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Asymmetric Synthesis of Iridoid Derivatives Using Resolved 2-Phenylindoline as a Chiral Auxiliary

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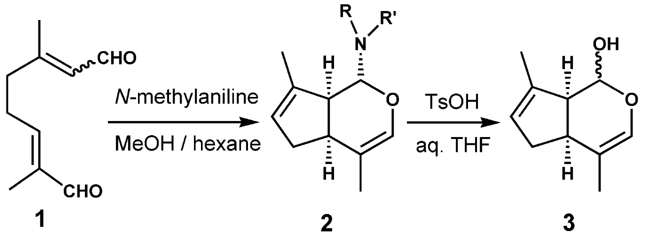
An asymmetric synthetic route to *cis*,*cis*-nepetalactol (component of the sex pheromone for the hop aphid, *Phorodon humuli*) is presented. 2-Phenylindoline was resolved to provide a chiral auxiliary for the cycloaddition of oxocitral. The resolution was made by chromatographic separation of the diastereomers of the urea derivative made from 2-phenylindoline and with (*R*)-(+)-α-methylbenzyl isocyanate, followed by reductive cleavage of the isolated diasteromers using diborane. The cycloaddition of oxocitral using (*S*)-2-phenylindoline yielded an enantiopure product after chromatography. Hydrolysis of the cycloaddition adduct yielded gastrolactol (**3**). As gastrolactol is a versatile synthon for the synthesis of iridoids, the overall procedure provides a general asymmetric route to elaborated iridoids.

Introduction

The iridoids constitute a group of natural products with a steadily increasing number of elucidated structures. The common carbon skeleton of these monoterpenes is (dimethylisopropyl)cyclopentane. The name derives from *Iridomyrmex*, a genus of ants that produces iridodial as a compound for chemical warfare. Apart from being used in the chemical defense in many insect species[1] some iridoids have antiviral and antibacterial properties.[2] Our interest in these molecules arose when we were trying to find good synthetic procedures for nepetalactols, common aphid sex pheromone components.[3] There are numerous syntheses of iridoids.[4] In a previous paper we published a synthesis of racemic gastrolactol **3** (Scheme 1),[5] where the key step is an enal-enamine [2+4]-cycloaddition and in a subsequent paper we used a dynamic acetylation/lipase mediated resolution procedure to resolve gastrolactol and converted it to chiral *cis*,*cis*-nepetalactone.[6]



Scheme 1. Synthesis of racemic gastrolactol (**3**).

In this paper, we describe an enantioselective variation of this intramolecular enal-enamine [2+4] cycloaddition using (*S*)-2-phenylindoline as the chiral auxiliary. During the course of this work both enantiomers of 2-phenylindoline were prepared for the first time.

Results and Discussion

In an initial attempt to cyclize oxocitral, we tried 2-*tert*-butyl-4-methyl-5-phenyloxazolidine (**4**) (as a 3:2 mixture) as chiral auxiliary (Scheme 2). This reagent was used as the chiral auxiliary in a synthesis of brefeldin C[7] and also as a catalyst for the enantioselective addition of diethylzinc to aryl aldehydes.[8]

Only one diastereomer of the product **5** can be seen in the ^{1}H NMR and the ^{13}C NMR spectrum, which indicates, not only that the product has been obtained in excellent diastereomerical excess, but also that one diastereomer of the oxazolidine acetal is selectively reacting or the oxazolidine acetal is equilibrating to the most stable configuration before, during, or after the reaction. All these scenarios would give rise to the *all-cis* configuration of the substitu-

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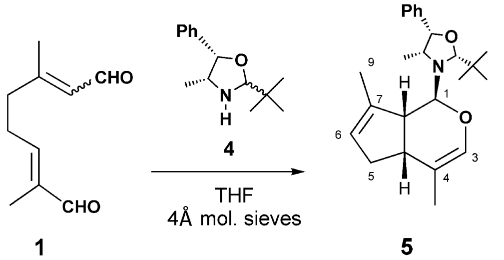


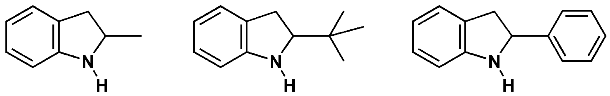
Scheme 2. Chiral cycloaddition.

ents on the oxazolidine ring in the product. The tentative assignment of the relative stereochemistry of compound **5** depicted in Scheme 2 was based on NMR experiments.

The yield in this asymmetric cycloaddition was low and it was not possible to get the cycloaddition reaction to go to completion. Still we believed that our approach could be very useful for iridoid and alkaloid synthesis therefore we looked for other chiral auxiliaries and decided to explore 2-substituted indolines.

Indolines as Chiral Auxiliaries

2-Methyl- (**6**) and 2-*tert*-butylindoline (**7**) were synthesized by the reaction of the indoles with sodium cyanoborohydride in glacial acetic acid at 15 °C to give the corresponding indolines in excellent yields. However, applying these conditions to 2-phenylindole did not result in a good yield of 2-phenylindoline (**8**) (Figure 1). Resistance of the highly stabilized indolenium ion towards reduction by sodium cyanoborohydride could possibly account for this result.[9] Instead, racemic 2-phenylindoline (**8**) was prepared from 2-phenylindole by reduction with Sn/HCl.[10]



6 **7** **8**

Figure 1. Indolines tried as chiral auxiliaries for the cycloaddition step.

Racemic 2-methyl- (**6**), 2-*tert*-butyl- (**7**), and 2-phenylindoline (**8**) were treated with oxocitral (**1**) and of the three auxiliaries only 2-phenylindoline (**8**), gave a pure diastereomer **9** with a *cis*-junction between the rings (*syn* or *anti*, Figure 2) according to NMR spectroscopy.

We then investigated the formation of **9** computationally.[11] Assuming that the ring closure is either a reversible equilibrium, or kinetically controlled but following a Bell–Evans–Polanyi relationship,[12] the energetically most favored product will be formed preferentially. For each of the four diastereomers of **9** (i. e. **9a**–**9d**), we have searched the conformational space fully[13] using two quite different force fields of high quality,[14] MM3*[15] and MMFFs,[16] as implemented in Macromodel.[17] With one exception (the highest energy diastereomer), the two force fields agreed on

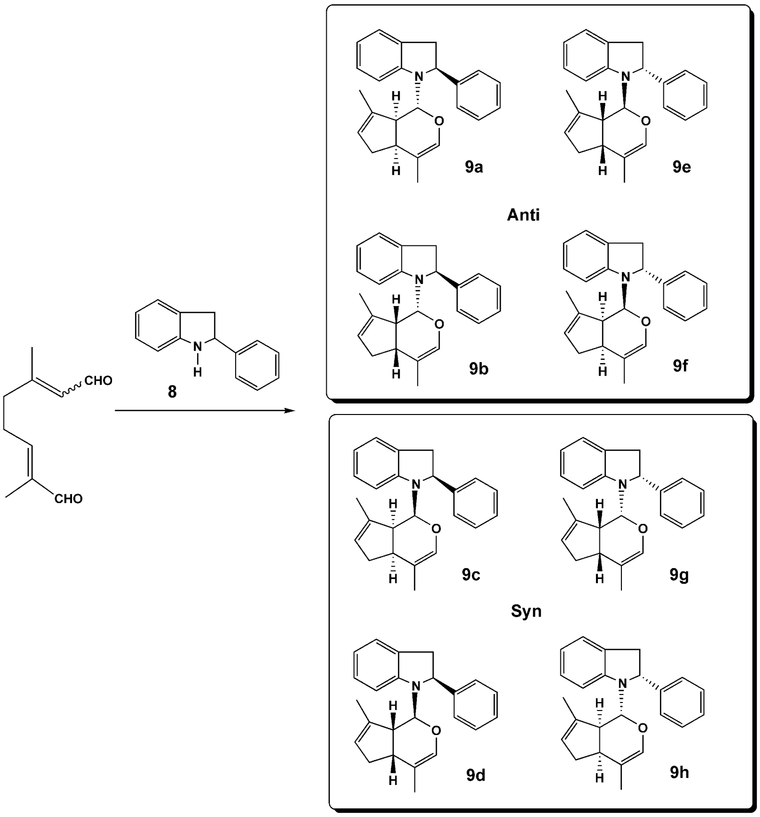
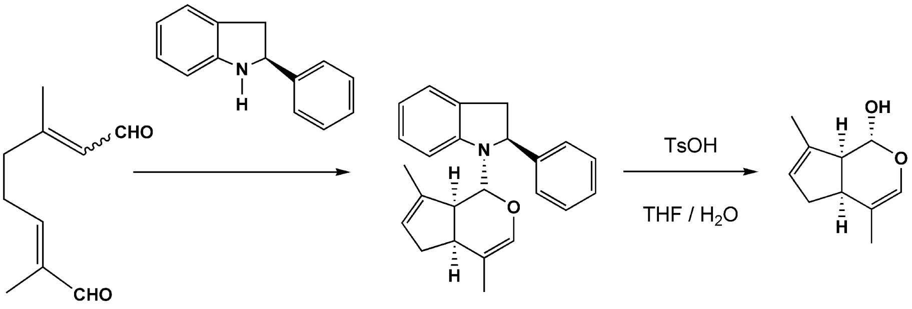


Figure 2. The stereoisomers that hypotetically can be formed by reaction of oxocitral with racemic 2-phenylindoline.



1 **9a** **3**

Scheme 3. Intramolecular cycloaddition using (*S*)-2-phenylindoline as an auxiliary.

the global energy minimum conformation for each diastereomer, and also on the ranking of the diastereomers. With both force fields, **9a** (Figure 2) was the most stable structure, by 4 kJ/mol in MMFFs, and by 10 kJ/mol in MM3*. This agreement would usually be sufficient to be fairly certain that **9a** is indeed the most stable structure, but because the structure contains an unusual mono-aza-acetal, for which the MM parameters may be less reliable, we also decided to check the results using a quantum-mechanical method. We thus subjected the minimum energy conformation of each diastereomer to optimization using B3LYP/6-31G*, a method that is generally believed to give accurate conformational energies.[14] Again, **9a** was identified to be the most stable structure, now by a safe 19 kJ/mol relative to the second most stable structure.

These results clearly indicated that the four isomers with a *cis,cis*-configuration at the atoms 4a-7a-1 are **not** formed, as found in earlier work by us[5–6] on very similar systems by NMR and it seemed evident that (*S*)-2-phenylindoline would give the cyclized *anti*-product **9a** in Figure 2 when reacted with oxocitral (**1**), (Scheme 3).

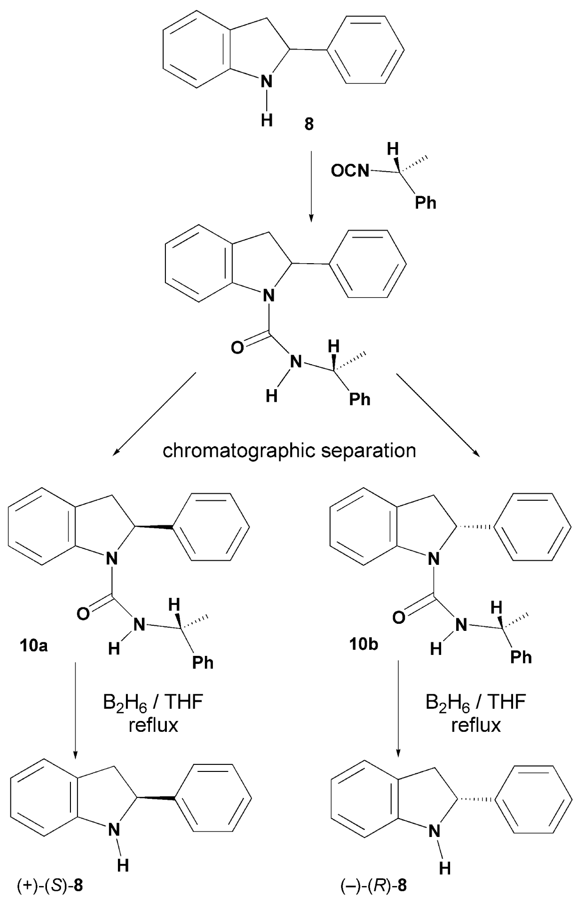
The synthetic strategy to produce the aphid sex pheromone *cis,cis*-nepetalactol would then be to do a regio- and stereoselective hydrogenation of the double bond in the five-membered ring in gastrolactol (**3**).[18]

With this synthetic route in mind, racemic 2-phenylindoline (**8**) was subjected to a resolution procedure (Scheme 4).

Racemic 2-phenylindoline (**8**) was treated with (*R*)-(+)-α-methylbenzyl isocyanate. The two diastereomers formed (**10a** and **10b**) were separated by an unusual variation of column chromatography silica gel.[19] The crystals were dissolved in hexane and pumped into a column saturated with hexane.

As the solubility of the urea derivatives was low in hexane the eluting solvent was recycled to adsorb all material on the column. The compounds were then eluted by increasing amounts of ethyl acetate in hexane via another column coupled in series. The two isolated diastereomers of the urea derivative **10a** and **10b** were separately transformed to the enantiomers of 2-phenylindoline by reduction with diborane and subsequent hydrolysis (Scheme 4).

The enantiomeric purities of the two resolved 2-phenylindoline enantiomers were $>$ 99% and 90% for **10a** and **10b** respectively, as analyzed by chiral gas chromatography. The lower enantiomeric purity for isomer **10b** could be traced back to the urea derivative in which the urea isomer **10a** could be detected.



Scheme 4. Resolution of racemic 2-phenylindoline (**8**).

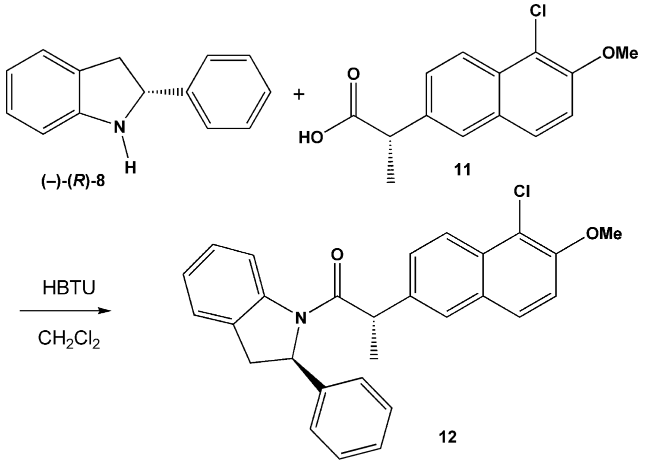
The urea derivative isomers **10a** and **10b** were both crystalline compounds and separately subjected to X-ray examination in order to determine the absolute configuration. Unfortunately, neither isomer gave crystals with crystalline lattices that were coherent enough for conclusive X-ray analysis.

The geometry of **10a** and **10b** structures were optimized using the hybrid density functional method B3LYP and the

6-31G(d) basis set. The NMR chemical shifts were calculated using GIAO method as implemented in Gaussian 94 using a larger basis set: 6-311G (d,p). The chemical shift calculated for the methyl protons of **10b** (*S*,*R*) was 0.3 ppm lower than for **10a** (*R*,*R*). Experimentally we found that the signals for the protons of the methyl group of **10b** (*S*,*R*) was 0.26 ppm to lower field than these of the other isomer.

To unambiguously assign the absolute configuration of the carbon bearing the phenyl group in **8b**, many derivatives were prepared. Of all tested, only the (*S*)-5-chloronaproxenyl derivative **12** gave crystals suitable for X-ray crystallographic analysis.

The X-ray analysis revealed, as depicted in Scheme 5, an (2*R*)-configuration at the C2 of the (–)-**8b**.



Scheme 5. Determination of the absolute configuration of (***R***)-(–)-2-phenylindoline.

Both enantiomers of 2-phenylindoline were used as chiral auxiliaries in the intramolecular cycloaddition reaction shown in Figure 2, providing a pure enantiomer for each reaction. When (*S*)-(+)-2-phenylindoline was used, **9a** was formed and when (*R*)-(–)-2-phenylindoline was used, **9e** was formed. The cycloaddition products **9a** and **9e** were hydrolyzed in separate reaction vials and after acetylation, the optical rotation of the acetates were compared with optical rotation data obtained previously, in order to determine the absolute configuration.[6] From these results we could confirm the results from our computer modeling experiments, that the *anti*-products **9a** and **9e** were formed in the cycloaddition reaction depicted in Figure 2.

Conclusions

In conclusion, a formal asymmetric synthesis leading to iridoids has been developed. It includes the resolution of 2-phenylindoline that hitherto has neither been resolved nor used as a chiral inductor.

Experimental Section

General Methods: All solvents were distilled before use unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone under nitrogen. Dichloromethane (CH_2Cl_2), toluene and triethylamine (Et_3N) were distilled from CaH_2 under nitrogen. Air- and moisture-sensitive reactions were carried out in oven- or flame-dried glassware, septum-capped under an atmospheric pressure of nitrogen. Commercially available compounds were used without further purification unless otherwise indicated. Analytical thin-layer chromatography was performed on Merck silica gel 60 F 254 plates, using UV and a solution of vanillin in ethanol containing sulfuric acid for visualization. The liquid chromatography technique used was the one described by Baeckström et al.[19] 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 amounts of ethyl acetate. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded with a 400- or 500-MHz instrument using the residual signals from $CHCl_3$, δ = 7.26 ppm and δ = 77.0 ppm, as internal references for ^{1}H and ^{13}C, respectively. Chemical shifts are reported in the δ scale with multiplicity (br. = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, sext. = sextett, m = multiplet), coupling constants [Hz] and integration. Optical rotations were measured at 20 °C using the sodium D-line (589 nm).

(4*R*,5*S*)-2-*tert*-Butyl-4-methyl-5-phenyloxazolidine (4): (+)-Norephedrine (6.80 g, 45.0 mmol) was heated to reflux with pivalaldehyde (3.96 g, 46.0 mmol) in benzene according to Senkus.[20] The condensed water was collected in a Dean–Stark trap. After 2 h the solvent was evaporated and the product was stored over molecular sieves in the freezer and was then used as such in the subsequent cyclization step. The product was obtained as a 2:3 mixture of α- and β-*tert*-butyl isomers in 95% yield (9.4 g).

Major Isomer: ^{1}H NMR: δ = 7.25–7.33 (m, 5 H), 4.93 (d, J = 8.1 Hz, 1 H), 4.25 (s, 1 H), 3.66 (dq, J = 8.1, J = 6.7 Hz, 1 H), 2.27 (br. s, 1 H), 1.15 (s, 9 H), 0.75 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR: δ = 140.3, 128.3 (2), 127.3 (2), 126.7, 98.0, 80.6, 57.7, 33.1, 25.8 (3), 16.8 ppm.

Minor Isomer: ^{1}H NMR: δ = 7.25–7.33 (m, 5 H), 4.96 (d, J = 4.9 Hz, 1 H), 4.72 (s, 1 H), 3.69 (app. quint., J = 6.7, J = 5.0 Hz, 1 H), 2.27 (br. s, 1 H), 1.03 (s, 9 H), 0.75 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR: δ = 140.1, 128.0 (2 C), 127.0 (2 C), 126.0, 98.7, 82.2, 57.4, 35.2, 25.7 (3 C), 15.6 ppm.

(2*R*,4*R*,5*S*)-2-*tert*-Butyl-3-[(1*S*,4a*R*,7a*R*)-1,4a,5,7a-tetrahydro-4,7-dimethylcyclopenta[*c*]pyran-1-yl]-4-methyl-5-phenyloxazolidine (5): 8-Oxocitral (**1**) (494 mg, 3.0 mmol) was dissolved in 3 mL of THF and molecular sieves and then added to (4*R*,5*S*)-2-*tert*-butyl-4-methyl-5-phenyloxazolidine (657 mg, 3.0 mmol) in hexane (5 mL). After 48 h at room temp. the solvents were evaporated. Compound **5** (349 mg, 1.39 mmol) was isolated after chromatography. The yield was 46.3%. ^{1}H NMR: δ = 7.22–7.35 (m, 5 H), 6.28 (d, J = 1.0 Hz, 1 H), 5.53 (d, J = 1.6 Hz, 1 H), 5.11 (d, J = 5.8 Hz, 1 H), 4.53 (s, 1 H), 4.05 (d, J = 10.3 Hz, 1 H), 3.82 (dq, J = 6.7, J = 5.8 Hz, 1 H), 2.67 (m, J = 8.7, J = 8.4 Hz, 1 H), 2.57 (ddt, J = 15.7, J = 8.4, J = 1.8 Hz, 1 H), 2.47 (t, J = 10.3, J = 8.7 Hz, 1 H), 2.06 (m, J = 15.8, J = 8.4 Hz, 1 H), 2.01 (s, 3 H), 1.62 (s, 3 H), 0.99 (s, 9 H), 0.74 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR: δ = 141.8, 138.8, 137.4, 128.0 (2 C), 126.91, 126.27 (2 C), 112.6, 100.6, 91.5, 82.1, 55.2, 48.5, 42.5, 38.1, 35.8, 29.7, 25.8 (3 C), 18.8, 17.6, 16.7 ppm.

Observed Nuclear Overhauser Effects (NOEs): NOEs between the phenyl group and *tert*-butyl group plus the CH-CH_3 methyl and between the Ph-C*H*-O proton, the C*H*-C$(CH_3)_3$ proton and the Me-C*H*-N proton suggested that the phenyl group, *tert*-butyl group and the CH-CH_3 methyl were all *cis* to each other.

The stereochemistry at the ring junction was concluded to be *cis* due to NOEs between the 4a and 7a protons. The anomeric proton has to be *trans* to 7a because the coupling constant was over 10 Hz (and accordingly no NOE was observed).

NOEs between the 7a and the Me-C*H*-N proton give the correct orientation of the two rings system in space.

2-Methylindoline (6): Sodium cyanoborohydride (322.5 mg, 5.13 mmol) was added at 17 °C in one portion to a magnetically stirred solution of 2-methylindole (300 mg, 2.29 mmol) in glacial acetic acid (4.5 mL) under N_2. The mixture was stirred for 2 h at 15 °C. Water (22.5 mL) was added and the mixture cooled in an ice bath and slowly made strongly basic with NaOH pellets. The mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with water and aq. NaCl and then dried with anhydrous K_2CO_3 and the solvent was removed under reduced pressure. After chromatography, 2-methylindoline (**6**) was isolated in 68% (206 mg, 1.55 mmol). ^{1}HNMR: δ = 7.09 (d, J = 7.2 Hz, 1 H), 7.03 (t, J = 7.6 Hz, 1 H), 6.72 (t, J = 7.2 Hz, 1 H), 6.63 (d, J = 7.7 Hz, 1 H), 4.01 (b sext, J = 7.9 Hz, 1 H), 3.87 (br. s, 1 H), 3.16 (dd, J = 15.4, J = 8.5 Hz, 1 H), 2.65 (dd, J = 15.4, J = 7.7 Hz, 1 H), 1.31 (d, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR: δ = 150.4, 129.0, 127.2, 124.7, 118.8, 109.5, 55.2, 37.7, 22.1 ppm.

1-[(1*S,4a*R**,7a*R**)-1,4a,5,7a-Tetrahydro-4,7-dimethylcyclopenta-[*c*]pyran-1-yl]-2-methylindoline:** 8-Oxocitral (400 mg, 2.4 mmol) in 3 mL of methanol was added to 2-methylindoline (320 mg, 2.4 mmol) in hexane (5 mL). After 48 h stirring at 20 °C, the hexane layer was concentrated under reduced pressure. The crude product was subjected to medium pressure column chromatography, yielding 40% (269 mg, 0.961 mmol) of a 7:3 mixture of diastereomers.

Major Isomer: ^{1}H NMR: δ = 7.05 (d, J = 7.8 Hz, 1 H), 7.02 (t, J = 7.7 Hz, 1 H), 6.68 (br. t, J = 7.3 Hz, 1 H), 6.64 (br. d, J = 7.8 Hz, 1 H), 6.21 (br. s, 1 H), 5.55 (br. s, 1 H), 4.55 (d, J = 10.5 Hz, 1 H), 4.02 (m, 1 H), 3.30 (m, 1 H), 3.1 (m, 1 H), 2.7 (m, 1 H), 2.5 (m, 1 H), 2.10 (m, 2 H), 1.75 (s, 3 H), 1.6 (s, 3 H), 1.26 (d, J = 6.38 Hz, 3 H) ppm.

***N*-(2-Methylphenyl)-2,2-dimethylpropanamide:** *o*-Toluidine (16.81 g, 79.2 mmol), trimethylacetyl chloride (9.55 g, 79.2 mmol) and anhydrous K_2CO_3 (7.60 g, 55.0 mmol) in 120 mL of anhydrous toluene was stirred and heated to reflux for 3 h and then allowed to stand for 6 h at room temperature. The resulting solid (mixture of products and salts) was filtered off and the filtrate was mixed with water (120 mL) and stirred at room temperature for 1.5 h. This mixture was extracted with dichloromethane and the solvents evaporated. Column chromatography and recrystallization (solvent: dichloromethane/toluene) yielded 12 g (62.5 mmol) of *N*-(2-methylphenyl)-2,2-dimethylpropanamide (79%). ^{1}H NMR: δ = 7.86 (d, J = 7.9 Hz, 1 H), 7.21 (t, J = 8.3 Hz, 1 H), 7.18 (d, J = 7.7 Hz, 1 H), 7.06 (br. t, J = 8.4 Hz, 1 H), 2.25 (s, 3 H), 1.34 (s, 9 H) ppm. ^{13}C NMR: δ = 176.4, 135.8, 130.3, 128.6, 126.8, 124.8, 122.7, 39.7, 27.7 (3 C), 17.6 ppm.

2-*tert*-Butyl-1*H*-indole: *N*-(2-Methylphenyl)-2,2-dimethylpropanamide (1.5 g, 7.98 mmol) was dissolved in 125 mL of THF and the mixture was stirred under argon in an ice bath. *n*BuLi (9.4 mL, 2.5 M) was added dropwise. After 16 h of stirring, the reaction mixture was cooled in an ice bath and neutralized with 2 M HCl. The organic layer was separated and the aqueous layer washed with CH_2Cl_2. The combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. After chromatography 1.16 g (6.70 mmol) of indole was obtained in 84% yield. ^{1}H NMR: δ = 7.95 (br. s, 1 H), 7.54 (br. d, J = 8.0 Hz, 1 H), 7.32 (br. d, J = 8.1 Hz, 1 H), 7.12 (br. t, J = 6.9 Hz, 1 H), 7.06 (br. t, J = 7.40 Hz, 1 H), 6.26 (br. s, 1 H), 1.40 (s, 9 H) ppm. ^{13}C NMR: δ = 148.7, 136.3, 128.5, 121.0, 119.9, 119.6, 110.3, 96.9, 30.3 (3 C), 27.7 ppm.

2-*tert*-Butylindoline (7): 2-*tert*-Butylindole (300 mg, 1.73 mmol) was reduced to 2-*tert*-butylindoline (**7**) using the same experimental procedure as described for **6**. The yield of **7** was 68% (204 mg, 1.18 mmol). ^{1}H NMR: δ = 7.13 (d, J = 7.3 Hz, 1 H), 7.06 (t, J = 7.6 Hz, 1 H), 6.72 (t, J = 7.3 Hz, 1 H), 6.63 (d, J = 7.7 Hz, 1 H), 3.75 (br. s, 1 H), 3.70 (br. t, J = 10.1, J = 9.3 Hz, 1 H), 3.02 (dd, J = 16, 9.2 Hz, 1 H), 2.88 (dd, J = 15.8, 10.3 Hz, 1 H), 1.0 (s, 9 H) ppm. ^{13}C NMR: δ = 151.4, 129.0, 127.1, 124.4, 118.0, 108.5, 69.4, 33.5, 31.2, 26.0 (3 C) ppm.

2-*tert*-Butyl-1-[(1*S,4a*R**,7a*R**)-1,4a,5,7a-Tetrahydro-4,7-dimethylcyclopenta[*c*]pyran-1-yl]indoline:** 8-Oxocitral (100 mg, 0.60 mmol) dissolved in 3 mL of methanol was added to 2-*tert*-butylindoline (105 mg, 0.60 mmol) in hexane (5 mL). After 48 h at room temperature the hexane layer was concentrated under reduced pressure. The crude product was subjected to medium pressure column chromatography yielding 46% (89 mg) of a 97:3 mixture of diastereomers.

Major Isomer: ^{1}H NMR: δ = 7.01 (t, J = 6.4 Hz, 1 H), 6.98 (d, J = 7.7 Hz, 1 H), 6.77 (d, J = 7.7 Hz, 1 H), 6.63 (t, J = 7.5 Hz, 1 H), 6.34 (s, 1 H), 5.54 (br. s, 1 H), 4.37 (d, J = 10.3 Hz, 1 H), 3.46 (dd, J = 10.4, J = 2.6 Hz, 1 H), 3.37 (m, 1 H), 3.23 (dd, J = 16, J = 10 Hz, 1 H), 2.9 (br. d, J = 14.8 Hz, 1 H), 2.74 (m, 1 H), 2.6 (m, 1 H), 2.0 (m, 1 H), 1.65 (s, 3 H), 1.51 (s, 3 H), 0.92 (s, 9 H) ppm. ^{13}C NMR: δ = 148.2, 141.2, 137.6, 130.4, 126.8, 126.7, 123.7, 117.5, 113.2, 110.4, 89.3, 73.0, 43.6, 42.5, 38.1, 37.0, 31.5, 26.0, 25.3 (2 C), 16.7, 15.6 ppm.

2-Phenylindoline (8): 2-Phenylindole (14 g, 72.5 mmol) in ethanol 350 mL and 10 N HCl (35 mL) was heated to reflux in the presence of Sn (30 g, 261 mmol) for 8 h. The mixture was decanted into 50% KOH solution, extracted with diethyl ether and concentrated. After chromatography, 12.4 g of 2-phenylindoline was obtained (yield 88%). ^{1}H NMR: δ = 7.44 (br. d, J = 6.8 Hz, 2 H), 7.38–7.28 (m, 3 H), 7.15–7.09 (m, J = 7.5 Hz, 2 H), 6.84 (br. t, J = 7.4 Hz, 1 H), 6.78 (br. d, J = 7.7 Hz, 1 H), 5.0 (br. t, J = 8.9 Hz, 1 H), 4.2 (br. s, 1 H), 3.48 (dd, J = 15.8, J = 9.0 Hz, 1 H), 3.07 (dd, J = 15.0, J = 8.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 150.9, 144.5, 128.4 (2 C), 128.0, 127.5, 127.3, 126.2 (2 C), 124.5, 118.8, 108.8, 63.4, 39.5 ppm.

2-Phenyl-*N*-[(*R*)-1-phenylethyl]indoline-1-carboxamide (10): 2-Phenylindoline (**8**) (4.6 g, 24 mmol) and (*R*)-(+)-α-methylbenzyl isocyanate (2.94 g, 20 mmol) in 25 mL of dry THF were mixed and stirred for 12 h. The yield was 86% (5.88 g). The two diastereoisomers formed were separated by liquid chromatography. One diastereomer (isomer I = **10a**) had an R_f-value of 0.44 on TLC-plates eluted with 20% EtOAc/hexane while the other (isomer II = **10b**) had an R_f-value of 0.34 using the same eluting system.

Isomer 1, (2*S*,1′*R*)-10a: ^{1}H NMR: δ = 8.04 (d, J = 8.1 Hz, 1 H), 7.37 (m, 3 H), 7.31 (m, 4 H), 7.20 (m, 4 H), 7.09 (d, J = 6.7 Hz, 1 H), 6.94 (t, J = 7.3 Hz, 1 H), 5.21 (dd, J = 10.54, J = 4.28 Hz, 1 H), 4.94 (quint, J = 7.05 Hz, 1 H), 4.61 (d, J = 7.05 Hz, 1 H), 3.75 (dd, J = 16.3, 10.57 Hz, 1 H), 3.00 (dd, J = 16.3, J = 4.28 Hz, 1 H), 1.12 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR: δ = 154.4, 144.2, 143.9, 142.8, 129.4 (2 C), 128.5 (2 C), 128.3, 128.0, 127.7, 127.0, 125.8 (2 C), 125.3 (2 C), 124.4, 122.1, 115.1, 62.6, 49.6, 39.1, 22.1 ppm.

Isomer 2, (2*R*,1′*R*)-10b: ^{1}H NMR: δ = 8.06 (d, J = 8.1 Hz, 1 H), 7.33–7.08 (m, 10 H), 6.94 (t, J = 7.2 Hz, 1 H), 6.65 (d, J = 3.0 Hz, 2 H), 5.25 (dd, J = 10.3, J = 3.5 Hz, 1 H), 4.96 (quint, J = 6.8 Hz, 1 H), 4.77 (d, J = 6.6 Hz, 1 H), 3.76 (dd, J = 15.8, 10.8 Hz, 1 H), 3.00 (dd, J = 16.0, J = 3.3 Hz, 1 H), 1.37 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR: δ = 154.2, 144.2, 143.8, 142.9, 129.5 (2 C), 128.3 (2 C), 128.2, 127.9, 127.7, 126.7, 125.4 (2 C), 125.3 (2 C), 124.4, 122.1, 115.1, 62.6, 49.6, 39.1, 23.0 ppm.

Reductive Cleavage of the Urea Derivatives 10a and 10b: The two diastereomers of the 2-phenylindoline urea derivatives (**10a** and **10b**) (1.5 g, 4.38 mmol) were heated to reflux separately in borane–DMS complex (2 M, 12 mL) overnight. Saturated Na_2CO_3 was added and the solution was extracted with EtOAc. After chromatography 734 mg of isomer 1 (**8a**) and 580 mg of isomer 2 (**8b**) of 2-phenylindoline was obtained (yields 86 and 68%, respectively).

The enantiomeric purity was measured by using chiral two-dimensional gas chromatography. The retention time on the first DB-wax column was 28.25 min using the programme 200 °C (1 min) followed by 210 °C (30 min). On the β-cyclodextrin chiral column the retention time for the first isomer was 70.84 min and for the second isomer 71.72 min using the temperature programme 120 °C (20 min) followed by 165 °C (180 min). The temperature in the interface between two columns was 200 °C. The enantiomeric purity of **8a** was 99.4% and 90.2% for **8b**.

Isomer 1, (*S*)-(+)-8a: The NMR spectrum was identical to the one of **8**. $[\alpha]_D^{20}$ = +93.8 (c = 0.75, benzene), ref.[21] $[\alpha]_D^{20}$ = +65.4 (c = 0.5, $CHCl_3$).

Isomer 2, (*R*)-(–)-8b: The NMR spectrum was identical to the one of **8**. $[\alpha]_D^{20}$ = –84.6 (c = 3, benzene).

(*S*)-2-(1-Chloro-2-methoxynaphthalen-6-yl)propanoic Acid (11): Sulfuryl chloride (290 mg, 2.19 mmol) was added dropwise to an ice cooled (5–20 °C) and vigorously stirred reaction solution of (*S*)-naproxen (471 mg, 1.99 mmol, $[\alpha]_D^{20}$ = +67.5 c = 0.17, $CHCl_3$, ref.[22] $[\alpha]_D^{25}$ = +66 c = 1, $CHCl_3$) in CH_2Cl_2 (10 mL). The reaction was then stirred at room temperature until all starting material was consumed (typically < 1 h). Compound **11** was obtained in 89% after recrystallization. ^{1}H NMR: δ = 8.18 (d, J = 8.8 Hz, 1 H), 7.73 (d, J = 8.9 Hz, 1 H), 7.7 (d, J = 1.5 Hz, 1 H), 7.53 (dd, J = 8.8, J = 1.8 Hz, 1 H), 7.29 (d, J = 9.0 Hz, 1 H), 4.0 (s, 3 H), 3.9 (q, J = 7.1 Hz, 1 H), 1.6 (d, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR: δ = 18.4, 45.1, 56.9, 113.9, 116.7, 131.0, 129.4, 127.8, 127.3, 126.1, 123.9, 136.4, 152.5, 174.8 ppm. $[\alpha]_D^{20}$ = +62.2 (c = 0.1, $CHCl_3$, ref.[23] $[\alpha]_D^{25}$ = +51).

(*S*)-2-(1-Chloro-2-methoxynaphthalen-6-yl)-1-[(*R*)-2-phenylindolin-1-yl]propan-1-one (12): *O*-Benzotriazole-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate (HBTU) (0.10 g, 0.27 mmol) and compound **11** (0.071 g, 0.027 mmol) were mixed in acetonitrile (10 mL) for 2–3 min. *N*,*N*-Diisopropylethylamine (DIPEA) (0.14 mL, 0.81 mmol) and the indoline **8b** (52 mg, 0.27 mmol) were added and the reaction mixture was stirred at room temperature overnight. After that, the mixture was impregnated in silica gel and submitted to MPLC, yielding compound **12** in 86%. ^{1}H NMR: δ = 8.35 (d, J = 7.9 Hz, 1 H), 7.92 (d, J = 8.7 Hz, 1 H), 7.46 (d, J = 8.9 Hz, 1 H), 7.24 (t, J = 7.8 Hz, 1 H), 7.19 (d, J = 9 Hz, 1 H), 7.18–7.08 (m, 7 H), 7.03 (br. t, J = 7.7 Hz, 1 H), 6.99 (s, 1 H), 5.68 (d, J = 9.7 Hz, 1 H), 4.0 (q, J = 6.8 Hz, 1 H), 3.9 (s, 3 H), 3.86 (dd, J = 15.8, J = 10.2 Hz, 1 H), 3.0 (d, J = 15.9 Hz, 1 H), 1.66 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR: δ = 173.6, 152.2, 143.5, 136.5, 130.7, 129.2, 129.0 (2 C), 127.84 (2 C), 127.76, 127.72, 127.68, 126.7 (2 C), 125.16 (2 C), 124.9, 124.3, 123.3, 117.4, 116.6, 113.5, 63.3, 56.9, 44.4, 39.0, 19.9 ppm. $[\alpha]_D^{20}$ = +143 (c = 0.6, benzene).

1-[(1*S,4a*R**,7a*R**)-1,4a,5,7a-Tetrahydro-4,7-dimethylcyclopenta-[*c*]pyran-1-yl]-(2*R**)-phenylindoline (9):** 8-Oxocitral (63 mg, 0.38 mmol) was dissolved in 3 mL of methanol and then added to 2-phenylindoline (**8**) (75 mg, 0.38 mmol) in 5 mL of hexane. 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 42% (54.9 mg, 0.16 mmol). The NMR analyses showed the presence of just one diastereomer (**9a** and **9e** in Figure 2). ^{1}H NMR: δ = 7.5–7.27 (m, 5 H), 7.19–7.12 (m, J = 6.5 Hz, 2 H), 6.85 (br. t, J = 7.3 Hz, 1 H), 6.80 (d, J = 7.8 Hz, 1 H), 6.25 (br. s, 1 H), 5.56 (br. s, 1 H), 5.12 (dd, J = 10.4, J = 5.6 Hz, 1 H), 4.66 (d, J = 10.3 Hz, 1 H), 3.75 (dd, J = 16.2, J = 10.32 Hz, 1 H), 3.06 (dd, J = 16.2, J = 5.6 Hz, 1 H), 2.76 (br. t, J = 9.8 Hz, 1 H), 2.67 (bq, J = 8.5 Hz, 1 H) 2.64–2.56 (m, 1 H), 2.14–2.06 (m, 1 H), 1.64 (br. s, 3 H), 1.53 (br. s, 3 H) ppm. ^{13}C NMR: δ = 150.4, 145.3, 137.0, 128.5, 129.3, 128.3 (2 C), 127.4, 127.2, 127.2, 126.5, 126.2, 124.5, 119.3, 112.5, 109.8, 88.1, 63.3, 46.2, 41.5, 39.8, 37.8, 16.8, 16.6 ppm.

X-ray Structure Analysis of (+)-12: The crystal was placed directly into the N_2 cold stream (Oxford Cryosystems Series 700) on a Bruker AXS SMART 2 K CCD diffractometer. Data were collected by means of 0.4°ω-scans in four orthogonal ϕ-settings using Mo-K_α radiation (λ = 0.71073 Å). Data collection was controlled using the program SMART, data integration using SAINT,[24] and structure solution and model refinement using SHELXS-97 and SHELXL-97, respectively.[25]

CCDC-678658 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, via www.ccdc.cam.ac.uk/data_request/cif.

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