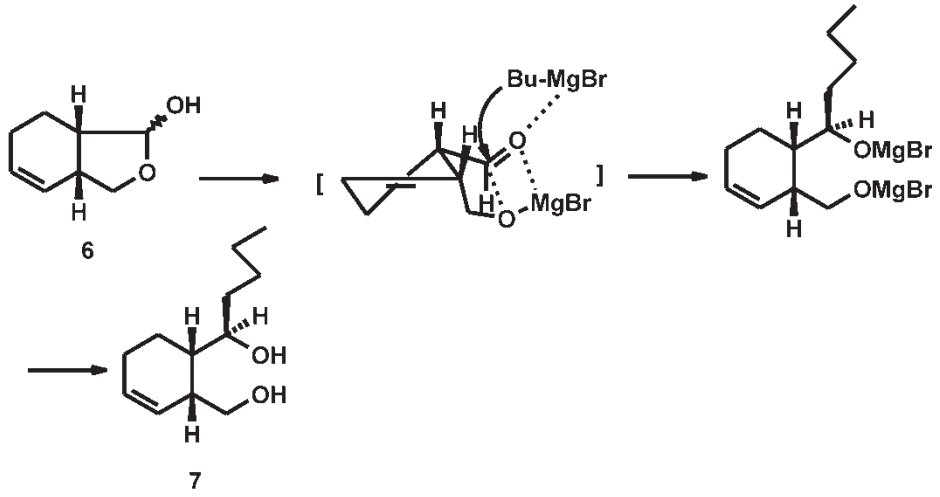
stereoselective reaction of **6** with *n*-BuMgBr could be explained by the following mechanism. Compound **6** can generate a Mg salt, the O–Mg part (with δ^-–δ^+) of which is parallel to the aldehydic C═O (with δ^+–δ^-). One of the two possible alignments has much less steric hindrance (by examination of molecular models), while in the other conformation the Mg atom is too close to the olefin's hydrogen. The favored alignment thus effectively shields one side of the C═O group (*Si*-face) from Bu^- attack. Hence compound **7** was formed as a single racemate as shown in Scheme 2.

The diol **7** was treated with NMO and a catalytic amount of tetrapropylammonium perruthenate (TPAP) in the presence of a molecular sieve in dichloromethane to give **8** in 50% yield [8].

The configuration of compound **8** shown in Fig. 2 was determined by use of the NOE. When irradiating H-3 (δ 4.21), H-7a (δ 3.18) had no NOE enhancement, demonstrating that H-3 was *trans* with H-7a. This is in accordance with the mechanism proposed in Scheme 2.



SCHEME 1 Synthesis of neocnidilide **1**. Reagents and conditions: (a) acrolein, pyridine, 75–80°C, 2.5 h; (b) $LiAlH_4$, Et_2O; (c) methyl acrylate, toluene, reflux, 7 days; (d) DIBAH, THF, N_2, −78°C, 2 h; (e) *n*-BuMgBr, Et_2O, N_2, room temp., 2.5 h; (f) NMO, TPAP, powdered molecular sieve, CH_2Cl_2, 2 h; (g) DBU, toluene, 24 h.



SCHEME 2 Mechanism of the highly stereoselective reaction.

Compound **8** was treated with DBU in refluxing toluene to give (±)-neocnidilide **1** by double bond migration.

EXPERIMENTAL

General Experimental Procedures

NMR spectra were recorded on Varian JEOL.FX-90Q, FX-300 or Varian INOVA-500 spectrometers with TMS as the internal reference. Mass spectra were obtained on a ZAB-2F spectrometer (EI). TLC was carried out on silica gel (GF_{254}). Column chromatography was run on silica gel (160–200 mesh) from Qing Dao Ocean Chemicals.

Compounds **3** *and* **4**. Under a nitrogen atmosphere, a solution of **2** (100 g, 0.96 mol) in pyridine (140 mL) was heated to 75–80°C and acrolein (81 mL, 1.2 mol) was added with stirring. Stirring was continued until the evolution of CO_2 ceased. The cooled solution was poured onto a mixture of 600 g of ice and 82 mL of 98% H_2SO_4, then extracted with CH_2Cl_2, and dried over Na_2SO_4 and evaporated to give **3** (33.6 g) as a slightly yellow solid.

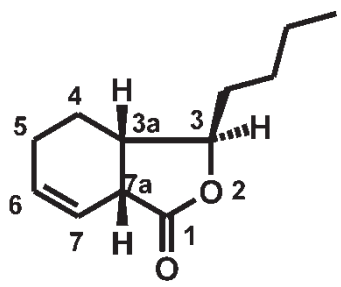


FIGURE 2 Configuration of compound **8**.

To a solution of $LiAlH_4$ (15 g, 0.395 mol) in dry Et_2O (300 mL) was added dropwise the solution of compound **3** (31 g, 0.316 mol) in Et_2O (90 mL) and THF (10 mL) while the temperature was controlled to keep the reaction mixture gently refluxing. The addition was completed within 1 h and the reaction mixture was cooled to 0°C. The reaction mixture was then sequentially treated with EtOAc (5 mL), water (5 mL) and 10% H_2SO_4 (*ca.* 450 mL). The organic phase was separated, then washed sequentially with brine (80 mL), saturated $NaHCO_3$ solution (80 mL), brine (80 mL), and dried over Na_2SO_4. After removal of the solvent, crude product (22 g) was obtained which was distilled *in vacuo* to afford a colorless oil **4** (8.8 g), 76–80°C/6 mmHg.

Compound **5**. To a 250 mL flask was added **4** (3 g, 35.7 mmol) and methyl acrylate (3.07 g, 35.7 mmol) and 150 mL toluene; the solution was then refluxed for 7 days and removal of the solvent gave the crude product (4 g) which was separated by column chromatography (CH_2Cl_2). Compound **5** (2.2 g) was obtained as a colorless oil in 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.92 (m, 1H, H-5), 5.56 (m, 1H, H-4), 4.33 (m, 1H, H-3), 4.03 (m, 1H, H-3), 3.06 (br, 1H, H-7a), 2.80 (m, 1H, H-3a), 2.03–1.76 (m, 4H, H-6, H-7).

Compound **6**. A solution of **5** (1.04 g, 7.5 mmol) in THF (20 mL) was cooled to −78°C under nitrogen. Then 1 mol L^{-1} DIBAH in hexane (11.25 mL, 11.25 mmol) was added dropwise over a period of 15 min. The mixture was stirred for 2 h, and the excess DIBAH destroyed by addition of 30 drops methanol, warmed to room temperature, and stirred for 20 min. Ether (16 mL), brine (16 mL) and saturated NH_4Cl solution (24 mL) were added, the mixture was filtrated and the resultant organic phase separated. The aqueous phase was extracted with ether (20 mL × 3) and the solid was washed with EtOAc. The combined solution was dried over Na_2SO_4; after removal of solvent and purification by column chromatography (PE:EtOAc = 4:1), **6** (842 mg) was obtained as a white solid in 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.80 (m, 1H, H-5), 5.64 (m, 1H, H-4), 5.25 (s, 1H, H-1), 4.25 (t, 1H, J = 7.8 Hz, H-3), 3.61 (t, 1H, J = 7.8 Hz, H-3), 2.95 (br., 1H, H-7a), 2.80 (br., 1H, −OH), 2.24 (m, 1H, H-3a), 2.04–1.50 (m, 4H, H-6, H-7).

Compound **7**. To a 50 mL three-necked flask was added Mg (184 mg, 7.67 mmol) and a little iodine in ether (10 mL), under nitrogen; a little *n*-butyl bromide (in ether) was added to initiate the reaction and the remaining *n*-butyl bromide (total 0.98 mL, 9.12 mmol) (in ether) was then added. After the Mg powder had disappeared, **6** (200 mg, 1.43 mmol) in ether was added at 0°C. After stirring for 2.5 h at room temperature, saturated NH_4Cl was added. The organic phase was separated and the aqueous phase extracted with ether (20 mL × 3). The combined organic phase was dried over Na_2SO_4 and evaporated to give the crude product (320 mg) which was separated by column chromatography (PE:Acetone = 3:1). Compound **7** was obtained as a colorless oil in 90% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.69 (m, 1H, H-1), 5.52 (m, 1H, H-2), 4.8–4.3 (br., 2H, −OH), 3.60–3.44 (m, 3H, H-1′, H-1″), 2.57–1.28 (m, 12H, H-3, H-4, H-5, H-6, H-2″, H-3″, H-4″), 0.92 (t, 3H, J = 7 Hz, H-5″). EI-MS *m*/*z* (%): 198 (M^+, 2), 149 (100), 94 (30), 79 (20).

Compound **8**. Solid TPAP (34 mg, 0.01 mmol) was added to a stirred mixture of the diol **7** (200 mg, 1.01 mmol), NMO (351 mg, 3 mmol) and activated powdered molecular sieves (500 mg) in CH_2Cl_2 at room temperature under argon. After stirring for 2 h, the reaction mixture was purified by column chromatography (PE:EtOAc = 10:1), and **8** (98 mg) was obtained as a colorless oil in 50% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.94 (m, 1H, H-6), 5.80 (m, 1H, H-7), 4.21 (m, 1H, H-3), 3.18 (m, 1H, H-7a), 2.40 (m, 1H, H-3a), 2.04–1.34 (m, 10H, H-4, H-5, H-8, H-9, H-10), 0.92 (t, 3H, J = 7 Hz, H-11). EI-MS *m*/*z* (%):194 (M^+, 43), 148 (100), 106 (28), 93 (82), 79 (99).

Compound **1**. Two drops DBU were added to a solution of **8** (25 mg, 0.13 mmol) in toluene (2 mL). After refluxing for 24 h, the solution was cooled and washed with water. The aqueous

phase was extracted with CH_2Cl_2, and the combined organic phase was dried over Na_2SO_4 and evaporated to give the crude product (30 mg) which was purified by column chromatography (PE:EtOAc = 10:1). Compound **1** (18 mg) was obtained as a colorless oil in 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.77 (m, 1H, H-7), 3.95 (m, 1H, H-3), 2.5–1.1 (m, 13H, H-4, H-5, H-3a, H-6, H-8, H-9, H-10), 0.91 (t, 3H, J = 7.2 Hz, H-11).

References

[1] Suzuki, H., Tanaka, A. and Yamashita, K. (1987), *Agric. Biol. Chem.* **51**, 3369–3373.
[2] Cocker, W., McMurry, T.B.H. and Sainsburg, D.M. (1966), *J. Chem. Soc. (C)*, 1152–1155.
[3] Wang, X.M., Li, S.B. and Li, Y.L. (1996), *Chem. Res. Appl.* **8**(1), 90–92.
[4] Schneider, M.P. and Goldbach, M. (1980), *J. Am. Chem. Soc.* **102**, 6114–6116.
[5] Corey, E.J. and Petrzilka, M. (1975), *Tetrahedron Lett.* **30**, 2537–2540.
[6] Grieco, P.A. (1972), *J. Org. Chem.* **37**(14), 2363–2364.
[7] Bloch, R. and Brillet, C. (1991), *Synlett*, 829–830.