Easy Access to (*E*)-β-Ocimene

Selma Yildizhan, Stefan Schulz*

Institut für Organische Chemie, TU Braunschweig, Hagenring 30, 38106 Braunschweig, Germany
Fax +49(531)3915272; E-mail: stefan.schulz@tu-bs.de

Received 23 September 2011

Abstract: β-Ocimene is one of the most common monoterpenes found in Nature, but a simple and reliable synthesis of the pure *E*-isomer has been missing. Here, we report a simple procedure involving a Grignard coupling as the key step that allows its synthesis on gram scales. The configuration of the double bond is fixed in the starting material.

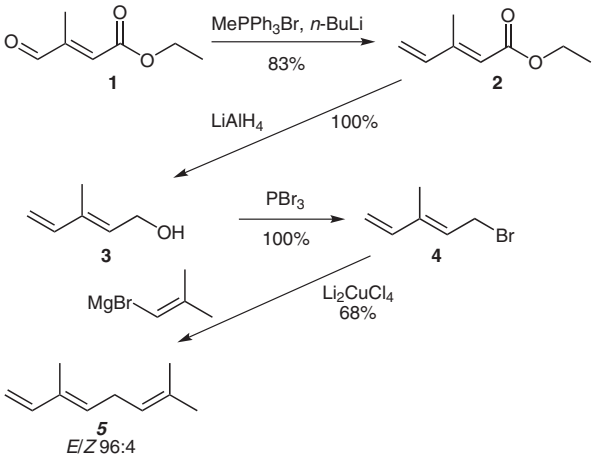
Key words: terpenoids, Grignard reaction, alkenes, hydrocarbons, coupling

(*E*)-β-Ocimene (**5**) is an acyclic monoterpene that is a widespread component of many essential oils. It is one of the most common flower volatiles known, occurring in more than 70% of plant families investigated.[1,2] In this context, it often functions as a pollination attractant of insects, together with other compounds.[2,3] Ocimene also plays important roles in chemical communication and trophic interactions. Several herbivores induce (*E*)-β-ocimene production in the host plant when feeding,[4] neighboring undamaged plants can thus be stimulated to enhance their own emission of volatiles.[5] These volatile signals indicating presence of herbivores can be exploited by parasitoids of the herbivores.[2,6,7] Male *Heliconius melpomene* butterflies use **5** as an antiaphrodisiac pheromone during courtship,[8] and it is also produced by other insects,[9] but no function has been described in these cases.

Pure and easily available compounds are a prerequisite for biological testing and are needed as analytical reference material. Unfortunately, **5** is only commercially available as a mixture of isomers, and not in pure form. (*E*)-β-Ocimene has been synthesized repeatedly, but a short, reliable and easy to reproduce synthesis is missing. An early metal-organic synthesis developed by Huo and Negishi, starting from geranyl acetate,[10] furnished ocimene in one step by treatment with propargyl zinc bromide. However, instead of the reported 75:25 *E*/*Z* mixture, the opposite, 29:71 *E*/*Z* ratio, was obtained in moderate yield in our hands. A related reaction using an allylindium reagent and palladium catalysis furnished **5** in good yield from ethyl geranyl carbonate, but no data on the *E*/*Z* ratio were reported.[11] Several substrates were tested for elimination reactions with allylpalladium reagents, but, again, mixtures of stereo- and regioisomers were formed.[12] Various procedures using thermal or other elimination protocols starting from linalool, pinene, or geraniol usually furnished only mixtures of products.[13] A synthesis developed by Nozaki et al. converts protected geraniol into a diol via an epoxide, and finally furnishes **5** by elimination.[14]

Because we needed **5** for several experiments and had received requests from other research groups, we developed a simple procedure to obtain gram quantities of pure (*E*)-β-ocimene, which is useful for further research, especially in chemical ecology.

Initial attempts at the synthesis of **5** via 2,6-dimethyl-2,5-heptadienal and Wittig methenylation were not satisfactory because of low *E*/*Z* selectivity and/or low yields. Therefore, we decided to introduce the conjugated double bond system early in the synthesis (Scheme 1). The terpene building block **1** is commercially available in stereochemically pure form. Wittig reaction with methyltriphenylphosphonium bromide furnishes the diene ester **2**. The ester can be quantitatively reduced with $LiAlH_4$ and converted into bromide **4** by treatment with PBr_3. This procedure is more convenient than the reported Appel bromination[15] because both column chromatography and Kugelrohr distillation of this sensitive bromide can be avoided. Finally, cross-coupling of **3** with commercially available 2-methyl-1-propenylmagnesium bromide under catalysis of Li_2CuCl_4 furnished (*E*)-β-ocimene (**5**) in good yield. The *E*/*Z* ratio was determined to be 96:4 by GC analysis. Careful analysis by GC showed that slight isomerization can take place during the bromination and cross-coupling steps, leading to the observed isomer ratio. The stereochemical purity of **5** can be further enhanced by argentation chromatography.[16] An extension of the methodology to the synthesis of (2*E*,6*E*)-α-farnesene failed because we could not obtain a Grignard reagent from 1-



Scheme 1

SYNLETT 2011, No. 19, pp 2831–2833
Advanced online publication: 11.11.2011
DOI: 10.1055/s-0031-1289869; Art ID: B08311ST

bromo-2,6-dimethylhept-1-ene, which was needed as a precursor.

In essence, the described synthesis[17] can be easily handled even in less experienced laboratories and opens the way for more investigations into the effects of this terpene in Nature.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank the State of Lower Saxony for funding and Marin Stürminger for technical assistance.

References and Notes

(1) Knudsen, J.; Eriksson, R.; Gershenzon, J.; Ståhl, B. *Botan. Rev.* **2006**, *72*, 1.
(2) Honda, K.; Omura, H.; Hori, M.; Kainoh, Y. In *Comprehensive Natural Products II*, Vol. 4; Mander, L. N.; Liu, H.-W., Eds.; Elsevier: Oxford, **2010**, 563.
(3) Kessler, D.; Baldwin, I. T. *Plant J.* **2007**, *49*, 840.
(4) (a) Pare, P. W.; Tumlinson, J. H. *Plant Physiol.* **1997**, *114*, 1161. (b) Navia-Gine, W. G.; Yuan, J. S.; Mauromoustakos, A.; Murphy, J. B.; Chen, F.; Korth, K. L. *Plant Physiol. Biochem. (Issy-les-Moulineaux, Fr.)* **2009**, *47*, 416.
(5) (a) Kost, C.; Heil, M. *J. Ecol.* **2006**, *94*, 619. (b) Piesik, D.; Lyszczarz, A.; Tabaka, P.; Lamparski, R.; Bocianowski, J.; Delaney, K. J. *Ann. Appl. Biol.* **2010**, *157*, 425.
(6) Khan, Z. R.; James, D. G.; Midega, C. A. O.; Pickett, J. A. *Biol. Control* **2008**, *45*, 210.
(7) (a) Du, Y.; Poppy, G. M.; Powell, W.; Pickett, J. A.; Wadhams, L. J.; Woodcock, C. M. *J. Chem. Ecol.* **1998**, *24*, 1355. (b) Mumm, R.; Dicke, M. *Can. J. Zool.* **2010**, *88*, 628.
(8) Schulz, S.; Estrada, C.; Yildizhan, S.; Boppré, M. L.; Gilbert, E. *J. Chem. Ecol.* **2008**, *34*, 82.
(9) Keegans, S. J.; Billen, J.; Morgan, E. D.; Gokcen, O. A. *J. Chem. Ecol.* **1993**, *19*, 2705.
(10) Matsushita, H.; Negishi, E. *J. Org. Chem.* **1982**, *47*, 4161.
(11) Lee, P. H.; Shim, E.; Lee, K.; Seomoon, D.; Sundae, K. *Bull. Korean Chem. Soc.* **2005**, *26*, 157.
(12) Keinan, E.; Kumar, S.; Dangur, V.; Vaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 11151.
(13) (a) Majetich, G.; Hicks, R.; Okha, F. *New J. Chem.* **1999**, *23*, 129. (b) Singh, S. A.; Kabiraj, S.; Khandare, R. P.; Nalawade, S. P.; Upar, K. B.; Bhat, S. V. *Synth. Commun.* **2010**, *40*, 74. (c) Reddy, P. V.; Bhat, S. V. *J. Indian Chem. Soc.* **1998**, *75*, 10.
(14) (a) Tanaka, S.; Yasuda, A.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1975**, *97*, 3252. (b) Yasuda, A.; Tanaka, S.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1752.
(15) Wu, Z.; Wouters, J.; Poulter, C. D. *J. Am. Chem. Soc.* **2005**, *127*, 17433.
(16) Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425.
(17) **Ethyl (*E*)-3-Methylpenta-2,4-dienoate(2)**: A solution of *n*-butyllithium (1.6 M in hexane, 14.4 mL, 23 mmol) was added dropwise at –78 °C to a solution of methyltriphenylphosphonium bromide (8.1 g, 22.7 mmol) in absolute THF (75 mL). The mixture was brought to 0 °C and stirred for 1 h. After cooling to –78 °C, ethyl (*E*)-3-methyl-4-oxo-2-butenoate (**1**; 3 g, 21.1 mmol) dissolved in absolute THF (30 mL) was added slowly. The mixture was stirred for 24 h at r.t., hydrolyzed with water, and extracted three times with Et_2O. The combined organic phases were dried with $MgSO_4$ and the solvent was removed. The residue was purified by flash chromatography (pentane–Et_2O, 40:1) to give **2** (83% yield, 2.43 g, 17.3 mmol). TLC: R_f = 0.24 (pentane–Et_2O, 40:1); ^{1}H NMR (400 MHz, $CDCl_3$): = 6.30–6.37 (ddd, *J* = 17.4, 10.6, 0.8 Hz, 1 H, CH), 5.74–5.71 (m, 1 H, CH), 5.54 (d, *J* = 17.4 Hz, 1 H, CH), 5.31 (d, *J* = 10.6 Hz, 1 H, CH), 4.11 (q, *J* = 7.2 Hz, 2 H, CH_2), 2.20 (d, *J* = 1.3 Hz, 3 H, CH_3), 1.22 (t, *J* = 7.1 Hz, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0 (s), 151.9 (s), 140.2 (d), 120.0 (d), 119.3 (t), 59.8 (t), 14.3 (q), 13.1 (q); MS (EI, 70 eV): *m*/*z* (%) = 140 (54)[M^+], 112 (78), 111 (76), 97 (41), 96 (12), 95 (100), 83 (10), 69 (17), 67 (91), 66 (27), 65 (35), 56 (12), 55 (13), 51 (13), 41 (60), 40 (13), 39 (57).
(*E*)-3-Methylpenta-2,4-dien-1-ol (3): Ethyl (*E*)-3-methylpenta-2,4-dienoate (**2**; 2.18 g, 15.57 mmol) was added to a suspension of $LiAlH_4$ (913 mg, 24 mmol) in absolute Et_2O (45 mL) under a N_2 atmosphere. The mixture was heated to reflux for 1 h and quenched by the addition of ice-cooled H_2O. The residue formed was dissolved by addition of 10% H_2SO_4. The phases were separated and the aqueous phase was washed with Et_2O. The combined organic phases were dried with $MgSO_4$ and the solvent was removed in vacuo. The residue of (*E*)-3-methylpenta-2,4-dien-1-ol (**3**; 1.53 g, 15.57 mmol, 100% yield) was sufficiently pure for use in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45–6.33 (m, 1 H, CH), 5.73–5.63 (m, 1 H, CH), 5.22 (d, *J* = 16.9 Hz, 1 H, CH), 5.07 (d, *J* = 10.6 Hz, 1 H, CH), 4.29 (d, *J* = 6.8 Hz, 2 H, CH_2), 1.82–1.77 (m, 3 H, CH_3), 1.45 (br. s., 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.7 (d), 136.4 (s), 130.4 (d), 113.2 (t), 59.4 (t), 11.8 (q); MS (EI, 70 eV): *m*/*z* (%) = 98 (30)[M^+], 97 (11), 83 (83), 80 (23), 79 (44), 70 (37), 69 (85), 65 (17), 55 (100), 53 (47), 51 (27), 43 (35), 41 (81), 39 (70).
(*E*)-5-Bromo-3-methylpenta-1,3-diene (4): Tribromophosphine (1.5 mL, 4.2 g, 15 mmol) was added dropwise at 0 °C to a solution of (*E*)-3-methylpenta-2,4-dien-1-ol (**3**; 2.67 g, 27.2 mmol) in absolute Et_2O (100 mL) under a N_2 atmosphere. An additional identical portion of tribromophosphine was added after 30 min if starting material was still present (TLC). After 30 min, the mixture was diluted by addition of Et_2O (50 mL) and hydrolyzed by addition of brine (100 mL). The organic phase was separated and dried with $MgSO_4$. The resulting (*E*)-5-bromo-3-methylpenta-1,3-diene (**4**; 4.38 g, 27.2 mmol, 10.2 mmol, 100% yield) was sufficiently pure for use in the next step. Because of its instability during purification, the compound was directly used in the following coupling reaction. The *E*/*Z* ratio was 97:3 (GC). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37 (ddd, *J* = 17.4, 10.7, 0.8 Hz, 1 H, CH), 5.78 (t, *J* = 8.8 Hz, 1 H, CH), 5.30 (d, *J* = 17.4 Hz, 1 H, CH), 5.12 (d, *J* = 10.6 Hz, 1 H, CH), 4.13 (d, *J* = 8.8 Hz, 2 H, CH_2), 1.84 (d, *J* = 1.3 Hz, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.1 (d), 139.8 (s), 126.7 (d), 114.8 (t), 28.9 (t), 11.4 (q); MS (EI, 70 eV): *m*/*z* (%) = 162 (5), 160 (5), 82 (7), 81 (100), 80 (11), 79 (33), 77 (9), 66 (9), 65 (8), 55 (5), 53 (27), 52 (7), 51 (11), 50 (8), 41 (21), 39 (18).
(*E*)-β-Ocimene (5): A solution of (*E*)-5-bromo-3-methylpenta-1,3-diene (**4**; 4.38 g, 27.2 mmol) in absolute 1,2-dimethoxyethane (8 mL) was treated with dilithium tetrachlorocuprate(II) (0.1 M in THF, 10.8 mL, 1.08 mmol). A solution of 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 70 mL, 35 mmol) was added at 0 °C and the mixture was stirred for 45 min. After an additional stirring period of 18 h at r.t., ice-cooled H_2O was added. The organic phase was washed with sat. NH_4Cl, and the aqueous phase

was extracted three times with pentane. The combined organic phases were dried with $MgSO_4$ and the solvent was removed. The product was purified by flash chromatography on silica(pentane). Pure (*E*)-β-ocimene (2.53 g, 18.6 mmol, 68% yield) was obtained in an *E*/*Z* ratio of 96:4 (GC). If needed, the *E*/*Z* ratio can be further enhanced by using argentation chromatography (5% $AgNO_3$ on silica in the dark) with pentane as solvent, but significant loss of material has to be considered. TLC: R_f = 0.75 (pentane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.42–6.31 (m, 1 H, CH), 5.45 (t, *J* = 7.5 Hz, 1 H, CH), 5.15–5.05 (m, 2 H, 2 × CH), 4.93 (d, *J* = 10.9 Hz, 1 H, CH), 2.82 (t, *J* = 7.2 Hz, 2 H, CH_2), 1.78–1.74 (m, 3 H, CH_3), 1.70 (d, *J* = 1.3 Hz, 3 H, CH_3), 1.64 (d, *J* = 0.6 Hz, 3 H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 141.5 (d), 133.7 (s), 132.2 (s), 131.8 (d), 122.2 (d), 110.6 (t), 27.3 (t), 25.7 (q), 17.7 (q), 11.6 (q); MS (EI, 70 eV): *m*/*z* (%) = 136 (6), 121 (17), 107 (8), 105 (21), 93 (100), 92 (25), 91 (55), 80 (33), 79 (51), 77 (42), 67 (13), 65 (12), 53 (20), 51 (11), 41 (32), 39 (32).