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Asymmetric Total Synthesis of Nigerone and *ent*-Nigerone: Enantioselective Oxidative Biaryl Coupling of Highly Hindered Naphthols

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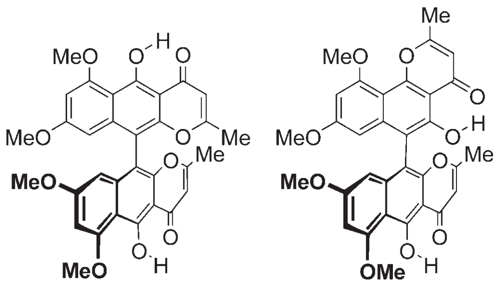
Abstract: An enantioselective synthesis of the chiral bisnaphthopyrone natural product nigerone and its enantiomer, *ent*-nigerone, has been realized. The use of constrained 2-naphthol substrates was critical to producing highly functionalized chiral 1,1′-binaphthols *via* asymmetric oxidative biaryl coupling with 1,5-diaza-*cis*-decalin copper complexes. The final natural product was formed *via* a key eight-step isomerization process of the coupling product, bisisonigerone, and proceeded with retention of the biaryl configuration. The axial configurations of bisisonigerone and nigerone were definitively established by a combination of circular dichroism (CD) measurements and quantum chemical CD calculations.

Keywords: chiral binaphthyls; configuration determination; naphthopyrones; nigerone; oxidative coupling; quantum chemical circular dichroism calculations

Introduction

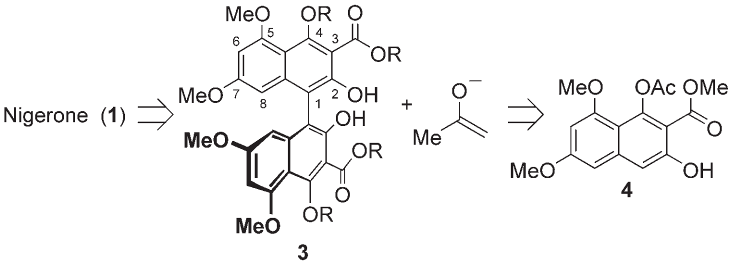
The number of natural products containing axial chirality has grown substantially in recent years.[1] While many methods for the generation of chiral biaryls[2] have been reported, the development of efficient synthetic routes to these architecturally interesting targets remains challenging. In addition, configurational assignment of these natural products is still difficult. While circular dichroism (CD) spectroscopy is a powerful and inexpensive method, the merely empirical interpretation of CD spectra can become difficult or even impossible if a novel type of structure or an unexpected conformational behaviour is involved. In numerous cases such difficulties can be overcome by quantum chemical CD calculations.[3–5] One such class of compounds, the bisnaphthopyrone natural products, includes nigerone (**1**) and isonigerone (**2**) (Figure 1),[6] mold isolates that display moderate antitumor[7] and antibacterial[8] activities. While these compounds have been characterized, no total synthesis efforts have as yet appeared.[9]

Nigerone (**1**) is formally – and from a biosynthetic point of view – the dimer of a tricyclic oxygen heterocycle, but retrosynthetically the heterocycle can be



Nigerone (**1**)   Isonigerone (**2**)

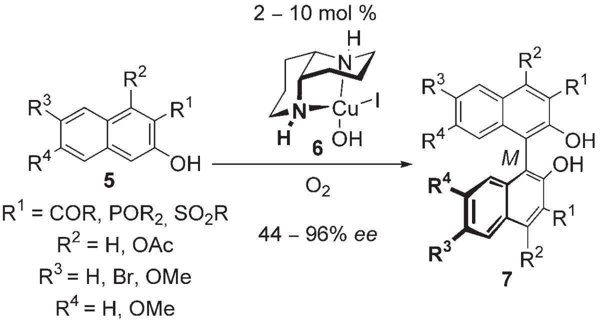
Figure 1. Structures of the axially chiral natural bisnaphthopyrones, nigerone (**1**) and isonigerone (**2**).



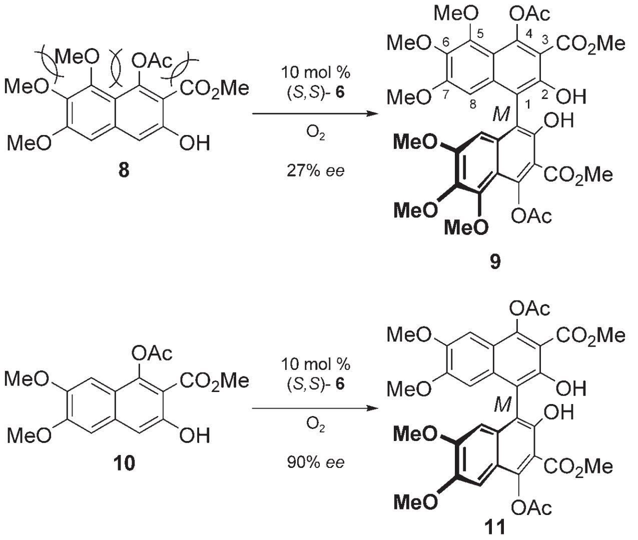
Scheme 1. Retrosynthetic analysis of (−)-nigerone (**1**).

formed last by a formal Claisen condensation with the enolate of acetone onto **3** followed by a dehydrative cyclization to **1** (Scheme 1). When this disconnection is exercised, the binaphthyl intermediate **3** maps directly onto the type of structures (**7**) assembled with our 1,5-diaza-*cis*-decalin copper catalyst (**6**) from simple naphthol substrates **5** (Scheme 2).[10] Thus, the synthetic plan is reduced to the formation of **3** from naphthol **4** (Scheme 1) by coupling to form the C-1–C-1′ bond (for the purposes of discussion, the atoms of all structures in the text are numbered as shown in Scheme 1).

However, in prior studies we observed an interesting effect with certain substitution patterns. In particular, the combination of C-4, C-5, and C-6 substituents as in naphthol **8** caused the coupling product **9** to be formed with low enantioselectivity (27% *ee*) (Scheme 3).[10d] Based upon the very different results observed with the closely related **10**, which provided the corresponding coupling product **11** in 90% *ee*,[10d] it is clear that centers distal from the forming bond can have a profound effect. We propose that the steric gearing illustrated for **8** places the C-3 methyl ester out of the plane of the aromatic ring. As a result, coordination of the catalyst *via* the C-2 OH and the C-3 methyl ester is compromised leading to a slower reaction rate and lower enantioselectivity (Scheme 3).[10d,e]



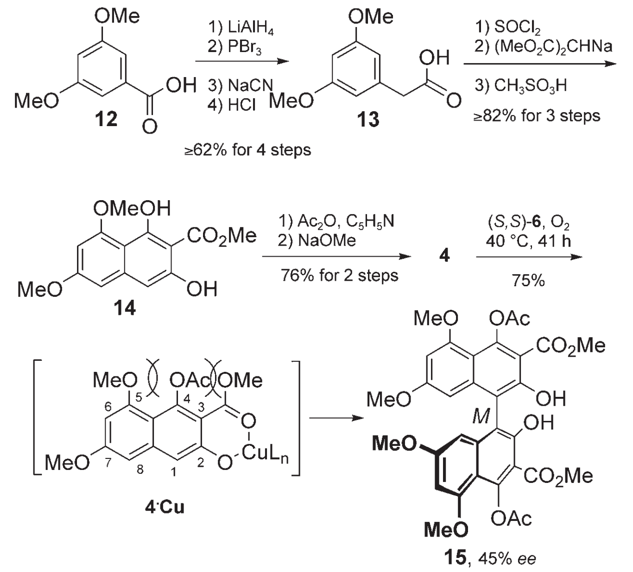
Scheme 2.



Scheme 3. Products of prior catalytic asymmetric oxidative couplings of highly functionalized naphthols.

Results and Discussion

In order to undertake the synthesis of nigerone (**1**), it was imperative to determine whether C-4 *and* C-5 substitution could be tolerated. Such a pattern would have less steric crowding than that found in compound **8**. To test whether the removal of the C-6 gearing substituent found in **8** would indeed be beneficial, naphthol **4** was synthesized (Scheme 4). Initially, a Wolff rearrangment was explored for generating **13** *via* the methyl ketone made from carboxylic acid **12**. While this route was shorter, the longer route in Scheme 4 was more efficient overall and allowed throughput of a large quantity of material. After addition of malonate anion to the acid chloride of **13**, the requisite naphthol ring of **14** was formed *via* an acid-catalyzed cyclization.[10d] Diacetylation and then selective deacetylation at the less hindered C-2 position provided **4**. Using the catalyst (*S,S*)-**6**, which reliably forms the (*M*)-binaphthols,[11] coupling of **4** proceeded well to form **15** with 45% *ee* as measured by HPLC on a chiral phase (see Experimental Section). As ex-



Scheme 4. Synthesis and dimerization of a functionalized monomer toward nigerone (**1**).

pected, the selectivity in coupling of **4** to **15** (45% *ee*) was better than that observed with the more crowded analog, **8** (27% *ee*),[10d] but the selectivity was still not sufficient to proceed. As a result, we had the opportunity to test directly our theory that steric inhibition of chelation (i.e., **4**·Cu) accounts for the low selectivity in the formation of **9** and **15**.[10e] Use of substrates with a cyclic protecting group (**16**, Figure 2) will align the C-3 carbonyl optimally for chelation to the copper catalyst and should furnish higher selectivity.

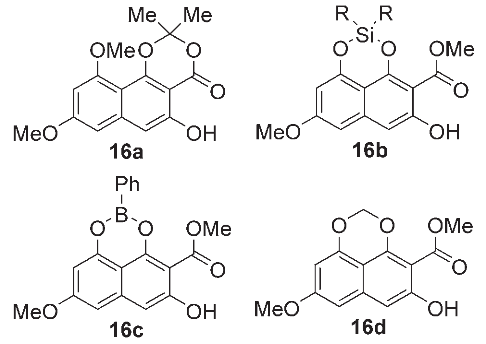
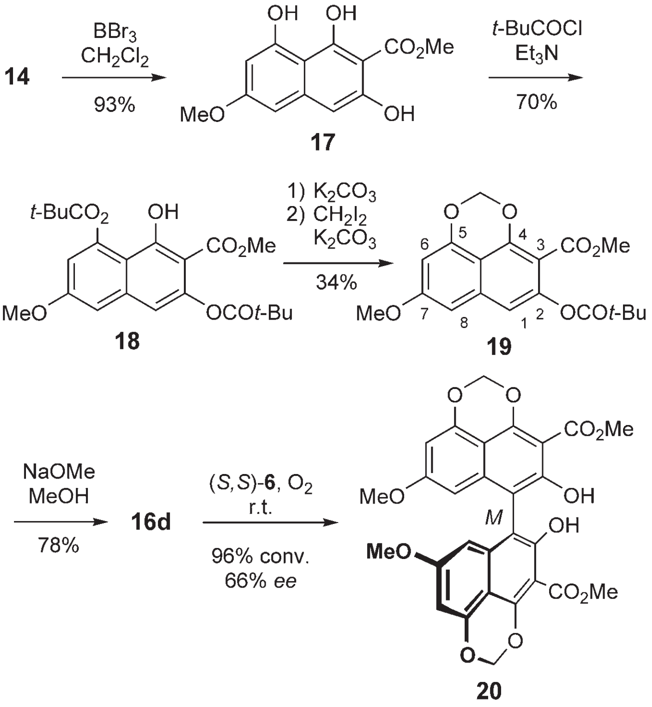


Figure 2. Attempted cyclic protecting groups to modify the steric parameters of the binaphthol coupling substrates.

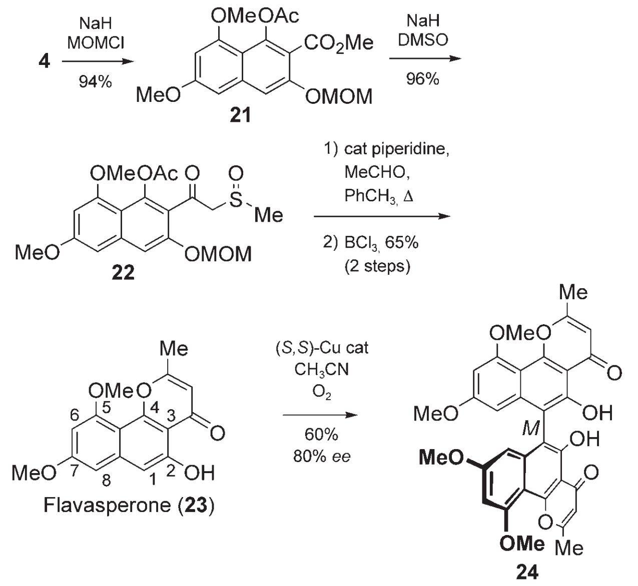
Unfortunately, our initial constrained candidates, **16a–c** (Figure 2), could not be formed (dioxenone) or were labile under the oxidative binaphthol coupling conditions (silylene, boronate).

On the other hand, **16d** with a methylene bridge proved to be stable and amenable to biaryl coupling with the copper catalyst. Substrate **16d** was generated from the intermediate **14**, described above (Scheme 4), as illustrated in Scheme 5. The methylenedioxy ring within **16d** renders this substrate more electron rich in comparison to **4** with the corresponding electron-withdrawing acetoxy group. As a result,[10e] coupling of **16d** proceeded readily even at room temperature (96% conversion in 4 h as measured by ^{1}H NMR and HPLC; see Experimental Section). Furthermore, the enantioselectivity was improved (66% *ee* as measured by HPLC on a chiral phase; see Experimental Section), over both **9** (27% *ee*, Scheme 3) and **15** (45% *ee*, Scheme 4). It appears that the reduced steric demand from the C-4/C-5 methylenedioxy protecting group relative to the C-4 acetoxy and C-5 methoxy of **15** results in better coordination to the copper catalyst and hence in greater enantioselectivity. Nonetheless, the length of the route to prepare these materials prompted us to explore a more concise route to nigerone (**1**) that would further reduce the steric inhibition to chelation and improve the enantioselectivity.

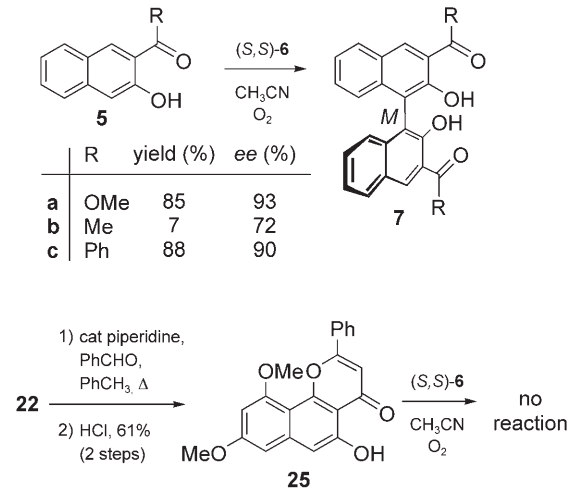


Scheme 5. Synthesis and coupling of the constrained naphthol substrate **16d**.

In this approach (Scheme 6), the pyrone ring system found in the product is used as the constraining element (i.e., **23**). An attractive feature of this route is that no protecting groups need to be installed or removed after the key binaphthol coupling. Compound **23** is itself a natural product,[12] flavasperone, which has been prepared previously[13] *via* a 10-step route. The yields from this route, however, would not provide sufficient quantities of **23**. Fortunately, we found that **23** could be rapidly prepared from **4** in an efficient four-step sequence (Scheme 6). The key step is reaction of **22** with a catalytic amount of piperidine



Scheme 6. A biomimetically inspired route to the nigerone intermediate, bisisonigerone (**24**), *via* C-3/C-4 constrained derivatives.



	R	yield (%)	*ee* (%)
a	OMe	85	93
b	Me	7	72
c	Ph	88	90

Scheme 7. Examination of a phenyl derived flavasperone analogue (**15**) in biaryl coupling.

in the presence of acetaldehyde. Under these conditions, the keto-sulfoxide is alkylated, cyclization occurs onto the C-4 OH, and the sulfoxide group eliminates. Subsequent BCl_3 treatment removes the MOM group to deliver **23**.

From the standpoint of an asymmetric coupling with 1,5-diaza-*cis*-decalin copper catalyst **6**, substrate **23** appears ideal. The heterocyclic ring constrains the C-3 carbonyl to align with the C-2 hydroxy for optimal chelation to copper. In addition, the group at C-4 is electron-withdrawing *via* conjugation to the C-3 carbonyl; electron-poor groups at C-4 suppress racemization of the binaphthol during the oxidative coupling.[10d] Surprisingly, however, the reaction of **23** with the chiral copper catalyst was sluggish. After one week at 40-45 °C with 10 mol% catalyst, only 36% of product **24** were isolated, still in a good selectivity (80% *ee*) as judged by HPLC on a chiral phase (see Experimental Section). As expected, no product racemization was observed over the time course of the reaction. For the attribution of the absolute configuration of the obtained bisisonigerone (**24**), see below.

Based on the higher selectivity for **23** in comparison to that observed with **4** (45% *ee*, Scheme 4), we have confirmed our hypothesis that a planar C-3 carbonyl and C-2 hydroxy arrangement provides superior asymmetric induction with the diaza-*cis*-decalin copper catalysts. However, the slow rate of reaction in the oxidative biaryl coupling of **23** was puzzling, but could be due to the enolizable protons. For example, the simple methyl ketone analogue **5b** in Scheme 7 was also problematic, whereas the methyl ester (**5a**) or phenyl ketone (**5c**) analogues underwent the asymmetric biaryl coupling to **7a** and **7c**, respectively, readily. To determine if enolization was the issue with **23**, the phenyl analogue **25** was synthesized (Scheme 7). However, no reaction with the chiral catalyst occurred after 5 d at 45 °C. This result may be a consequence of the electron-withdrawing nature of the phenyl ring.[10e]

From the above results, it is clear that steric bulk at both C-4 and C-5 is not favorable since the required conformation of the C-3 carbonyl is not readily accessible. On the other hand, generation of a rigid analogue with the C-3 carbonyl locked into the required conformation is not ideal, either. It appears that the optimal systems possess a C-3 chelating group (i.e., the carbonyl) that is slightly strained in the requisite planar orientation. Under these circumstances a planar copper chelate can form and undergo reaction, but is not so stable that product dissociation is inhibited.

Reasoning that this optimized chelation inhibits turnover, greater amounts of the diaza-*cis*-decalin copper oxidant were employed, which improved the yield (60%), while maintaining the selectivity (80% *ee*). With increasing amounts of the chiral coupling catalyst, C-1 iodination became problematic accounting for the moderate yield. Use of copper catalyst variants with different counterions (Cl, BF_4) gave the product without the iodination by-product, but resulted in a diminished enantioselectivity (60–72% *ee*).

Due to the key role of the intermediate **24** thus obtained, its absolute axial configuration was determined by means of circular dichroism (CD) spectroscopy. Because of the constitutionally symmetrical structure of **24**, it should be possible to assign its configuration by the classical exciton chirality method.[14] In bisisonigerone (**24**), with its two interacting flavasperone (**23**)[12] chromophores, the UV band at 285 nm gave rise to an exciton couplet in the CD spectrum with the first, negative Cotton effect at 300 nm and the second, positive one at 280 nm (Figure 3 a/b), indicating a negative chirality of **24**, i.e., an (*M*)-configuration.

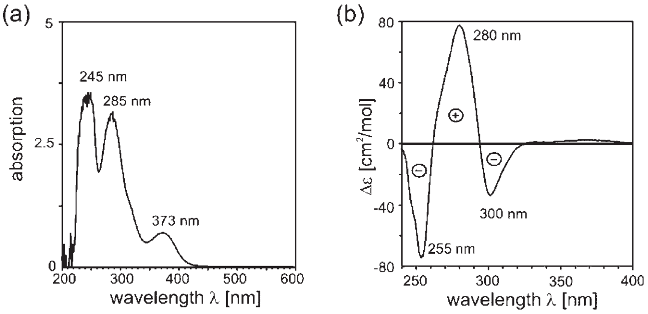


Figure 3. (a) The experimental UV and (b) CD spectra of (+)-bisisonigerone (**24**).

On the other hand, the presence of a third band at 255 nm with a strong negative Cotton effect raised some uncertainty, making an independent interpretation of the experimental CD spectra of **24** by quantum chemical CD calculations[3–5] a rewarding task. Arbitrarily starting with the (*P*)-enantiomer of **24**, a DFT (RI-BLYP/SVP)[15–17] based conformational analysis was performed. The calculations revealed that the two hydroxy functions adopt only one energetically preferable array, with strong hydrogen bonds (*d*H−O *ca.* 1.60 Å) to the adjacent respective carbonyl groups, and that the two methoxy substituents at C-5 and C-5′ orient with a maximum distance from the pyrone ring. The other two methoxy groups at C-7 and C-7′ revealed two energetically relevant orientations each, thus resulting in four possible input structures for further calculations.

The single CD and UV spectra were calculated using the semiempirical CNDO/S[18] and OM2[19] approaches (Figure 4 a/a′), and by the time-dependent DFT (B3LYP/TZVP)[20,21] method (Figure 4 b/b′). The resulting Bolzmann-weighted overall spectra (for details, see Experimental Section) were then compared with the experimental CD and UV curves of (+)-bisisonigerone (**24**). The calculated CD spectra for the (*P*)-enantiomer of **24** clearly showed an opposite behavior, while the spectra predicted for *M* reasonably reproduced the experimental features. Within the semiempirical approaches the rotatory strength values for the band at 300 nm were underestimated to a remarkably strong degree, while in the TDDFT based spectrum the band at 255 nm was predicted with a too low intensity, so that these two bands were not considered for the attribution of the absolute configura-

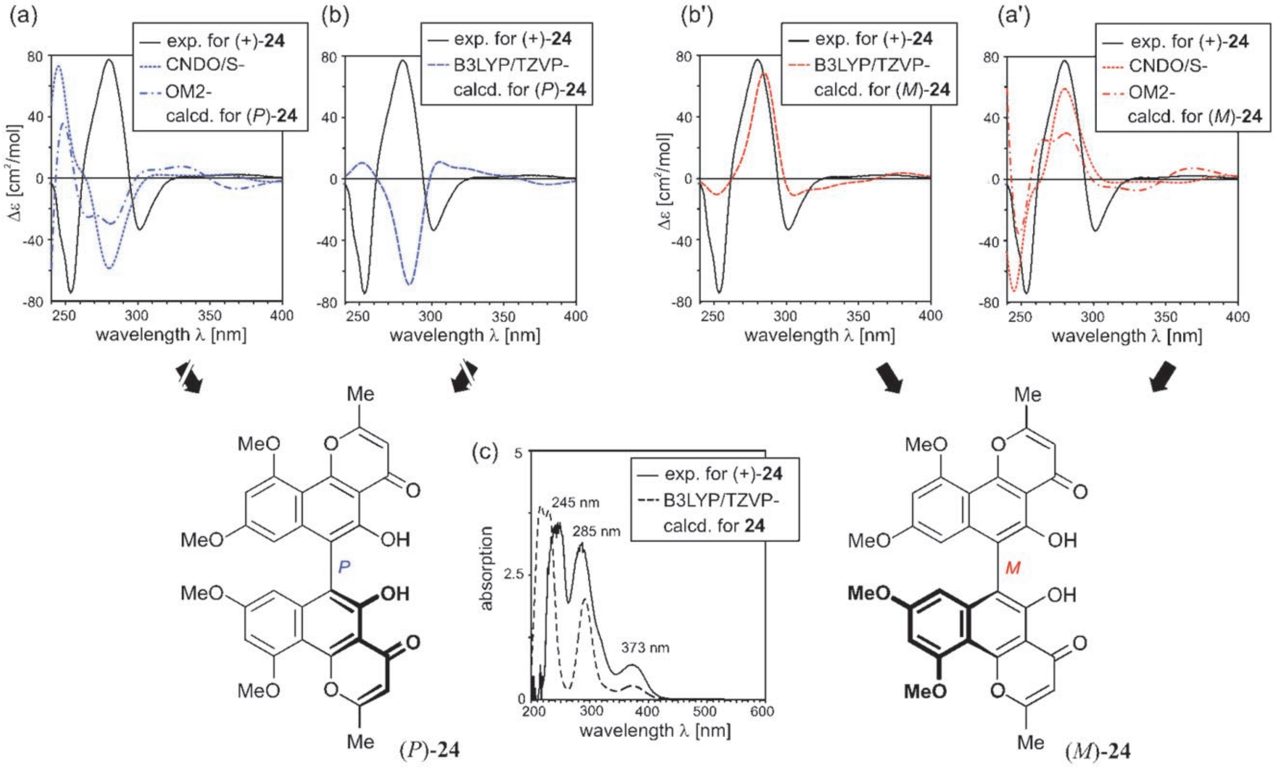


Figure 4. Comparison of the experimental CD spectrum of (+)-bisisonigerone (**24**) (a/a′) with the semiempirically (CNDO/S, OM2) predicted curves, and (b/b′) with the TDDFT based spectra; (c) comparison of the experimental UV profile of **24** with the TDDFT based UV spectrum.

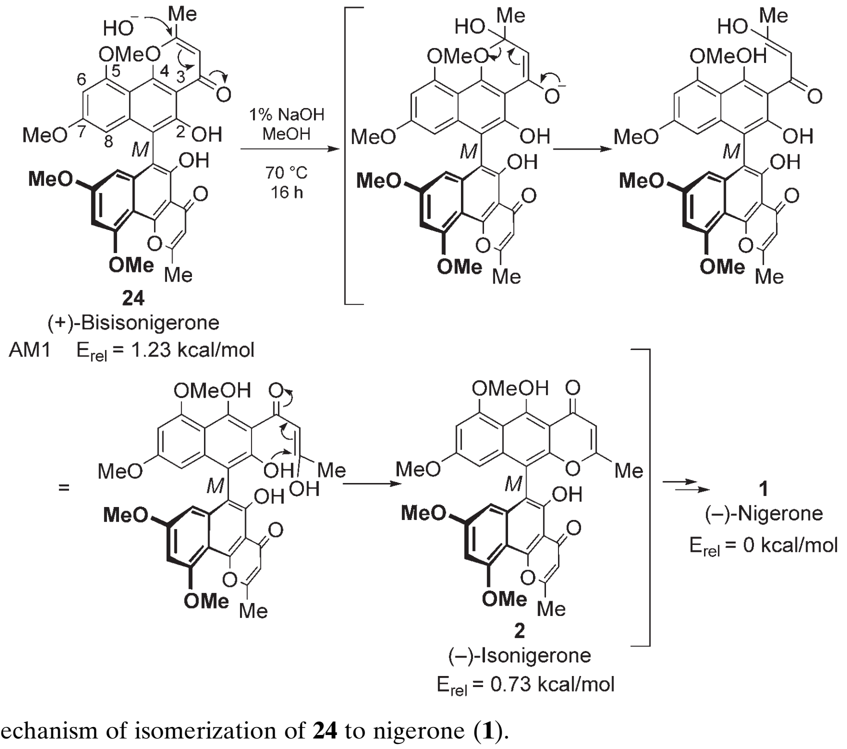
tion. On the other hand, all of the calculation methods reproduced the strong, characteristic band at 280 nm most accurately, predicting a negative Cotton effect for the (*P*)-configured atropo-enantiomer of bisisonigerone (**24**) and a positive one for *M*.

With (*M*)-**24** in hand and unambiguously characterized stereochemically, isomerization of the naphthopyrones *via* 1,4-addition to the enones with catalytic base[22] was investigated (Scheme 8). Equilibration of **24** under these conditions was proposed to favor nigerone (**1**) since the C-2 position of the binaphthyl is less hindered compared to C-4 (the C-5 group is coplanar to C-4 while the C-1 biaryl is 70° out of plane) and should better accommodate the heterocyclic portion. In addition, NMR evidence indicates that the intramolecular hydrogen bond found in **24** would be weaker than that found in the linear array of **1**.[6a] Energy calculations (AM1[23,24]) of the low-energy conformers of the three possible nigerone isomers supported these assumptions (Scheme 8): **24**, $E_{rel} = 1.23\ kcal\,mol^{-1}$, isonigerone (**2**) (half-isomerized), $E_{rel} = 0.73\ kcal\,mol^{-1}$, nigerone (**1**), $E_{rel} = 0.00\ kcal\,mol^{-1}$. Implementation of this plan using a base-catalyzed isomerization in methanol at 70 °C overnight succeeded in formation of (*M*)-nigerone in 50 % yield (for the configurational assignment of **1**, see below). During the isomerization, an intermediate is observed which is consumed by the time all the bisisonigerone (**24**) reacts. We propose that this intermediate is isonigerone (**2**), which is ultimately converted to the more stable nigerone (**1**). Given that isomerization of **24** to **1** is feasible, a reasonable question is whether the nigerone (**1**) obtained from natural sources is actually a secondary product of the isolation protocol. Since the isolation protocol does not utilize any base, it is difficult to imagine the isomerization occurring under those conditions. However, it is entirely possible that **24** is a biosynthetic precursor to **1** and **2**.

The enantiomeric purity of the compound decreased only slightly during this process (< 3% *ee*), which likely occurs during the isomerization step due to the loss of rigidity created by the γ-pyrone ring. It would appear that nigerone (**1**) itself is configurationally stable at high temperature as it has been refluxed in acetic acid for 3 h with no loss of optical activity.[6c] By the same route, except for using the enantiomeric diaza-*cis*-decalin catalyst,[11] (*P*)-nigerone (**1**) was also produced. Pleasingly, trituration of the 70–80 % *ee* nigerone (**1**) thus obtained with 50 % ethyl acetate/hexanes readily proceeded to provide **1** with 90 % *ee*.

The NMR data for the synthesized (−)-nigerone (**1**) were in complete accordance with those of the isolated natural product.[6a] In addition, the data for the bisisonigerone (**24**) differed markedly from those of nigerone (**1**) confirming the isomeric identity of the natural material (see Supporting Information).

As above for **24**, the absolute stereostructures of two atropo-enantiomers of the synthetically obtained nigerone (**1**) were also elucidated by CD calculations. This seemed an urgent task because the direct comparison of the experimental CD spectrum of (*M*)-(+)-bisisonigerone (**24**) with the CD curve of (*M*)-(−)-ni-



Scheme 8. Proposed mechanism of isomerization of **24** to nigerone (**1**).

gerone (**1**) showed a substantial difference, revealing the first negative and the second positive Cotton effects of (*M*)-**24** to be red-shifted by 16 and 18 nm, respectively (Figure 5 a/c). Furthermore, previous attempts to attribute the absolute configuration of natural nigerone (**1**) were contradictory. The comparison of its CD and ORD data with those of other bisnaphthopyrones of known absolute configuration[6a] (erroneously) led to a *P*-configuration, while the interpretation by using the exciton chirality approach[6c] (correctly) gave *M*.

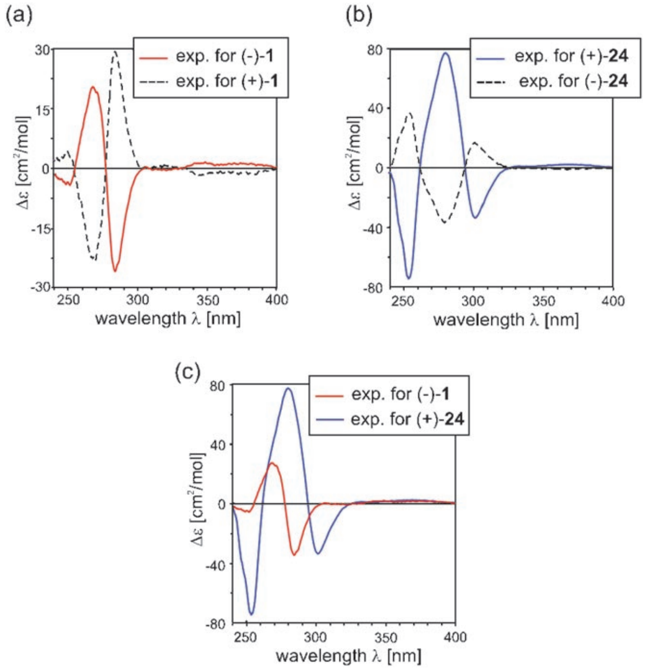


Figure 5. The measured CD spectra (in CH_2Cl_2) of two atropo-enantiomers of (a) nigerone (**1**) and of (b) bisisonigerone (**24**); (c) comparison of the experimental CD spectra of (−)-nigerone (**1**) and (+)-bisisonigerone (**24**).

As before for bisisonigerone (**24**), the conformational analysis of **1** was performed for the (*P*)-enantiomer, revealing the same respective four conformers, differing only in the orientation of two methoxy substituents at C-7 and C-7′. In this case, the spectra were immediately calculated at the TDDFT (B3LYP/TZVP)[20,21] level. The comparison of the calculated CD spectrum for the (*P*)-enantiomer of **1** with the experimental curve of (−)-nigerone (**1**) showed a fully opposite behavior, while the spectrum predicted for the (*M*)-atropisomer reproduced the experimental curve with a very high accuracy (Figure 6). This firmly corroborated the previous attribution based on the exciton coupling method,[6c] thus indicating that the natural product (−)-nigerone (**1**) has the *M*-configuration. Consequently, the absolute configuration of the synthetically obtained (+)-nigerone (**1**) was assigned to be *P*.

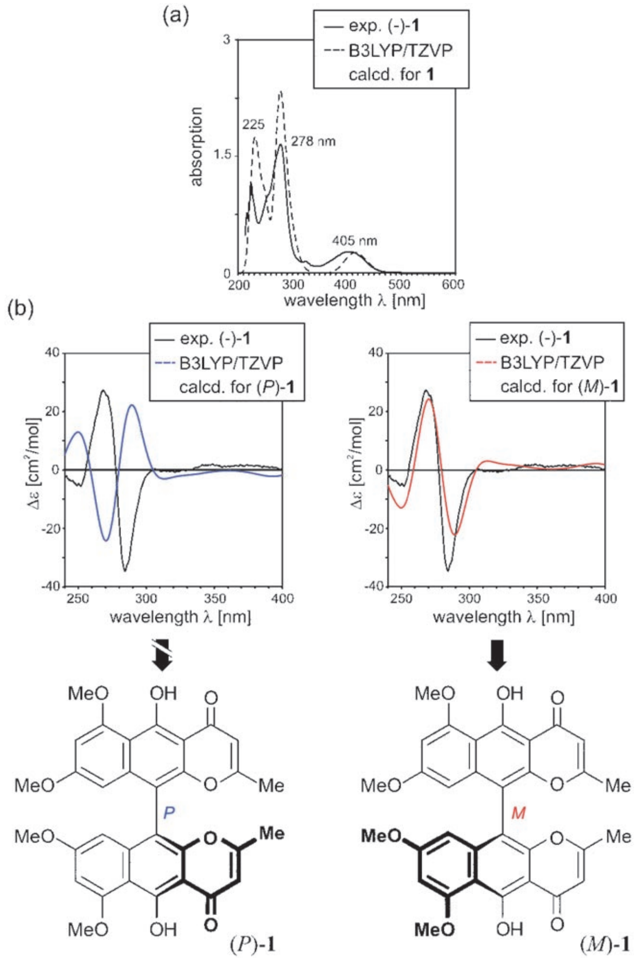


Figure 6. Determination of the absolute configuration of (−)-nigerone (**1**) by comparison of the experimental CD curve with the theoretically (TDDFT/B3LYP/TZVP) predicted CD spectra; (a) comparison of the UV spectra; (b) comparison of the CD spectra.

Conclusions

In summary, the first, atropo-enantiodivergent total synthesis of the axially chiral bisnaphthopyrone natural product nigerone has been achieved. Constrained 2-naphthol substrates were critical to producing highly functionalized chiral 1,1′-binaphthols *via* asymmetric oxidative biaryl coupling with 1,5-diaza-*cis*-decalin copper complexes. From the biaryl coupling product, an isomerization *via* a sequence of eight conjugate addition/elimination reactions gave rise to nigerone (**1**). With this asymmetric synthesis, both enantiomers of nigerone (**1**) have been generated with good enantioselectivity. The absolute configurations of the natural product, (−)-nigerone (**1**) and the key intermediate, bisisonigerone (**24**) have been unambiguously assigned by quantum chemical CD calculations.

Experimental Section

General Considerations

Solvents for the preparation of the catalyst complexes and for the oxidative coupling reactions were usually used without purification although acid-free halogenated solvents are required (if necessary, trace acid can be removed by filtering through basic Al_2O_3). Enantiomerically pure diaza-*cis*-decalin was prepared as previously described.[25] The Cu(TMEDA)Cl(OH) catalyst was prepared[26] and used in the oxidative biaryl coupling reactions to prepare the racemic samples of the biaryl products.

Chromatography was performed using a forced flow of the indicated solvent system on EM Reagents Silica Gel 60 (230–400 mesh). Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC), performed on a Waters 600 HPLC with UV detection at 254 nm. Optical rotations were measured on a Perkin–Elmer Polarimeter 341 with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T}$, (*c* in g/100 mL, solvent).

2-(3,5-Dimethoxyphenyl) acetic Acid (13)

A solution of 3,5-dimethoxybenzoic acid (5.6 g, 30.7 mmol) in THF (250 mL) was cooled to 0 °C. $LiAlH_4$ (2.33 g, 61.4 mmol) was slowly added. After 3 h at room temperature a saturated solution of Na/K tartrate (50 mL) was added. After 1 h at room temperature the layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The benzylic alcohol was obtained as an oil; yield: 5.0 g (97 %). The ^{1}H NMR spectrum matches that of the reported compound.[27]

A solution of the above benzylic alcohol (5.0 g, 29.7 mmol) in CH_2Cl_2, was cooled to 0 °C, at which time PBr_3 (3.07 mL) was added. After 1 h at room temperature, $NaHCO_3$ was added dropwise and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford the benzylic bromide as an oil; yield: 5.9 g (86 %). The ^{1}H NMR spectrum matches that reported.[28]

To a solution of the above benzylic bromide (5.9 g, 25.5 mmol) in DMF, was added NaCN. After 1 h water was added and the aquous layer was extracted with EtOAc. The organic layers were washed three times with water and brine, dried over $MgSO_4$ and concentrated to afford the benzylic cyanide as a white solid; yield: 3.7 g (83 %). The ^{1}H NMR spectrum matches that reported.[29]

A concentrated solution of HCl was added to the above benzylic cyanide (3.7 g, 21.6 mmol). After 2.5 h at reflux, water (100 mL) was added and the reaction mixture was cooled to room temperature. The aqueous phase was extracted three times with CH_2C1_2, dried over $MgSO_4$, filtered and concentrated. Crystallization from EtOAc/hexanes gave phenylacetic acid **13** as white crystals; yield: 3.8 g (90 %). The ^{1}H NMR spectrum matches that reported.[30]

Methyl 1,3-Dihydroxy-6,8-dimethoxynaphthalene-2-carboxylate (14)

To a solution of phenylacetic acid **13** (0.429 g, 2.19 mmol) in CH_2Cl_2, thionyl chloride (0.319 mL) was added. After 1 h at reflux, the solution was concentrated. To a suspension of NaH (0.156 g, 6.5 mmol) in THF (51 mL) dimethyl malonate (0.838 g, 6.35 mmol) was added. After stirring for 1 h, a solution of the unpurified acid chloride in THF was added. After 1 h at room temperature, 1 M HCl and EtOAc were added. The layers were separated and the aqueous layer was extracted three times with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2; 85 % hexanes/EtOAc) to afford the intermediate tricarbonyl (0.650 g) as a clear oil.

To a solution this tricarbonyl in methanesulfonic acid (10 mL), was added P_2O_5 (0.600 g). After 3 h at room temperature, ice was added and the resulting precipitate was filtered and dried in an oven overnight to yield the naphthalenediol **14** as a grey solid; yield: 0.500 g (82 %); mp 162–164 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 11.13$ (s, 1 H), 10.70 (s, 1 H), 6.64 (s, 1 H), 6.48 (d, $J = 2.2$ Hz, 1 H), 6.28 (d, $J = 2.2$ Hz, 1 H), 4.05 (s, 3 H), 4.02 (s, 3 H), 3.89 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 171.3$, 160.7, 158.8, 157.7, 141.1, 105.1, 102.0, 97.9, 97.4, 95.8, 56.1, 55.3, 52.4; IR (film): $\nu = 3443$, 3304, 2953, 1664, 1594 cm^{-1}; HR-MS (ES): *m/z* = 279.0880, calcd. for $C_{14}H_{14}O_6$ $[M+H]^+$: 279.0868.

Methyl 1-Acetoxy-3-hydroxy-6,8-dimethoxynaphthalene-2-carboxylate (4)

To a round-bottom flask containing the above naphthalenediol **14** (0.50 g, 1.80 mmol), Ac_2O (2.54 mL), pyridine (2.50 mL), and a catalytic amount of DMAP were added. After 4 h at room temperature, ethyl acetate was added and the organic layer was washed with a saturated solution of Cu_2SO_4 until the aqueous layers were no longer purple. The organic layer was subsequently washed with water, brine, dried over $MgSO_4$, filtered, and concentrated. Methanol was added to this material along with enough 1 M NaOMe solution until TLC analysis indicated no remaining diacetate compound. 1 M HCl was subsequently added and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (30 % EtOAc/hexanes) to afford the monoacetate **4** as a yellow solid; yield: 0.44 g (76 %); mp 168–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 10.83$ (s, 1 H), 7.06 (s, 1 H), 6.52 (d, $J = 2.2$ Hz, 1 H), 6.29 (d, $J = 2.2$ Hz, 1 H), 3.98 (s, 3 H) 3.89 (s, 3 H), 3.88 (s, 3 H), 2.37 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.0$, 169.5, 161.1, 158.1, 157.4, 149.9, 141.1, 111.2, 109.3, 107.3, 97.8, 97.1, 56.1, 55.4, 52.9, 20.9; IR (film): $\nu = 1760$, 1671, 1629, 1571 cm^{-1}; HR-MS (ES): *m/z* = 343.0797, calcd. for $C_{16}H_{16}O_7$ $[M+Na]^+$: 343.0794.

(*M*)-(−)-Dimethyl 4,4′-Diacetoxy-2,2′-dihydroxy-5,7,5′,7′-tetramethoxy-[1,1′]-binaphthalenyl-3,3′-dicarboxylate (15)

To a solution of **4** (0.10 g, 0.31 mmol) in CH_3CN (3 mL) (*S,S*)-**6** (0.10 g, 0.031 mmol) was added. After 48 h under an O_2 atmosphere at 40 °C, 1 M HCl was added and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (60% hexanes/EtOAc) to afford **15** as a reddish solid; yield: 0.70 g (75%); mp 227–230 °C; $[\alpha]_D^{23}$: −9.21 (*c* 0.38, 45% *ee*, $CHCl_3$); CSP HPLC (Chiralpak AD, 1.0 mL min^{-1}, hexanes:*i*-PrOH = 90:10): t_R (*P*) = 26.1 min, t_R (*M*) = 38.3 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.04 (s, 1H), 6.32 (d, *J* = 2.2 Hz, 1H), 6.08 (b, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 3.53, (s, 3H), 2.40, (s, 3H); ^{13}C NMR (125 MHz, $CHCl_3$): δ = 170.2, 169.5, 161.3, 158.5, 155.1, 150.1, 140.3, 114.3, 110.2, 97.7, 95.7, 60.3, 56.2, 55.2, 53.0, 21.0; IR (film): ν = 1764, 1668, 1621, 1575 cm^{-1}; HR-MS (ES): *m/z* = 661.1526, calcd. for $C_{32}H_{30}O_{14}$ $[M+Na]^+$: 661.1534.

Methyl 5-Hydroxy-8-methoxy-2phenylnaphthol[1,8-*de*][1,3,2]dioxaborinine-4-carboxylate (16c)

A solution of the naphthalene diol **14** (0.050 g, 0.179 mmol) in CH_2Cl_2 was cooled to 0 °C, at which time a 1 M BBr_3 solution in CH_2Cl_2 (0.358 mL) was added. After 1 h, water was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford the naphthalenetriol **17** as a yellow solid; yield: 0.044 g (93%); mp 180–185 °C, decomposition; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.10 (bs, 1H), 9.42 (s, 1H), 8.80 (bs, 1H), 6.61 (s, 1H), 6.42 (d, *J* = 2.2 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H), 4.12 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2, 163.2, 158.4, 153.2, 141.4, 104.9, 102.8, 101.5, 99.8, 97.7, 94.7, 55.3, 53.1; IR (film): ν = 3474, 3405, 3281, 1660, 1621, 1517 cm^{-1}; HR-MS (ES): *m/z* = 287.0535, calcd. for $C_{13}H_{12}O_6$ $[M+Na]^+$: 287.0532.

To a solution of the above naphthalenetriol (0.030 g, 0.114 mmol) in CH_2Cl_2, $PhB(OH)_2$ (0.014 g, 0.114 mmol) was added. After 1 h at room temperature, diethyl ether and NaCl were added. After 10 min, the mixture was filtered and concentrated. The resulting solution was crystallized from chloroform/hexanes to obtain **16c** as white crystals; yield: 0.022 g (55%); mp 202–204 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.16 (s, 1H), 8.11 (d, *J* = 7.0 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 2H), 6.74 (s, 2H), 6.53 (d, *J* = 2.2 Hz, 1H), 6.49 (d, *J* = 2.2 Hz, 1H), 4.12 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9, 161.4, 155.9, 154.9, 154.4, 137.9, 131.5, 127.1, 127.0, 106.3, 101.2, 98.9, 97.3, 95.6, 54.9, 51.8; IR (film): ν = 3370, 1668, 1644, 1606, 1586 cm^{-1}; HR-MS (ES): *m/z* = 352.0950, calcd. for $C_{20}H_{16}O_6$ $[M+Na]^+$: 352.0947.

Methyl 8-Methoxy-5-(pivaloyloxy)naphtho[1,8-*de*][1,3]dioxine-4-carboxylate (19)

A solution of naphthalenetriol **17** (0.020 g, 0.075 mmol) in CH_2Cl_2 (500 μL) was cooled to 0 °C. Trimethylacetyl chloride was added (26 μL in 50 μL of CH_2Cl_2) followed by triethylamine (29 μL in 50 μL of CH_2Cl_2). After 30 min, the same portions of trimethylacetyl chloride and triethylamine were added again. After a further 1 h at 0 °C, 1 M HCl was added and the mixture was extracted with CH_2Cl_2. The organic layers were combined, dried with Na_2SO_4, and concentrated. The bispivaloyl product was obtained; yield: 0.023 g (70%).

A 0 °C solution of this bispivaloyl material (0.020 g, 0.046 mmol) in CH_2Cl_2 (500 μL) was added to a 0 °C solution of K_2CO_3 (0.006 g) in MeOH (300 μL). After 1 h the reaction mixture was allowed to warm to room temperature. After 30 min, 1 M HCl was added and the reaction mixture was extracted with CH_2Cl_2. The organic layers were combined, dried with Na_2SO_4, and concentrated. The monopivaloyl product was obtained; yield: 0.016 g (100%).

To a solution of the above monopivaloyl product (0.015 g, 0.043 mmol) in dimethylformamide (400 μL) CH_2I_2 (30 μL) was added, followed by K_2CO_3 (0.029 g). The resulting reaction mixture was heated to 60 °C. After 8 h, 1 M HCl was added and the mixture was extracted with EtOAc. The organic layers were combined, dried with Na_2SO_4, and concentrated. The residue was chromatographed (25% EtOAc/hexanes) to afford **19** as a yellow solid; yield: 0.044 g (34%); mp 133–135 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.05 (s, 1H), 6.76 (d, *J* = 1.7 Hz, 1H), 6.61 (d, *J* = 1.6 Hz, 1H), 5.58 (s, 2H), 3.89 (s, 6H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.7, 164.1, 161.1, 151.7, 150.6, 147.7, 136.3, 112.2, 108.2, 107.3, 101.3, 100.1, 91.2, 55.6, 52.3, 39.2, 27.1; IR (film): ν = 2976, 2937, 1752, 1725, 1640, 1594, 1467 cm^{-1}; HR-MS (CI): *m/z* = 360.1202, calcd. for $C_{19}H_{20}O_7$ $[M]^+$: 360.1209.

(*M*)-(−)-Dimethyl 5,5′-Dihydroxy-8,8′-dimethoxy-[6,6′]bi[naptho[1,8-de][1,3]dioxinyl]-4,4′-dicarboxylate (20)

A solution of **19** (0.024 g, 0.067 mmol) in THF/MeOH (700 μL/200 μL) at 0 °C was treated with a solution of NaOMe/MeOH (140 μL, 2.5 M). After slowly warming to ambient and then stirring 30 min, the reaction was quenched with 1 M HCl. After extracting with EtOAc, the organic layers were combined, dried over Na_2SO_4, and concentrated. The residue was chromatographed (15% EtOAc/hexanes) to afford the free naphthol **16d** as a yellow solid; yield: 0.014 g (78%).

To a solution of naphthol **16d** (0.002 g, 0.007 mmol) in CH_2Cl_2 (200 μL) was added (*S,S*)-**6** (0.003 g, 0.0007 mmol). The mixture was sonicated and allowed to stir at room temperature under air. After 4 h, 1 M HCl was added, and the mixture was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated, to afford the product in 96% conversion (measured by ^{1}H NMR and HPLC) and 66% *ee* (measured by HPLC); CSP HPLC (Chiralpak ODH, 1.0 mL min^{-1}, hexanes:*i*-PrOH = 92:8): t_R (**16d**) = 15.5 min, t_R (*P*-**20**) = 43.5 min, t_R (*M*-**20**) = 56.2 min; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.40 (s, 2H), 6.41 (d, *J* = 2.2, 2H), 6.11 (d, *J* = 2.2, 2H), 5.70 (d, *J* = 5.0, 2H), 5.62 (d, *J* = 5.0, 2H), 3.99 (s, 6H), 3.59 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 162.2, 156.1, 154.1, 152.6, 138.8, 108.8, 105.1, 98.6, 98.1, 97.6, 90.8, 55.4, 52.5; IR (film): ν = 3053, 2926, 2856, 1664, 1633, 1586, 1444 cm^{-1}; HR-MS (ES): *m/z* = 573.0999, calcd. for $C_{28}H_{22}O_{12}Na$ $[M+Na]^+$: 573.1100.

Methyl 1-Acetoxy-6,8-dimethoxy-3-(methoxymethoxy)naphthalene-2-carboxylate (21)

A solution of **4** (0.250 g, 0.780 mmol) in DMF (4 mL) was cooled to 0 °C, at which time NaH (0.028 g, 1.17 mmol) was added. After 20 min, MOM-Cl (0.099 mL) was added in one portion. After 2 h at room temperature, EtOAc and 1 M HCl were added. The organic layer was washed three times with water and brine to remove DMF. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (70% hexanes/EtOAc) to afford **21** as a white powder; yield: 0.270 g (94%); mp 140–141 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.22$ (s, 1H), 6.65 (d, $J = 2.2$ Hz, 1H), 6.39 (d, $J = 2.2$ Hz, 1H), 5.28 (s, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.51 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 169.3$, 165.8, 159.9, 157.3, 152.5, 145.6, 138.8, 116.8, 110.4, 107.9, 98.8, 98.6, 95.1, 56.6, 56.3, 55.6, 52.7, 20.9; IR (film): $\nu = 3067$, 2989, 1772, 1714, 1629, 1586 cm^{-1}; HR-MS (ES): $m/z = 364.1164$, calcd. for $C_{18}H_{20}O_8$ $[M+Na]^+$: 364.1158.

1,3-Dimethoxy-6-(methoxymethoxy)-7-(2-(methylsulfinyl)acetyl)-8-hydroxynaphthalene (22)

Benzene (10 mL) and DMSO (3.1 mL) were added to a round-bottom flask containing NaH (0.296 g, 12.33 mmol). After 1 h at reflux, the reaction mixture was allowed to cool to room temperature and a solution of **21** (0.642 g, 1.76 mmol) in benzene was added. After 1 h at 45 °C, the solution was concentrated at which time water and acetic acid were added dropwise until a precipitate formed. The precipitate was filtered and dried to afford **22** as a yellow powder; yield: 0.600 g (96%); mp 145–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 14.05$ (s, 1H), 6.73 (s, 1H), 6.54 (d, $J = 2.2$ Hz, 1H), 6.36 (d, $J = 2.2$ Hz, 1H), 5.35 (q, $J = 6.8$, 2H), 4.84 (d, $J = 14$ Hz, 1H), 4.30 (d, $J = 14$ Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 3.56 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 194.6$, 165.3, 162.3, 160.7, 154.0, 141.6, 108.1, 107.3, 100.2, 99.1, 97.2, 94.8, 68.6, 56.8, 56.2, 55.4, 39.9; IR (film): $\nu = 3003$, 2968, 3397, 1625, 1583 cm^{-1}; HR-MS (ES): $m/z = 368.0937$, calcd. for $C_{17}H_{20}O_7S$ $[M+Na]^+$: 368.0930.

Flavasperone (23)

To a solution of **22** (0.192 g, 0.523 mmol) in toluene (10 mL), one drop of piperidine was added. The solution was warmed to 45 °C and newly purchased acetaldehyde (0.375 mL) was added. After 3 h at reflux, the mixture was allowed to cool to room temperature upon which time EtOAc and 1 M HCl were added. The organic layer was washed with water and brine. To the unpurified product was added CH_2Cl_2 (3.80 mL) and the reaction mixture was cooled to −78 °C. To the cooled solution was added BCl_3 (0.476 mL, 3.00 mmol), and was allowed to stir for 20 min at which time $NaHCO_3$ was added. The reaction mixture was then allowed to warm to room temperature. The organic layer was washed with water and brine. The residue was chromatographed (4% EtOAc/CH_2Cl_2) to afford **23** as a yellow solid; yield: 0.036 g (65%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 12.83$ (s, 1H), 6.89 (s, 1H), 6.60 (d, $J = 2.2$ Hz, 1H), 6.41 (d, $J = 2.2$ Hz, 1H), 6.29 (s, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 182.9$, 166.4, 161.7, 159.6, 155.9, 154.7, 140.6, 110.6, 110.4, 108.6, 105.2, 97.0, 96.8, 56.0, 55.2, 20.5. ^{1}H NMR matches that of the reported compound.[6a]

(*M*)-(+)-Bisisonigerone (24)

To a solution of **23** (0.027 g, 0.094 mmol) in 1,2-dichloroethane (3 mL), (*S,S*)-**6** (0.031 g, 0.094 mmol) was added. After 6 d under air at 50 °C, 1 M HCl was added and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (60% hexanes/EtOAc) to afford recovered **23** (0.009 g) along with **24** as a yellow solid; yield: 0.012 g (60%, 80% *ee*); mp 180–185 °C decomposition; $[\alpha]_D^{23}$: +72.6 (*c* 0.25 g/100 mL, 80% *ee*, $CHCl_3$); CSP HPLC (Chiralpak AD, 1.0 mL min^{-1}, hexanes:*i*-Pr-OH = 90:10): t_R (*P*) = 40.6 min, t_R (*M*) = 109.9 min; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 13.19$ (s, 1H), 6.45 (d, $J = 2.2$ Hz, 1H), 6.33 (s, 1H), 6.21 (d, $J = 2.2$ Hz, 1H), 4.02 (s, 3H), 3.55 (s, 3H), 2.56 (s, 3H); ^{13}C NMR: (125 MHz, $CDCl_3$): $\delta = 182.9$, 166.4, 161.7, 159.7, 156.1, 154.6, 140.5, 110.5, 110.3, 108.6, 104.3, 96.9, 96.7, 56.0, 55.2, 29.7, 20.5; IR (film): $\nu = 3366$, 3003, 2926, 1656, 1610, 1579, 1517 cm^{-1}; HR-MS (ES): $m/z = 571.1624$, calcd. for $C_{32}H_{26}O_{10}$ $[M+Na]^+$: 571.1604.

5-Hydroxy-8,10-dimethoxy-2-phenyl-4*H*-benzo[*h*]chromen-4-one (25)

To a solution of **22** (0.100 g, 0.271 mmol) in toluene (5 mL) one drop of piperdine was added. The solution was warmed to 45 °C and benzaldehyde (0.276 mL) was added. After 3 h at reflux, the solution was allowed to cool to room temperature at which time EtOAc and 1 M HCl were added. The layers were separated and the organic layer was washed with brine. The residue was chromatographed (90% hexanes/EtOAc) to afford **25** as yellow solid; yield: 0.580 g (61%); mp 232–234 °C; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 12.79$ (s, 1H), 8.07 (dd, $J_{ab} = 1.34$ Hz, $J_{bc} = 7.9$ Hz, 2H), 7.56 (m, 3H), 6.85 (s, 1H), 6.82 (s, 1H), 6.52 (s, $J = 2.2$ Hz, 1H), 6.39 (s, $J = 2.2$ Hz, 1H), 4.03 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 182.7$, 163.6, 161.4, 158.6, 156.5, 155.2, 141.3, 131.8, 131.3, 129.0, 126.4, 109.3, 106.5, 106.0, 104.9, 98.1, 96.9, 55.9, 55.4; IR (film): $\nu = 3343$, 2968, 2926, 1706, 1664, 1613, 1583 cm^{-1}; HR-MS (ES): $m/z = 348.0993$, calcd. for $C_{21}H_{16}O_5$ $[M+Na]^+$: 348.0998.

(*M*)-(−)-Nigerone (1)

A solution of **24** (0.026 g, 80% *ee*) in MeOH (22 mL) was heated with saturated aqueous NaOH solution (0.22 mL) and was placed in a 70 °C oil bath. After 18 h, 1 M HCl was added and the aqueous layer was extracted three times with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2; 60% hexanes/EtOAc) to afford **1** as yellow solid; yield: 0.013 g (50%, 77% *ee*); mp >200 °C decomposition; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 15.31$ (s, 1H), 6.44 (d, $J = 7$ Hz, 2H), 6.07 (d, $J = 7$ Hz, 1H), 6.00 (s, 1H), 4.06 (s, 3H), 3.49 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 184.5$, 167.6, 163.1, 161.9, 161.2, 151.3, 140.7, 108.8, 107.3 105.5, 104.3, 97.2, 96.5, 56.2, 55.2, 20.6; IR (film): $\nu = 3377$, 2930, 2853, 1652, 1610, 1586, 1409 cm^{-1}; HR-MS (ES): $m/z = 571.1624$, calcd. for $C_{32}H_{26}O_{10}Na$ $(M+Na^+)$: 571.1604; CSP HPLC (Chiralpak AD, 1.0 mL min^{-1}, 90:10 hexanes:*i*-PrOH): t_R (*S*) = 31.7 min, t_R (*R*) = 38.7 min.

Trituration of this material with 50% EtOAc/hexanes provided **1** with 90% *ee*: $[\alpha]_D^{23}$: −223 (*c* 0.018 g/100 mL, CH_2Cl_2, 90% *ee*), literature $[\alpha]_D^{20}$:[6a] −287.7 (*c* 1.00, $CHCl_3$).

Measurements of the Optical Rotation and Circular Dichroism

During the measurements of the optical rotation of synthetic (*P*)-nigerone (**1**), the sign and magnitude of the rotation were found to change with concentration. At low concentrations ($c = 0.012$–0.024 g/100 mL), self-consistent values were obtained (the α_D values changed linearly with concentration in this range): (*P*)-**1** $[\alpha]_D^{23}$: +172 (*c* 0.025 g/100 mL, CH_2Cl_2, 68% *ee*); (*M*)-**1** $[\alpha]_D^{23}$: −170 (*c* 0.020 g/100 mL, CH_2Cl_2, 67% *ee*). By trituration with EtOAc/hexanes, 90% *ee* material was obtained: (*P*)-**1** $[\alpha]_D^{23}$: +227 (*c* 0.0092 g/100 mL, CH_2Cl_2, 90% *ee*); (*M*)-**1** $[\alpha]_D^{23}$: −223 (*c* 0.018 g/100 mL, CH_2Cl_2, 90% *ee*). For bisisonigerone (**24**), a similar phenomenon was observed, and optical rotation measurements were therefore again made at low concentration: (*P*)-**24** $[\alpha]_D^{23}$: −70.0 (*c* 0.050 g/100 mL, CH_2Cl_2, 70% *ee*); (*M*)-**24** $[\alpha]_D^{23}$: +72.6 (*c* 0.120 g/100 mL, CH_2Cl_2, 67% *ee*).

CD spectra were recorded on a Jasco J-720 spectrophotometer equipped with a NESLAB RTE-111 variable temperature circulator. (*M*)-Nigerone (**1**) of 67% *ee* and (*P*)-nigerone (**1**) of 68% *ee*, as judged by chiral HPLC, were employed. Each sample was dissolved in CH_2Cl_2 (4.20 E–4M) at 23 °C. CD measurements were performed at 20 °C using a 1-mL quartz cuvette of 0.1 cm path length and the following parameters: scanned optical range, 240–400 nm; scan band width, 1 nm; scanning speed, 100 nm min^{-1}; response, 1 sec; accumulations, 5. Data were processed using Jasco Spectra Manager V. 1.51. For a table with CD data of (+)- and (−)-nigerone (**1**), and of (+)- and (−)-**24**, see Supporting Information.

Computational Methods

The conformational analyses of nigerone (**1**) and bisisonigerone (**24**) were performed on a Linux AMD MP 2800+ workstation using the DFT/RI-BLYP/SVP[15–17] approach within the TURBOMOLE[31] suite of programs. The wave functions of the ground and excited states were obtained by semiempirical CNDO/S-CI[18] and OM2-CI[19] computations with a CI expansion including 576 and 900 occupied configurations, respectively, and the ground state determinant. Within a time-dependent DFT approach 30 excited states being lowest in energy were calculated using the B3LYP[20] functional and a TZVP[21] basis set. In all approaches the oscillator and rotatory strengths were computed using the dipole-length formalism.[32] The rotatory and oscillator strengths calculated for the single conformers (bar spectra) were added up according to the Boltzmann statistic. The spectra were then simulated as sums of Gaussian functions centered at the wavelengths of the corresponding electronic transitions and multiplied by the respective overall rotatory or oscillator strengths. For both, UV and CD spectra, an empirically chosen exponential half width of 0.1 eV (CNDO/S, TDDFT) and 0.15 eV (OM2) was used. The CD spectra thus obtained for bisisonigerone (**24**) were then submitted to a 'UV correction',[3] requiring a red-shift of 5 nm for the CNDO based spectra, a red-shift of 35 nm for the OM2 based spectra, and a blue-shift of 20 nm for the TDDFT based spectra. The calculated spectra for nigerone (**1**) were not shifted.

Supporting Information

NMR spectral data, Table with CD data of **1** and **24**.

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