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Studies on Agarofurans
IV. The Synthesis of 4-Substitutioned Agarofurans

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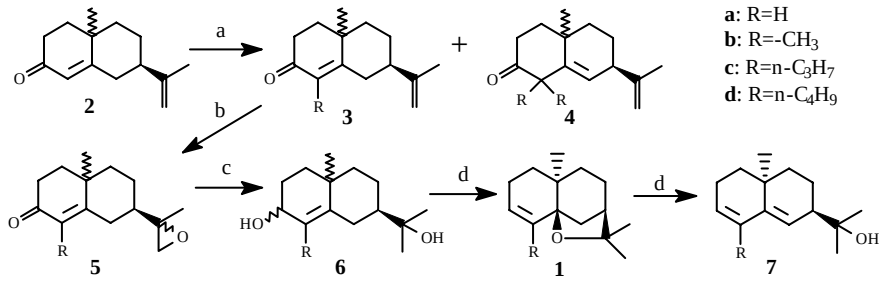
Abstract: A new synthetic route for α-agarofuran(**1b**) is described. Several agarofuran derivatives were synthesized in similar way. Derivative **1d** was also synthesized in a novel way, in which the substitution at C-4 was performed quantitatively. An ideal condition for cyclization of diol **7** to agarofuran (**1**) was found.

Keywords: Agarofuran, synthesis.

Agarowood oil was found to be bioactive in pharmacological screening for the nervous system in our institute. Agarofurans are one structural type of the important constituents of agarowood oil. α-Agarofuran (**1b**), one of the many constituents of the oil, is suspected of being an important contributor to the bioactivity. Although several synthesis of α-agarofuran (**1b**) have been described[1-3], they are not suitable for the synthesis of its analogs. The bioactivities prompted us to develop a new route to α-agarofuran (**1b**) and its analogs.

Scheme 1



a) RX, t-BuOK, t-BuOH; b) m-CPBA, CH_2Cl_2; c) LAH, ether, d) HCl/MeOH

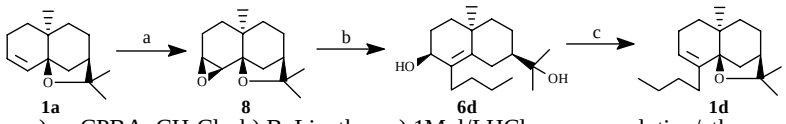
Earlier synthesis of α-agarofuran(**1b**), without exception, employed (-)epi-α-cyperone as starting material[1-3]. Our route outlined in **Scheme 1**, was to use epimeric mixture **2** as starting material. The key step is substitution at C-4 to compound **3b**. Reaction of **2** with CH_3I in t-BuOH solution of t-BuOK[5] and chromatography gave mono-substituted product **3b** in 50% yield and di-substituted product **4b** in 10% yield

along with some starting material. Epoxidation of **3b** with m-CPBA followed by reduction with LAH[2], diol mixture **6b** was obtained. Treatment of **6b** with HCl/MeOH[6], the 10α-diol **6b** cyclized to α -agarofuran (**1b**) and 10β-diol **6b** could not cyclize because of the steric constraint. The overall yield for the last three steps was 40%. Since **1b** can be changed to **7b** under the same condition, the time of cyclization should be strictly controlled.

In a similar manner, analogues **1a**, **1c**, **1d** were obtained in similar yield.

This route is capable of synthesis of analogues, but the overall yield is not satisfactory. The yield is restricted by two key steps. First, di-substitution at C-4 can not be avoided. The second concerns the conversion of diol **6** to agarofuran(**1**), where part of the product reverse to a diene[3,4].

Scheme 2



1a **8** **6d** **1d**

a) m-CPBA, CH_2Cl_2; b) BuLi, ether; c) 1Mol/LHCl aqueous solution/ether

When **1d** was chosen as a drug candidate, the amounts for pharmacological tests became larger and larger. A synthetic route for analogue **1d** in comparatively high yield was developed to meet the demand (**Scheme 2)**. Epoxidation of olefin **1a** with m-CPBA yielded β -epoxide **8** in 80% yield[7]. Reaction of **8** with BuLi in ether under ice-bath cooling for half an hour and quenching with aqueous 1Mol/LHCl afforded diol **6d** quantitatively. The two phase solution was allowed to stand over night, and the ether layer gave compound **1d** with no trace of side product.

The conversion of diol to agarofuran by treatment with acid has been widely studied by Huffman[4] and other researchers[6, 8]. A variety of acid-solvent combinations have been used, but all with low yields. There is a paradox that should be solved: cyclization needs acid catalysis, but the acid is detrimental to agarofurans by destructive diene formation. This difficulty was apparently circumvented by the two-phase reaction system where the relatively hydrophobic product like **1d** proved immune to interfacial acid catalysis which prevailed for the hydrophilic diol.

Acknowledgment

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References and notes

1. H. C. Barrett *et al*., *J. Am. Chem. Soc.*, **1967**, *89*, 5665.
2. J. A. Marshall *et al*., *J. Org. Chem*., **1968**, *33*, 435.
3. A. Asselin *et al*., *Can. J. Chem*., **1968**, *46*, 2817.
4. J. W. Huffman *et al*., *J. Org. Chem*., **1982**, *47*, 3254.
5. N. W. Atwater, *J. Am. Chem. Soc*., **1960**, *82*, 2847.
6. Q. Liu *et al*., *Chin Chem. Lett*., **1991,** *2*, 425.
7. W. Y. Zhang *et al*., *Chin Chem. Lett*., **1997**, *8 (1)*, 25.
8. X. Chen, Doctoral Thesis of Lan Zhou University, **1993.**
9. **1a**: oil, $[\alpha]_D^{20}$+15. 6. (c, 1. 5, acetone); **1b**: oil, $[\alpha]_D^{20}$+40, (c, 1. 8, acetone).
1c: oil, $[\alpha]_D^{17}$+17. 4. (c, 0. 73, EtOH); MS: 248 (M+, 31), 57 (100); ^{1}H-NMR ($CDCl_3$) δ: 0. 9 (m, 6H, $2CH_3$), 1. 24 (s, 3H, CH_3), 1. 36 (s, 3H, CH_3), 5. 56 (br, 1H, -C=C-H).
1d: mp: 24°C, $[\alpha]_D^{20}$+16. 8 (c, 1. 3, acetone).

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