Chinese Chemical Letters Vol. 11, No. 4, pp. 301–304, 2000

Studies on Agarofurans
III. The Synthesis of 3-Substituted Agarofurans

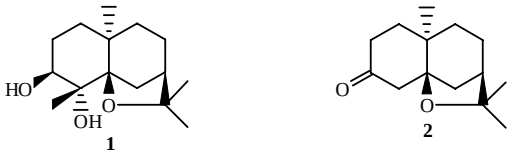
Wu Yan ZHANG, Ji Yu GUO*, Xiao Tian LIANG

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

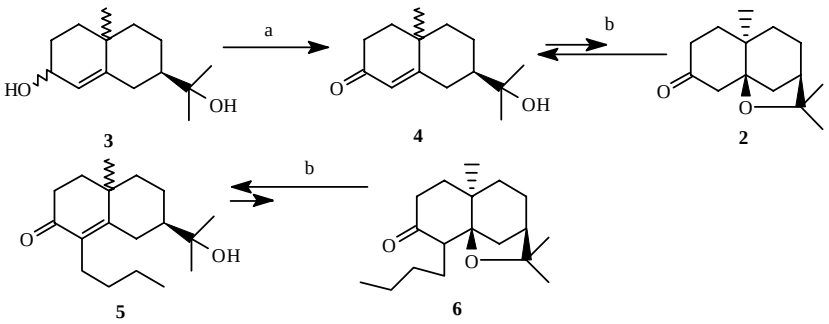
Abstract: 14-Nor-3-oxodihydroagarofuran (**2**) was prepared in high yield. From **2**, derivatives**12** and **13** were synthesized by Grignard addition. In order to identify the configuration of C-3 in compound **12** and **13**, the sterospecific synthesis of compound **12** has been carried out in 5 steps from octalone (**14**).

Keywords: Agarofuran, synthesis.

Agarofurans were found to be bioactive on nervous system. 3,4-dihydroxy dihydro agarofuran (**1**)[1] is only one of this group of natural products, which has substituent on C-3 position.



Scheme 1



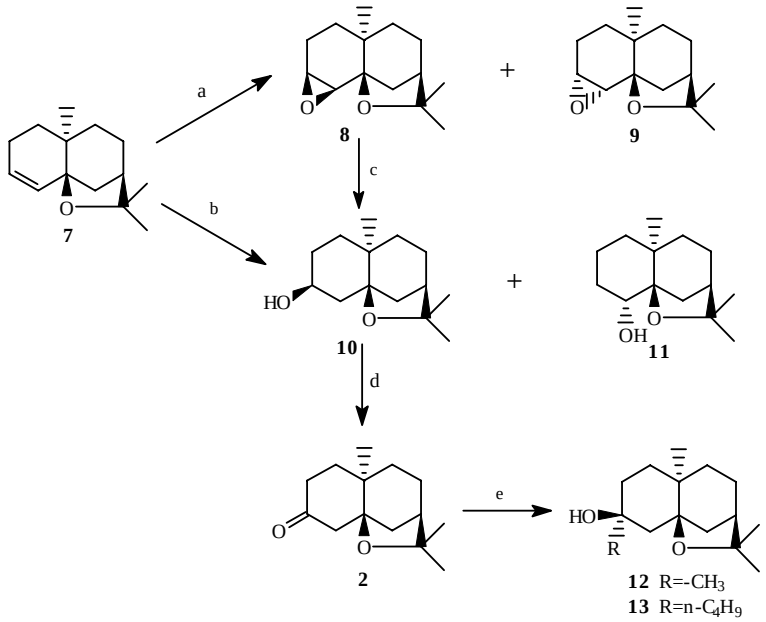
a) PCC, CH_2Cl_2; b) TsOH, benzene

We synthesized this compound by the reported method[1] and found it to possess some

specific bioactivity on nervous system. In order to search for more active compounds, we decided to modify agarofurans on C-3 position beginning with the synthesis of 14-nor-3-oxodihydroagarofuran (**2**).

In the initial stage of the synthesis (**scheme 1)**, the diol **3** was converted to hydroxy ketone **4** by oxidation with PCC. Treatment of **4** with p-toluenesulfonic acid in benzene at room temperature for one day and chromatography according to Asselin[2] gave ketone **2** in 20% yield and 70% of the starting material **4** were recovered. The attempt to improve the yield *via* prolonging the time failed. We assumed there is an equilibrium between ketone **2** and hydroxy ketone **4**. In order to confirm this assumption, treatment of ketone **2** with TsOH in benzene indeed afforded hydroxy ketone **4** in 70% yield. In order to study the effect of substituent on C-4 to the equilibrium, we treated the hydroxy ketone **5** with TsOH and obtained very small amounts of ketone **6**. The substituent on C-4 makes the reverse reaction more facile.

Scheme 2

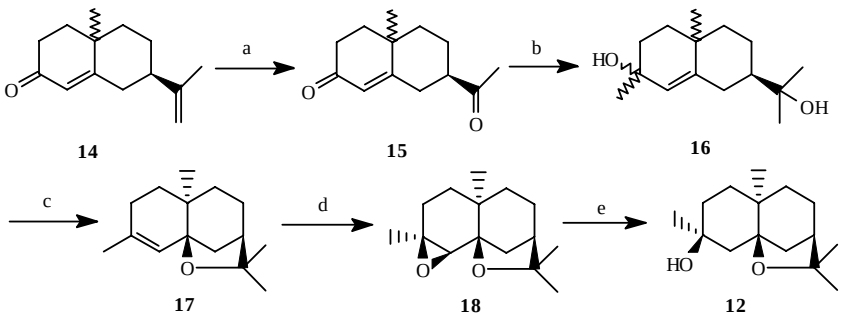


a) m-CPBA, CH_2Cl_2; b) 1. $Hg(OAc)_2$, THF, H_2O; 2. 3Mol/LNaOH, 3Mol/L$NaBH_4$; c) LAH, ether; d) PCC, CH_2Cl_2; e) CH_3MgI or C_4H_9MgBr, ether

We had to abandon this approach and designed another synthetic route (**scheme 2**). Epoxidation of olefin **7** gave β -epoxide **8** and α -epoxide **9** in a 4:1 ratio[3]. Reduction of epoxide **8** afforded alcohol **10**. Oxidation of alcohol **10** with PCC in dichloromethane gave ketone **2** in 90% yield. The overall yield based on olefin **7** was 65%. Since ketone **2** would reverse to hydroxy ketone **4**, the neutral oxidant should be used. The alcohol **10** could also be obtained directly involving oxymercuration of olefin **7**, which afforded

alcohol **10** and alcohol **11** in a 10:1 ratio in 90% yield. But when we use the olefin with substituent on C-4 position, such as methyl and butyl, many attempts of oxymercuration failed.

Scheme 3



a) OsO_4/KIO_4, dioxane, H_2O; b) CH_3MgI, ether; c) HCl/MeOH; d) m-CPBA, CH_2Cl_2; e) LAH, ether

Reaction of ketone **2** with Grignard reagents afforded alcohols **12** and **13**. NMR spectra indicated they are exclusively one epimer. However, the configuration of C-3 is not easy to determine. We designed a stereospecific route to absolutely identify the configuration (**scheme 3**). Agarofuranoid **17** was obtained by oxidation of octalone **14** with OsO_4/KIO_4, followed by addition of CH_3MgI and cyclization with HCl/MeOH. Epoxidation of **17** with m-CPBA give the β-epoxide **18** . The sterospecificity in this epoxidation is determined by the hindrance of angular methyl and a directing effect by the proximate oxygen atom in the tetrahydrofuran ring. Reduction of epoxide **18** with LAH gave exclusively alcohol **12**, of which the physical data and NMR spectrum is entirely consistent with the compound obtained previously. Hence the configuration of C-3 in compounds **12** and **13** were determined as hydroxyl in 3β orientation and alkyl in 3α orientation.

Acknowledgment

This work was supported by the National Natural Science Foundation of China.

References and notes

1. M.L.Maheshwari *et al*., *Tetra*. **1963**, *19*, 1519
2. A.Asselin *et al*., *Can.J.Chem.*, **1968**, *46*, 2817
3. Wu Yan Zhang *et al*., *Chin. Chem. Lett.*, **1997**, *8 (1)*, 25
4. **2**: mp: 60-61°C; $[\alpha]_D^{17}$ -22.9 (c, 0.55, EtOH); MS: 222 (M^+,3), 207 (100), 189 (5), 164 (30). 149 (20); ^{1}H-NMR ($CDCl_3$) δ: 1.20 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); IR:2940,2870,1710(C=O),1460,1381,1362,1305,1235,1135,970,895;
Anal. Cacld. for $C_{14}H_{22}O_2$: C,75.63; H, 9.97. Found: C, 75.74; H, 9.72
6: mp:64-66°C; $[\alpha]_D^{10}$ -10.3 (c, 0.58, $CHCl_3$); MS: 278 (M^+, 85), 263 (55), 235 (75), 164 (100);

^{1}H-NMR ($CDCl_3$) δ:0.92 (t, 3H, J=7.4 Hz, CH_3), 1.19 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), Anal. Cacld. for$C_{18}H_{30}O_2$: C,77.65; H,10.86. Found: C,77.89; H,10.94

12: mp: 68-70°C; $[\alpha]_D^{17}$ -62.2 (c, 1.8, EtOH); MS:239(M+1,11),238(M^+,46),153(100)
^{1}H-NMR ($CDCl_3$) δ:0.96(s, 3H, CH_3), 1.16(s, 3H, CH_3), 1.20(s, 3H, CH_3), 1.35(s, 3H, CH_3), Anal. Cacld. for $C_{15}H_{26}O_2$: C,75.58; H,10.99. Found: C, 75.57; H,11.19

13: mp: 25-26°C; $[\alpha]_D^{17}$ -30.8 (c, 0.61, EtOH); MS: 280 (M^+, 39), 205 (23), 195(100);
^{1}H-NMR ($CDCl_3$) δ: 0.96(t, 3H, J=7.4 Hz, CH_3), 1.20 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.36 (s, 3H, CH_3),

17: mp: 38-39°C; $[\alpha]_D^{10}$ +45.8 (c, 0.47, $CHCl_3$); MS: 220 (M+,15), 205 (50), 187 (14), 162 (31), 147 (50), 31 (100); ^{1}H-NMR ($CDCl_3$) δ: 0.90 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 5.16 (s, 1H, -C=C-H)

18: mp: 97-98°C; $[\alpha]_D^{10}$ +45.8 (c, 0.47, $CHCl_3$); MS: 236 (M+, 2), 221(100), 203 (15), 175 (23);
^{1}H-NMR ($CDCl_3$) δ: 0.84 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.32(s, 3H, CH_3), 1.35(s, 3H, CH_3), 2.74 (s, 1H, -O-CH-)

Received 25 January 2000