Chinese Chemical Letters Vol.11, No.11, pp.971–974, 2000

The Synthesis of a Novel Lignan

Xiu Xiang QI[1], Jun Biao CHANG[2]*, Rui Yun GUO[2], Rong Feng CHEN[2]

[1]Chemistry Department of Zhengzhou Univeristy, Zhengzhou 450052
[2]Henan Institute of Chemistry, Henan Academy Sciences, Zhengzhou 450002

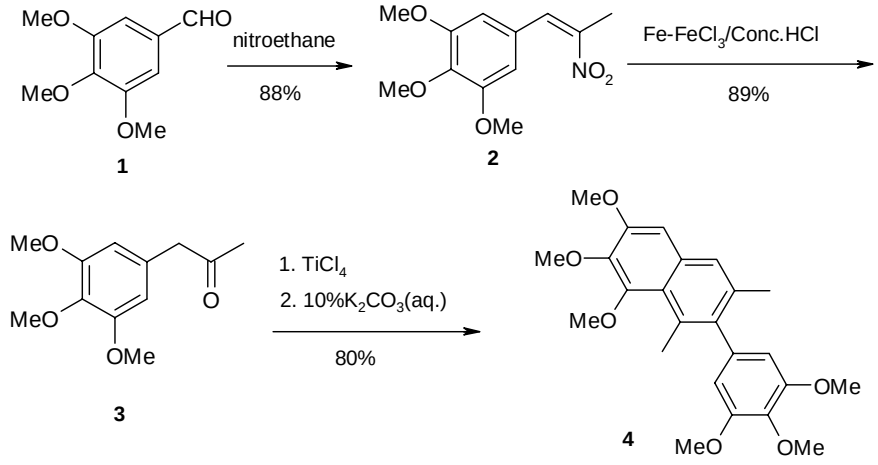
Abstract: A short convenient synthesis of a novel lignan, 2-(3',4',5'-trimethyoxyphenyl)-1,3-dimethyl-6,7,8-trimethoxy-naphthalene has been accomplished by the condensation of key intermediates, 3,4,5-trimethoxybenzyl methyl ketone with $TiCl_4$.

Keywords: Lignan, analogues, synthesis, condensation.

Lignans have attracted much interest over the years on account of their widespread ocurrence in nature[1], and on account of their broad range of biological activity[2]. Thus, several lignans are known to exhibit anti-tumor activity[3-7], while others function as growth inhibitors and antifungal agents[8,9]. The importance is the isolation of lignans from animals, including human beings[10-12], which has led to the suggestion that such compounds may be an example of a novel class of hormone controlling cell growth.

Lignans can possess many varied types of structure. So to synthesize lignans has presented a considerable challenge to organic chemists. Many elegant synthetic methods have been reported[13]. In ref.13, the synthetic methods of lignans are classified according to the types of compound prepared. Thus, it can be seen that most of the synthesis depend upon the condition of reactions, for example, phenolic oxidative coupling[14], non-phenolic oxidative coupling[15], Diels Alder and related reactions[16]. As a part of our drug discovery program for anti-tumor agents, we needed to synthesize the isopodophyllotoxin analogues of naturally occurring compounds which possess a arylnaphthalene skeleton. To prepare these class of lignans, the key intermediate compound **3**[17] was required(S**cheme 1**). The compound **3** was synthesized by reduction of the nitrostyrenes **2** with Fe-$FeCl_3$, and then hydrolysis with conc.HCl.Compound 3 was prepared from the 3,4,5-trimethoxy benzaldehyde **1** in yield 78.3%. Condensation of two molecules of the benzyl methyl ketone **3** with $TiCl_4$ in tetrahydrofuran (THF) afforded 2-(3',4',5'-trimethyoxyphenyl)-1,3-dimethyl-6,7,8-trimethoxy-naphthalene **4**[18] in high yield. The mechanism of reaction showed as S**cheme 2**.

Scheme 1 Route of Synthesis of Compound **4**



Scheme 2 The mechanism of the condensation of two molecules of 3,4,5-trimethoxyphenyl methyl ketone **3** with $TiCl_4$

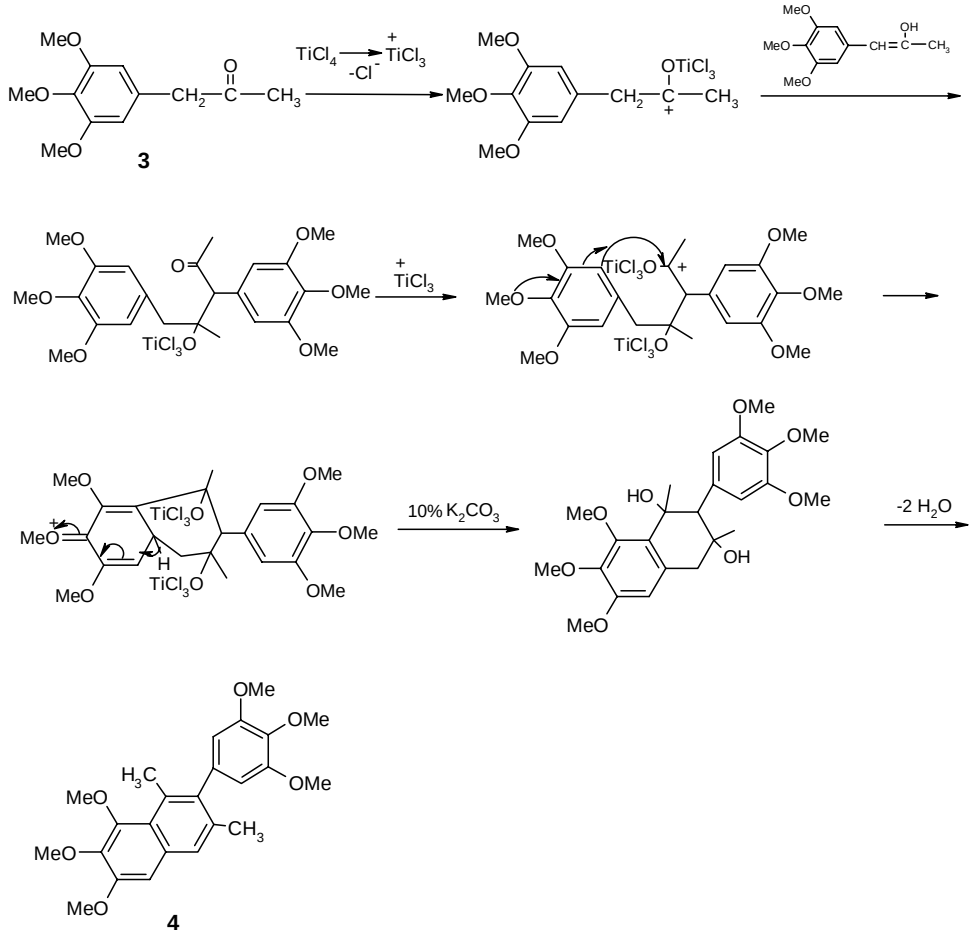
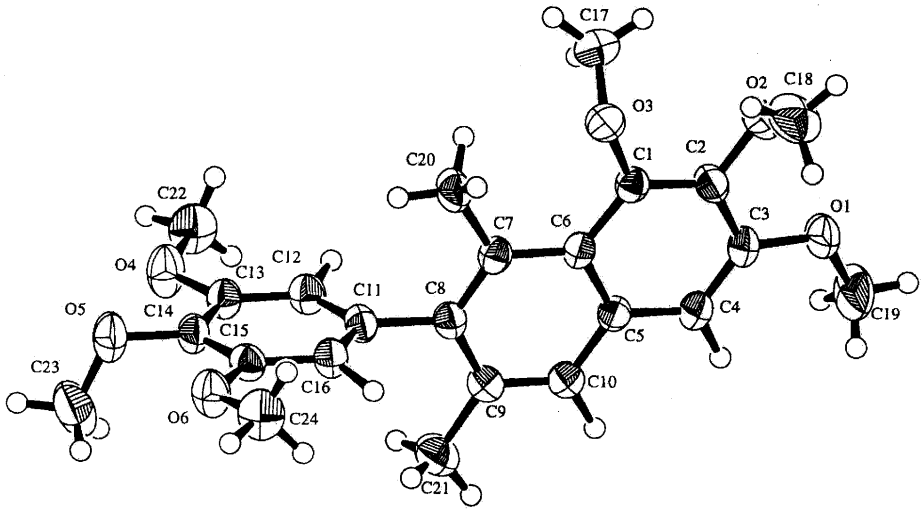


Figure 1.ORTEP Drawing of Compound **4**



Mass spectrometry and elemental analysis established the molecular formula $C_{24}H_{28}O_6$. The ^1H NMR spectrum showed the presence of two methyl groups (δ 2.12, 2.58), six methoxy groups. The ^{13}C NMR spectrum also supported the structure **4**, and the structure **4** has been confirmed by x-ray crystallography (**Figure 1**).The biological evaluations of the compound **4** is in progress in our laboratories.

Acknowledgment

This research was supported by Natural Science Foundation of Henan Province (9940317004) and The National Natural Science Foundation of China(29972009).

References and Notes

1. J. R. Cole, R. M. Wiedkopf, *Chemistry of lignans*, Andhra University Press, **1978**
2. Y. Landais, J. P. Robin, A. Lebrum, *Tetrahedron*, **1991**, *47*(23), 3787.
3. M. Sainsbury, *Tetrahedron*, **1980**, *36*, 3327.
4. S. M. kupchan, R. W. Britton, M. F. Ziegler, C. J. Gilmore, R. J. Restivo, R. F. Bryan, *J.Am.Chem.Soc.*, **1973**, *95*, 1335.
5. S. G. Weiss, M. Tin-wa, R. E. Perdue, N. R. Farnsworth, *J.Pharm.Sci*., **1975**, *64*, 95.
6. S. K. Carter, R. B. Livingston, *Cancer treat Rep*., **1976**, *60*, 1141.
7. J. B. Chang, J. X. Xie, *Science in China(Series B)*, **2000**, *43*(3), 323.
8. T. Kamikado, C. F. Chang, S. Murakoshi, A. Sakurai, S. Tamura, *Agric.Biol.Chem.(Jpn)*, **1975**, *39*, 833.
9. G. B. Russell, P. Singh, P. G. Fenemore, *Aust.J.Biol.Sci.*, **1976**, *29*, 99.
10. S. R. Stitch, P. D. Smith, D. Lllingworth, K. Toumba, *J.Endocrinol.*, **1980**, *85*, 239.
11. S. R. Stitch, J. K. Toumba, M. B. Groen, C. W. Funke, J. Leembuis, J. Vink, G. F. Woods, *Nature*, **1980**, *287*, 738.
12. K. D. R. Setchell, R. Bull, H. Adlercreutz, *J.Steroid Biochem.*, **1980**, *12*, 375.
13. J. B. Chang, J. X. Xie, R. F. Chen, P. Liu, *Acta Pharmaceutica Sinica*, **1999**, *34*(12), 913.
14. C. J. Sih, P. R. Ravikumar, F. C. Huang, C. Buckner, H. Whitlock, *J.Am.Chem.Soc.*, **1976**, *98*,

5412.
15. J. B. Chang, J. X. Xie, *Chin.Chem.Lett.*, **1996**, *9*, 801.
16. T. L. Holmes, R. Stevenson, *J.Org.Chem.*, **1971**, *36*, 3450 and *J.Chem.Soc.(C)*, **1971**, 2091.
17. Compound **2**: mp, 91-92℃; UV (EtOH) λ_{max} (log ε): 339.6 (0.95), 211.6 (3.03) nm; IR (KBr): 1640, 1580, 1520 cm^{-1}; ^{1}HNMR (400 MHz $CDCl_3$) δ ppm: 2.51 (3H, d, J=1.5Hz, CH=C-CH_3), 3.95 (9H, s, 3×OCH_3), 6.65 (2H, s, ArH), 8.06 (1H, brs, CH=C-H); Anal.Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53; Found: C, 56.90; H, 6.00; N, 5.51.
Compound **3**: mp.61-62℃; UV (EtOH) λ_{max} (log ε): 270.7 (0.35); 220 (3.49) nm; IR (KBr): 1700, 1582 cm^{-1}; ^{1}HNMR (400 MHz $CDCl_3$), δ ppm: 2.11 (3H, s, $COCH_3$); 3.52 (2H, s, $ArCH_2$), 3.80 (9H, s, 3×$ArOCH_3$), 6.30 (2H, s, ArH). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19, Found: C, 64.30; H, 7.25.
18. Compound **4**: mp, 159-160℃; UV (EtOH) λ_{max} (log ε): 242.7 (1.96), 205.9 (0.95) nm; IR (KBr): 3000, 2850, 1580, 1010 cm^{-1}; ^{1}HNMR (400 MHz $CDCl_3$) δ ppm: 2.12 (3H, s, CH_3), 2.58 (3H, s, CH_3), 3.84 (6H, s, 2×$COCH_3$), 3.94 (6H, s, 2×OCH_3), 3.95 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 6.90 (2H, s, 2×ArH), 6.93 (1H, s, ArH), 7.42 (1H, s, ArH); ^{13}CNMR (400 MHz $CDCl_3$) δ: 19.55, 21.56 (CH_3), 55.67, 56.08, 60.94, 60.95, 61.13 (6×OCH_3), 102.81, 106.48, 121.97 (Ar-CH), 124.98, 131.31, 131.37, 134.09, 136.49, 137.67, 139.71, 142.15, 151.06, 152.30, 153.21 (Ar); MS(*m/z*) (%): 412 (M^+, 100), 366 ([M-C_2H_6O]$^+$, 38), 351 ([M-C_3H_9O]$^+$, 28); Anal.Calcd for $C_{24}H_{28}O_6$: C, 69.90; H, 6.80; Found: C, 69.78; H, 6.75.

Received 11 May 2000