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A Convergent Route for the Synthesis of AF-5

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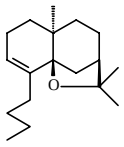
Abstract: AF-5 was synthesized through a convergent method. The key step was the Robinson annulation using a key intermediate pentyl vinyl ketone.

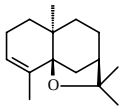
Keywords: AF-5, synthesis, Robinson annulation.

AF-5(**1**) is a synthetic derivative of sesquiterpinoid agarofuran that has potential biological activity on the central nerve system[1]. We have developed a linear synthetic route for the synthesis of AF-5[2]. In this report, we disclose a convergent synthesis of this molecule.

Figure 1 The structure of AF-5 and α-agarofuran



AF-5 (**1**)



α-agarofuran (**2**)

In the linear pathway, AF-5 was synthesized from dihydrocarvon in six steps (**Scheme** 1)[2]. The disubstituted by-product was almost equal to the amount of the desired product. It was unavoidable in the alkylation step. So we designed a convergent synthetic route based on the method for α-agarofuran **2** synthesis (**Scheme** 2)[3] to skip the alkylation step. For α-agarofuran synthesis, both starting materials are commercially available. But the substitution of methyl group by butyl group in A-ring of α-agarofuran is needed for this purpose.

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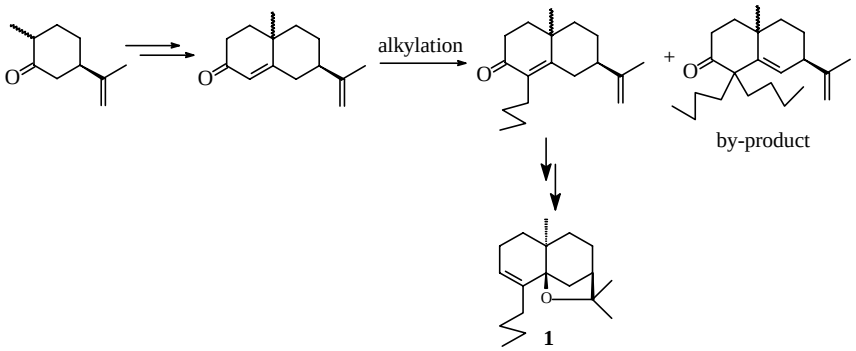
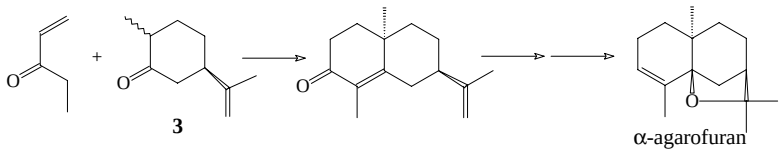
Scheme 1 Outline of the linear synthesis of AF-5



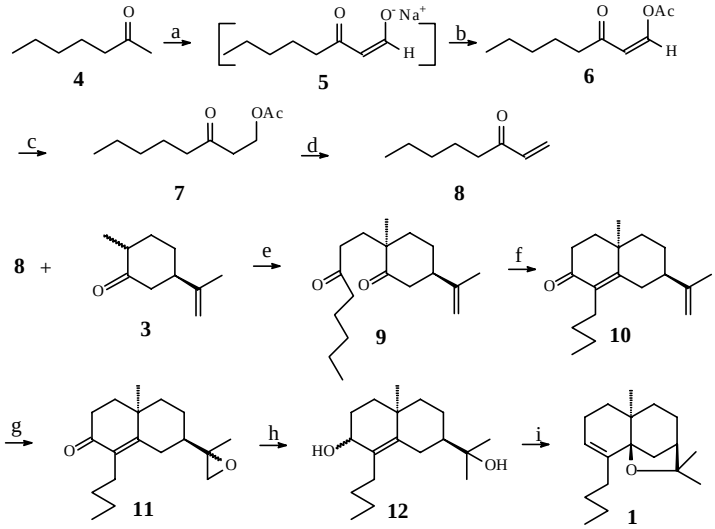
Scheme 2 Outline of the synthesis of α-agarofuran



Adaptation of the above method gives a synthetic route of AF-5, in which a key step is the Robinson annulation with pentyl vinyl ketone **8** and (+)dihydrocarvone **3** (**Scheme 3**). Pentyl vinyl ketone is not readily available and needs to be prepared from 2-heptanone **4**. Thus, condensation of 2-heptanone with ethyl formate gave **5** as its sodium salt, which was acetylated *in situ* to afford **6**. Hydrogenation of **6** with H_2/Pd-C gave **7**. When compound **7** was heated in triethylamine, elimination of acetic acid gave pentyl vinyl ketone **8**. When **8** and **3** were treated with sodium ethoxide in toluene at room temperature, **9** was obtained in 28.0% yield. After being heated with KOH in methanol, compound **9** could be cyclized to **10** in 59.4 % yield. Oxidation of **10** with *m*-CPBA gave oxirane **11**. Then reduction with $LiAlH_4$ produced diol **12**, which was treated with dilute hydrochloric acid to form AF-5(**1**)[2]. The over all yield of compound **1** was 10.8%(from **3**).

In conclusion, we have designed a convergent synthetic method for the synthesis of AF-5. In this route, a key intermediate, pentyl vinyl ketone, was synthesized from heptanone. This method may be used to synthesize alkyl vinyl ketone or aryl vinyl ketone to expand the scope of Robinson annulation reaction.

Scheme 3 The convergent synthetic route of AF-5



a. EtONa, Toluene, $HCOOC_2H_5$, 55°C, 3h; b. Ac_2O, DMF, 0°C-r.t., 2h, 55.4% (two steps); c. H_2, 10% Pd/C, EtOAc, r.t.,, 3h, 64.5%; d. Et_3N, 60°C,7h, 55.4%; e. EtONa, Toluene, -15°C, 3h, 28.0%; f. MeOH, KOH, reflux, then r.t.,6h, 59.4%; g. *m*-CPBA, CH_2Cl_2, 1h; h. Ether, $LiAlH_4$, 1h; i. MeOH, Petroleum ether, 1 mol·L^{-1} HCl (aq.), 1h, 50% (three steps).

Acknowledgments

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References and Notes

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3. (a) H. C. Barrett, G. Büchi, *J. Am. Chem. Soc.*, **1967**, *89*, 5665.
   (b) J. A. Marshall, M. T. Pike, *J. Org. Chem.*, **1968**, *33*(1), 435.
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4. **6**: oil, ^{1}H NMR($CDCl_3$, δ ppm): 0.89(t, 3H, *J*=7.2), 1.29(m, 4H), 1.62(m, 2H), 2.22(s, 3H), 2.52(t, 2H, *J*=7.4), 6.00(d, 1H, *J*=12.8), 8.24(d, 1H, *J*=12.8). MS(EI):*m/z* 169(M+H). **7**: oil, ^{1}H NMR($CDCl_3$, δ ppm): 0.88(t, 3H, *J*=7.2), 1.29(m, 4H), 1.57(m, 2H), 2.01(s, 3H), 2.41(t, 2H, *J*=7.6), 2.72(t, 2H, *J*=6.3), 4.31(t, 2H, *J*=6.3). **8**: oil, ^{1}H NMR($CDCl_3$, δ ppm): 0.89(t, 3H, *J*=7.2), 1.30 (m, 4H), 1.60(m, 2H), 2.58(t, 2H, *J*=4.8), 5.81(dd, 1H, *J*=10.5, 1.4), 6.21(dd, 1H, *J*=17.7, 1.4), 6.35(dd, 1H, *J*=17.7, 10.5). **9**: oil, ^{1}H NMR($CDCl_3$, δ ppm): 0.87(t, 3H, J=7.2), 1.03(s, 3H), 1.15-1.35(m, 4H), 1.45-1.70(m, 4H), 1.75(s, 3H), 1.70-1.90(m, 3H), 2.05-2.20(m, 3H), 2.30-2.50(m, 5H), 4.71(s, 1H), 4.76(s, 1H). The ^{1}H NMR data of compounds **10**, **11** and **12** are identical with those in reference 2.

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