Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4609–4615

TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of (−)-γ-jasmolactone

Lauri J. Missio and J. Valdir Comasseto*

Instituto de Química, Universidade de São Paulo, C. P. 26077, 05599-070 São Paulo SP, Brazil

Received 26 October 2000; accepted 31 October 2000

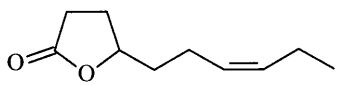
Abstract

The title compound was prepared in seven steps starting from the commercially available 4-ketopimelic acid. The key step features an enantioselective lactonization promoted by PPL. © 2000 Published by Elsevier Science Ltd.

1. Introduction

The γ-butyrolactone backbone is present in a number of biologically active natural products. Recent reports in the literature illustrate this fact.[1] The physiological activity of such lactones often depends on the configuration of the stereogenic centers present in their structure.[2–6]

According to a patent[7] the organoleptic properties of γ-jasmolactone (*Z*-7-decen-4-olide) **1** are described as fruity, flowery, green, creamy, sweet and juicy. This compound has an association with peaches and tropical fruits and can enhance the fruit flavor in food stuffs or drinks.[7]



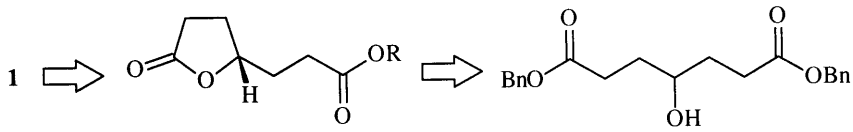
1

Several syntheses of **1** were described in the literature,[8–12] however, none of them were enantioselective. In 1993, Fuganti et al. reported that (*R*)-**1**, obtained from linolenic acid by action of *Pichia stipitis* and *ohmeri*, was identified as one of the main aroma constituents of white peaches.[13] In that work it was only mentioned that the (*S*)-**1** isomer was a minor constituent of the mixture.

As part of an ongoing program on the enantioselective synthesis of γ-butyrolactones in course in our laboratory, we devised the synthesis of (*S*)-**1** according to the retrosynthetic analysis shown in Scheme 1.

* Corresponding author. E-mail: jvcomass@iq.usp.br

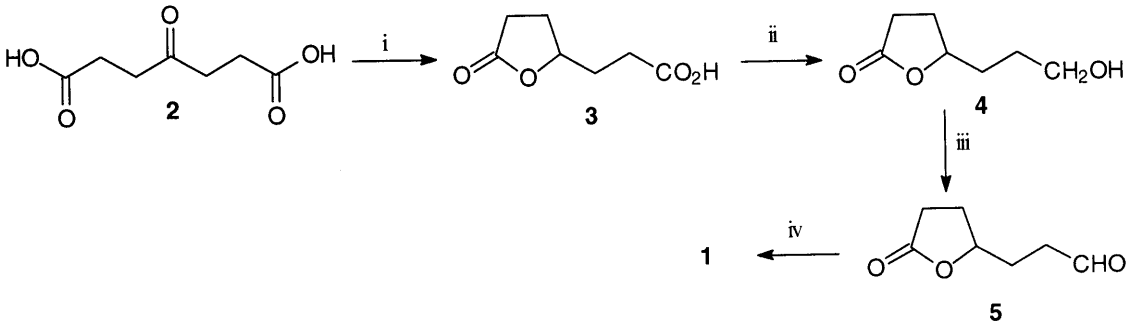
0957-4166/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0957-4166(00)00444-4



Scheme 1.

2. Results and discussion

Initially we synthesized racemic **1** in four steps, starting from the commercially available 4-ketopimelic acid **2**. Reduction of the keto group of **2** with sodium borohydride gave lactone **3** on acidic work up. Reduction of **3** with borane·dimethylsulfide (BMS) gave alcohol **4** which was oxidized to aldehyde **5** by PCC. A Wittig olefination completed the sequence giving racemic **1** (Scheme 2).

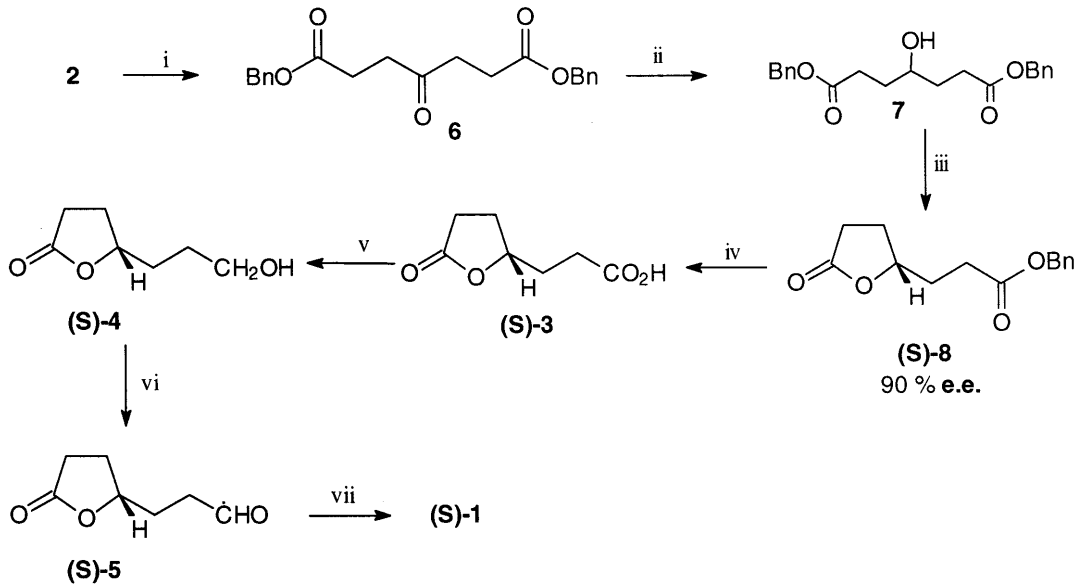


Scheme 2. Reagents and conditions: (i) $NaBH_4$, THF, 3 h, rt (90%); (ii) BMS, THF, 2 h, rt (92%); (iii) PCC, CH_2Cl_2, 2 h, rt (91%); (iv) $C_3H_7PPh_3Br$, LHMDS, THF (55%)

(*S*)-**1** was prepared according to Scheme 3. The key step was the synthesis of (*S*)-**8** lactone, which featured a lipase enantioselective lactonization of the prochiral diester **7**.[14] Compound **7** was prepared by benzylation of **2** followed by reduction of the keto group with sodium borohydride. Lactone (*S*)-**8** was obtained in 90% e.e. by pig pancreatic lipase (PPL) lactonization of **7**, as shown by chiral HPLC analysis. The (*S*) configuration of the stereogenic center of lactone **8** was attributed by comparison of its specific rotation with the literature data.[14] The benzyl group of lactone **8** was hydrogenolysed by H_2/Pd giving (*S*)-**3**. The measured specific rotation for compound (*S*)-**3** was compared with the published one,[14] showing that racemization did not occur. The compound was allowed to stand for 4 days at room temperature and the specific rotation was measured again. No change was observed, showing that no racemization occurred. Compound (*S*)-**3** was submitted to BMS reduction followed by PCC oxidation to give (*S*)-**5**. A Wittig olefination led to (*S*)-**1**. The enantiomeric excess of the final product (87%) was determined by means of gas chromatography.

The Wittig olefination step gave (*S*)-**1** as a 85:15 mixture of *Z*:*E* isomers which were separated by column chromatography on silica gel impregnated with $AgNO_3$,[15] eluting with hexane:ethyl acetate (7:3). The product is a colorless oil presenting an odor of peaches.

In conclusion, we have described the first enantioselective synthesis of the γ-jasmolactone. Using the common intermediate **7** the enantioselective syntheses of other γ-butyrolactones are underway in our group.



Scheme 3. Reagents and conditions: (i) $CsCO_3$, DMF/MeOH, pH 7.0, BnBr, 17 h, rt (84%); (ii) $NaBH_4$, Et_2O/MeOH, 2 h, –20°C (95%); (iii) PPL, Et_2O, 24 h, 30°C (74%); (iv) Pd/C 10%, H_2, 1 atm, 3 h (95%); (v) BMS, THF, 2 h, rt (90%); (vi) PCC, CH_2Cl_2, 2 h, rt (90%); (vii) $C_3H_7PPh_3Br$, LHMDS, THF, (55%)

3. Experimental

3.1. General

The NMR spectra were recorded on Bruker DRX-400, 500 and Varian FT-300 spectrometers using TMS as internal reference (^{1}H NMR) and the central peak of the $CDCl_3$ signal (^{13}C NMR). IR spectra were obtained with a Perkin–Elmer 1600 grating infrared spectrophotometer. The GC analyses were performed on a Hewlett–Packard 5890(II) instrument with a capillary crosslinked 5% Ph-Me silicone column (25 m×0.20 mm×0.33 um) and with a chiral column packed with β-cyclodextrin. The mass spectra were performed on GC-MS HP 5890/5988A. Optical rotations were measured on a Jasco, DIP 370 Digital polarimeter. Enantiomeric excesses were determined by chiral HPLC analysis with Shimadzu LC10AD.

3.2. 3-(5-Oxotetrahydro-2-furanyl)propanoic acid **3**

4-Ketopimelic acid **2** (1.0 g; 5.74 mmol) was dissolved in dry THF (30 mL) and then sodium borohydride (0.8 g; 24 mmol) was added. The mixture was stirred for 3 h at room temperature. The solvent was evaporated and to the residue was added 8 M HCl (10 mL). The aqueous phase was extracted with methylene dichloride (3×50 mL). The organic phase was dried with $MgSO_4$ and the solvent was evaporated, giving pure **3**. Yield: 0.816 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.86–1.95 (m, 1H); 1.97–2.06 (m, 2H); 2.36–2.44 (m, 1H); 2.53–2.60 (m, 4H); 4.59 (dddd, J=8.16 Hz, J=8.15 Hz, J=6.78 Hz, J=5.02 Hz, 1H); 10.67 (sl, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 177.5; 177.2; 79.8; 30.2; 29.8; 28.4; 27.5; IR (KBr) (cm^{-1}): 3489; 2933, 1768; 1727; MS: (m/z) (%rel.): 44 (51.8); 85 (100); 98 (0.4); 112 (1.1).

3.3. 3-(5-Hydroxypropyl)tetrahydro-2-furanone **4**

In a three necked flask, under nitrogen, compound **3** (2.12 g; 13.44 mmol) was dissolved in dry THF (90 mL). Then $BH_3{\cdot}SMe_2$ (1.61 mL; 16.12 mmol, $c=10$ M) was added via a syringe. The mixture was allowed to stir at room temperature for 2 h. Then methanol (30 mL) was added and distilled afterwards. The residue was dissolved in methanol (10 mL), dried with $MgSO_4$, the solvent was evaporated and the residue was purified by silica gel column chromatography eluting with ethyl acetate. Yield: 1.78 g (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.63–1.94 (m, 5H); 2.32–2.46 (m, 1H); 2.53–2.57 (m, 2H); 3.65 (t, $J=5.45$ Hz, 2H); 4.56 (dddd, $J=7.58$ Hz, $J=7.05$ Hz, $J=6.50$ Hz, $J=5.41$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 177.8; 81.2; 61.8; 32.0; 28.9; 28.4; 28.0; IR (KBr) (cm^{-1}): 3464; 2938, 1763; MS: (m/z) (%rel.): 31 (88.2); 44 (70.3); 60 (5.1); 85 (100); 113 (1.6).

3.4. 3-(5-Oxotetrahydro-2-furanyl)propanal **5**

PCC (0.621 g, 2.76 mmol) and sodium acetate (0.044 g; 0.52 mmol) were dissolved in dry CH_2Cl_2 (10 mL). Then alcohol **4** (0.2 g; 1.38 mmol), dissolved in dry CH_2Cl_2 (5 mL), was added. The initially yellow solution turned brown and was stirred for 2 h at room temperature. Then the solution was filtered through a column containing Celite and activated charcoal. The solvent was evaporated and the residue was used without purification. Yield: 0.18 g (91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.83–1.96 (m, 2H); 2.01–2.09 (m, 1H); 2.33–2.42 (m, 1H); 2.53–2.58 (m, 2H); 2.67–2.71 (m, 2H); 4.54 (dddd, $J=9.36$ Hz, $J=8.32$ Hz, $J=6.65$ Hz, $J=4.14$ Hz, 1H); 9.82 (t, $J=0.95$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 200.8; 176.8; 79.5; 39.7; 30.4; 28.6; 27.7; IR (KBr) (cm^{-1}): 2948, 1765; 1720; MS (m/z) (%rel.): 41 (61.6); 56 (58.9). 85 (100); 98 (23.3); 114 (15.1).

3.5. (±)-γ-Jasmolactone **1**

To a suspension of propyltriphenyl phosphonium bromide (0.51 g; 1.25 mmol) in dry THF (2 mL) was added lithium bis(trimethylsilyl)amide (LHMDS) (1.5 mL; 1.5 mmol). The resulting purple solution was stirred for 10 min at 0°C and the aldehyde **5** (0.142 g; 1.1mmol), dissolved in dry THF (2 mL), was added. The THF was evaporated and the residue was dissolved with ethyl acetate (3×30 mL). The organic phase was washed with ammonium chloride solution and brine, dried with $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography eluting with hexane:ethyl acetate (7:3). Yield: 0.082 g (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.96 (t, $J=7.56$ Hz; 1H); 1.61–1.68 (m, 1H); 1.76–1.91 (m, 2H); 2.02–2.08 (m, 2H); 2.17–2.21 (m, 2H); 2.30–2.36 (m, 1H); 2.52–2.55 (m, 1H); 4.50 (dddd; $J=8.12$ Hz; $J=6.76$ Hz; $J=6.65$ Hz; $J=5.17$ Hz; 1H); 5.31 (dtt; $J=10.75$ Hz; $J=7.29$ Hz; $J=1.54$ Hz, 1H); 5.43 (dtt; $J=10.75$ Hz; $J=7.29$ Hz; $J=1.54$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 177.0; 132.7; 126.9; 80.1; 35.3; 28.5; 27.7; 22.7; 20.2; 14.0; IR (KBr) (cm^{-1}): 2936, 1775; MS (m/z) (%rel.): 68 (100); 85 (40.9), 108 (11.4); 168 (M^+).

The spectroscopic data are in agreement with those of the literature.[2]

3.6. Dibenzyl 4-ketoheptanoate **6**

Compound **2** (0.82 g; 4.75 mmol) was dissolved in methanol:water (10:1) (22 mL). Then a 20% aqueous solution of $CsCO_3$ was added until pH 7.0. The solvents were evaporated under

vacuum. DMF (2×50 mL) was added and distilled afterwards. Then dry DMF (50 mL) was added under nitrogen. To the solution was added recently distilled benzyl bromide (1.24 mL; 10.45 mmol) and the mixture was stirred for 17 h. The solvent was evaporated and then aqueous $NaHCO_3$ (2×10 mL) was added. The aqueous phase was extracted with methylene dichloride and dried with $MgSO_4$. The product was used without further purification. Yield: 1.74 g (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.64 (t, $J=6.40$ Hz, 4H); 2.77 (t, $J=6.40$ Hz, 4H); 5.10 (s, 4H); 7.30–7.37 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.8; 172.5; 135.9; 128.6; 128.2; 66.5; 37.1; 28.0; IR (KBr) (cm^{-1}): 2948, 1731; 1706; 1327; 625, 726.

3.7. Dibenzyl 4-hydroxyheptanodiate **7**

Compound **6** (0.3 g; 1.3 mmol) was dissolved in a mixture of ether:methanol 4:1 (25 mL). Sodium borohydride (0.05 g, 1.2 mmol) was added at −20°C. The reaction was monitored by TLC eluting with ether:hexane (6:4) and by ^{1}H NMR. After 2 h, 5% aqueous $NaHCO_3$ (10 mL) was added and the reaction mixture was extracted with cold ether (3×20 mL). The organic phase was dried with $MgSO_4$, evaporated and the residue was purified by silica gel chromatography eluting with ether:hexane (6:4).

Yield: 0.29 g (95%). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.61–1.89 (m, 10H); 2.51 (t, $J=8.00$ Hz, 4H); 3.63–3.69 (m, 1H); 5.30 (s, 4H); 7.22–7.48 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 173.7; 135.7; 128.4; 128.1; 70.1; 65.0; 32.1; 30.5; IR (KBr) (cm^{-1}): 3454; 2931, 1733; 1497; 698, 747.

3.8. (S)-Dibenzyl 3-(5-oxotetrahydro-2-furanyl)propanoate **8**

In a round bottomed flask compound **7** (0.117 g, 0.32 mmol) was dissolved in dry ether (3 mL) and then PPL (0.3 g) was added. The mixture was further stirred for 24 h at 30°C. The reaction was monitored by TLC eluting with ether:hexane (6:4). The enzyme was filtered and the product was purified by silica gel column chromatography eluting with ether:hexane (6:4).

Yield: 0.059 g (74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.81–1.92 (m, 1H); 1.94–2.07 (m, 2H); 2.30–2.38 (m, 1H); 2.49–2.58 (m, 4H); 4.53 (dddd, $J=8.19$ Hz, $J=7.60$ Hz, $J=7.02$ Hz, $J=5.27$ Hz, 1H); 5.13 (s, 2H); 7.25–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 176.5; 172.1; 135.5; 128.2; 128.0; 127.9; 79.2; 66.0; 30.2; 29.8; 28.3; 27.4; IR (KBr) (cm^{-1}): 2929, 1773; 733; 699.

The enantiomeric excess of the lactone was determined by chiral HPLC. Stationary phase: amylose tris[(*S*)-1-phenylethylcarbamate] coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w); mobile phase: [hexane:isopropanol (8:2)]; flow rate: 0.5 mL/min). The enantiomeric excess was 90%. The $[\alpha]_D$ measured was compared with the published one: $[\alpha]_D^{25}$ found: −42.15 (*c* 0.74, CH_2Cl_2), $[\alpha]_D^{25}$ literature:[14] −40.86 (*c* 0.74, CH_2Cl_2).

3.9. (S)-3-(5-Oxotetrahydro-2-furanyl)propanoic acid **3**

Compound (*S*)-**8** (0.41 g, 1.64 mmol) was dissolved in MeOH (5 mL). Then Pd/C 10% (0.2 g) was added and the mixture was stirred under a H_2 atmosphere for 3 h at room temperature. The catalyst was filtered through silica gel and Celite. The solvent was evaporated and the product was used without further purification. Yield: 0.245 g (95%). The spectral data are identical to those observed for racemic **3** (Section 3.2) and are in agreement with those of the

literature.[14] The $[\alpha]_D^{25}$ measured was compared with the published one: $[\alpha]_D^{25}$ found: −42.86 (*c* 0.77, H_2O), $[\alpha]_D^{25}$ literature:[14] −39.86 (*c* 0.77, H_2O).

3.10. (S)-3-(5-Hydroxypropyl)tetrahydro-2-furanone 4

(*S*)-**4** was prepared by a procedure similar to that described for racemic **4** (Section 3.3). The spectral data agree with those of racemic **4** and are in agreement with those of the literature.[14]

3.11. (S)-3-(5-Oxotetrahydro-2-furanyl)propanal 5

(*S*)-**5** was prepared by a procedure similar to that described for racemic **5** (Section 3.4). The spectral data agree with those of racemic **5** and are in agreement with those of the literature.[14]

3.12. (S)-(−)-γ-Jasmolactone 1

(*S*)-**1** was prepared by a procedure similar to that described for racemic **1** (Section 3.5). The spectral data agree with those of racemic **1**. The enantiomeric excess (87%) was measured by using a gas chromatograph equipped with a β-cyclodextrin (Supelco™) capillary column (30 m, 0.25 mm, i.d. 0.25 μm film thickness); the carrier gas was H_2 set at 14 KPa column head pressure and the column temperature program was 30 min at 100°C, 1°C min^{-1} to 180°C and held at 180°C for 20 min. The on-column injector and the detector were at 250 and 300°C, respectively. $[\alpha]_D^{25}$: −22.35, $c = 0.85$; $CHCl_3$.

Acknowledgements

The authors thank FAPESP and CNPq for support.

References

1. (a) Bertus, P.; Ratovelomanana-Vidal, V.; Genêt, J. P.; Touati, A. R.; Homri, T.; Hassine, B. B. *Tetrahedron: Asymmetry* **1999**, *10*, 1369; (b) Wang, G.; Hollingsworth, R. I. *Tetrahedron: Asymmetry* **1999**, *10*, 1895; (c) Ramachandran, P. V.; Krzeminski, M. P.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron: Asymmetry* **1999**, *10*, 11; (d) Pansare, S. V.; Jain, R. P.; Ravi, R. G. *Tetrahedron: Asymmetry* **1999**, *10*, 3103; (e) Upadhya, T. T.; Gurunath, S.; Sudalai, A. *Tetrahedron: Asymmetry* **1999**, *10*, 2899.
2. Mori, K. *Chem. Commun.* **1997**, 1153.
3. Iino, Y.; Tanaka, A.; Yamashita, K. *Agric. Biol. Chem.* **1972**, *36*, 2505.
4. Ku, T. W.; McCarthy, M. E.; Weichman, B. M.; Gleason, J. G. *J. Med. Chem.* **1985**, *28*, 1847.
5. Sanière, M.; Charvet, I.; Le Merre, Y.; Depezay, J.-C. *Tetrahedron* **1995**, *51*, 1653.
6. Tumlinson, J. H.; Klein, M. G.; Doolittle, R. E.; Ladd, T. L.; Proveaux, A. T. *Science* **1977**, *197*, 789.
7. Vlas, A. EP Patent 0473842A1, 1990.
8. Bellini, R.; Petrini, M.; Marotta, E. *Synth. Commun.* **1989**, *19*, 575.
9. Yamashita, M.; Tashika, H.; Uchida, M. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1257.
10. Tetsuo, M.; Hidetaka, T. JP Patent 0687844, 1994.
11. Gavin, D.; Geraghty, N. W. A. *Synth. Commun.* **1994**, *24*, 1351.

12. (a) Matsuda, I.; Murata, S.; Izumi, Y. *J. Org. Chem.* **1980**, *45*, 237; (b) Hidetaka, T. *Yukagaku* **1987**, *36*, 362; (c) Hidetaka, T. JP Patent 63119480, 1988; (d) Tetsuo, M. *Yukagaku* **1988**, *37*, 19; (e) Hidetaka, T. *Yukagaku* **1989**, *38*, 1019; (f) Tetsuo, M.; Hidetaka, T.; Akira, S. JP Patent 02059563A228, 1990; (g) Keiichi, T.; Ito, M. JP Patent 02282377A2; (h) Keiichi, T.; Yasuhiro, K.; Naoto, Y. JP Patent 02282376A2, 1990.
13. (a) Fuganti, C.; Grasselli, P.; Zucchi, G.; Allegrone, G.; Barbeni, M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2777 and references cited therein; (b) Berger, R. G. *Aroma Biotechnology*; Springer-Verlag: Berlin, 1995; p. 70; (c) Teranishi, *Flavor Chemistry-Trends and Developments* ACS Symposium Series, *388*, American Chemical Society: Washington, DC, 1989, pp. 01–06.
14. Gutman, A. L.; Zuobi, K.; Bravdo, T. *J. Org. Chem.* **1990**, *55*, 3546.
15. Tumlinson, J. H.; Heath, R. R.; Dollitle, R. E. *J. Chrom. Sci.* **1977**, *15*, 10.