Resolution of an Iridoid Synthon, Gastrolactol, by Means of Dynamic Acetylation and Lipase-Catalyzed Alcoholysis

Ellen M. Santangelo, Didier Rotticci, Ilme Liblikas, Torbjörn Norin, and C. Rikard Unelius*,†

Department of Organic Chemistry, Royal Institute of Technology, SE -100 44 Stockholm, Sweden

rikard.unelius@hik.se

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A short synthetic route to asymmetric iridoids was developed. The three key steps were an intramolecular [4 + 2] cycloaddition reaction of an enamine derivative of 8-oxocitral (**2**), a dynamic acetylation, and an enzymatic resolution of the gastrolactyl acetates **5a** and **5b**, iridoids with three stereocenters. Some regio- and stereoselective heterogeneous catalytic hydrogenations of double bonds in iridoid aglucones were discussed.

Introduction

Iridoids (Figure 1), an important class of terpenoids widespread in Nature, often in the form of glycosides, were first studied in the middle of the last century. The interest in them was intensified about 1970, when chemists started studying the origin of the nontryptophan moieties of indole alkaloids.[1] In the 1990s, some iridoids were identified as sex pheromones of host-alternating aphids (**II**, Figure 1).[2] Iridodial (**III**, Figure 1) was found to serve in the chemical defense systems of many insect species.[3] Some iridoids possessing antiviral and antibacterial properties[4] were isolated as a result of pharmacognostic studies of medicinal plants used since ancient times.[5]

Numerous syntheses of iridoids have been described in the literature.[6] Our synthetic strategy in the preparation of the racemic gastrolactol (**4**) is based on an intramolecular enal−enamine [2 + 4] cycloaddition within the *N*-methylaniline derivative of (8)-oxocitral **2** (Figure 2). This strategy resembles the one used by Schreiber et al.,[7] but our starting material has the advantage of giving a double bond in the five-membered ring of the product (**4**).

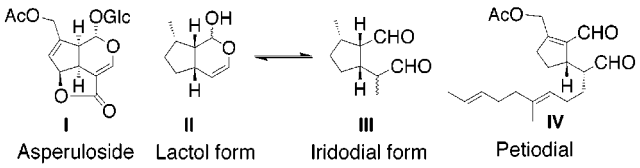

Figure 1. Some iridoid structures.

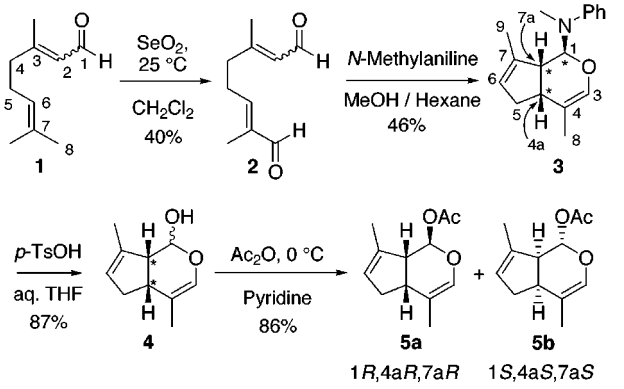

Figure 2. Synthetic route to racemic gastrolactyl acetate (**5a** plus **5b**).

The double bond in the five-membered ring of gastrolactol (**4**) could be used for further reactions such as allylic oxidations and halogenations. We anticipated, in analogy with earlier findings (Figure 3), that it should be possible on hydrogenation to predetermine the con-

† Present address: Department of Chemistry and Biomedical Sciences, University of Kalmar, SE-391 82 Kalmar, Sweden.

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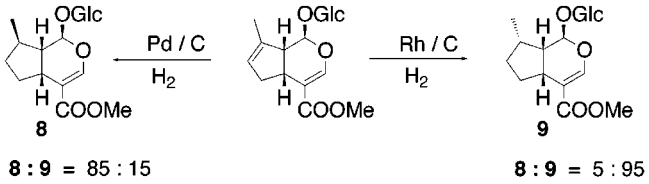

Figure 3. Stereoselective hydrogenation of deoxygeniposide (from literature).[8]

figuration at the C7 methyl group by the choice of hydrogenating agent.[8]

To obtain the optically pure iridoid synthon **5a** we planned to use a lipase-catalyzed kinetic resolution of the racemic gastrolactyl acetate (**5a** plus **5b**). Lipase-catalyzed resolution is a well-established method for the preparation of enantiomericly enriched acids or alcohols,[9] although only a limited number of acetals have been enzymatically resolved.[10]

Results and Discussion

Synthesis of Gastrolactol (4). Citral (**1**) was oxidized to 8-oxocitral (**2**) using stoichiometric amounts of selenium dioxide (Figure 2). The catalytic method of Umbreit and Sharpless[11] was abandoned after we experienced difficulties in obtaining reproducible high yields of the reaction.

The oxidation was followed by the preparation of the enamine derivative of 8-oxocitral, which underwent an intramolecular Diels−Alder reaction, forming compound **3**. Careful hydrolysis of compound **3** with *p*-toluenesulfonic acid provided the lactol **4** in good yield. The assignment of the relative stereochemistry of compound **4** depicted in Figure 2 was based on NMR experiments. Compound **4** was called gastrolactol since it could be regarded as a reduction product of gastrolactone **6** (Figure 7). Gastrolactol (**4**) had been suggested as an intermediate in the biosynthesis of iridoids.[12]

Enzymatic Acetylation of Gastrolactol (4). Gastrolactol (**4**) is a mixture of two enantiomeric pairs. Both pairs have a cis configuration at the ring junction. The pairs differ as regards the relative configuration of the proton at position 7a and the proton at position 1. The enantiomeric pair with the trans configuration is the major pair in the equilibrium mixture. The minor cis pair constitutes approximately 15−20% of the diastereomeric mixture.

A lipase-catalyzed irreversible acetylation of the four stereoisomers of gastrolactol (**4**) shown in Figure 4 was performed in CH_2Cl_2, using vinyl acetate as the acyl donor. Amano I, PS-C (lipase from *Pseudomonas cepacia*)

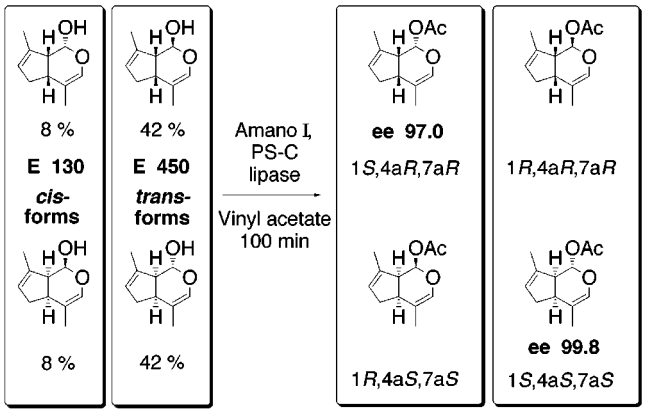

Figure 4. Acetates formed after 100 min of enzymatic acetylation of four stereoisomers of gastrolactol.

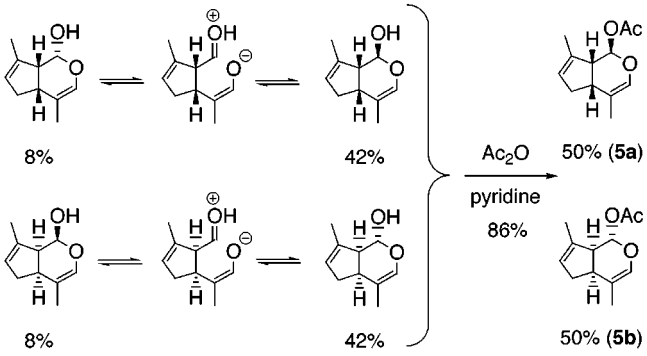

Figure 5. Dynamic chemical acetylation of gastrolactol (**4**).

was the most efficient catalyst of the enzymes tested, and the reaction reached 50% conversion in less than 2 h. The enantiomeric purity of the products was measured by means of chiral gas chromatography, and the enantiomeric ratio (*E*) was calculated according to Rakels.[13] The biocatalyst showed good enantioselectivity toward both the cis and the trans racemates. The *E* value of the trans racemate was 450 and that of the *cis*-racemate was 130 (Figure 4). Note that the 1*R* lactols became 1*S* acetates after acetylation due to the Cahn−Ingold−Prelog rules.

We observed that the faster reacting enantiomer in the trans racemate reacted approximately twice as fast as the fastest reacting enantiomer in the cis racemate. To obtain a product not contaminated by the cis isomer, we switched to a different synthetic strategy, in which compound **4**, prior to the enzymatic step, was transformed to a diastereochemically pure gastrolactyl acetate (**5a** plus **5b**) by a dynamic chemical acetylation.

Dynamic Chemical Acetylation of Gastrolactol (4). Acetylation of four stereoisomers of gastrolactol (**4**) in pyridine and acetic anhydride at 0 °C to room temperature yielded two of four possible acetates (**5a** plus **5b**). Only one diastereomer of **5** could be seen in the ^{1}H and the ^{13}C NMR spectra. We assumed that the hemiacetal had equilibrated during the reaction, resulting in the **5a** and **5b** configurations shown in Figure 5.

Enzymatic Resolution of the Gastrolactyl Acetates 5a and 5b. The enzymatic kinetic resolution of the gastrolactyl acetates **5a** and **5b** was investigated. The lipase preparation "Amano I, PS-C" catalyzed the alcoholysis of **5b**. The reaction was carried out in *tert*-butyl methyl ether in the presence of an excess of 1-butanol.

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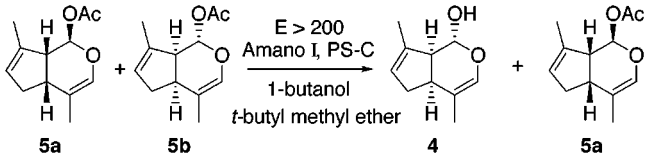

Figure 6. Enzymatic resolution of **5a** and **5b**.

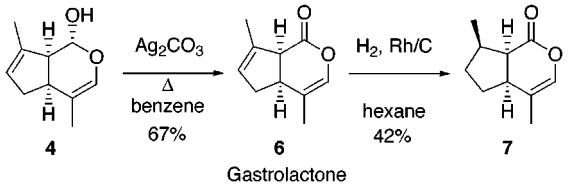

Figure 7. Synthesis of *cis*,*cis*-nepetalactone **7**.

Table 1. Changes in Enantiomeric Excess (ee) during the Resolution of the Gastrolactyl Acetates 5a and 5b

time (min)	substrate (% ee)	product (% ee)	conversion (%)
30	56	>99	36
55	87	99	47
140	98	97	50
180	>99	97	51

Under these reaction conditions, this lipase displayed an excellent enantioselectivity (E > 200). The substrate **5a** and the product **4** were isolated in high enantiopurity and chemical yields (Figure 6 and Table 1).

Determination of the Absolute Configuration of the Products Formed in the Enzymatic Resolution. To determine the absolute configuration of the chiral lactol **4** obtained and the acetate **5a** remaining after by the resolution procedure (Figure 6), lactol **4** was oxidized using silver carbonate on Celite, providing gastrolactone **6** (Figure 7), which had been isolated from the larval defense secretion of the chrysomelid beetle *Gastrophysa cyanea*.[14] Gastrolactone (**6**) had been synthesized before by Jones and Blum, but in more than 10 steps and in 4% overall yield.[15]

The double bond in the five-membered ring of **6** was stereoselectively hydrogenated using rhodium/C as a catalyst, providing *cis*,*cis*-nepetalactone **7** together with some over-reduced material. The use of Pd/C provided a 2:1 mixture of the two *cis*,*cis*-nepetalactones and the corresponding 7-epimer (*cis*,*trans*-nepetalactone). Our conclusion from this experiment was that Rh/C was a more selective catalyst than Pd/C and that the hydrogenating metal approached the double bond from the less hindered side. The result of Damtoft et al. (1989) in their analogous experiment (Figure 3) might, therefore, have been incorrect and it seemed likely that they had made a mistake in the assignment of the stereochemistry of their product.[8]

The *cis*,*cis*-nepetalactone (**7**) obtained in the Rh/C-catalyzed hydrogenation was analyzed by chiral GC and the chromatogram was compared with the chromatograms of the two enantiomers of racemic nepetalactone (which had been synthesized separately, see below) and with that of the natural product (4a*R*,7*S*,7a*S*)-*cis*,*cis*-nepetalactone isolated from *Nepeta racemosa*.[16] We found that we had obtained the antipode of the natural product. The optical rotation was in accordance with the one reported by Jones and Blum.[6f] From this result we concluded that the absolute configurations of **5a** and **4** were as depicted in Figure 6.

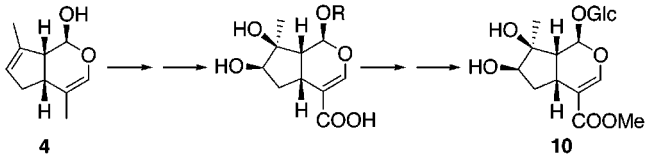

Figure 8. Tentative schematic synthetic route to caryoptoside (**10**).

Conclusions

We have explored the enzymatic kinetic resolution of iridoid hemiacetals and acetals as a means of resolving the stereocenters at the ring junction. A versatile strategy for the preparation of optically pure iridoid synthons has been developed. In a synthetic sequence, including a dynamic acetylation (Figure 5) and an enantioselective transesterification mediated by the lipase Amano I, PS-C (Figure 6), we have resolved a lactol with three chiral centers. This is an important achievement as the optically pure iridoid precursors **4** and **5a** are useful synthetic intermediates in the synthesis of more elaborate iridoids such as loganin or caryoptoside (**10**, Figure 8).

Experimental Section

General Methods. The liquid chromatography technique used was the one described by Baeckström et al.[17] It was performed on silica gel (Merck 60, 0.040−0.063 mm) in 15 or 25 mm inner diameter glass columns with gradient elution, using hexane and increasing proportions of ethyl acetate. ^{1}H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded at 400 and 100 MHz, respectively, using a Bruker AM spectrometer. Chemical shifts were expressed in ppm relative to tetramethylsilane, followed by multiplicity (s, singlet; d, doublet: t, triplet; q, quartet; quint, quintet; m, multiplet; bs, broad singlet; bd, broad doublet; bt broad triplet; td, triple doublet; tt, triple triplet; dt, double triplet), coupling constant (Hz), and number of protons. High-resolution mass spectra were obtained via electron impact (70 eV, 7000 resolution) on a VG 70-SE 250 spectrometer. Optical rotations were measured at 20 °C in a Perkin-Elmer 343 polarimeter. GC−MS analyses were performed by means of a Finnigan SSQ 7000 mass spectrometer, connected to a Varian 3400 GC, with electronic ionization (EI). A DB-5 MS fused silica column (J&W Scientific, 30 m, 0.25 mm ID, 0.25 μm coating layer) and a DB-WAX column (J&W Scientific, 30 m, 0.25 mm i.d., 0.25 μm coating layer) were used. The temperature program was 70 °C (1 min), followed by an increase of 7 °C/min to 220 °C, remaining at 220 °C for 15 min. The injector was a split/splitless type, closed for 0.5 min at isothermal 225 °C.

The tetrahydropyran was treated with sodium/benzophenone and distilled immediately before use. The dichloromethane was treated with calcium hydride and distilled immediately before use. The other starting materials employed were p.a. grade, purchased from commercial suppliers and used without further purification. The reactions involving anhydrous solvents were carried out under an atmosphere of argon.

3,7-Dimethyl-2,6-octadiene-1,8-dial (2). A mixture of geranial and neral ("citral") (**1**) (8.88 g, purity 95%, 55.5 mmol) and SeO_2 (6.17 g, 55.5 mmol) was stirred in dichloromethane (500 mL). The reaction mixture was filtered and concentrated

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after 3 days at room temperature. The yield after chromatography was 40% (3.7 g). Data of (2*E*,6*E*)-**2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (d, J = 7.8 Hz, 1H), 9.33 (bs, 1H), 6.37 (m, 1H), 5.89 (bd, J = 7.7 Hz, 1H), 2.50−2.57 (m, 2H), 2.37 (bt, J = 7.6 Hz, 2H), 1.70 (bs, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.95, 191.13, 161.60, 151.74, 140.32, 127.79, 38.80, 26.41, 17.68, 9.43. Data of (2*Z*,6*E*)-**2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (d, J = 8.0 Hz, 1H), 9.34 (bs, 1H), 6.40 (m, 1H), 5.84 (dt, J = 7.8 Hz, J = 1.1 Hz, 1H), 2.74 (bt, J = 7.8 Hz, 2H), 2.50−2.57 (m, 2H), 2.15 (d, J = 1.1 Hz, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.89, 190.23, 161.75, 151.26, 140.53, 129.08, 31.16, 27.77, 24.95, 9.43.

1,4a,5,7a-Tetrahydro-*N*,4,7-trimethyl-*N*-phenylcyclopenta(c)pyran-1-amine (3). Compound **2** (494 mg, 3.0 mmol) was dissolved in MeOH (3 mL) and then added to *N*-methylaniline (317 mg, 3.0 mmol) in hexane (5 mL). After the mixture was stirred for 48 h at 20 °C, the hexane layer was concentrated under reduced pressure. The crude compound was subjected to medium-pressure column chromatography and the yield was 46% (349 mg, 1.39 mmol). Data of **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24(dd, J = 8.7, 7.3 Hz, 2H), 6.92-(bd, J = 8.7 Hz, 2H), 6.84(bt, J = 7.3 Hz, 1H), 6.25(bs, 1H), 5.52(bs, 1H), 4.80(d, J = 9.9 Hz, 1H), 3.00(s), 2.81(10.0, 8.3 Hz, 1H), 2.75(ddd, 8.6 Hz, 1H), 2.62(m, 1H), 2.11(m, 1H), 1.75-(bs, 3H), 1.63(bs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.25, 140.83, 137.36, 128.97, 126.84, 119.28, 116.02, 113.14, 87.92, 46.78, 42.04, 38.08, 32.58, 16.71, 16.43; HRMS (EI) calcd 255.16231, found 255.16226.

Gastrolactol (4). The reagent *p*-toluenesulfonic acid monohydrate (246 mg, 1.30 mmol) was added to a solution of **3** (332 mg, 1.32 mmol) in water/THF (1:9, 10 mL), and the mixture was stirred for 24 h at room temperature. The reaction mixture was then washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. After chromatography, gastrolactol (**4**) was isolated as a 5:1 mixture of anomeric isomers, the 1*R**,-4a*S**,7a*S** form dominating. The total yield was 87% (190 mg, 1.14 mmol). Data for the 1*R**,4a*S**,7a*S** isomer *trans*-**4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (t, J = 1.6 Hz, 1H), 5.47 (bs, 1H), 4.72 (d, J = 8.0 Hz), 3.18 (bs, 1H), 2.70 (bq, J = 8.0 Hz, 1H), 2.57−2.50 (m, 1H), 2.40 (bt, J = 8.0 Hz, 1H), 2.08−2.00 (m, 1H), 1.83 (d, J = 1.6 Hz, 3H), 1.57 (t, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.03, 134.86, 126.19, 114.22, 95.40, 51.78, 40.29, 37.74, 16.51, 16.43. Data for the 1*S**,4a*S**,-7a*S** isomer *cis*-**4**:^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (t, J = 1.2 Hz, 1H), 5.58 (bs, 1H, CCH=), 5.37 (d, J = 4.0 Hz, 1H, OCHO), 2.80−2.40 (m, 3H), 2.23−2.16 (m, 1H), 1.79−1.78 (m, 3H), 1.60 (t, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.31, 132.46, 127.49, 113.70, 90.93, 49.73, 38.18, 37.32, 16.86, 15.46; HRMS (EI) calcd 166.10054, found 166.09938.

Enzymatic Kinetic Resolution of Gastrolactol (4). The immobilized enzyme preparation Amano I, PS-C (from *P. cepacia*) was equilibrated against a saturated aqueous NaCl solution for 2 days (water activity a_w = 0.7). Racemic gastrolactol (**4**) (249 mg, 1.5 mmol) was added in a sealed flask to a mixture of vinyl acetate (690 μL, 7.5 mmol) and an enzyme preparation (400 mg) suspended in CH_2Cl_2 (1.5 mL, previously dried over molecular sieves). The reaction mixture was stirred at 23 °C and monitored by chiral GC (Chrompack CP Chiralsil-dex CB 25 m × 0.32 mm, FID detector). The reaction was quenched after 100 min by removal of the enzyme by filtration. The substrates and products were purified by medium-pressure chromatography and the isolated yields were 29% (89 mg) of the remaining hemiacetal **4** and 25% (77 mg) of the acetal **5**, respectively. The products were analyzed by chiral GC. The proportions of the acetates formed are shown in Figure 4.

1*R*,4a*R*,7a*R*-Gastrolactyl Acetate (5a) and 1*R*,4a*S*,7a*S*-Gastrolactyl Acetate (5b). Gastrolactol (**4**) (160 mg, 0.99 mmol) was stirred in acetic anhydride and pyridine (0.6 mL, 1:2 v/v) at 0 °C for 1 h and at room temperature for 2 h. The reaction mixture was washed with water (2 × 25 mL), the aqueous phases were extracted with diethyl ether, and the combined organic phases were dried ($MgSO_4$). The yield of **5a** plus **5b** after chromatography was 86% (170 mg). Data of **5a** and **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (t, J = 1.1 Hz, 1H), 5.82 (d, J = 4.0 Hz), 5.48 (bs, 1H), 2.75 (q, J = 8 Hz, 1H), 2.67 (t, J = 8.0 Hz, 1H), 2.57−2.50 (m, 1H), 2.19−2.13 (m, 1H), 2.11 (s, 3H), 1.75 (bs, 3H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.97, 138.26, 134.83, 127.02, 113.96, 91.80, 49.32, 40.29, 36.77, 21.24, 16.28, 15.69; HRMS (EI) calcd 208.11038, found 208.10994.

Enzymatic Kinetic Resolution of 1*R*,4a*R*,7a*R*-Gastrolactyl Acetate (5a). The immobilized enzyme preparation (Amano I, PS-C) was equilibrated against a saturated aqueous NaCl solution for 2 days (a_w = 0.7). The racemic gastrolactyl acetates **5a** and **5b** (208 mg, 1 mmol), 1-butanol (296 μL, 4 mmol) and the enzyme preparation [300 mg in *tert*-butyl methyl ether (9.5 mL), previously dried over molecular sieves] were mixed in a stoppered round-bottomed flask. The reaction mixture was stirred at 25 °C and monitored by chiral GC (Chrompack CP Chiralsil-dex CB 25 m × 0.32 mm, FID detector). The reaction was quenched after 3 h by removal of the enzyme by filtration, whereafter the substrates and products were purified by medium-pressure chromatography. The isolated yields of the remaining acetate **5a** and the hemiacetal **4** were 40% (83 mg, ee >99%) and 45% (75 mg, ee 98%), respectively, and the optical rotations were $[\alpha]^{20}_D$ +25.50 (*c* 0.076, CH_2Cl_2) and $[\alpha]^{20}_D$ +71.16 (*c* 0.036, CH_2Cl_2).

Gastrolactone (6). A reaction mixture containing gastrolactol (**4**) (64 mg, 0.39 mmol), benzene (5 mL), an excess of Fetizon's reagent (silver carbonate on Celite), and freshly dried molecular sieves (4 Å) was heated with reflux during 4 h. The reaction mixture was then filtered and chromatographed. Gastrolactone (**6**) was isolated in 67% yield (43 mg, 0.26 mmol). Data for **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (t, J = 1.2 Hz, 1H), 5.50 (bs, 1H), 3.44 (bd, J = 8.0 Hz, 1H), 2.97 (bd, J = 8.0 Hz, 1H), 2.65−2.58 (m, 1H), 2.24 (ddq, J = 16.0, 8.0, 2.0 Hz, 1H), 1.86 (bs, 3H), 1.60 (bs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.81, 137.16, 133.55, 126.37, 115.18, 50.47, 40.29, 37.55, 15.85, 15.84; HRMS (EI) calcd 164.08154, found 164.08373; $[\alpha]^{20}_D$ +113.82 (*c* 0.019, hexane).

(4a*R*,7*S*,7a*S*)-Nepetalactone (7) (*cis*,*cis*-Nepetalactone). Gastrolactone (**7**) (193 mg, 1.17 mmol) was dissolved in hexane (10 mL), Rh/C 5% (20 mg) was added, and the reaction flask was flushed with hydrogen. The hydrogenation process was monitored by GC, and it was stopped when less than 2% starting material remained. The reaction mixture was poured on the top of a silica gel column, and the product was eluted with increasing amounts of ethyl acetate in hexane. The combined fractions yielded 42% (82 mg) of the *cis*,*cis*-nepetalactone (**7**). Data of **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (bs, 1H), 3.10 (t, J = 9.6 Hz, 1H), 3.00−2.76 (m, 1H), 2.65−2.59 (m, 1H), 1.89−1.78 (m, 3H), 1.56 (s, 3H), 1.36−1.24 (m, 1H), 0.98 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.80, 134.13, 115.40, 46.16, 39.32, 38.31, 32.66, 30.40, 17.17, 14.76; HRMS (EI) calcd 166.09755, found 166.09938; $[\alpha]^{20}_D$ −41.14 (*c* 0.0039, hexane).

Racemic Gastrolactone (6). Compound **6** was prepared as described by Unelius et al.[18] The racemic gastrolactone (**6**) was reduced to *racemic cis*,*cis*-nepetalactone as described above for the enantiopure gastrolactone.

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Supporting Information Available: MS fragments of compounds **3**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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