Simplified Isolation Procedure and Interconversion of the Diastereomers of Nepetalactone and Nepetalactol

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Three nepetalactones were isolated from *Nepeta racemosa (mussinii)* by traditional methods. An improved method was developed to isolate nepetalactones from *N. faassénii*. An epimerization procedure was used to prepare the fourth 7*S*-nepetalactone diastereomer. The *cis*-fused nepetalactols were prepared by reduction of the corresponding nepetalactones, while the *trans*-fused nepetalactols were unstable and found to undergo ring-opening reactions yielding iridodials. The characterizations and structural assignments by means of NMR agree with quantum chemical density functional calculations.

Aphids are ubiquitous insects. Some species cause severe damage to arable crops. A prerequisite for finding environmentally safe methods of controlling the noxious aphid species is the ability to interpret the chemical language of aphids. In recent years nepetalactones and related iridoids have been identified as sex pheromones of host-alternating aphids. As an example, the sex pheromone of the aphid *Megoura viciae* has been characterized as a synergistic mixture of the (4a*S*,7*S*,7a*R*)-nepetalactone (**1**; Figure 1) and (4a*S*,7*S*,7a*R*)-nepetalactols (**5** and **9**; Figure 5).[1,2] The nepetalactols appear to act as aphrodisiacs and the nepetalactone as an attractant.[3] Compounds **1**, **5**, and **9** combined or as single compounds have also been identified as sex pheromone components in host-alternating aphids such as the greenbug, *Schizaphis graminum*,[4] the pea aphid, *Acyrthosiphon pisum*,[5] the black bean aphid, *Aphis fabae*,[5] the bird-cherry aphid, *Rhopalosiphum pad*,[6] the peach-potato aphid, *Myzus persicae*,[5] and the potato aphid, *Macrosiphum euphorbiae*.[7] The hop aphid, *Phorodon humuli,* has been reported to use the *cis*−*cis*-isomer of a nepetalactol, a diastereomer not found in blends of other species, as a single sex pheromone component.[8]

Dawson et al.[9] and Hardie et al.[10] have reported that the configuration at C-7 is crucial for the biological activity on aphids. However, it is still not clear if the aphid pheromone glands produce the thermodynamic equilibrium of nepetalactol anomers or if the aphids use one or both anomers in their chemical communication. Bates and Sigel[11] reported that *cis*−*trans* and *trans*−*cis* nepetalactones are attractive to cats, and Mori et al.[12] reported that both enantiomers of *cis*−*trans* nepetalactone have similar degrees of arousing effects on cats.

We needed all four diastereomers of the 7*S*-nepetalactones for an investigation of the chemical communication of the aphids and aphid predators. As these were seemingly difficult to obtain by total synthesis, we developed a synthetic method of using extracts from readily available *Nepeta* (catmint) species. Some aspects of the chemistry and structures of nepetalactols and nepetalactones will also be discussed. For a more extensive review on the occurrence and synthesis of iridolactones in general, see the work by Nangia et al.[13]

Nomenclature

Nepetalactones are named after the plant genus *Nepeta*, which consists of more than 280 species. Since there are different ways of naming nepetalactones and the corresponding lactols, clarifying schemes, using the IUPAC nomenclature, are shown in Figures 1 and 5. In the short names, i.e., *cis*−*trans*, *cis*−*cis*, *trans*−*cis*, and *trans*−*trans*, the first part of the name refers to the configuration at the ring junction (4a−7a) and the second part to the configuration of the 7a−7 bond. The configuration at carbon 7 is generally *S*. We have found only one exception in a report about *Nepeta elliptica* by Bottini et al.,[14] who rely on work by Trave et al.[15] for the assignment of the 7*R*-configuration.

Results and Discussion

1. Isolation of Nepetalactones from *Nepeta* Species. The nepetalactones **1**, **2**, and **3** were isolated from the aerial parts of the plant *Nepeta racemosa* (mussinii). The total amount of isolated nepetalactones was 1.5 g per 100 g of plant material (dry weight) and the relative amounts of the lactones were as follows: **1** (13%), **2** (32%), and **3** (55%).

Nepeta faassenii is a very common garden plant in Sweden. It is a hybrid of *N. racemosa* and *N. nepetella*. Soxhlet extraction of the green parts with CH_2Cl_2, followed by chromatography, yielded, predominantly, the nepetalactone **1**. The relative amounts of nepetalactones were as follows: **1** (98.5%), **2** (1.5%). The amount of isolated nepetalactones per 100 g dry weight was 230 mg.

Even considering the somewhat different methods of isolation (see Experimental), the differences in the amounts of the nepetalactones obtained from 100 g dry weight of the two plant materials were significant, 1.5 g for N. *racemosa* while only 230 mg from *N. faassénii*. One explanation for this could be plant variety. Further, Velasco-Negueruela et al.[16] have reported that the amount of nepetalactones (e.g. in *Nepeta teydea*) decreased continuously during the flowering period. Thus, the fact that the hybrid was harvested one month later than the *N. mussinii* (in October, shortly before wilting) probably explained part of the difference.

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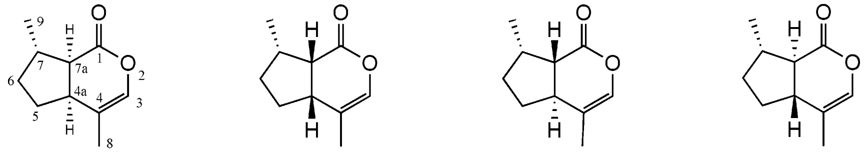


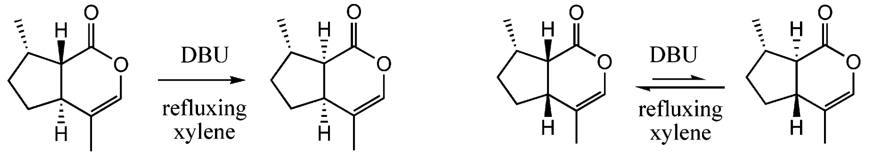
1 **2** **3** **4**

4a*S*,7*S*,7a*R* **4a*R*,7*S*,7a*S*** **4a*S*,7*S*,7a*S*** **4a*R*,7*S*,7a*R***

cis-trans ***cis-cis*** ***trans-cis*** ***trans-trans***

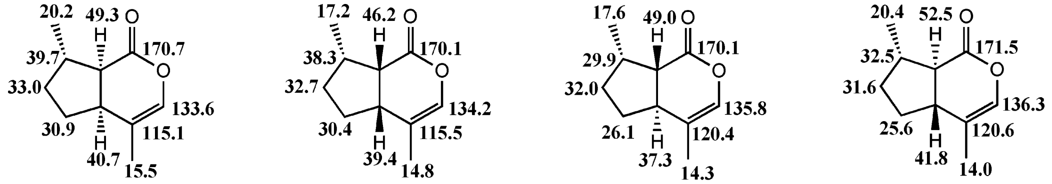
4aα,7α,7aα **4aβ,7α,7aβ** **4aα,7α,7aβ** **4aβ,7α,7aα**

Figure 1. All nepetalactone 7*S*-diastereomers.



3 **1** **2** **4**

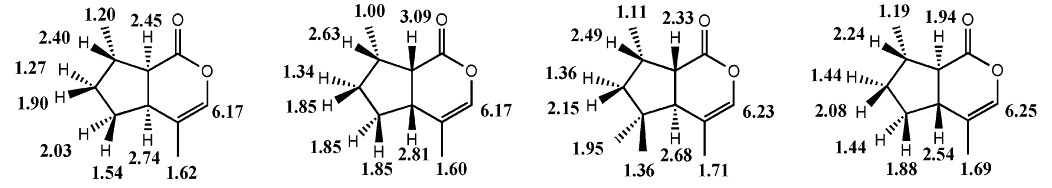
Figure 2. Epimerization of nepetalactones.



1 **2** **3** **4**

cis-trans *cis-cis* *trans-cis* *trans-trans*

Figure 3. Unambiguously assigned ^{13}C NMR shifts of all nepetalactones.



1 **2** **3** **4**

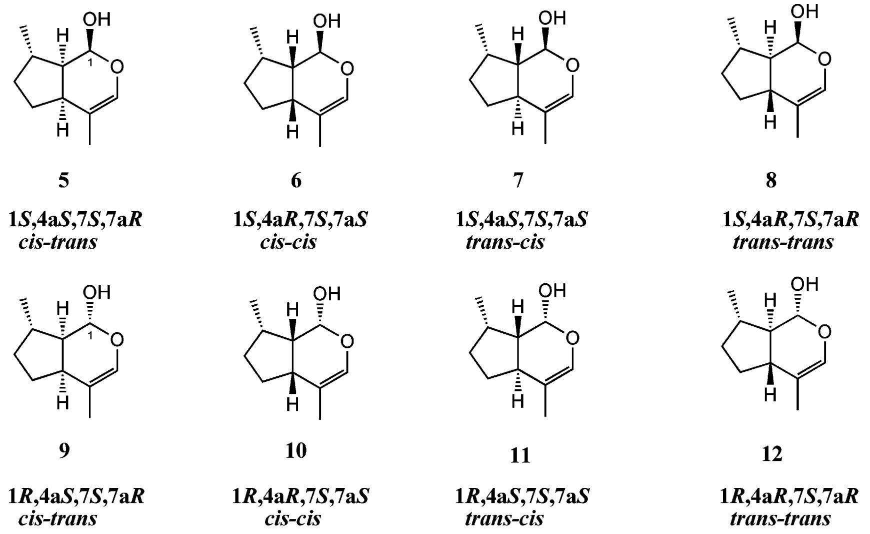
cis-trans *cis-cis* *trans-cis* *trans-trans*

Figure 4. ^{1}H NMR shifts of all nepetalactones.

2. Development of a Simplified Isolation Procedure and Its Comparison with a Traditional Extraction Method. Some years back, Baeckström[17] and Jirón[18] developed a procedure for isolating azadirachtin by grinding the oily seeds of *Azadirachta indica* with silica gel. The extraction was performed in a column by passing the extract through a fresh adsorbent using gradient elution. By means of this method, sequential extraction with different solvents could be replaced by one operation, called combined extraction and chromatography. The time-saving aspect of this method made it especially interesting to see if nepetalactones could be isolated from fresh plant material in a similar way. The efficiency of extraction would then be compared to more traditional methods. The same batch of plant material was used for both experiments. Grinding the fresh plant material with 1.5 times by weight of silica gel in a household meat grinder gave sufficiently dry material for the combined extraction and chromatography. This procedure gave partially separated diastereomers of nepetalactone in a yield of 1.05 g/100 g dry weight of the plant material. This amount was 8 times more than that obtained with the more traditional method (extraction of the minced fresh plant material with CH_2Cl_2).

3. Epimerization of Nepetalactones and Synthesis of the *trans*–*trans*-Nepetalactone 4. The fourth nepetalactone (**4**) is reported to be present in the essential oil of *Nepeta nuda*.[19] We produced it by epimerization of nepetalactone **2** (see Experimental Section). A literature report indicated the possibility of epimerizing nepetalactones by treatment with K_2CO_3 in xylene.[20] We subjected the four lactones **1**–**4** to epimerization attempts using the base DBU (1,8-diaza-bicyclo[5.4.0]undec-7-ene). The *trans*-fused nepetalactone **3** was completely converted into the *cis*-fused **1**, and the proportion of the *cis*-fused lactone **2** to the *trans*-fused lactone **4** was 9:1 in the equilibrium mixture (Figure 2). The *cis*-fused nepetalactones were thermodynamically the most stable ones. Attempts to epimerize nepetalactone **1** to nepetalactone **3** failed (i.e., nepetalactone **1** was recovered).

In accordance with these experimental results, quantum chemical density functional calculations by the B3LYP method using the 6-31G* basis set[21–23] (benzene as the solvent) revealed that the *cis*-fused lactones were more stable than the *trans*-fused ones. The calculations matched the empirical values well for the nepetalactone epimers **1** and **3** (the energy difference was 4.5 kcal, which corresponds to a 99.9:0.1 equilibrium ratio), while the calculated



5 1*S*,4a*S*,7*S*,7a*R* *cis-trans*

6 1*S*,4a*R*,7*S*,7a*S* *cis-cis*

7 1*S*,4a*S*,7*S*,7a*S* *trans-cis*

8 1*S*,4a*R*,7*S*,7a*R* *trans-trans*

9 1*R*,4a*S*,7*S*,7a*R* *cis-trans*

10 1*R*,4a*R*,7*S*,7a*S* *cis-cis*

11 1*R*,4a*S*,7*S*,7a*S* *trans-cis*

12 1*R*,4a*R*,7*S*,7a*R* *trans-trans*

Figure 5. All 7*S*-nepetalactol diastereomers.

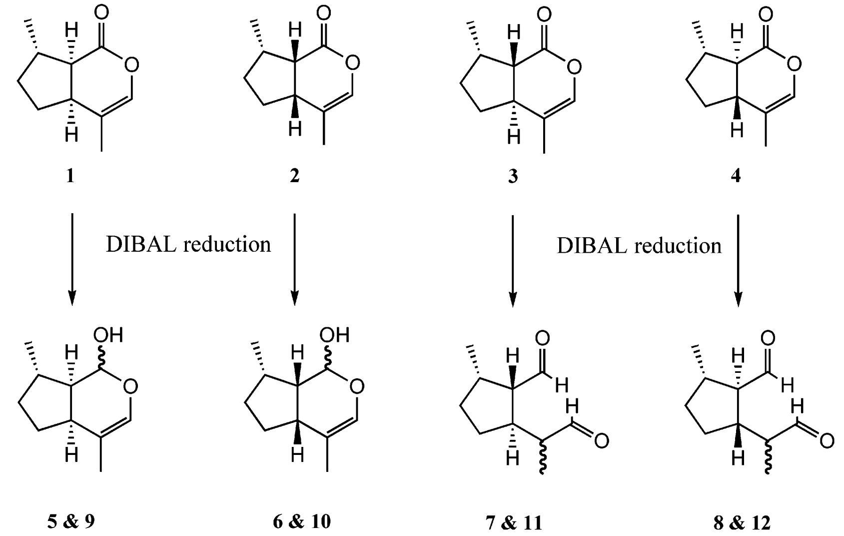


Figure 6. Products from hydride reduction of nepetalactones.

equilibrium proportion between the lactones **2** and **4** was 8:2 (0.76 kcal energy difference) in comparison to the experimental value of 9:1.

4. NMR Studies of Nepetalactones. An unambiguous assignment of the NMR spectra of the four nepetalactones has been achieved using COSY and NOESY NMR techniques, and the results are shown in Figures 3 and 4.

When comparing our NMR data with reported data, we found that the ^{13}C NMR shift of carbon atoms 6 and 7 in the *trans*–*cis* isomer should be δ 32.0 and 29.9, respectively, and not vice versa, as tentatively suggested by Eisenbraun et al.[24] and later by De Pooter et al.[19]

The shift of the C4-methyl group in *cis*–*cis*-nepetalactone is δ 1.60, not 1.70 as reported by Eisenbraun et al.[24]

5. Synthesis of Nepetalactols. Initially we intended to produce the eight diastereomeric 7*S*-nepetalactols (Figure 5). However, only the *cis*-fused nepetalactols **5**, **6**, **9**, and **10** could be obtained (Figure 6). Reduction of the *cis*-fused nepetalactones with DIBAL (diisobutylaluminum hydride) or TBABH4 (tetrabutylammonium borohydride) yielded the corresponding lactols. In agreement with some literature reports[2] the *trans*-fused nepetalactones yielded dialdehyde (iridodial) isomers upon DIBAL reduction.

6. Nepetalactol–Iridodial Equilibrium. It is most likely that the equilibration process between the anomeric forms of *cis*-fused nepetalactols proceeds via a charged intermediate, while it is not clear if the mutarotation proceeds via equilibrium with the iridodial form (Figure 7 and Murai et al.[25]).

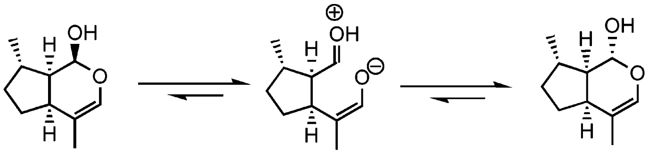


Figure 7. Nepetalactol–iridodial equilibrium.

This equilibrium between the *cis*-fused nepetalactols, in which the substituents at the ring junction are *cis*-oriented, is apparently solvent-dependent, as it is possible to extract the *cis*-fused dialdehyde from acidic water solutions.[2] In organic solvents the equilibrium is shifted toward the lactol.

We have found that the anomeric forms of *cis*-fused nepetalactols tend to equilibrate to different fixed ratios. The 1*R*/1*S* ratio (**9**/**5** ratio, see Figure 7) of the *cis*–*trans*-lactol is ~93:7, while the *cis*–*cis*-isomer reaches a 1*R*/1*S* ratio (**10**/**6** ratio, see Figure 5) of ~30:70. The difference between these ratios is most probably due to steric interactions between the ring substituents.

The separation of the nepetalactol anomers may not be possible if the equilibration is fast. In an attempt to visualize the rate of the process we acetylated the mixture of *cis*−*cis*-nepetalactol anomers (30% **10**:70% **6**, Figure 5). When the acetylation reaction was performed at −70 °C, the ratio was preserved in the product acetates, while the acetylated product composition was 10:90 when the reaction was run at room temperature. This indicates that at room temperature the more sterically accessible hydroxyl group in **6** is acetylated and that the mutarotation during these conditions is fast enough to partially epimerize the nepetalactol during the time span of the acetylation reaction.

7. Molecular Modeling and Quantum Mechanic Studies of Nepetalactols. Although the NMR shifts give an indication of the configuration of the hemiacetal function, we have further confirmed the assignment using molecular mechanics. As mentioned earlier the *cis*−*trans*-lactol anomers **5/9** have an S/R ratio at equilibrium of ∼1:15, while the *cis-cis*-anomers **6/10** have an S/R ratio of ∼2:1. These ratios correspond with the energy differences found by molecular modeling and quantum chemical density functional calculations by the B3LYP method using the 6-31G* basis set.[21−23] The calculations predict the same trend in the stability ratios between the two *cis*−*trans*-lactol anomers **5/9** and the two *cis*−*cis*-lactol anomers **6/10** as the experiments do. The energy difference calculated is 0.9 kcal/mol between **5** and **9** (lowest for **9**) and 1.8 kcal/mol between **6** and **10** (lowest for **6**).

Experimental Section

General Experimental Procedures. The NMR spectra were recorded in CDCl$_3$ on Bruker 500 or 400 spectrometers, and the CHCl$_3$ peak was set at δ 77.0 in the ^{13}C NMR spectra and at δ 7.26 in the ^{1}H NMR spectra. Liquid chromatography was performed on silica gel[26] (Merck 60, 0.040−0.063 mm) in 15 or 25 mm inner diameter glass columns with gradient elution, using hexane and increasing amounts of EtOAc. TLC was carried out on silica gel (Merck 60, HF precoated aluminum foil) using 40% EtOAc in hexane as the eluent. The plates were checked under UV and developed with vanillin and H_2SO_4 in EtOH.

Analysis of Nepetalactones and Nepetalactols by Gas Chromatography (GC). Analytical GC was performed with an FID detector by use of a polar (30 m DB-WAX) phase fused silica capillary column. The elution order was *trans*−*trans*, *cis*−*trans, trans*−*cis*, and *cis*−*cis*. The retention times were 15.5, 16.2, 18.2, and 18.9 min, respectively, using the following temperature program: injection temperature 80 °C (1 min hold), 20 °C/min to 160 °C (11 min hold), and 4 °C/min to 200 °C.

Extraction of *N. racemosa*. Fresh material (900 g, ca. 200 g dry weight) of the aerial parts of *N.* racemosa (syn. *mussinii)* was minced in H_2O, from which the organic components were then extracted with CH_2Cl_2. The material extracted was subjected to liquid chromatography. The total amount of eluted organic material was 6.25 g, of which the amount of isolated nepetalactones (**1**, **2**, and **3**) was 3.05 g. The proportions of the nepetalactones were **1**, 409 mg (13%); **2**, 975 mg (32%); and **3**, 1670 mg (55%).

***cis*−*trans*-Nepetalactone (1):** ^{1}H NMR (CDCl$_3$) δ 6.17 (1H, pentet, J = 1.5 Hz), 2.74 (1H, quartet, J = 8.4 Hz), 2.45 (1H, dd, J = 9.1, 8.4 Hz), 2.40 (1H, m), 2.03 (1H, m), 1.90 (1H, m), 1.62 (3H, t, J = 1.2 Hz), 1.54 (1H, m), 1.27 (1H, m), 1.20 (3H, d, J = 6.6 Hz); ^{13}C NMR (CDCl$_3$) δ 170.7 (C1), 133.6 (C2), 115.1 (C3), 49.3 (C7a), 40.7 (C4a), 39.7 (C7), 33.0 (C6), 30.9 (C5), 20.2 (C9), 15.5 (C8).

***cis-cis*-Nepetalactone (2):** ^{1}H NMR (CDCl$_3$) δ 6.17 (1H, pentet, J = 1.7 Hz), 3.09 (1H, t, J = 9.6 Hz), 2.81 (1H, m), 2.63 (1H, m), 1.85 (3H, m), 1.60 (3H, t, J = 1.3 Hz), 1.34 (1H, m), 1.00 (3H, d, J = 7.23 Hz); ^{13}C NMR (CDCl$_3$) δ 170.1 (C1), 134.2 (C2), 115.5 (C3), 46.2 (C7a), 39.4 (C4a), 38.3 (C7), 32.7 (C6), 30.4 (C5), 17.2 (C9), 14.8 (C8).

***trans*−*cis*-Nepetalactone (3):** ^{1}H NMR (CDCl$_3$) δ 6.23 (1H, sextet, J = 1.6 Hz), 2.68 (1H, m), 2.49 (1H, m), 2.33 (1H, dd, J = 15.0, 6.8 Hz), 2.15 (1H, m), 1.95 (1H, m), 1.71 (3H, t, J = 1.5 Hz), 1.36 (2H, m), 1.11 (3H, d, J = 7.0 Hz); ^{13}C NMR (CDCl$_3$) δ 170.1 (C1), 135.8 (C2), 120.4 (C3), 49.0 (C7a), 37.3 (C4a), 32.0 (C6), 29.9 (C7), 26.1 (C5), 17.6 (C9), 14.3 (C8).

Extraction of *N. faassénii*. Soxhlet extraction with CH_2Cl_2 was used to extract 5600 g (ca. 800 g dry weight) of aerial parts of fresh *N. faass*énii (hybrid *N. racemosa* × *nepetella*). The organic material extracted was dried (MgSO$_4$) and mixed with silica gel (120 g), and the solvent was then evaporated. The impregnated gel was subjected to liquid chromatography. The total amount of organic material eluted was 28.43 g, of which the total amount of isolated nepetalactones was 1.82 g. The proportions of the nepetalactones were **1**, 1793 mg (98.5%); **2**, 27.9 mg (1.5%).

Comparison of Isolation Methods. (A) The Baeckström Method. Fresh aerial parts of *N. faass*énii (120 g) were minced with silica (180 g) by means of a household meat grinder. The material was passed through the grinder three times to produce a free-flowing powder. The combined extraction and partial separation was achieved by use of a 50 mm inner diameter glass column (Baeckström SEPARO AB) sealed with pistons that could be adjusted to the resulting bed length. The sample-containing powder followed by 60 g of silica gel was added to the column. Hexane (∼250 mL) was pumped to the lower end of the column until all air was expelled, after which the column was turned upside down. The compounds were eluted at a flow rate of ∼60 mL/min, using 250 mL each of solutions containing 1.25%; 2.5%; 5.0%; 7.5%; 10.0%; 15.0%; 20.0%; 30.0%; 50.0%; and 80.0% EtOAc in hexane via a constant volume mixing chamber containing 100 mL of hexane from the start. The yield of nepetalactones was 334 mg, and the relative amounts were **1**, 272 mg (85.0%); **2**, 62 mg (15.0%), which corresponds to a yield of 1.05 g/100 g of dry plant material (dry weight).

(B) Traditional Extraction. Fresh aerial parts of *N. faassénii* (400 g) were minced with H_2O (2000 mL) by means of an electric (food) mincer. The H_2O was filtered off and the solid plant material extracted with CH_2Cl_2 (500 mL). The water phase was extracted with CH_2Cl_2 (3 × 500 mL), and the combined organic phases were dried over MgSO$_4$ and concentrated under reduced pressure. The crude mixture was subjected to preparative liquid chromatography using silica gel and the solvent gradient used in method A.

The relative amounts of nepetalactones isolated were the same as found by method A, and the yield from 400 g of fresh plant material was 142 mg, which corresponded to 134 mg/100 g of dry weight.

Epimerization of *trans*−*cis*-Nepetalactone (3). The *trans*−*cis*-nepetalactone (**3**) (300 mg, 1.81 mmol) was transformed into the *cis*−*trans*-nepetalactone (**1**) by reaction with DBU (1.97 mmol) in refluxing xylene for 2 h (Figure 2). The epimerization reaction was stopped when no **3** was present according to GC analysis (2 h). The diastereomer **1** was isolated in 93% yield (280 mg, 1.69 mmol) by liquid chromatography.

Syntheses of *trans*−*trans*-(4a*R*,7*S*,7a*R*)-nepetalactone (4). *cis*−*cis*-Nepetalactone (**2**) (940 mg, 5.66 mmol) was refluxed in xylene in the presence of DBU (950 mg, 6.25 mmol). The epimerization reaction was stopped when the ratio between the diastereomers was constant (**2**/**4** ≈ 9:1). The diastereomers could easily be separated by liquid chromatography, and the yield of the *trans*-fused nepetalactone **4** was 7.2% (68 mg, 0.41 mmol) while the yield of recovered *cis*−*cis*-nepetalactone (**2**) was 85.8% (807 mg, 4.86 mmol).

***trans*−*trans*-Nepetalactone (4):** ^{1}H NMR (CDCl$_3$) δ 6.25 (1H, quartet, J = 1.5 Hz), 2.54 (1H, m), 2.24 (1H, m), 2.08 (1H, m), 1.94 (1H, dd, J = 14.7, 10.4 Hz), 1.88 (1H, m), 1.44 (2H, m), 1.69 (3H, t, J = 1.6 Hz), 1.19 (3H, d, J = 6.6 Hz); ^{13}C NMR (CDCl$_3$) δ 171.5 (C1), 136.3 (C2), 120.6 (C3), 52.5 (C7a), 41.8 (C4a), 32.5 (C7), 31.6 (C6), 25.6 (C5), 20. (C9), 14.0 (C8).

Syntheses of *cis*−*trans*-Nepetalactols 5 and 9. Procedure 1. DIBAL (1.56 M solution in hexane, 0.4 mL, 0.61 mmol) was added to a mixture of nepetalactones (100 mg, 71% of *cis*−*trans*- and 22% of *trans*-*cis*-nepetalactone) in 6 mL of hexane during 20 min at −70 °C. After 10 min, a saturated solution of tartaric acid in EtOH (1.2 mL) was added. The cooling bath was removed, and the mixture was allowed to reach room temperature. Baeckström reagent (Na$_2$SO$_4$·10H$_2$O:Celite, 1:1, v/v) (0.75 g) was added, and when the color had changed from gray to white, the reaction mixture was filtered. The organic solution was further dried and the solvent evaporated. The residue was subjected to chromatography to yield 52 mg (52%) of *cis*−*trans*-nepetalactols.

Procedure 2. DIBAL (1.56 M solution in hexane, 1.5 mL, 2.34 mmol) was added to a solution of *cis*−*trans*-nepetalactone (251 mg, 1.51 mmol) in 10 mL of hexane during 5 min at −70 °C. After 2 h the cooling bath was removed and the mixture was allowed to reach room temperature. Baeckström reagent (Na$_2$SO$_4$·10H$_2$O:Celite, 1:1, v/v) (2.5 g) was added, and when the color had changed from gray to white, the mixture was filtered. The organic solution was further dried and the solvent evaporated. The residue was subjected to chromatography to yield 211 mg (83%) of *cis*−*trans*-nepetalactols.

(1*R*,4a*S*,7*S*,7a*R*)-Nepetalactol (9): ^{1}H NMR (CDCl$_3$) δ 6.00 (1H, s), 4.84 (1H, d, J = 5.5 Hz), 2.93 (1H, s), 2.45 (1H, dd, J = 7.6, 7.9 Hz), 1.87 (3H, m), 1.64 (1H, dd, J = 6.4, 6.7 Hz), 1.54 (3H, s), 1.36 (1H, m), 1.15 (1H, m), 1.07 (3H, d, J = 6.4 Hz); ^{13}C NMR (CDCl$_3$) δ 134.9, 113.7 (C4), 94.4 (C1), 50.5 (C7a or 4a), 38.8 (C5), 35.8 (C7a or 4a), 33.3, 30.8, 20.6 (C8 or 9), 16.3 (C8 or 9).

Synthesis of *cis*−*cis*-Nepetalactols 6 and 10. DIBAL (1.56 M solution in hexane, 1.5 mL, 2.34 mmol) was added to a solution of *cis*−*cis*-nepetalactone (340 mg, 2.05 mmol) in 10 mL of hexane during 5 min at −70 °C. After 2 h the cooling bath was removed and the mixture was allowed to reach room temperature. Baeckström reagent (Na$_2$SO$_4$·10H$_2$O:Celite, 1:1, v/v) (2.5 g) was added, and when the color had changed from gray to white, the mixture was filtered. The organic solution was further dried and the solvent evaporated. The residue was subjected to chromatography to yield 300 mg (87%) of *cis*−*cis*-nepetalactols **6** and **10**.

6: ^{1}H NMR (CDCl$_3$) δ 6.01 (1H, dd, J = 1.2, 1.4 Hz), 5.01 (1H, t, J = 5.8 Hz), 2.85 (1H, d, J = 5.8 Hz), 2.46 (1H, dd, J = 7.3, 7.6 Hz), 2.21 (2H, m), 2.14 (1H, m), 1.79 (3H, m), 1.54 (3H, s), 1.30 (1H, m), 1.08 (3H, dd, J = 3.1, 7.0 Hz); ^{13}C NMR (CDCl$_3$) δ 169.8, 132.5, 114.2, 89.6, 42.6, 36.9, 36.4, 32.7, 30.6, 21.5, 17.1, 15.0.

10: ^{1}H NMR (CDCl$_3$) δ 5.98 (1H, dd, J = 1.2, 1.5 Hz), 5.32 (1H, t, J = 3.4 Hz), 2.64 (1H, dd, J = 4.6, 7.6 Hz), 2.14 (2H, m), 2.0 (2H, m), 1.79 (1H, m), 1.59 (3H, s); ^{13}C NMR (CDCl$_3$) δ 170.0, 134.5, 113.4, 90.9, 42.5, 38.8, 35.2, 32.2, 29.0, 21.3, 16.2, 16.0.

Synthesis of *cis*−*cis*-Nepetalactyl Acetate. Procedure 1. DIBAL (1.56 M solution in hexane, 1.3 mL, 2.03 mmol) was added to *cis*−*cis*-nepetalactone **10/6** (250 mg, 1.5 mmol) in 13 mL of hexane for 20 min at −70 °C. After stirring for 0.5 h, Ac$_2$O (1.0 g, 9.8 mmol), DMAP (366 mg, 3 mmol), and pyridine (1.5 mL) were added at −70 °C. The mixture was allowed to reach RT overnight. Workup and chromatography yielded 300 mg (95%) of a 30/70 mixture of *cis*−*cis*-nepetalactyl acetates (the **6**-OAc dominating as determined by GC).

Procedure 2. A sample of the above cold reaction mixture was allowed to reach room temperature before the acetylating reagents were added. This procedure gave a 10/90 mixture of *cis*−*cis*-nepetalactyl acetates and more byproducts than procedure 1.

10-OAc: ^{1}H NMR (CDCl$_3$) δ 6.19 (1H, d, J = 3.3 Hz), 5.96 (1H, d, J = 1.2 Hz), 2.33 (1H, m), 2.25 (1H, dd, J = 3.3, 7.4 Hz), 2.06 (3H, s), 1.59 (3H, s), 1.01 (3H, d, J = 7.0 Hz); ^{13}C NMR (CDCl$_3$) δ 169.8, 132.5, 114.2, 89.6, 42.6, 36.9, 36.4, 32.7, 30.6, 21.5, 17.1, 15.0.

6-OAc: ^{1}H NMR (CDCl$_3$) δ 6.04 (1H, d, J = 3.6 Hz), 6.01 (1H, d, J = 1.3 Hz), 2.25 (1H, dd, J = 3.3, 7.6 Hz), 2.08 (3H, s), 1.59 (3H, s), 1.01 (3H, s); ^{13}C NMR (CDCl$_3$) δ 170.0, 134.5, 113.4, 90.9, 42.5, 38.8, 35.2, 32.2, 29.0, 21.3, 16.2, 16.0.

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