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New Stereoselective Synthesis of 4-Butyl-α-agarofuran

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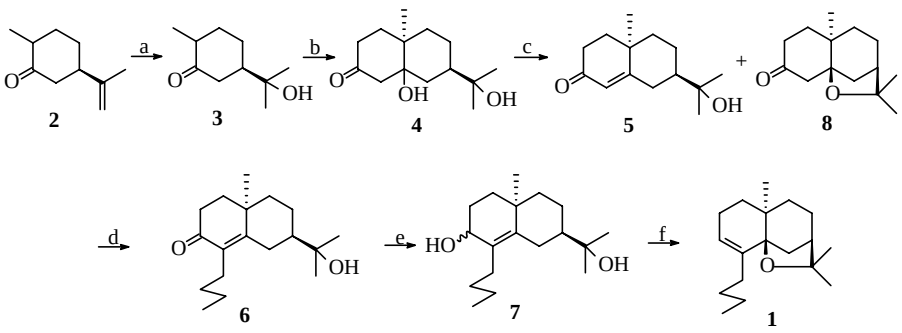
Abstracts: A potent anxiolytic 4-butyl-α-agarofuran (AF-5) was synthesized from (+)dihydrocarvone. Acid catalyzed hydration of (+)dihydrocarvone and interconversion with β-*O*-ketone **8** and the key intermediate α,β-unsaturated ketone **5** made this synthesis more practical.

Keywords: AF-5, stereoselective synthesis.

4-Butyl-α-agarofuran (AF-5, **1**) is an agarofuran derivative that possesses pharmacological activity on the central nervous system and is currently under active development as anxiolytic. A series of α-agarofuran derivatives were synthesized and tested on some CNS models, among which, AF-5 was found to be active on anxiolytic models[1]. Here we report the method for stereoselective synthesis of AF-5.

The synthesis of AF-5 was designed starting from (+)dihydrocarvone **2** possessing the *iso*-propenyl substituent at 5-position. The configuration of *iso*-propenyl group is *R* which is coincident with that of AF-5 (**Scheme 1**). In our previous report[1], AF-5 was

Scheme 1



a) dilute H_2SO_4, 74.8%; b) MVK, KOH, *i*-Pro_2O, -10°C, 35.4%; c) KOH, H_2O, hexane, reflux, 97.8%; d) *n*-BuBr, *t*-BuOK/*t*-BuOH, 49.9%; e) $NaBH_4$, MeOH; f) dilute HCl, 82%(two steps).

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prepared in 6 steps featured with Robinson annulation, alkylation, *m*CPBA epoxidation, $LiAlH_4$ reduction of the epoxide and, finally, acid catalyzed cyclization. One methyl group was found lost during the synthesis caused by over oxidation of the *iso*-propenyl to form acetyl group. After reduction and cyclization, demethyl-AF-5 was formed. This by-product is very difficult to separate from AF-5 either by column chromatography or by low temperature recrystallization. Then we tried to introduce the oxygen functionality on the *iso*-propenyl at an early stage by acid catalyzed hydration. This strategy (**Scheme 1**) may avoid over-oxidation and inconvenient reagent of $LiAlH_4$ in large scale preparation.

Thus, (+)dihydrocarvone **2** was hydrated with dilute sulfuric acid to form 8-hydroxy-*p*-menthan-2-one **3**. Robinson annulation of **3** was treated with methyl vinyl ketone (MVK) at –10 ^{o}C to form **4** as the major product and its β-angular methyl epimer as the minor product[2]. Fortunately, the β isomer suffered spontaneous dehydration under the reaction conditions, and dissolved in the reaction medium, while the desired **4** precipitated from the diisopropyl ether solution. When **4** was heated in KOH solution, **5** was obtained in 28.1% yield, and **1** was prepared from **5** following the similar procedure of our previous report[1]. During dehydration of **4**, a major by-product **8** was formed in 60% yield. It may be formed by intramolecular Michael addition of **5** under the basic conditions. When weaker base such as $Ca(OH)_2$ was used, **8** was still unavoidably formed, the yield reduced to 20% though, and **5** was obtained in 60% yield.

Because **8** is much less polar than **5**, hexane extraction was used to separate **8** from **5** once it was formed. This treatment can give pure products in both (76.9% of **8**, 20.9% of **5**). It is interesting to note that **5** and **8** can convert to each other under the basic conditions. If **5** and **8** are in equilibrium, when alkylation of **5** in the presence of **8** under the basic conditions, **8** will be drived to convert to **5**. When the mixture of **5** and **8** was used directly for alkylation without previous separation under the same conditions as that for **5**, **6** was obtained in 49.9% yield (45% from pure **5**). The procedure was much simplified. Compound **6** was reduced with $NaBH_4$ to give **7**, which was cyclized to form the final compound **1**. The overall yield of compound **1** was 10.2%.

In conclusion, we have found an efficient method for the synthesis of AF-5. The mixture of **5** and **8** could be used directly to produce **6**, therefore the separation of **5** and **8** is not necessary. The introduction of the hydroxyl group by hydration at an early stage, alkylation at the α-position of α,β-unsaturated ketone, and the discovery of interconversion of **5** and **8** made the process more practical.

References

1. Q. Liu, D. H. Wang, C. Li, *et al. Chin. J. Med. Chem.*,(in Chinese), to be published.
2. B. S. M. Tenius, E. R. de Oliveira, H. M. C. Ferraz, *Tetrahedron: Asymmetry*, **1993**, *4* (4), 633.

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