A FACILE SYNTHESIS OF (±)–FRONTALIN

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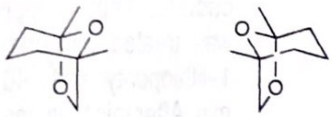
Abstract: Frontalin was prepared by the epoxidation and intramolecular cyclization of 6–methyl–6–hepten–2–one. The latter was synthesized by 1,2–addition of a mixed cuprate, formed from methallyl magnesium chloride, and methyl vinyl ketone. The overall yield was 56%.

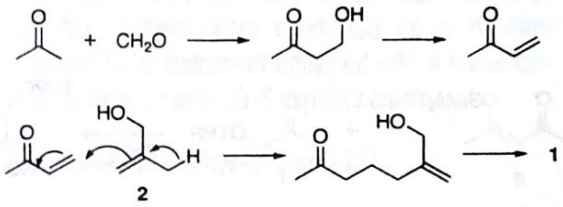
Frontalin **(1)** is an aggregation pheromone of several species of *Dendroctonus* bark bettles. These pests are responsible for timber losses in coniferous forests. Pheromone provokes mass colonization of trees, which are used as breeding sites. Frontalin was identified as the principal component of the pheromone of the female southern pine beetle *Dendroctonus frontalis*[1], and its structure was elucidated as 1,5–dimethyl–6,8–dioxabicyclo [3.2.1] octane **(1)** *(Figure 1)*. It has been shown that in the case of the western pine beetle *Dendroctonus brevicomis* , both exo-brevicomin and (S)–(–)–frontalin are active pheromone components[2] *(Figure 1)*. However, racemic frontalin is very active for practical applications.



(S)-(-)-Frontalin (R)-(+)-Frontalin

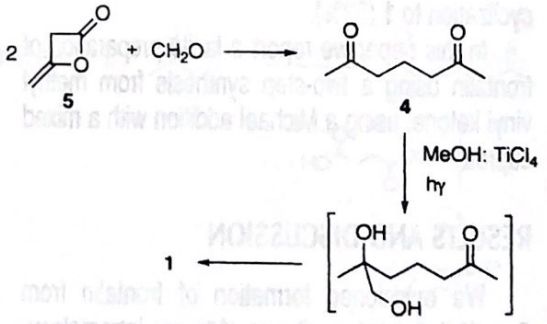
Figure 1

The need for operational use of frontalin for detection and management of bark beetle populations, has resulted in the development of about thirty different syntheses[3] of racemic and chiral frontalin. Among the short racemic syntheses are D'Silva's one pot procedure[4], wherein a mixture of formaldehyde, excess acetone and methallyl alcohol **(2)** is heated in an autoclave at 250–275° for 1 h. Methyl vinyl ketone **(3)** has been proposed as an intermediate in this reaction, probably formed from acetone and paraformaldehyde *(Scheme 1)*. Finally, reaction between **2** and **3** produces frontalin in 35% yield, based on methallyl alcohol **(2)**. The major drawback of this procedure is the use of drastic reaction conditions and the low yield obtained.



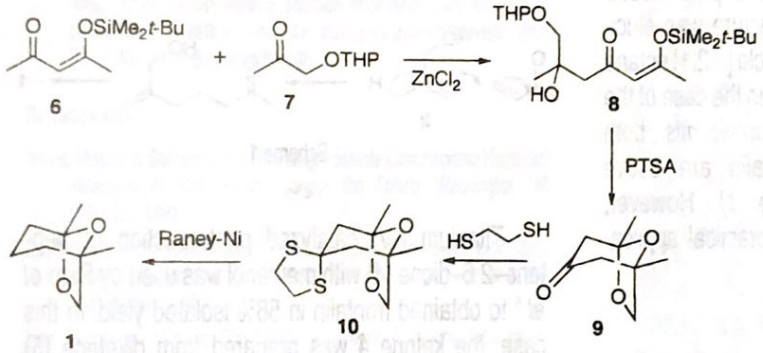
Scheme 1

Titanium (IV) catalyzed photoreaction of heptane–2,6–dione **(4)** with methanol was used by Sato *et al* [5] to obtained frontalin in 58% isolated yield. In this case, the ketone **4** was prepared from diketene **(5)** and formalin *(Scheme 2)*. The overall yield from diketene is 23%. The use of large amounts of the highly toxic titanium chloride (molar ratio ketone: $TiCl_4$; 2:1) and the low overall yield obtained, makes this procedure enviromentally bendenson for large scale preparations.



Scheme 2

Hagiwara and Uda prepared frontalin using a zinc chloride-assisted cross-aldol condensation between 4–(*tert*-butyldimethylsiloxy) pent–3–en–2–one (**6**) and 1–tetrahydropiranyloxy acetone (**7**). Thus, siloxyenone **6** was first treated with lithium diisopropylamine (LDA) and then with protected α–ketol **7** in the presence of zinc chloride to afford, after hydrolysis, the condensation product **8**. Treatment of the latter with *p*-toluene sulphonic acid, removed the protecting groups and catalyzed an intramolecular acetal formation to give the 5–methyl–6,8–dioxabicyclo [3.2.1] octan–3–one derivative **9** in 36% yield, based on the enone **6** *(Scheme 3)*. Thioacetalisation of **9**, followed by the reductive removal of the thioacetal of **10**, with Raney-Ni gave frontalin in 67% yield *(Scheme 3)*. The overall yield from **6** was 16%.



Scheme 3

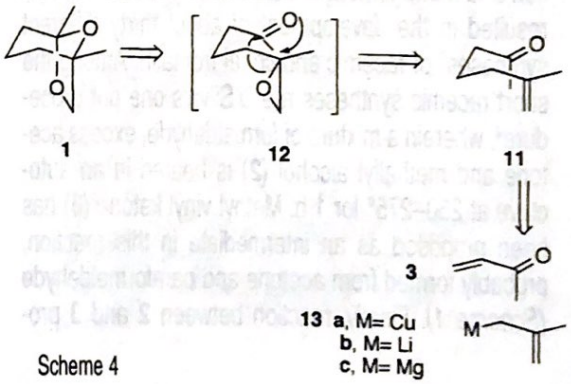
Reaction of methallyl bromide with methyl vinyl ketone (**3**), under sonochemical aqueous conditions, was used to obtain 6–methyl–6–hepten–2–one (**11**) in 80%[6]. The latter ketone was epoxidized prior to cyclization to **1** (52%).

In this paper we report a facile preparation of frontalin using a two-step synthesis from methyl vinyl ketone, using a Michael addition with a mixed cuprate.

RESULTS AND DISCUSSION

We envisioned formation of frontalin from 6–methyl–6–hepten –2–one (**11**), *via* intramolecular cyclization of its epoxide **12** *(Scheme 4)*. Enone **11** was envisioned to be available from methyl vinyl ketone (**3**) and a metallic methallyl derivative (**13**).

Initial reactions focused on the preparation of **11**, by 1,4–addition of a methallyl cuprate (**13a**) to methyl vinyl ketone (**3**). Formation of a methallyl cuprate from the corresponding organollithium reagent (**13b**) and a Cu(I) salt was difficult, because of formation of the organolithium compound from the corresponding halide. Allylic halides undergo competitive Wurtz-type coupling reaction and are, therefore, of limited use in the metal-halogen exchange reactions[7]. We decided to prepare a mixed cuprate reagent from a Cu(I) salt and an organomagnesium (**13c**), rather than an organolithium reagent (**13b**). Indeed addition of one equivalent of methallylmagnesium chloride to one equivalent of copper cyanide in THF at –40 °C resulted in the formation of a yellow solution, which upon cooling to –78 °C, was treated with one equivalent of methyl vinyl ketone (**3**), at the same temperature for 2.5 hours. Surprisingly, analysis of the crude reaction mixture revealed the 1,2 addition adduct, allylic alcohol **14**, as the major product (*Table 1*, entry 1). To change the regiochemistry of the reaction, we used a mixed higher order cuprate. Thus, copper cyanide was treated with one equivalent 1–lithiopentyne at –40 °C for 30 min. After this time one equivalent of methallyl magnesium chloride was added to the above solution and stirred for 1 h. The mixed cuprate was reacted with one equivalent of methyl vinyl ketone at –78 °C for 2.5 h. GC analysis of the crude reaction

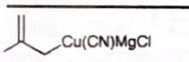
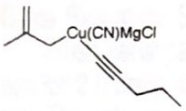
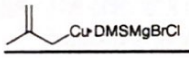


Scheme 4

evidenced the formation of a 2:1 mixture of alcohol **14** and the desired ketone **11** (*Table 1*, entry 2). Although ketone **11** was obtained, the regiochemistry of the reaction was poor. To further increase the "softness" of the cuprate we prepared a similar reagent from methallyl magnesium chloride and one equivalent of copper bromide dimethylsulfide complex at –40 °C for 30 min. After cooling to –78 °C, this reagent was treated with one equivalent of methyl vinyl ketone for 2.5 h. GC analysis of the crude reaction mixture revealed the formation of ketone **11**, the 1,4–addition product, with a regioselectivity of 98% (*Table 1*, entry 3). The reaction was repeated on a bigger scale and the product was isolated in 67% yield.

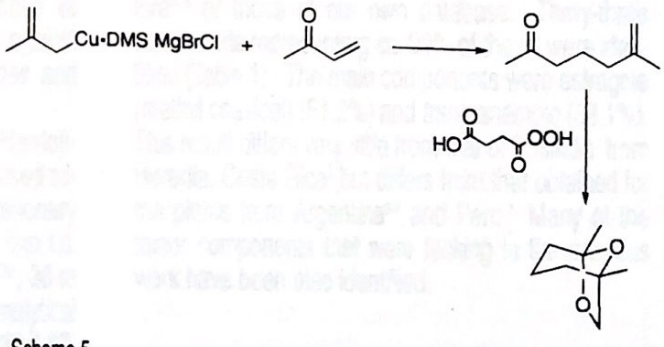
TABLE 1

ADDITION OF CUPRATES OVER METHYL VINYL KETONE (3) AT –78 °C

CUPRATE	Products (ratio) 14	11	%Yield
	96	4	76[a]
	67	33	72[a]
	2	98	67[b]

a. Calculated by GC.
b. Isolated yield.

Conversion of **11** into frontalin (**1**), was carried out by a one-pot procedure. Thus, treatment of ketone **11** with maleic anhydride and hydrogen peroxide, resulted in the *in situ* formation of the corresponding epoxide, which underwent an intramolecular cyclization to frontalin. Distillation gave frontalin in 90% yield. Overall yield from methyl vinyl ketone (**3**) was 60% *(Scheme 5)*.



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Scheme 5

EXPERIMENTAL SECTION

General Methods for reactions involving the use of cuprates:

Glassware and syringes were dried overnight in an oven at 140 °C and flushed with nitrogen immediately prior to use. Liquid transfers were performed with syringes equipped with stainless-steel needles. CuBr•DMS and CuCN were weighed in a glove bag under nitrogen. Reactions were carried out under positive pressure of nitrogen. THF was refluxed and freshly distilled from potassium/benzophenone ketyl under argon atmosphere. Grignard reagents were titrated according to the method of Watson and Easthman[8].

^{1}H– and ^{13}C–NMR spectra were recorded on a Varian Mercury 400 spectrometer, operating at 400,13 MHz and 100,62 MHz respectively. Gas chromatographic analyses were conducted on a Hewlett-Packard 5892 instrument equipped with a flame ionization detector and DB–5 capillary column.

6-METHYL-6-HEPTEN-2-ONE (11)

A solution of methallylmagnesium chloride (17,2 mL, 6 mmol) was added dropwise to a cold (–40 °C) suspension of CuBr·DMS (1,23 g, 6 mmol) in THF (8 mL) and the resulting solution stirred at this temperature for 40 min. After this time, the reaction mixture was cooled to –78 °C and reacted with methyl vinyl ketone (0,5 mL, 6 mmol) and stirred for 2,5 h. The reaction was quenched by addition of NH_4Cl, and allowed to warm to room temperature. The reaction was extracted with ethyl ether and dried over $MgSO_4$. Solvents were removed by fractional distillation using a 10 cm Vigreaux column. The residue obtained was

purified by Kugelrohr distillation to afford 0,51 g of **11** (67%).

^{1}H–NMR ($CDCl_3$, 400 MHz) 1,70 (s, 3H); 1,72 (tt, 2H, J= 7,5 Hz); 2,05 (t ancho, 2H, J= 7,5 Hz); 2,13 (s, 3H); 2,42 (t, 2H, J= 7,5 Hz); 4,66 (m, 1H); 4,72 (m, 2H); ^{13}C–NMR ($CDCl_3$, 100 MHz); 21,5; 22,2; 30,0; 37,0; 42,9; 110,4; 144,7; 208,6; IR (film) 3074, 2938, 1715, 1648, 1445, 1364, 1158, 888 cm^{-1}.

Frontalin (1)

In a 50 ml flask was dissolved maleic anhydride (4,37 g, (44 mmol) in 25 mL of dichloromethane. The solution was cooled to 0 °C and a 30% H_2O_2 solution added dropwise (5,0 g, 44 mmol), the cooling bath was removed and the mixture was allowed to reach room temperature (30 min.). Ketone **11** (3,3 g; 26 mmol), dissolved in CH_2Cl_2 (5 mL), was added and the mixture stirred overnight. The reaction was quenched by addition of water (10 mL) and was extracted with diethyl ether. The organic solvents were dried ($MgSO_4$) and evaporated by fractional distillation, the residue was purified by vacuum distillation to afford 3,1 g of **1** (84%).

^{1}H–NMR ($CDCl_3$, 400 MHz) 1,33 (s, 3H); 1,43 (s, 3H); 1,50–1,68 (m, 5H); 1,80–1,95 (m, 1H). 3,45 (dd, 1H, J = 7,0; 2,0 Hz); 3,91 (d, 1H, J = 7,0 Hz); ^{13}C–NMR ($CDCl_3$, 100 MHz) 18,1; 23,1; 24,8; 34,0; 34,6; 74,1; 80,0; 107,9; IR (film) 2935, 2876, 1452, 1382, 1242; 1202, 1172, 1119, 1028, 930, 893, 84, 820 cm^{-1}.

References

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