Chinese Chemical Letters Vol. 14, No. 2, pp 127 – 129, 2003
http://www.imm.ac.cn/journal/ccl.html

Stereoselective Synthesis of (±) Neocnidilide

Xiao Zhen JIAO, Ping XIE*, Lian Suo ZU, Xiao Tian LIANG

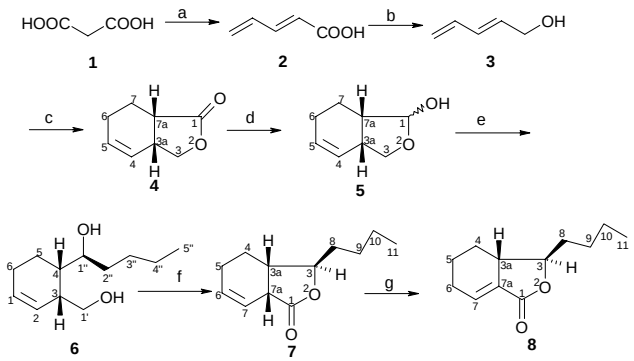
Institute of Materia Medica, Chinese Academy of Medical Sciences
& Peking Union Medical College, Beijing 100050

Abstract: The racemic neocnidilide has been synthesized by stereoselective reaction of hemiacetal **5** with *n*-BuMgBr.

Keywords: Neocnidilide, stereoselective, synthesis.

The lactone neocnidilide **8** occur in the roots of *Cnidilide officinale*[1] which is shown to inhibit the growth and toxin production of mycotoxin-producing fungi[2]. Although The synthesis of lactones **7,** which is stereoisomer of cnidilide, and **8** had been reported by others[3, 4], we would like to report the highly stereoselective synthesis of its racemic isomer **8** as shown in **Scheme 1**.

Scheme 1



Reagents and Conditions: a)acrolein, pyridine, 75-80°C; b)$LiAlH_4$, Et_2O; c)methyl acrylate, toluene, reflux; d)DIBAH, toluene, N_2, -78°C; e)*n*-BuMgBr, THF, r.t.; f)NMO, TPAP, powdered molecular sieve, CH_2Cl_2; g) DBU, toluene.

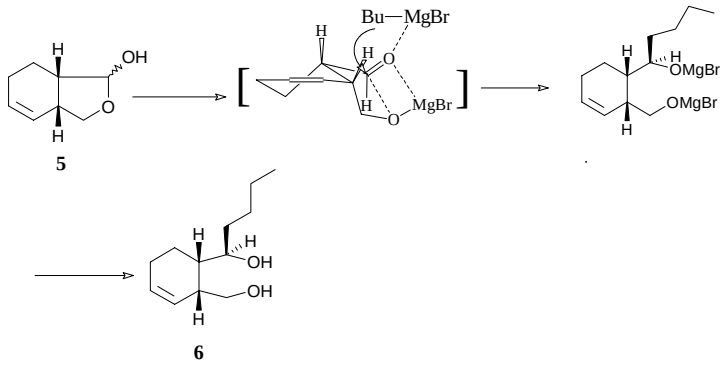
Compound **3** was prepared according to the literature[5]. Diels-Alder reaction of **3** and methyl acrylate in refluxing toluene over one week gave 1(3H)-isobenzofuranone **4** in 45% yield[6]. Reduction of **4** with diisobutylaluminum hydride (DIBAH) in THF at -78°C under nitrogen gave hemiacetal **5** in 80% yield[7]. The hemiacetal **5** with

*E-mail: pingx@imm.ac.cn

n-BuMgBr in dry ether under nitrogen at room temperature yielded diol **6** stereoselectively in 90% yield. Oxidation and cyclization of diol **6** with NMO and catalytic amount of tetrapropylammonium perruthenate (TPAP) in the presence of molecular sieve in CH_2Cl_2 gave **7** in 50% yield[9]. Treatment of compound **7** with DBU in refluxing toluene gave (±)neocnidilide **8** by a double bond migration.

The highly stereoselective reaction of **5** with *n*-BuMgBr could be explained by the following mechanism:[8] Compound **5** can generate a Mg salt, the O-Mg part (with δ^-—δ^+) of which is aligned parallel to the aldehydic C=O (with δ^+-δ^-). One of the two possible alignments has much less steric hindrance(by examination of molecular structure models), in the other conformation, the Mg atom is too close to the olefin hydrogen, thus effectively shields one side of the C=O group from Bu^- attack. So compound **6** was formed as a single racemate as shown in **Scheme 2**.

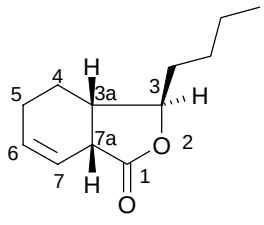
Scheme 2



5 **6**

The configuration of compound **7** shown in **Figure 1** was determined by NOE . When irradiating H-3 (4.21 ppm), H-7a (3.18 ppm) had no NOE enhancement, this demonstrated that H-3 was *trans* with H-7a. It is in accordance with the result from the mechanism which was proposed in **Scheme 2**.

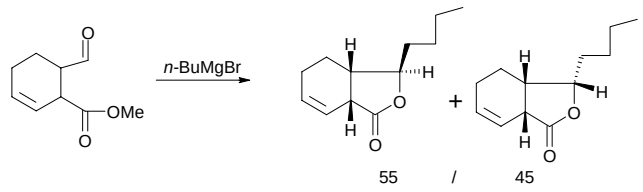
Figure 1



References and Notes

1. H. Mitsuhashi , T. Muramatsu, *Tetrahedron*, **1964**, *20*, 1971.
2. S. Morozumi, T. Wauke, H. Hitokoto, *Tokyo Eiken Nenpo*, **1984**, *35*, 31 [CA, 103,3570s (1985)].
3. By Wesley Cocker, T.B.H. McMurry, D.M. Sainsburg, *J.Chem.Soc. (c)*, **1966**, 115*2*.

4. XM. Wang, SB Li, YL Li, *Chemical Research and Application*, **1996**, *8* (1), 90.
5. M. P. Schneider , M. Goldbach, *J. Am. Chem. Soc.*, **1980**, *102*, 6114.
6. E.J. Corey , Martin Petrzilka, *Tetrahedron. Lett.*, **1975**, *30*, 2537.
7. Paul A. Grieco, *J. Org. Chem.*, **1972**, *37* (14), 2363.
8. In reference 4, the low stereoselecive reaction was shown as :



9. R. Bloch, C. Brillet, *Synlett.* **1991**, 829.
10. Data of the compounds:

Compound 4: colorless oil, ^{1}H-NMR(300Hz, $CDCl_3$, δ ppm, JHz), 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 5: white solid, ^{1}H-NMR(300Hz, $CDCl_3$, δ ppm, JHz), 5.80 (m, 1H, H-5), 5.64 (m, 1H, H-4), 5.25 (s, 1H, H-1), 4.25 (t, 1H, J=7.8Hz, H-3), 3.61 (t, 1H, J=7.8Hz, 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 6: colorless oil, ^{1}H-NMR(500Hz, $CDCl_3$, δ ppm, JHz), 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=7Hz ,H-5″).

EI-MS *m/z*(%): 198 (M^+, 2), 149 (100), 94 (30), 79 (20).

Compound 7: colorless oil, ^{1}H-NMR(500Hz, $CDCl_3$, δ ppm, JHz), 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=7Hz, H-11).

EI-MS *m/z*(%):194 (M^+, 43), 148 (100), 106 (28), 93 (82), 79 (99).

Compound 8: ^{1}H-NMR(300Hz, $CDCl_3$, δ ppm, JHz), 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=7.2Hz, H-11).

Received 15 April, 2002