Pergamon

Tetrahedron Letters 42 (2001) 3757–3758

TETRAHEDRON LETTERS

Two-step synthesis of (±)-stigmolone, the pheromone of *Stigmatella aurantiaca*

Oleg L. Epstein and Oleg G. Kulinkovich*

Department of Organic Chemistry, Belarussian State University, 4, Skariny av., 220050 Minsk, Belarus

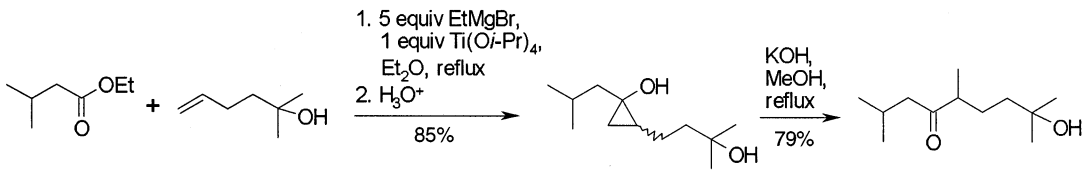
Received 18 January 2001; accepted 5 April 2001

Abstract—Racemic stigmolone (8-hydroxy-2,5,8-trimethyl-4-nonanone), the pheromone of myxobacterium *Stigmatella aurantiaca*, was synthesised in 67% overall yield, using titanium-mediated hydroxycyclopropanation of 2-methyl-5-hexen-2-ol with ethyl isovalerate followed by the base-induced ring opening of the resulting 2-(3-hydroxy-3-methylbutyl)-1-isobutyl-1-cyclopropanol.

Myxobacteria are Gram-negative aerobic bacteria that occur anywhere in soils and under nutrient deficient conditions aggregate to form myxospores and macroscopic coloured fruiting bodies.[1] Among myxobacteria, *Stigmatella aurantiaca* has the most elaborate fruiting body structure and produces a pheromone that possesses fruiting body inducing activity.[2] In 1998 Plaga et al. isolated and identified this pheromone as 8-hydroxy-2,5,8-trimethyl-4-nonanone **1**, named it stigmolone,[3] and synthesised it in four steps in 16% overall yield.[4] Recently, Mori et al. synthesised racemic stigmolone **1** in 48% yield in five steps.[5] They have also obtained both of the enantiomers of **1**[6] and showed that the racemic mixture exhibits nearly the same bioactivity as the individual enantiomers.[7]

We report herein a convenient and efficient two-step synthesis of (±)-stigmolone **1**. The formation of the α-methyl ketone moiety of compound **1** was based on regioselective C_1–C_3 cleavage of 1,2-disubstituted cyclopropanol **2**[8] (Scheme 1). The latter was readily prepared by hydroxycyclopropanation[9] of the bishomoallylic alcohol **3** with ethyl isovalerate promoted by the EtMgBr/Ti(O*i*-Pr)$_4$ reagent.[9–11] Slow addition of 5 equivalents of EtMgBr to a refluxing ethereal solution of equimolar amounts of ethyl isovalerate, 2-methyl-5-hexen-2-ol **3** and Ti(O*i*-Pr)$_4$ led, after aqueous workup, to 2-(3-hydroxy-3-methylbutyl)-1-isobutyl-1-cyclopropanol **2** as a mixture of diastereomers in 72% yield.[12] When *i*-PrMgBr, *n*-BuMgBr and *c*-C_6H_{11}MgBr were used in place of EtMgBr, the yields of **2** were 63, 62 and 33%, respectively.[13] The use of a slight excess (1.2 equiv.) of ethyl isovalerate in the reaction with alkene **3** promoted by EtMgBr/Ti(O*i*-Pr)$_4$ allowed an increase in the yield of cyclopropanol **2** to 85%.

Treatment of the cyclopropanol **2** with an excess of potassium hydroxide in dry THF[8] for 3 hours at reflux afforded in a 90% yield an equimolecular mixture of **1** and the isomeric product of C_1–C_2 cyclopropane ring cleavage. The selectivity of the formation of the desired ketone **1** was significantly improved to 94:6 (GC–MS analysis) when methanol was employed as the solvent, and the target product (±)-**1** was isolated by column chromatography on silica gel in 79% yield.[14] NMR, IR and mass-spectral data were in good accordance with the data described in the literature.[3–7] Preparation of



Scheme 1.

* Corresponding author. Fax: (375)-17-226-4998; e-mail: kulinkovich@chem.bsu.unibel.by

0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)00564-0

(±)-stigmolone **1** was also performed without isolation of the intermediate cyclopropanol **2** in 62% overall yield.

References

1. Dawid, W. *FEMS Microbiol. Rev.* **2000**, *24*, 403–427.
2. Stephens, K.; Hegeman, G. D.; White, D. *J. Bacteriol.* **1982**, *149*, 739–747.
3. Plaga, W.; Stamm, I.; Schairer, H. U. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 11263–11267.
4. Hull, W. E.; Berkessel, A.; Plaga, W. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 11268–11273.
5. Domon, K.; Mori, K. *Eur. J. Org. Chem.* **1999**, 979–980.
6. Mori, K.; Takenaka, M. *Eur. J. Org. Chem.* **1998**, 2181–2184.
7. Morikawa, Y.; Takayama, S.; Fudo, R.; Yamanaka, S.; Mori, K.; Isogai, A. *FEMS Microbiol. Lett.* **1998**, *165*, 29–34.
8. Epstein, O. L.; Kulinkovich, O. G. *Tetrahedron Lett.* **1998**, *39*, 1823–1826.
9. Kulinkovich, O. G.; Savchenko, A. I.; Sviridov, S. V.; Vasilevskii, D. A. *Mendeleev Commun.* **1993**, 230–231.
10. Savchenko, A. I.; Kulinkovich, O. G. *Zh. Org. Khim.* **1997**, *33*, 913–915.
11. For recent reviews, see: Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834. Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835–2886.
12. The solution of EtMgBr derived from EtBr (2.05 ml, 27 mmol) and magnesium turnings (0.6 g, 25 mmol) in 15 ml of Et_2O was added dropwise over 30 min to the solution of ethyl isovalerate (0.90 ml, 6 mmol), 2-methyl-5-hexen-2-ol **3** (0.68 ml, 5 mmol) and titanium(IV) isopropoxide (1.50 ml, 5 mmol) in 10 ml of ether at reflux. The reaction mixture was stirred for an additional 10 min and then poured into 50 ml ice-cold 5% H_2SO_4. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×15 ml). The combined organic extracts were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography on silica gel to provide 0.85 g (85%) of 2-(3-hydroxy-3-methylbutyl)-1-isobutyl-1-cyclopropanol **2** as a mixture of diastereomers: IR (neat) 3360, 3074, 2920, 1460, 1365, 1250, 1200, 925, 905 cm^{-1}. MS (70 eV) 182 (M^+-H_2O), 167, 149, 140, 127, 121, 113, 111, 107, 97, 95, 91, 85 (100%) 69, 57, 43, 29. (*E*)-isomer ^1H NMR (200 MHz, $CDCl_3$) 0.04–0.13 (m, 1H), 0.78–0.88 (m, 2H), 0.96 (d, $J=6.9$ Hz, 3H), 0.97 (d, $J=6.9$ Hz, 3H), 1.19 (s, 6H), 1.35–1.64 (m, 4H), 1.65–2.06 (m, 3H), 2.88 (br s, 2H). (*Z*)-isomer ^1H NMR (200 MHz, $CDCl_3$) δ 0.27–0.35 (m, 1H), 0.48–0.61 (m, 2H), 0.93 (d, $J=6.9$ Hz, 3H), 0.95 (d, $J=6.9$ Hz, 3H), 1.20 (s, 3H), 1.23 (s, 3H), 1.35–1.42 (m, 2H), 1.50–1.62 (m, 4H), 1.98 (sept, $J=6.8$ Hz, 1H), 2.67 (br s, 2H).
13. For the use of various Grignard reagents for hydroxycyclopropanation of olefins, see also: (a) Epstein, O. L.; Savchenko, A. I.; Kulinkovich, O. G. *Tetrahedron Lett.* **1999**, *40*, 5935–5938; (b) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291–292; (c) Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079–6082; (d) Kasatkin, A.; Kobayashi, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1849–1852; (e) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198–4199; (f) Lee, J.; Kim, Y. G.; Bae, J. G.; Cha, J. K. *J. Org. Chem.* **1996**, *61*, 4878–4879.
14. The solution of cyclopropanol **2** (0.85 g, 4.25 mmol) and KOH (0.8 g, 14.2 mmol) in 7 ml of dry MeOH was refluxed for 3 hours. Then the reaction mixture was concentrated to half-volume under reduced pressure, and water (15 ml) was added. The mixture was extracted with ethyl acetate (3×10 ml). The combined organic layers were washed twice with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford 0.67 g of (±)-**1**: IR (neat) 3460, 2955, 2870, 1705, 1460, 1365, 1265, 1170, 950, 920 cm^{-1}. MS (70 eV) 185 (M^+-CH_3), 182 (M^+-H_2O), 167, 141, 127, 125, 114, 103, 97, 85, 72, 69, 57 (100%), 43, 29. ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, $J=6.5$ Hz, 3H), 0.91 (d, $J=6.9$ Hz, 3H), 1.09 (d, $J=7$ Hz), 1.21 (s, 6H), 1.28–1.50 (m, 3H), 1.61–1.80 (m, 2H), 2.04–2.25 (m, 1H), 2.27–2.34 (m, 2H), 2.38–2.52 (m, 1H). The hydroxy ketone (±)-**1** was unstable to storage decomposing to give the corresponding pyran derivatives.[3–6]