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Studies on Agarofurans VI. The Introduction of Substituents to C-1 and C-2 Positions of Agarofurans

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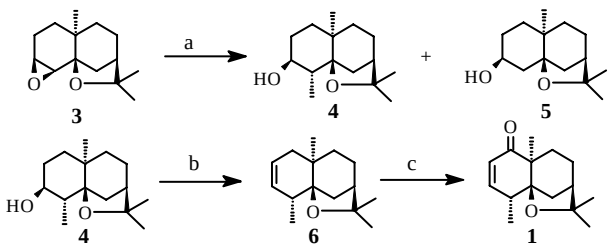
Abstract: Agarofuranoids with oxygen functions at C-1 and C-2 were synthesized by allylic oxidation. Ketone **2** gave compound **8** and **9** by Grignard reaction. The configuration of C-2 in **8** and **9** were identified by the CD spectroscopy of the benzoate **10**.

Keywords: Agarofuran, synthesis.

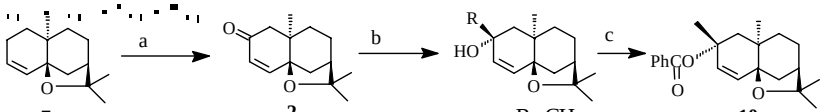
Agarofurans have been found to be active on the nervous system in our institute. Since no member of natural agarofurans has C-1 or C-2 substituents, we decided to synthesize ketone **1** and **2**, for the convenience of further modification.

Our synthetic design for ketone **1**, outlined in **Scheme 1**, was to employ β-epoxide **3** as starting material. Reaction of epoxide **3** with CH_3MgI cooled with ice-bath afforded alcohol **4** in 50% yield and reductive product **5** in 40% yield. The structure of **5** has been determined in our previous work[1]. 3β-Hydroxydihydroagarofuran has been reported by Hoffman[2], but its oxidation product is the known 3-keto-isodihydroagarofuran[3] with the methyl in 4β configuration. Dehydration of **4** with thionyl chloride and pyridine in ice-bath gave olefin **6** in 70% yield, with no trace of the alternative dehydration product α-agarofuran. The regioselectivity of this reaction is attributed to the fact that *trans*-diaxial elimination is predicted to lead to the formation of **6**. The regioselective dehydration also verifies the α-orientation of 4-Me. Our strategy for introducing an oxygen onto C-1 was allylic oxidation of olefin **6**. In general the double bond would shift and oxygen atom comes to C-2 position[4]. However allylic oxidation with t-BuOOH/SeO_2, the double bond seldom shifts[5]. Oxidation of olefin **6** with t-BuOOH/SeO_2 at 10℃ for 10 days and chromatographic separation gave ketone **1** in 30% yield, 40% of recovered starting material **6**, and no double bond shifted product was found.

Scheme 1: a) MeMgI, ether, ice-bath; b) $SOCl_2$, pyridine, ice bath; c) SeO_2, t-BuOOH, CH_2Cl_2



Scheme 2: a) $CrO_3.Py_2$, CH_2Cl_2; b) RMgX, ether; c) 1. BuLi, THF; 2. PhCOCl



7 **2** **8** R=CH_3 **9** R=n-C_4H_9 **10**

Ketone **2** was likewise obtained by allylic oxidation (**Scheme 2**). Oxidation of olefin **7** with $CrO_3.Py_2$ complex in dichloromethane at 10 ℃ for 3 days and chromatographic separation, gave ketone **2** in 70% yield and 20% of starting material **7**. Reaction of **2** with Grignard reagents yielded quantitatively alcohols **8** and **9** respectively. NMR spectra indicate both **8** and **9** are epimerically pure. In order to establish the configuration of C-2, alcohol **8** was converted to benzoate **10**, by the normal method for tert-hydroxyl[6]. The + Cotton effect in the CD spectrum of the benzoate **10** indicates the allylichydroxyl in alcohol **8** is in α orientation, according to the rules summarized by N.Harda[7]. The exclusive production of C-2 α-OH epimer indicates that the α-face of this molecular is significantly more hindered than the β-face, attributable to the angular methyl group.

Acknowledgment

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References and notes

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8. **1**: MS: 234 (M^+); ^{1}H-NMR($CDCl_3$)δ: 1.07 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 5.98 (dd, 1H, J_1=9.8Hz, J_2=1.1Hz, H-C=C-), 6.45 (d, 1H, J=9.8 Hz, -C=C-H); IR υ(KBr)cm^{-1}: 2965, 2927, 2880, 1684 (-C=C-C=O), 1458, 1384, 1370, 1144, 1013
   2: mp: 63-65°C; $[\alpha]_D^{20}$ –65.7 (c, 0.74, EtOH); MS: 221 (M+1), 220 (M^+); ^{1}H-NMR($CDCl_3$)δ: 1.07 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 5.95 (d, 1H, J=9Hz, H-C=C-), 6.44 (d, 1H, J=9Hz, H-C=C-); IR υ(KBr)cm^{-1}: 2970, 2940, 2880, 1680(-C=C-C=O), 1460, 1390, 1370, 1250, 1150, 865; Anal. Cacld. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.57; H, 9.17
   4: mp: 76-77°C; $[\alpha]_D^{10}$ –86.9 (c, 0.16, $CHCl_3$); MS: 223 (M-15); ^{1}H-NMR($CDCl_3$)δ: 1.24 (s, 3H, CH_3), 1.31 (s, 3H, CH_3),1.40 (s, 3H, CH_3), 4.19 (br.s, 1H, HOCH)
   8: mp: 100-102°C; $[\alpha]_D^{10}$ +45.4 (c, 0.63, $CHCl_3$); MS: 236 (M^+); ^{1}H-NMR($CDCl_3$)δ: 1.18 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 5.52 (d, 1H, J=9.7Hz, H-C=C-), 5.76 (dd, 1H, J_1=9.7Hz, J_2=1Hz, -C=C-H); Anal. Cacld. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.46; H, 10.23
   9: mp: 65-67°C; $[\alpha]_D^{20}$ +25.8 (c, 0.63, EtOH); MS: 279 (M+1); ^{1}H-NMR($CDCl_3$)δ: 0.96 (t, J=7.6Hz, CH_3), 1.08 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 5.44 (d, 1H, J=9.7Hz, H-C=C-), 5.68 (dd, 1H, J_1=9.7Hz, J_2=1Hz, -C=C-H); IR υ(KBr)cm^{-1}: 3480 (OH), 2960, 2940, 2880, 1460, 1385, 1370, 1150, 875; Anal. Cacld. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.93; H, 11.08
   10: mp: 142-144°C; MS 340 (M^+); ^{1}H-NMR($CDCl_3$)δ: 1.10 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 5.63 (d, 1H, J=9.9Hz, H-C=C-), 6.43 (dd, 1H, J_1=9.9Hz, J_2=1.5Hz, -C=C-H), 7.40 (td, 2H, J_1=7.4Hz, J_2=1.2Hz, Ph-H), 7.51 (tt, 1H, J_1=7.4Hz, J_2=1.2Hz, Ph-H), 7.96 (dd, 2H, J_1=7.4Hz, J_2=1.2Hz, Ph-H); IR υ(KBr)cm^{-1}: 2969, 2930, 1711, 1603, 1451, 1285, 1211, 1092, 1064, 711; UV (nm): 227, 272; CD: 220nm (Δε+)

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