Chinese Chemical Letters Vol. 13, No. 1, pp 19 – 22, 2002
http://www.imm.ac.cn/journal/ccl.html

Studies on Agarofurans VIII. Synthesis of the Metabolites of 4-Butyl-α-agarofuran

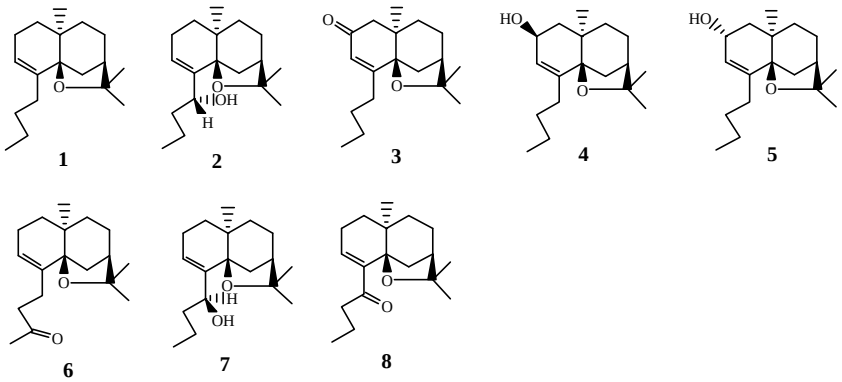
Chun Li, Wu Yan Zhang, Ji Yu Guo*, Xiao Tian Liang

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

Abstract: The structures of five metabolites (**2**-**6**) of agarofuran **1** were confirmed by synthesis. The configuration of the secondary hydroxyl in **7** was determined by Horeau's method. The configuration of C-2 in compound **4** and **5** was determined by their stereochemistry and NMR.

Keywords: Agarofuran, metabolite, synthesis.

Agarofurans have been found to be active on the nervous system in our institute. 4-Butyl-α-agarofuran **1** is a promising drug candidate. In order to explore the pharmacokinetics of **1**, the metabolism of **1** in *vitro* was studied with liver microsomes from rats. Five metabolites were isolated and structures were identified as compounds **2**-**6**. But the absolute configuration of **2**,**4**,**5** and the position of carbonyl in **3** could not be unambiguously determined. Further determination was limited by the small amount of the isolated metabolites. This prompted us to synthesize the compounds with these proposed structures and other plausible structures **7** and **8**.

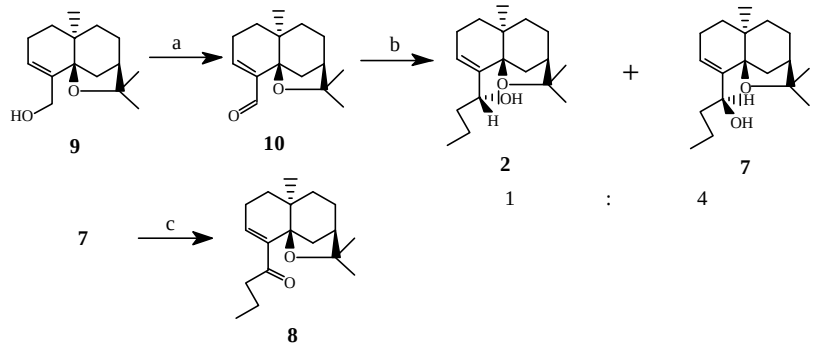


The approachs to **2**, **7** and **8**, were outlined in **Scheme 1**, using dehydrobaimuxiangchun **9**[1] as the starting material, thus the resultant hydroxyl or carbonyl group would be established undoubtedly at 1′. The position of oxidation of **9**

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

with PCC provided aldehyde **10**. Subsequent reaction of **10** with propyl magnesium bromide yielded alcohols **2** and **7** in a ratio 1:4, **2** is much less polar than **7** on TLC. The NMR of **2** is identical with that of the metabolite, so the structure **7** could be ruled out. Further oxidation of **7** with PCC afforded ketone **8**. Compound **8** could be excluded from the metabolites as the absence of the correspoding signals in its NMR spectrum.

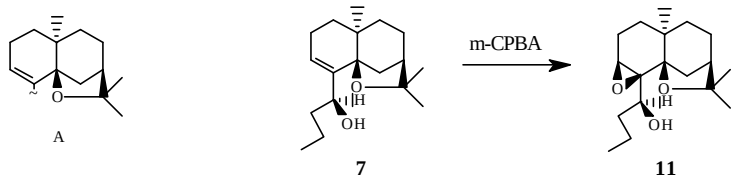
Scheme 1



a) PCC, CH_2Cl_2; b) C_3H_7MgBr, Et_2O; c) PCC, CH_2Cl_2

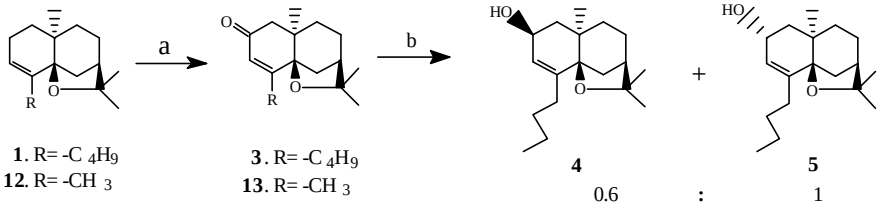
The absolute configuration of **7** was determined according to Horeau's method[2]. Alcohol **7** (30 mg) and 2-phenylbutyric anhydride (77 mg) were dissolved in pyridine. After standing at 5°C for 12 h, the mixture was titrated with 0.1 mol/L aqueous NaOH solution. The aqueous layer was separated and washed with chloroform, then neutralized with 1 mol/L HCl and extracted with benzene. The benzene solution was concentrated and the residue was redissolved in 1.3 mL of benzene. The rotation of the resulting solution in 1 dm vessel at 15°C under sodium D light is -0.54, so the configuration of C-1′ in **7** is S, thereby the configuration in metabolite **2** is R. In order to accentuate the bulk of group A, we epoxidized **7** to **11** (**Figure 1**) and repeated the above procedure. The final rotation was again minus.

Figure 1



It was reported that 4-CH_3 of α-agarofuran **12** was oxidized with SeO_2 as oxidant[3]. When we used SeO_2/t-BuOOH[4] to oxidize **1** and **12** (**Scheme 2**), allylic oxidation occured specifically on 2 position and afforded ketones **3** and **13** respectively. Reduction of **3** with $NaBH_4$ gave **4** and **5** in the ratio 0.6:1. The NMR spectra of **3, 4** and **5** are identical with those of the metabolites. The result of reduction agrees with that α-face of the ketone is more hindered than β-face[5].

Scheme 2



1. R= -C $_4$H$_9$
12. R= -CH $_3$

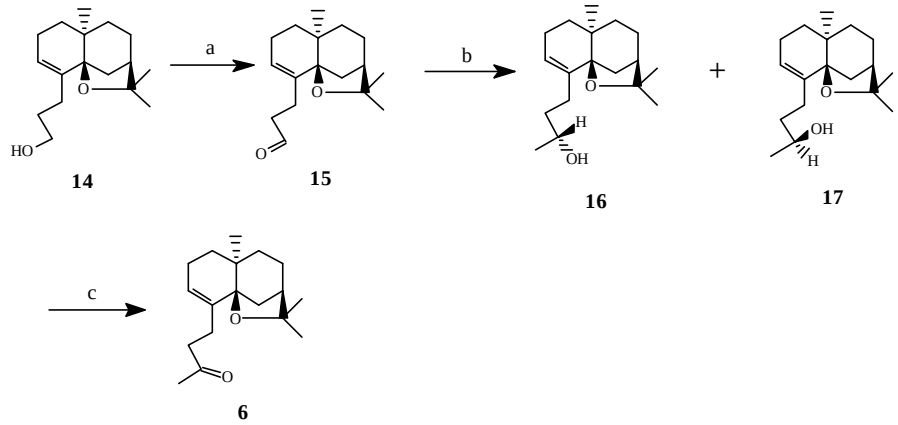
3. R= -C $_4$H$_9$
13. R= -CH $_3$

4 : **5**
0.6 : 1

a) SeO_2/t-BuOOH, CH_2Cl_2; b) $NaBH_4$, MeOH

$NaBH_4$ favored to attack from β-face and produced **5** more than **4**. The stereochemistry is also evidenced by the NMR spectra of the vinyl proton. In compound **5**, the vinyl proton is a broad single peak, very similar to the proton in compound **1**. While in compound **4**, the vinyl proton is split by the carbinylic proton with a coupling constant of 4.7 Hz. This indicates that the conformation of A ring of **4** is significantly different from compound **1** and **5**. It is conceivable that the intramolecular hydrogen bond between 2β-OH and the oxygen in tetrahydrofuran ring causes the conformational distortion.

Scheme 3



14 **15** **16** **17**

6

a) PCC, CH_2Cl_2; b) CH_3MgI, Et_2O; c) PCC, CH_2Cl_2

The synthesis of metabolite **6** is shown in **Scheme 3**. Oxidation of alcohol **14**[6] with PCC followed by Grignard reaction using methyl magnesium iodide in ether afforded alcohols **16** and **17**, which could be separated on TLC. Without separation, these two alcohols were subjected to PCC oxidation to furnish ketone **6**. Its NMR spectrum is identical with the metabolite. Thus, the structures of metabolites **2-6** were confirmed by the synthesis.

Acknowledgment

This work was supported by the National Natural Science Foundation of China. We also appreciate the heavy involvement of Dr. Wen Jiang Zhang in the work on metabolism studies and spectrometric identification of the metabolites.

References and Notes

1. Q. Liu, *et al*., *Chin. Chem. Lett*., **1991**, *2*, 425.
2. J. C. Fiaud, *Stereochemistry (Fundamentals and Methods)*, Stuttgart, **1977**, Vol *3*, 55.
3. X. Chen, *Synthesis of Natural Agarofurans*, Ph.D. Dissertation, Lanzhou University, **1993.**
4. M. A. Umbreit, *et al*., *J. Am. Chem. Soc*., **1977**, *99*, 5526.
5. W. Y. Zhang, *et al*., *Chin. Chem. Lett*., **2000**, *11*(10), 873.
6. W. Y. Zhang, *et al*., *Chin. Chem. Lett*., **2000**, *11*(5), 399.
7. **2**: $[\alpha]_D^{10}$+50.0 (c, 0.05, $CHCl_3$); MS *m/z* (%): 278 (M^+, 17), 245 (25), 235 (85), 217 (60), 41 (100); ^{1}H-NMR ($CDCl_3$, δ ppm): 0.91 (s, 3H, CH_3), 0.92 (t, 3H, J=7.2 Hz, CH_3), 1.26 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 4.15 (dd, 1H, J_1=5.5 Hz, J_2=7.9Hz, HO-C-H), 5.94 (dd, 1H, J_1=3.9 Hz, J_2=3.6 Hz, -C=C-H). **3**: $[\alpha]_D^{10}$-41.3 (c, 0.24, $CHCl_3$); MS *m/z* (%): 276 (M^+, 40), 153 (80), 81 (100); ^{1}H-NMR ($CDCl_3$, δ ppm): 0.93 (t, 3H, J=7.2 Hz, CH_3), 1.04 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.98 (d, 1H, J=15.5 Hz, CH), 2.76 (d, 1H, J=15.5 Hz, CH), 5.91 (br.s, 1H, C=C-H). **4**: mp: 75-76°C, $[\alpha]_D^{10}$+40.7 (c, 0.14, $CHCl_3$); MS *m/z* (%): 278 (M^+,40), 261 (100), 243 (49), 203 (23); ^{1}H-NMR ($CDCl_3$, δ ppm): 0.93 (t, 3H, J=7.2 Hz, CH_3), 1.09 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 4.22 (ddm, 1H, J_1=5.2 Hz, J_2=4.7 Hz, HO-C-H), 5.72 (dd, 1H, J_1=4.7 Hz, J_2=1.4 Hz, -C=C-H). **5**: $[\alpha]_D^{10}$-5 (c, 1.37, $CHCl_3$); MS *m/z* (%): 279 (M+1, 22), 261 (100), 243 (46), 187 (87); ^{1}H-NMR ($CDCl_3$, δ ppm): 0.93 (t, 3H, J=7.2 Hz, CH_3), 0.95 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 4.12 (m, 1H, HO-C-H), 5.64 (br.s, 1H, -C=C-H). **6**: mp: 59-61°C, $[\alpha]_D^{10}$+17.1 (c, 0.21, $CHCl_3$); MS *m/z* (%): 277 (M+1, 100), 259 (90), 2219 (18); ^{1}H-NMR ($CDCl_3$, δ ppm): 0.90 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.32 (m, 2H, CH_2), 2.57 (m, 2H, CH_2), 5.55 (br.s, 1H, -C=C-H). **7**: $[\alpha]_D^{10}$-176.7 (c, 0.1, $CHCl_3$); MS *m/z* (%): 279 (M+1, 10), 243 (79), 236 (62), 200 (95), 157 (100); ^{1}H-NMR ($CDCl_3$, δ ppm): 0.90 (s, 3H, CH_3), 0.94 (t, 3H, J=7.2 Hz, CH_3), 1.28 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 4.26 (t, 1H, J=5.7 Hz, HO-C-H), 6.06 (dd, 1H, J_1=3.9 Hz, J_2=3.6 Hz, -C=C-H). **8**: MS *m/z* (%): 277 (M+1, 10), 218 (70), 175 (100); ^{1}H-NMR ($CDCl_3$, δ ppm): 0.91 (t, 3H, J=7.2 Hz, CH_3), 0.92 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.60 (tq, 2H, J_1=7.1 Hz, J_2=1.8 Hz, CH_2), 6.65 (dd, 1H, J_1=4.1 Hz, J_2=3.5 Hz, -C=C-H). **11**: MS *m/z* (%): 294 (M^+, 2), 279 (40), 207 (45), 55 (100); ^{1}H-NMR ($CDCl_3$, δ ppm): 0.87 (s, 3H, CH_3), 0.96 (t, 3H, J=7.3 Hz, CH_3), 1.26 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 3.22 (s, 1H, CH), 3.96 (d, 1H, J=9.5 Hz, HO-C-H).

Received 15 May, 2001