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Studies on Agarofurans V. Studies on the Reductive Ring-Opening of 3,4-Epoxide of Agarofurans

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Abstract: Reduction of epoxides **1**, **2**, **3** with LAH and LAH/$AlCl_3$ has been studied. The products of reduction with LAH were controlled by steric and stereoelectronic effects. The reduction with LAH/$AlCl_3$ seemed to involve an intermediate in which one aluminum ion was shared by both oxygen atoms from the epoxide and the tetrahydrofuran ring.

Keywords: Agarofuran, synthesis.

The nature of reductive ring-opening of epoxide has been widely studied. But epoxides of agarofurans with rigid skeleton have their own specificity. Agarofurans have been found to be active on the nervous system in our institute. Reduction of epoxides may afford different types of agarofurans. This prompted us to investigate the reaction.

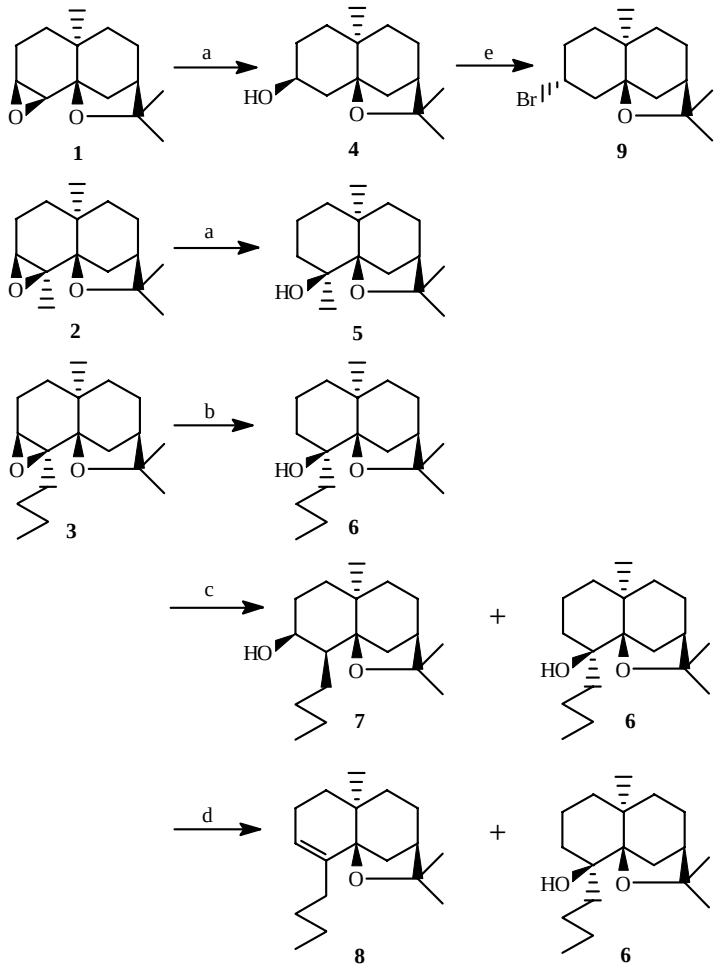
Epoxides **1**, **2**, **3** were prepared by oxidation of their corresponding olefins[1]. Generally, the nature of the reduction of epoxides with LAH depends on the steric hindrance. But for the structure of our compound, stereoelectronic effect is also important. If the reduction proceeds by stereoelectronically favored axial attack, it will afford 3β-OH products; if governed by steric hindrance, it will afford 4β-OH. We have reduced different epoxides with LAH (**Figure 1**). Reduction of **1** was carried out with ice-bath cooling to give exclusively 3β-OH **4**. The difference of steric hindrance in epoxide **1** at 3α and 4α positions is not significant and the stereoelectronic effect plays a key role. The splitting pattern of the carbinylic proton signal of **4** as a triplet at δ 3.92 (J=3.6Hz) seems to indicate a 3β-axial hydroxyl. In order to establish the site and configuration of hydroxyl unambiguously, we substituted Br for OH in a S_N2 procedure to compound **9**. The NMR spectrum of **9** showed 3-H as a triplet of triplets (J_{aa}=12.3Hz and J_{ae}=6.4Hz), in complete agreement with the previously assigned stereochemistry.

Reduction of epoxide **2** with LAH proceeded with ice-bath cooling only to afford 4β-OH **5**, agreeing with that reported[2]. Because of the angular methyl and the methyl in 4β position, the steric hindrance becomes a key role.

Reduction of **3** with LAH is complicated. Refluxing in ether even for one day gave only a trace of **6** with 4β-OH. The difficulty of this reaction is caused by the long C-chain at 4 position. Because of the presence of the space-demanding angular methyl and H-6, the C-chain mostly stands below the epoxide. This assumption was confirmed by

computer-aided MM2 calculation. So the long C-chain prevents LAH of approaching both 3 α and 4 α positions.

Figure 1



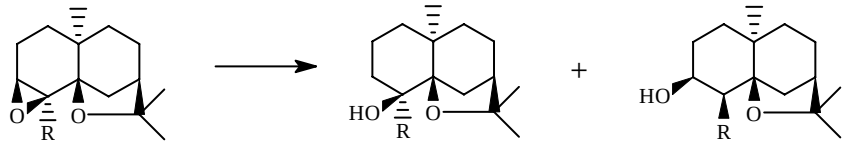
a) LAH, ether, ice-bath; b) LAH, ether, reflux; c) LAH, THF, reflux;
d) LAH, DME, reflux;e) PBr_3, PPh_3, THF

Raising the reaction temperature, refluxing in THF, reduction of compound **3** with LAH quantitatively gave **6** and **7** in a 1:1 ratio. In this case, the steric hindrance and stereoelectronic effect are both vitally important. Continuously raising the temperature, refluxing in DME yielded **8** and **6** in a 3:1 ratio. The easy production of **8** is due to a path of *trans*-diaxial elimination (**Figure 2**), which indicated both the hydroxyl and H-4 are in axial orientation at the same time. Raising the temperature makes reagent LAH more active and the C-chain spin more freely, so stereoelectronic effect becomes more

important.

Reduction of epoxide with LAH and $AlCl_3$ (**Figure 2**) gave products independent of the proportions (1:3 to 1:1) of LAH and $AlCl_3$ in the reaction mixture. **1** was reducted in ice-bath to give **10** and **4** in a 9:1 ratio, while at room temperature afforded **10** and **4** in a

Figure 2



1: R=H **10** **4**

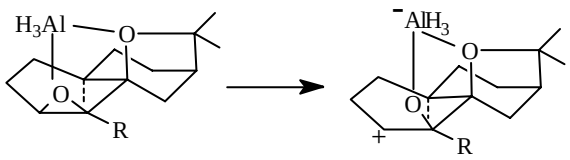
reaction condition	product composition		
ice-bath	9	:	1
r.t.	2	:	1

2: R=CH_3 ice-bath **5**

3: R=C_4H_9 ice-bath **6**

ratio of about 2:1. Reduction of **2** and **3** at the same temperature provided exclusively **5** and **6** with 4β-OH. The reduction with ice cooling proceeded smoothly and gave 4β-OH as the major product regardless of the C-chain at 4 position. In this path, a ring opening appears to occur at 4 position carbon atom. The reaction mixture presumably contains AlH_3 as the active reducing reagent. With this reagent, reduction seems to proceed by forming of complex **I** in which aluminum ion bonded with both oxygen atoms from the epoxide and the tetrahydrofuran ring (**Figure 3**). Since the oxygen in the tetrahydrofuran ring pulls the aluminum ion, reduction is through intermediate **II** and give products with hydroxyl in 4β position. For compound **1**, the reduction gave a small amount of compound **4**, by favored axial attack of 4α position of **1** .

Figure 3



I **II**

Acknowledgement

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References and notes:

1. W. Y. Zhang *et al*., *Chin Chem. Lett*., **1997**, *8* (1), 25
2. M. L. Maheshwari *et al*., *Tetra*., **1963**, 19, 1519
3. **4**: mp: 58-59°C; $[\alpha]_D^{17}$ –37.7 (c, 0.73, EtOH); MS *m/z*(%): 224 (M^+, 4), 209 (75), 191 (56), 43 (100); ^{1}H-NMR ($CDCl_3$) δ: 0.99 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 3.92 (t, 1H, J=3.6Hz, HO-CH-), 4.30 (br.s, 1H, OH)
   5: oil; $[\alpha]_D^{20}$ –67 (c, 0.52, EtOH); ^{1}H-NMR ($CDCl_3$) δ: 1.09 (s, 3H, CH_3), 1.18(s, 3H, CH_3), 1.23(s, 3H, CH_3), 1.36(s, 3H, CH_3)
   6: oil; $[\alpha]_D^{17}$ –57.4 (c, 1.7, $CHCl_3$); MS *m/z*(%) 280 (M^+, 3), 263 (2), 219 (2), 205 (2), 198 (20), 98 (20), 43 (100); ^{1}H-NMR ($CDCl_3$) δ: 0.90 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.29 (s, 3H, CH_3)
   7: mp: 47-48°C; $[\alpha]_D^{17}$ –22.7 (c, 0.44, $CHCl_3$); MS *m/z*(%) 278 (M+, 85), 263 (55), 235 (75), 164 (100); ^{1}H-NMR ($CDCl_3$) δ: 0.92 (t, 3H, J=7.4Hz, CH_3), 1.19(s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.32 (s, 3H, CH_3)
   9: MS *m/z:* 287 (M+, 4), 285 (M+, 4), 274 (15), 273 (100), 272 (15), 271 (100), 230 (20), 228 (20), 207 (42), 191 (30), 149 (60); ^{1}H-NMR ($CDCl_3$) δ: 1.04 (s, 3H, CH_3), 1.16(s, 3H, CH_3), 1.32 (s, 3H, CH_3), 3.34 (tt,Jaa=12.3Hz, Jae=6.4Hz, Br-CH)
   10: mp: 50-52°C; $[\alpha]_D^{10}$ –42.1 (c, 0.86, $CHCl_3$); MS *m/z*(%): 209(M-15, 100), 191 (35), 173(35); ^{1}H-NMR($CDCl_3$)δ: 0.96 (s, 3H, CH_3), 1.20(s, 3H, CH_3), 1.36 (s, 3H, CH_3), 3.50 (m, 1H, CHOH)

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