J. Sci. Soc. Thailand 13 (1987) 239-242

A SHORT, EFFICIENT SYNTHESIS OF (±) FRONTALIN AND ITS ANALOGUE

NGAMPONG KONGKATHIP, BOONSONG KONGKATHIP AND RONGSAN SOOKKHO
Department of Chemistry, Faculty of Science, Kasetsart University, Bangkhen, Bangkok 10900, Thailand.

(Received 13 November 1987)

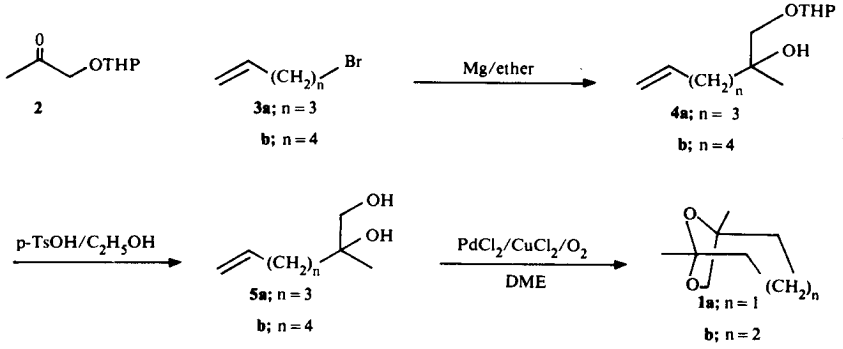
Abstract

(±)-Frontalin and its analogue were synthesized employing the Wacker oxidation as the key-step.

Frontalin **(1a)** has been shown to possess aggregation pheromone activity in several species of *Dendroctonus* bark beetle[1]. Several groups have synthesized this compound in both racemic[2] as well as enantiomeric[3] forms.

As a part of our continuing study on the palladium(II) catalyzed intramolecular cyclisation of alkenyl diols, we have developed a novel method for the synthesis of brevicomin[4], frontalin[5], and 1, 3-dimethyl-2, 9-dioxabicyclo [3.3.1] nonane[6], by using a Wacker catalyst system.

We wish to report here a short and more convenient synthetic method for frontalin and its analogue **(1b)** as shown by the following sequence of reactions.



The protected α -hydroxy ketone **(2)** was easily prepared according to the procedure reported previously[7].

A Grignard reaction between the ketone **(2)** and alkenyl bromide **(3)** led to compound **(4)**. Acidic hydrolysis afforded the desired diol **(5)** which was cyclised directly to bicyclic acetal **(1)** using palladium chloride as catalyst in 1, 2-dimethoxyethane with copper(II) chloride as reoxidant for the palladium.

A typical procedure is illustrated by the synthesis of frontalin from 5-bromo-1-pentene and the results were summarized in Table 1.

TABLE 1. PERCENTAGE YIELDS OF ALCOHOLS, DIOLS, FRONTALIN AND ITS ANALOGUE

Halide (3)	4[c] %	5[a,b] % (b.p.)	1[a,b] % (b.p.)
3a: n = 3	**4a:** 64	**5a:** 47 (81-84/1Torr)	**1a:** 45 (60-62/16Torr)
3b: n = 4	**4b:** 65	**5b:** 58 (90-94/1Torr)	**1b:** 34 (58-60/17Torr)

[a]Isolated yields

[b]Satisfactory elemental analyses and spectroscopic data

[c]Spectroscopic data satisfactory. Products were used without further purification.

IR spectra were recorded on Jasco A-302 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Jeol FX-200 spectrometer. Chemical shift are given in ppm relative to internal TMS (δ scale). MS data were obtained at 70ev on a VG-Micromass 7070e instrument.

2-Hydroxy-2-methyl-6-heptenyl tetrahydropyranyl ether **(4a)**

A solution of 5-bromopentene (1.60g, 10.8 mmol) in 3 ml of anhydrous ether was slowly added to a stirred suspension of magnesium turning (0.24g, 10 mmol) and a few crystal of iodine in anhydrous ether (10 ml) at such a rate to keep a gentle reflux under a nitrogen atmosphere. After the addition was completed, the resulting mixture was refluxed for 40 min then cooled to room temperature. A solution of acetonyl tetrahydropyranyl ether (1.37g, 8.67 mmol) in 10 ml of anhydrous ether was added and then refluxed for 2 h. The reaction mixture was cooled to room temperature and crush ice was added, acidified with dilute sulphuric acid then extracted with ether. The combined ether layer was washed with water and dried over anhydrous sodium sulphate. Solvent was removed to give a colorless liquid product **(4a)** (1.27g, 64%) which was used in the next step without further purification ^{1}H NMR ($CDCl_3$) δ : 1.10 (s, 3H, CH_3), 1.27-1.77 (m, 10H, 5xCH_2), 1.93-2.23 (m, 2H, CH_2), 2.77 (s, 1H, OH), 3.20-4.00 (m, 5H, CH_2-O-CH-O-CH_2), 4.70-5.13 (m, 2H, C = CH_2), 5.40-6.07 (m, 1H, C = CH).

1, 2-Dihydroxy-2-methylhepta-6-ene **(5a)**

A mixture of 2-hydroxy-2-methyl-6-heptenyl tetrahydropyranyl ether (5.10g, 24.30 mmol), p-toluene sulfonic acid (1.44g, 8.37 mmol) and 95% ethanol (160 ml) was refluxed for 2h, then most of ethanol was evaporated off. The residue was extracted with ethyl acetate, washed with sat.brine, dried (Na_2SO_4) and concentrated under vacuum. The residue was distilled to afford diol **(5a)** (1.50g, 47%), b.p. 81-84°C/1 Torr. IR (neat): 3350, 1640, 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ : 1.19 (s, 3H, CH_3), 1.50 (m, 4H, 2xCH_2),

1.98 (br.s, 2H, OH), 2.09 (m, 2H, CH_2), 3.42 and 3.50 (d, J = 10Hz, 1H each, CH_2-O), 4.94-5.10 (m, 2H, C = CH_2), 5.72-5.92 (m, 1H, C = CH); MS(m/e): 144 (M^+, 0.36), 129(4.27), 113(100); Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.39; H, 11.16.

Frontalin **(1a)**

A mixture of palladium chloride (0.11g, 0.61 mmol) and anhydrous cupric chloride (0.19g, 1.44 mmol) in dry dimethoxyethane (30 ml) was stirred and heated at 65°C while oxygen was bubbled through the solution. A solution of 1, 2-dihydroxy-2-methylhepta-6-ene (1.57g, 10.9 mmol) in dry dimethoxyethane (5 ml) was added dropwise and stirred at 65°C for a further 6 h then cooled to room temperature. The reaction mixture was filtered through a short neutral alumina column and eluted with ether. After removal of the solvent, the residue was distilled to give frontalin as a colorless liquid (0.71g, 45%) b.p. 60-62°C/16Torr; IR (neat) 2900, 1120 and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ : 1.33 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.47-1.72 (m, 6H, 3xCH_2), 3.46 and 3.81 (d, J = 7Hz, 1H each); ^{13}C NMR ($CDCl_3$) 108.42 (s), 80.01 (s), 77.64 (t), 34.52 (t), 33.90 (t) 24.68 (q), 23.01 (q), 17.99 (t) ppm. MS(m/e):142 (M^+, 8.72), 112(14), 100(23), 92(8), 84(12), 72(36), 70(81), 56(13), 43(100).

Acknowledgment

The authors would like to thank Prof. R.W. Rickards, Research School of Chemistry. The Australian National University, Canberra, for recording the ^1H, ^{13}C NMR, MS, and elemental analysis. The authors are also grateful for the help given by the Network for the Chemistry of Biologically Important Natural Products.

References

1. Hughes, P.R., Renwick, J.A.A. and Vite, J.R. (1976) *Environ. Entomol.* **5**, 1165; Wood, D.L., Browne, L.E., Ewing, B., Lindahl, K., Bedard, W.D., Tilden, P.E., Mori, K., Pitman, G.B. and Hughes, P.R. (1976) *Science* **192**, 896; Renwick, J.A.A. and Vite, J.P. (1969) *Nature* **224**, 1222; Pitman, G.B. and Vite, J.P. (1970) *Ann. Entomol. Soc. Am.* **63**, 661; Dyer, E.D.A. (1975) *Can. Entomol.* **107**, 979; Renwick, J.A.A., Hughes, P.R. and Vite, J.P. (1975) *J. Insect Physiol.* **21**, 1097.

2. Mundy, B.P., Otzenberger, R.D. and Debernaridis, A.R. (1971) *J. Org. Chem.* **36**, 2390; D'Silva, T.D.J. and Peck, D.W. (1972) *J. Org. Chem.* **37**, 1828; Mori, K., Kobayashi, S. and Matsui, M. (1979) *Agr. Biol.* Chem. **39**, 1889; Phaik-Eng Sum and Weiler, L. (1979) *Can. J. Chem.* **57**, 1475; Sato, T., Kaneko, H. (1979) *Tetrahedron Lett.* 1863; Marshall, R. and Rekers, W. (1981) *J. Am. Chem. Soc.* **103**, 205; Joshi, N.N., Mamdapur, V.R. and Chadha, M.S. (1983) *J. Chem. Soc.*, Perkin-I, 2963; Utaka, M., Makino, H., Oota, Y., Tsubol, S., and Takeda, A. (1983) *Tetrahedron Lett.* 2567; Hagiwara, H. and Uda, H. (1985) *J. Chem. Soc.*, Perkin-I, 283.

3. Mori, K. (1975) *Tetrahedron* **31**, 1381; Ohrui, H. and Emoto, S. (1976) *Agric. Biol. Chem.* **40**, 2267; Sakito, Y. and Mukaiyama, T. (1979) *Chem. Lett.*, 1027; Fraser-Reid, B., Hicks, D.R. and Jarsoz, S. (1982) *J. Org. Chem.* **47**, 935; Naef, R. and Seebach, D. (1983) *Ann. Chem.*, 1930; Meister, C. and Scharf, H.D. (1983) *Ann. Chem.*, 913; Lee, A.W.M. (1984) *J. Chem. Soc. Chem. Comm.*, 578; Johnston, B.D.

and Oehlschlager, A.C. (1984) *Can. J. Chem.* **62**, 2148; Yadav, J.S., Joshi, B.V. and Sahasrabudhe, A.B. (1985) *Synth. Comm.* **15**, 797; Hosokawa, T., Makabe, Y., Shinohara, T. and Murahashi, S.I. (1985) *Chem. Lett.*, 1529.

4. Byrom, N.T., Grigg, R. and Kongkathip, B. (1976) *J. Chem. Soc. Chem. Comm.*, 216; Byrom, N.T., Grigg, R., Kongkathip, B., Reimer, G. and Wade, A.R. (1984) *J. Chem. Soc.*, Perkin-I, 1643.
5. Kongkathip, B., Sookkho, R. and Kongkathip, N. (1985) *Chem. Lett.*, 1849.
6. Kongkathip, B., Kongkathip, N. (1984) *Tetrahedron Lett.*, 2175.
7. Hagiwara, H. and Uda, H. (1984) *J. Chem. Soc.*, Perkin-I, 91; Bernady, K.F., Floyd, M.B., Poletto, J.F. and Weirs, M.J. (1979) *J. Org. Chem.* **44**, 1438.

บทคัดย่อ

ได้บรรยายถึงวิธีการสังเคราะห์สารประกอบ *frontalin* และสารประกอบคล้ายคลึง โดยใช้ปฏิกิริยา *Wacker* เป็นขั้นตอนสำคัญในการสังเคราะห์