Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 8551–8553

TETRAHEDRON

Efficient synthesis of beetle aggregation pheromone frontalin and its analogues

Xiaobao Yang,[a,b] Shengjun Luo,[a] Chengwen Hua[b] and Hongbin Zhai[a,*]

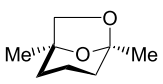
[a]*Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*
[b]*Department of Chemistry, Northwest University, Xi'an City, Shaanxi Province 710069, China*

Received 28 August 2003; revised 2 September 2003; accepted 4 September 2003

Abstract—(−)-Frontalin is an aggregation pheromone that has found application in selective exterminating of certain harmful insects. This paper discloses an expedite synthesis of (±)-frontalin from a symmetric molecule, 2,6-dimethyl-1,6-heptadiene, in 64% yield. The one-flask operation consists of double dihydroxylation, mono-cleavage, and acid-catalyzed intramolecular acetalation. Our unique strategy was also successfully applied to additional diene substrates such as **4a** and **4b**.

1. Introduction

(1*S*,5*R*)-(−)-Frontalin ((−)-**1**) is an aggregation pheromone secreted from the southern pine beetle (*Dendroctonus frontalis*), the western pine beetle (*Dendroctonus brevicomis*), and the Douglas-fir beetle (*Dendroctonus pseudotsugae*).[1] It possesses the aggregation activity and has found application in selective exterminating of certain harmful insects while imposing minimal environmental impact. Because of the relatively simple structure containing a 6,8-dioxabicyclo[3.2.1]octane framework and the unique bioactivity, both non-asymmetric[2] and asymmetric[3] syntheses of frontalin have drawn tremendous attention in the synthetic community. Remarkably, efficient assembly of this pheromone remains a great challenge. Now we wish to disclose an expedite synthesis of (±)-frontalin ((±)-**1**) starting from a symmetric diene, via a one-flask operation consisting of double dihydroxylation, mono-cleavage, and acid-catalyzed intramolecular acetalation.

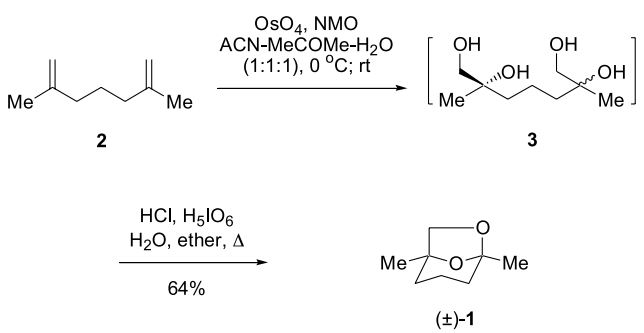


(-)-**1**: (1*S*,5*R*)-(-)-frontalin

2. Results and discussion

As depicted in Scheme 1, our new synthesis of (±)-frontalin ((±)-**1**) commenced from 2,6-dimethyl-1,6-heptadiene (**2**), which was prepared by the Li_2CuCl_4-catalyzed coupling of (2-methallyl)magnesium chloride and 4-bromo-2-methyl-1-butene according to a literature method.[4] The symmetric diene **2** was subject to double dihydroxylation with osmium tetroxide (catalytic amount) and 4-methylmorpholine *N*-oxide in MeCN–MeCOMe–H_2O (1:1:1).[5] Removal of most of the organic solvents generated crude tetraol **3**. After dilution with concentrated aqueous hydrochloric acid (2 equiv.), water and ether, crude **3** was treated with aqueous periodic acid (1 equiv.) while being heated at reflux. This effected sequential mono cleavage and acid-catalyzed intramolecular acetalation. After standard workup and vacuum distillation, (±)-**1** could be obtained as a colorless oil in 64% yield over the whole operation. The spectroscopic data of our synthetic sample of (±)-**1** were in accord with those reported.[2,3]

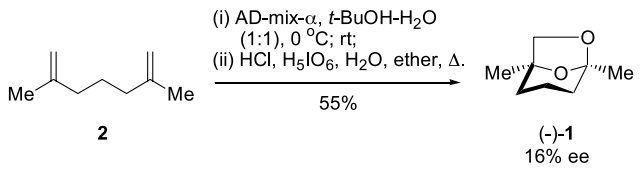
Several issues are worth pointing out concerning the synthesis of frontalin. (i) Double dihydroxylation presumably produced a mixture of two pairs of possible stereoisomers. (ii) During the second stage of the process, sufficient (but not too high) acidity has to be maintained so as to favor the intramolecular acetalation over the formation



Scheme 1. Synthesis of (±)-frontalin.

Keywords: aggregation pheromone; double dihydroxylation; frontalin; intramolecular acetalation; synthesis.
* Corresponding author. Tel.: +86-21-64163300; fax: +86-21-64166128; e-mail: zhaih@mail.sioc.ac.cn

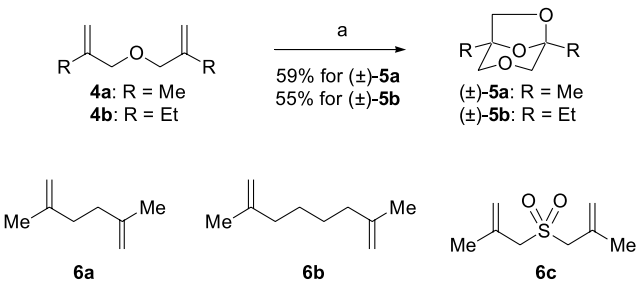
0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.09.029



Scheme 2. Asymmetric synthesis of (−)-frontalin.

of heptadione, the double cleavage product resulted from tetraol **3**. (iii) An attempt to accomplish an asymmetric synthesis of (−)-frontalin ((−)-**1**) by employing AD-mix-α[6] in double dihydroxylation step did not turn out to be so rewarding (Scheme 2). The final product was afforded in only 16% ee. Perhaps the second dihydroxylation of **2** proceeded in lower facial selectivity than the first one, because of the interference of the newly generated tertiary hydroxyl group. It seems unlikely that the low enantioselectivity in the formation of (−)-**1** originated from the epimerization of tetraol **3** under the acidic media required for the intramolecular acetalation. Our two trials of the same experiment led to the product with the same ee values.

Finally, five additional symmetric diene substrates were examined in an effort to understand the application scope of our method. By following the same protocol described for (±)-**1**, symmetric 1,6-dienes **4a**[7] and **4b**[8] could be converted to frontalin analogues (±)-**5a**[9] and (±)-**5b** in 59 and 55% yields, respectively (Scheme 3). On the other hand, no desired bicycles were formed from **6a**,[10,11] **6b**,[11] and **6c**.[12] The outcomes for **6a** and **6b** might be accounted for by less favorable intramolecular acetalation compared to the case of **2**. But the observed chemical behavior of the sulfone **6c** remains puzzling to us at present.



Scheme 3. Synthesis of frontalin analogues. (a) (i) OsO_4, NMO, ACN–MeCOMe–H_2O (1:1:1), 0°C; rt; (ii) HCl, H_5IO_6, H_2O, ether, △.

3. Conclusion

In summary, we have presented an expedite synthesis of (±)-frontalin from a symmetric molecule, 2,6-dimethyl-1,6-heptadiene, in 64% yield. The one-flask operation consists of double dihydroxylation, mono-cleavage, and acid-catalyzed intramolecular acetalation. Our unique strategy was also successfully applied to certain other substrates such as **4a** and **4b**.

4. Experimental

4.1. General

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$, DMSO-d_6 or D_2O (^1H at 300 MHz and ^{13}C at 75.47 MHz), using TMS as the internal standard when appropriate. Column chromatography was performed on silica gel.

4.1.1. (±)-Frontalin ((±)-1). To a stirred mixture of 2,6-dimethyl-1,6-heptadiene (1.214 g, 9.77 mmol) in MeCN–MeCOMe–H_2O (1:1:1, 45 mL) at 0°C were added NMO (aqueous solution, 50% w/w, 4.16 mL, 20.1 mmol) and OsO_4 (aqueous solution, 4% w/w, 0.10 mL, 0.016 mmol). The reaction mixture was allowed to warm up to rt over 20 min, stirred at rt for an additional 20 h, and concentrated in vacuo to give a slurry that was used directly in the next manipulation. Usual workup and chromatography (SiO_2, MeOH–EtOAc, 1:8) at this stage furnished the analytical sample of **3** as a colorless viscous oil: ^1H NMR (D_2O, 300 MHz) δ 0.88 (s, 6H, $2CH_3$), 1.09–1.20 (m, 6H, $3CH_2$), 3.15 (s, 4H, $2OCH_2$), 4.58 (s, 4H, 4OH); ^1H NMR (DMSO-d_6, 300 MHz) δ 0.96 (s, 6H, $2CH_3$), 1.25 (s, 6H, $3CH_2$), 3.11 (dd, J=5.3, 2.6 Hz, 4H, $2OCH_2$), 3.96 (s, 2H, 2OH), 4.45 (t, J=5.7 Hz, 2H, 2OH). The above slurry was diluted with a solution of concentrated hydrochloric acid (1.7 mL, 20 mmol) in water (3 mL) and Et_2O (150 mL), stirred for 5 min, and then treated with a solution of H_5IO_6 (2.343 g, 10.28 mmol) in water (20 mL) over 30 min while kept at reflux. After further reflux for 20 min, the two layers were separated and the aqueous layer was extracted with ether (50 mL×3). The combined organic layers were washed with saturated $NaHCO_3$ solution, dried over anhydrous magnesium sulfate, and filtered. The solvents were distilled off at the atmospheric pressure to give a residue, vacuum distillation of which afforded (±)-**1** (890 mg, 64%) as a colorless oil: bp 91°C/96 mm Hg; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.54–1.68 (m, 5H, $2.5CH_2$), 1.84–1.87 (m, 1H, $0.5CH_2$), 3.44 (dd, J=5.4, 1.5 Hz, 1H, $0.5CH_2$), 3.92 (d, J=6.6 Hz, 1H, $0.5CH_2$); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 18.0, 23.0, 24.6, 33.8, 34.5, 74.1, 80.0, 108.0. MS (EI) 143 (26, M+1), 142 (13, M^+), 100 (45), 43 (100); HRMS (EI) calcd for $C_8H_{14}O_2$ (M^+) 142.0994. Found: 142.1030.

4.1.2. (−)-Frontalin ((−)-1). 2,6-Dimethyl-1,6-heptadiene (679 mg, 5.48 mmol) was added to a suspension of AD-mix-α (15.4 g) in *t*-BuOH–H_2O (1:1, 110 mL) at 0°C. The mixture was stirred at 0°C until the reaction reached completion as judged by analytical TLC. Evaporation of the volatiles in vacuo gave a slurry that was immediately subjected to the next manipulation, in which the same procedure as described in Section 4.1.1 was followed. Thus (−)-**1** (414 mg, 55%) was obtained as a colorless oil: bp 60°C/30 mm Hg; 16% ee (determined by comparing the measured specific rotation with the literature value, see below); $[\alpha]_D^{20}$=−8.4 (*c* 1.4, ether) {lit.[3i] $[\alpha]_D^{30}$=−53.8 (*c* 0.5, ether)}. The rest of the spectrometric data can be found in Section 4.1.1.

4.1.3. 1,5-Dimethyl-3,6,8-trioxabicyclo[3.2.1]octane ((±)-5a). By following the same procedure as described for preparing (±)-**1**, frontalin analogue (±)-**5a** (2.230 g, 59%) was synthesized from **4a** (3.315 g, 26.27 mmol). (±)-**5a**,[9] a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 3.51–3.55 (m, 3H, $1.5CH_2$), 3.58 (s, 2H, CH_2), 4.24 (d, J=6.3 Hz, 1H, $0.5CH_2$); ^{13}C

NMR ($CDCl_3$, 75.47 MHz) δ 17.6, 19.6, 71.7, 72.7, 73.3, 79.4, 105.6. MS (EI) 144 (4, M^+), 114 (15), 72 (64), 43 (100).

4.1.4. 1,5-Diethyl-3,6,8-trioxabicyclo[3.2.1]octane ((±)-5b). By following the same procedure as described for preparing (±)-**1**, frontalin analogue (±)-**5b** (1.972 g, 55%) was synthesized from **4b** (3.200 g, 20.74 mmol). (±)-**5b**, a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91–1.00 (m, 6H, $2CH_3$), 1.61–1.68 (m, 4H, $2CH_2$), 3.51–3.68 (m, 5H, $2.5CH_2$), 4.20–4.23 (dd, J=6.6, 2.4 Hz, 1H, $0.5CH_2$); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 6.5, 7.6, 25.0, 26.0, 71.4, 71.6, 72.0, 81.8. MS (EI) 172 (5, M^+), 86 (37), 57 (100); HRMS (EI) calcd for $C_9H_{16}O_3$ (M^+) 172.1099. Found: 172.1101.

Acknowledgements

We thank the following agencies for financial support: Chinese Academy of Sciences ('Hundreds of Talent' Program); Science & Technology Commission of Shanghai Municipality ('Venus' Program); National Natural Science Foundation of China (20102008).

References

1. (a) Kinzer, G. W.; Fentiman, A. F., Jr.; Page, T. F., Jr.; Foltz, R. L.; Vite, J. P.; Pitman, G. B. *Nature* **1969**, *221*, 477–478. (b) Payne, T. L.; Richerson, J. V.; Dickens, J. C.; West, J. R.; Mori, K.; Berisford, C. W.; Hedden, R. L.; Vite, J. P.; Blum, M. S. *J. Chem. Ecol.* **1982**, *8*, 873–881. (c) Dickens, J. C.; Payne, T. L.; Ryker, L. C.; Rudinsky, J. A. *J. Chem. Ecol.* **1985**, *11*, 1359–1370. (d) Perrin, T. E.; Rasmussen, L. E. L.; Gunawardena, R.; Rasmussen, R. A. *J. Chem. Ecol.* **1996**, *22*, 207–221. (e) Huber, D. P. W.; Gries, R.; Borden, J. H.; Pierce, H. D., Jr. *J. Chem. Ecol.* **1999**, *25*, 805–816.
2. Selected references since 1990: (a) Jun, J. G.; Lee, I. S. *Synth. Commun.* **2000**, *30*, 1159–1165. (b) Yus, M.; Ramon, D. J. *J. Org. Chem.* **1992**, *57*, 750–751. (c) Weichert, A.; Hoffmann, H. M. R. *J. Org. Chem.* **1991**, *56*, 4098–4112. (d) Imamoto, T.; Hatajima, T.; Takiyama, N.; Takeyama, T.; Kamiya, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3127–3135. (e) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595–4612.
3. Selected references since 1990: (a) Chenevert, R.; Caron, D. *Tetrahedron: Asymmetry* **2002**, *13*, 339–342. (b) Kanada, R. M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2000**, *41*, 3631–3635. (c) List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, A.; Bui, T.; Anderson, J.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1999**, *121*, 7283–7291. (d) Scholl, M.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 1425–1428. (e) Kouklovsky, C.; Dirat, O.; Berranger, T.; Langlois, Y.; Tran-Huu-Dau, M. E.; Riche, C. *J. Org. Chem.* **1998**, *63*, 5123–5128. (f) Nishimura, Y.; Mori, K. *Eur. J. Org. Chem.* **1998**, 233–236. (g) Majewski, M.; Nowak, P. *Tetrahedron: Asymmetry* **1998**, *9*, 2611–2617. (h) Chen, S. T.; Fang, J. M. *J. Org. Chem.* **1997**, *62*, 4349–4357. (i) Taniguchi, T.; Nakamura, K.; Ogasawara, K. *Synthesis* **1997**, 509–511. (j) Kroutil, W.; Osprian, I.; Mischitz, M.; Faber, K. *Synthesis* **1997**, 156–158. (k) Chan, T. H.; Chen, L. M.; Wang, D.; Li, L. H. *Can. J. Chem.* **1993**, *71*, 60–67. (l) Santiago, B.; Soderquist, J. A. *J. Org. Chem.* **1992**, *57*, 5844–5847. (m) Turpin, J. A.; Weigel, L. O. *Tetrahedron Lett.* **1992**, *33*, 6563–6564. (n) Mori, K.; Fukamatsu, K. *Liebigs Ann. Chem.* **1992**, 1191–1193. (o) Mash, E. A.; Fryling, J. A. *J. Org. Chem.* **1991**, *56*, 1094–1098. (p) Nemoto, H.; Yamada, T.; Ishibashi, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3149–3151. (q) Sugai, T.; Kakeya, H.; Ohta, H. *J. Org. Chem.* **1990**, *55*, 4643–4647. (r) Ibrahim, N.; Eggimann, T.; Dixon, E. A.; Wieser, H. *Tetrahedron* **1990**, *46*, 1503–1514.
4. Berkowitz, W. F.; Wu, Y. *J. Org. Chem.* **1997**, *62*, 1536–1539.
5. For alkene dihydroxylation with OsO_4/NMO, see: Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* **1998**, *63*, 6094–6095.
6. For Sharpless asymmetric dihydroxylation, see: Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768–2771.
7. For the synthesis of **4a**, see: Olson, W. T.; Hipsher, H. F.; Buess, C. M.; Goodman, I. A.; Hart, I.; Lamneck, J. H., Jr.; Gibsons, L. *J. Am. Chem. Soc.* **1947**, *69*, 2451–2454.
8. Diene **4b** was synthesized in 80% yield by the etherification of 2-ethylallyl alcohol and 2-ethylallyl bromide (1 equiv.) in the presence of KOH (2 equiv.) in refluxing THF, by following the procedure for preparing **4a**.[7]
9. The synthesis of 1,5-dimethyl-3,6,8-trioxabicyclo[3.2.1]octane (**5a**) was previously reported. See: Calinaud, P.; Gelas, J. *Can. J. Chem.* **1978**, *56*, 2292–2300.
10. For the synthesis of **6a**, see: Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1985**, *41*, 5779–5789.
11. For the synthesis of **6b**, see: Irrgang, B.; Mayr, H. *Tetrahedron* **1991**, *47*, 219–228.
12. For the synthesis of **6c**, see: Cao, X.-P.; Chan, T.-L.; Chow, H.-F.; Tu, J. *J. Chem. Soc., Chem. Commun.* **1995**, 1297–1299.