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Aromatic annulation on the *p*-menthane monoterpenes: enantiospecific synthesis of the trans and cis isomers of calamenene and 8-hydroxycalamenene

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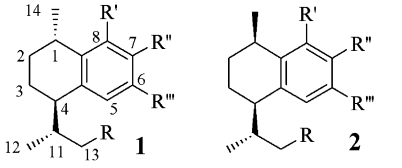
Abstract—A new enantiospecific route to sesquiterpenes of the calamenene family is described. The synthetic pathway starts from easily available 3-oxygenated-*p*-menthane monoterpenes and affords the title compounds by a homologation–benzannulation sequence. The trans and cis isomers of the natural compounds calamenene and 8-hydroxycalamenene were obtained in enantiopure form starting from (−)-menthone and (+)-isomenthone, respectively.

The chiral substituted tetrahydronaphthalene derivatives of type **1** and **2** (Fig. 1) are important natural products, which have attracted considerable attention because of their remarkable properties. The sesquiterpene calamenene[1] is widespread in plants and is a component of a number of essential oils. The oxygenated constituents display a wide range of biological activities. (+)-8-Hydroxycalamenene is the active principle of the seeds of *Dysoxylum acutangulum*[2] that have been traditionally known as fish-poisonous plant material in Indonesia. Otherwise, some serrulatane[3] and pseudopterosin[4] diterpenoids possess anti-mycobacterial,[5] analgesic and anti-inflammatory activities.[6]



Calamenene (R=R'=R"=H; R'''=Me)
8-Hydroxycalamenene (R=R"=H; R'=OH; R'''=Me)
Serrulatane and Pseudopterosins diterpenoids (R=C_5H_9)

Figure 1.

Compounds with structure **1** and **2** share the difficult accessibility by synthesis especially in enantiopure form. Their preparation could be accomplished by two different approaches. The first starts with a functionalised aromatic ring and then builds up the chiral cyclohexane ring.[7] The second approach is based on the use of chiral cyclic precursors on which the aromatic ring is created by an annulation reaction.[8] In both cases the major problem is due to the difficulty in introducing the stereocentres in the benzylic position and the epimerisation of existing stereocentres, respectively. The benzannulation approach has received growing interest since the preparation of highly substituted compounds could be performed straightforwardly in few regiospecific steps. In this field, we have previously developed a method for annulation that allows the construction of substituted phenols starting from substituted 3-alkoxycarbonyl-3,5-hexadienoic acids[9] and from 3-alkoxycarbonyl-3-en-5-ynoic acids.[10] The latter process is very flexible and can be used for the preparation of chiral tetrahydronaphthalenes[11] and for the enantiospecific synthesis of various natural products.[12] Moreover, we have recently shown that enantiomer-enriched 3-[13] and 3,9-oxygenated[14] *p*-menthane monoterpenes are easily obtainable by means of enzymes mediated resolution of racemic materials. We envisaged that the combination of the latter finding could be applicable to the preparation of compounds **1** and **2** starting from *p*-menthane derivative of type **3** (Fig. 2) through homologation to hexadienoic acid **4** and benzannulation reaction.

Keywords: Annulation; Terpenes; Calamenene; Enantiospecific; Tetralins.
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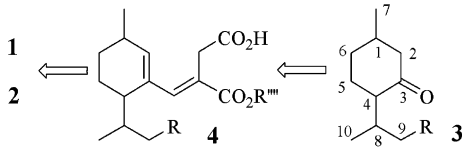
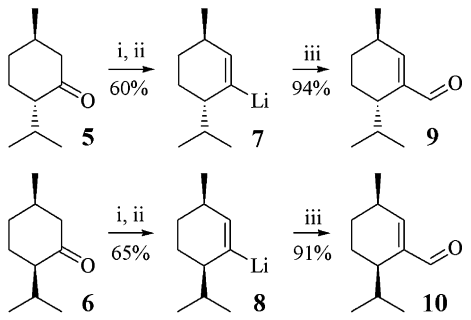


Figure 2. Retrosynthesis of **1** and **2**.

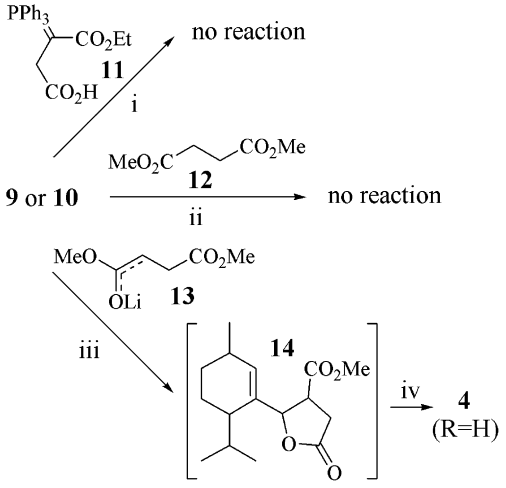
Herein we communicate a preliminary accomplishment of this synthetic plan. We used (−)-menthone **5** and (+)-isomenthone[15] **6** as starting materials for the preparation of sesquiterpenes of the calamenene family. The latter compounds are the most simple *p*-menthane derivatives of type **3** (R = H) and are easily available in high enantiomeric purity. According to our retrosynthetic analysis, we needed hexadienoic acid **4**, which was prepared from **3** by stepwise C1–C4 homologation. The regioselective introduction of the double bond at the C2(3) carbon was performed by the Shapiro reaction (Scheme 1).[16]

In order to avoid epimerisation at C(4) of the *p*-menthane framework, the tosylhydrazones of ketones **5** and **6** were prepared following the careful conditions described by Garner et al.[17] The lithium derivatives **7** and **8** were treated with DMF to give the isomerically pure aldehydes **9**[18] and **10**,[19] respectively. An essential aspect of our approach is the regioselective conversion of the latter compounds into the corresponding mono esters mono acids of type **4**. In our previous work this kind of transformation has been achieved straightforwardly by Wittig reaction[20] or by Stobbe condensation[21] of the starting α,β-unsaturated aldehydes with triphenyl-(α-ethoxy-carbonyl-β-carboxyethyl)phosphonium ylide **11** or with dimethyl succinate **12**, respectively. Unfortunately, the application of the latter procedures on aldehydes **9** and **10** was disappointing since no reaction took place under the usual conditions (Scheme 2). This behaviour is probably due to the steric hindrance of the isopropyl group. Therefore, we settled on the more nucleophilic lithium enolate **13** to accomplish this homologation step.

According to this finding, aldehydes **9** and **10** reacted with **13** at low temperature (−60 °C) to afford the corresponding bicyclic condensation product of type **14**.[22] The latter intermediates do not rearrange spontaneously



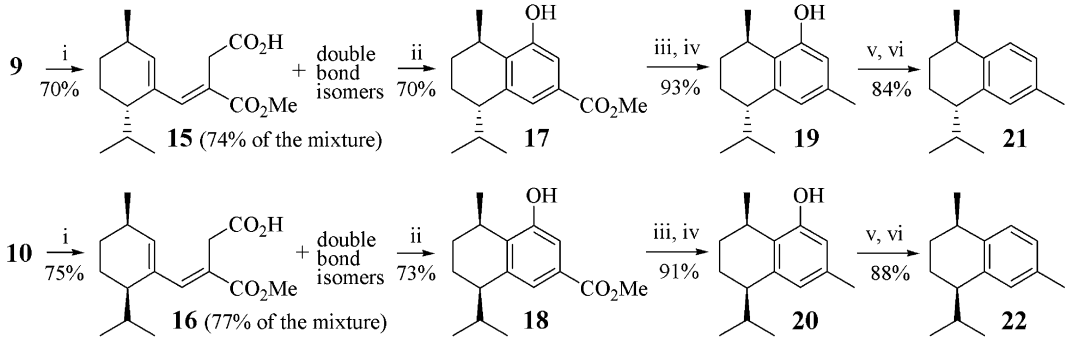
Scheme 1. Reagents and conditions: (i) $TsNHNH_2$, CH_2Cl_2, 0 °C, 2 h; (ii) BuLi (5 equiv), hexane/TMEDA, −78 °C 10 min then 1 h at rt; (iii) DMF (10 equiv), −78 °C 10 min, 10 min at rt then NH_4Cl aq.



Scheme 2. Reagents and conditions: (i) **11**, CH_2Cl_2, reflux, 48 h; (ii) **12**, ^{t}BuOH, ^{t}BuOK, 50 °C 4 h; (iii) **13** (1.1 equiv), −60 °C, 1 h; (iv) LDA (1 equiv), −60 °C 10 min, 1 h at rt then NH_4Cl aq.

to give **4**. Therefore the reaction mixtures were treated with an equimolar amount of LDA at low temperature followed by warming to 0 °C. When employed the above condensation protocol, **9** and **10** afforded the homologated dienoic acids in satisfactory yields (70–75%) although as a mixture of isomers. In effect, the analysis of the reaction mixture[23] revealed that even if acids of type **4** were the major components (74–77%), their 3-(*Z*) isomers (18–19%) and the 2,5-hexadienoic acids (5–8%) were also formed. Since the isomers were not separable by chromatography and only 3-(*E*)-hexadienoic acids are able to give benzannulation reactions, the whole isomeric mixtures were used in the next step. Hence, the impure acids **15** and **16** were obtained from aldehydes **9** and **10**, respectively (Scheme 3). They were treated at 0 °C with trifluoroacetic anhydride as activating agent, in the presence of an excess of triethylamine.[9] After a short reaction time at rt (1 h), work up and chromatographic separation afforded annulated phenols **17**[24] and **18**[25] as nicely crystalline compounds and as single isomers. Some polymeric tar materials were also observed. The latter are conceivably derived from the isomeric dienoic acids as confirmed by the yield of the annulated products, corresponding to a quantitative conversion of **15** and **16**.

Reduction of the ester group to a methyl substituent was accomplished in two steps in nearly quantitative yield. Reduction of **17** and **18** with $LiAlH_4$ gave the corresponding benzyl alcohols that were further reduced to phenols **19**[26] and **20**[27] by hydrogenation in the presence of Pd/C as catalyst. The latter (−)-*trans*- and (+)-*cis*-8-hydroxycalamenene showed identical NMR spectral data to those reported for the natural compounds isolated from *D. acutangulum*,[2] *Leminda millecra*,[28a] *Dysoxylum schiffner*[28b] and *Bazzania trilobata*,[29] respectively. The comparison of the optical rotation data showed that **19** had identical value and opposite sign to that reported for the natural product.[2,28] Moreover, **20** showed the same sign and superior optical rotation value ($[\alpha]_D^{20}$ +67.9, *c* 1, $CHCl_3$) to that reported[29a] ($[\alpha]_D^{20}$



Scheme 3. Reagents and conditions: (i) **13** (1.1 equiv), −60 °C 1 h, LDA (1 equiv) −60 °C 10 min, 1 h at rt then NH_4Cl aq; (ii) $(CF_3CO)_2O$ (1.9 equiv), THF, Et_3N (4 equiv), 0 °C 10 min then 1 h at rt; (iii) $LiAlH_4$ (1 equiv), Et_2O, 0 °C 30 min; (iv) H_2 (1 equiv), 10% Pd/C (cat.), MeOH; (v) NaH (1.2 equiv), THF, $(EtO)_2POCl$ (1.1 equiv), 2 h at rt then NH_4Cl aq; (vi) Li (1.5 equiv), NH_3 liq., −60 °C 1 h then NH_4Cl dry.

+31, *c* 4.2, $CHCl_3$). These results confirm their previous assigned absolute and relative stereochemistries and show that *cis*-8-hydroxycalamenene isolated from nature is not enantiomerically pure. The next step was the deoxygenation of the phenol functionality to the corresponding aromatic hydrocarbon. This transformation was accomplished by conversion of phenols **19** and **20** to their corresponding diethyl phosphate esters.[30] Reductive cleavage by mean of lithium in liquid ammonia smoothly afforded the (−)-*trans*- and (+)-*cis*-calamenene **21**[31] and **22**,[32] respectively. The spectral and optical rotation data of the latter compounds were in good accord with those of earlier studies that assigned unambiguously their absolute stereochemistry.[8a,33]

In summary, we have demonstrated that the benzannulation approach on the 3-oxygenated-*p*-menthane framework allows the straightforward construction of substituted calamenene sesquiterpenes in stereospecific fashion. The trans and cis isomers of the natural compounds calamenene and 8-hydroxycalamenene were synthesised in enantiopure form starting from (−)-menthone and (+)-isomenthone, respectively. Since (+)-menthone and (−)-isomenthone are easily available by synthesis,[34] the preparation of their enantiomeric forms is also possible. Our synthetic path compares favourably with those reported previously both in terms of selectivity, length and overall yield. Further application of this methodology for the preparation of *seco*-pseudopterosin and related diterpenes are underway.

Acknowledgements

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18. Aldehyde **9**: $[\alpha]_D^{20}$ +103.1 (*c* 3, $CHCl_3$). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.55; H, 10.90; ^1H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 6.65 (br s, 1H), 2.58–2.23 (m, 3H), 1.98–1.80 (m, 1H), 1.76–1.59 (m, 1H), 1.55–1.36 (m, 1H), 1.20–1.04 (m, 1H), 1.10 (d, J = 7.3 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.69 (d, J = 6.9 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 194.4, 158.3, 143.8, 37.6, 31.4, 28.7, 27.9, 20.6, 20.6, 20.5, 17.0; EI-MS *m/z* 166 (61), 151 (11), 137 (12), 123 (100), 109 (49),

95 (74), 81 (36), 67 (23); IR (neat) cm^{-1} 1690, 1628, 1460, 1368, 1162, 705.

19. Aldehyde **10**: $[\alpha]_D^{20}$ −12.8 (*c* 3, $CHCl_3$). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.60; H, 10.90; ^1H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 6.63 (d, J = 3.4 Hz, 1H), 2.48–2.33 (m, 2H), 2.00–1.88 (m, 1H), 1.86–1.78 (m, 1H), 1.77–1.69 (m, 1H), 1.50–1.33 (m, 2H), 1.14 (d, J = 7.2 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 194.5, 157.2, 144.1, 36.5, 31.9, 29.9, 27.5, 22.5, 21.3, 20.1, 19.6; EI-MS *m/z* 166 (76), 151 (19), 137 (23), 123 (100), 109 (68), 95 (90), 81 (48), 67 (27); IR (neat) cm^{-1} 1687, 1633, 1458, 1171, 695.
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22. The compounds of type **14** were identified by quenching the reaction at low temperature followed by GC–MS analysis of the crude reaction mixture.
23. Acids of type **4**; their 3-(*Z*) isomers and the 2,5-hexadienoic acids were identified by NMR and GC–MS analysis of the purified mixture of dienoic acids.
24. Hydroxy-ester **17**: mp 129–130 °C; $[\alpha]_D^{20}$ −71.9 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.15; H, 8.45; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 1.5 Hz, 1H), 7.32 (d, J = 1.5 Hz, 1H), 5.28 (s, 1H), 3.89 (s, 3H), 3.24–3.14 (ddq, J = 2.3, 6.6, 7 Hz, 1H), 2.59–2.53 (ddd, J = 2.7, 5.5, 5.9 Hz, 1H), 2.10–1.92 (m, 2H), 1.91–1.75 (m, 2H), 1.54 (dm, J = 13.3 Hz, 1H), 1.21 (d, J = 7 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.0, 153.7, 141.5, 135.7, 126.9, 123.3, 113.2, 52.1, 43.1, 33.2, 27.2, 26.8, 21.9, 20.8, 19.4, 19.0; EI-MS *m/z* 262 (24), 231 (8), 219 (100), 187 (40), 160 (10), 145 (11), 131 (4), 115 (7), 105 (2), 91 (3); IR (nujol) cm^{-1} 3420, 1698, 1582, 1438, 1421, 1294, 1239, 1029, 767.
25. Hydroxy-ester **18**: mp 122–123 °C; $[\alpha]_D^{20}$ +85 (*c* 2, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.30; H, 8.40; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (br s, 1H), 7.31 (br s, 1H), 5.32 (s, 1H), 3.89 (s, 3H), 3.24–3.12 (m, 1H), 2.81–2.72 (m, 1H), 2.51–2.38 (m, 1H), 1.80–1.60 (m, 4H), 1.24 (d, J = 7 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 0.68 (d, J = 6.9 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) 168.0, 153.6, 141.7, 136.2, 127.6, 121.5, 112.8, 52.1, 43.4, 30.9, 28.4, 27.2, 20.9, 20.0, 17.2, 16.3; EI-MS *m/z* 262 (22), 231 (10), 219 (100), 187 (69), 160 (24), 145 (44), 131 (20), 115 (39), 105 (6), 91 (20); IR (nujol) cm^{-1} 3400, 1698, 1584, 1438, 1349, 1273, 1245, 1032, 773.
26. (−)-*trans*-8-Hydroxycalamenene **19**: $[\alpha]_D^{20}$ −37.9 (*c* 2, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.60; H, 10.20; ^1H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1H), 6.44 (s, 1H), 4.54 (s, 1H), 3.08 (ddq, J = 2.1, 7, 6.7 Hz, 1H), 2.48 (ddd, J = 2.9, 5.8, 5.8 Hz, 1H), 2.25 (s, 3H), 2.07–1.94 (m, 2H), 1.91–1.73 (m, 2H), 1.52 (dm, J = 13.4 Hz, 1H), 1.21 (d, J = 7.1 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.1, 141.1, 135.0, 126.2, 122.9, 113.5, 43.2, 33.1, 27.4, 26.7, 22.0, 21.2, 21.0, 19.6, 19.4; EI-MS *m/z* 218 (29), 203 (2), 175 (100), 160 (13), 147 (12), 141 (4), 128 (4), 121 (5), 115 (6), 105 (2), 91 (4); IR (neat) cm^{-1} 3460, 1619, 1579, 1464, 1287, 1239, 1164, 1029, 974, 841.
27. (+)-*cis*-8-Hydroxycalamenene **20**: mp 71–73 °C; $[\alpha]_D^{20}$ +67.9 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.65; H, 10.15; ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (s, 1H), 6.42 (s, 1H), 4.52 (s, 1H), 3.12–3.02 (m, 1H), 2.74–2.66 (m, 1H), 2.45–2.32 (m, 1H), 2.25 (s, 3H), 1.82–1.56 (m, 4H), 1.23 (d, J = 7.1 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.71 (d, J = 6.9 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.0, 141.3, 135.7, 126.7, 120.9, 112.8, 43.3, 30.9, 28.8, 26.5, 21.1, 21.1, 20.5, 17.4, 16.4; EI-MS *m/z* 218 (15), 203 (2), 175 (100), 160 (11), 147 (12), 141 (4), 128 (5), 121 (6), 115 (9), 105 (4), 91 (7); IR (nujol) cm^{-1} 3405, 1619, 1583, 1459, 1377, 1271, 1170, 839.
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31. (−)-*trans* Calamenene **21**: $[\alpha]_D^{20}$ −75.2 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.15; H, 11.00; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 7.9 Hz, 1H), 7.01 (s, 1H), 6.93 (d, J = 7.9 Hz, 1H), 2.81–2.70 (m, 1H), 2.72–2.64 (m, 1H), 2.29 (s, 3H), 2.28–2.16 (m, 1H), 2.00–1.91 (m, 1H), 1.88–1.78 (m, 1H), 1.65–1.54 (m, 1H), 1.39–1.27 (m, 1H), 1.26 (d, J = 7 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 140.1, 139.9, 134.4, 128.8, 126.8, 126.3, 44.1, 32.6, 32.1, 30.9, 22.3, 21.7, 21.3, 21.1, 17.6; EI-MS *m/z* 202 (10), 159 (100), 144 (9), 128 (16), 115 (9), 105 (7), 91 (6); IR (neat) cm^{-1} 1614, 1497, 1463, 1384, 1366, 1319, 880, 814.
32. (+)-*cis*-Calamenene **22**: $[\alpha]_D^{20}$ +42.6 (*c* 1, $CHCl_3$). Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 89.20; H, 11.05; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 7.8 Hz, 1H), 7.01 (s, 1H), 6.92 (d, J = 7.8 Hz, 1H), 2.90–2.80 (m, 1H), 2.63–2.51 (m, 1H), 2.29 (s, 3H), 2.31–2.20 (m, 1H), 1.87–1.55 (m, 4H), 1.25 (d, J = 7 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 139.9, 139.7, 134.4, 128.7, 128.4, 126.3, 43.8, 32.6, 31.2, 28.9, 23.2, 21.4, 21.1, 20.1, 17.7; EI-MS *m/z* 202 (10), 159 (100), 144 (9), 128 (15), 115 (9), 105 (7), 91 (5); IR (neat) cm^{-1} 1614, 1499, 1464, 1384, 1261, 1038, 880, 814.
33. (a) Bunko, J. D.; Ghisalberti, E. L.; Jefferies, P. R. *Aust. J. Chem.* **1981**, *34*, 2237–2242; (b) Croft, K. D.; Ghisalberti, E. L.; Hocart, C. H.; Jefferies, P. R.; Raston, C. L.; White, A. H. *J. Chem. Soc., Perkin Trans. 1* **1978**, *2*, 1267–1270.
34. (+)-Menthone are available by oxidation of commercially available (+)-menthol according to the procedure described in Ref. 15. (−)-Isomenthone is available by hydrogenation of (+)-piperitone; see for instance: Wagner, H. *Chem. Ber.* **1941**, *74*, 657–660.