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Concise Synthesis of Arnottin I and (−)-Arnottin II

Fujiko Konno,[†] Tsutomu Ishikawa,*[,†] Masatoshi Kawahata,[‡] and Kentaro Yamaguchi[‡]

Graduate School of Pharmaceutical Sciences, Chiba University, 1−33 Yayoi, Inage, Chiba 263-8522, Japan, and Faculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University, 1314-1 Shido, Sanuki, Kagawa 769-2193, Japan

benti@p.chiba-u.ac.jp

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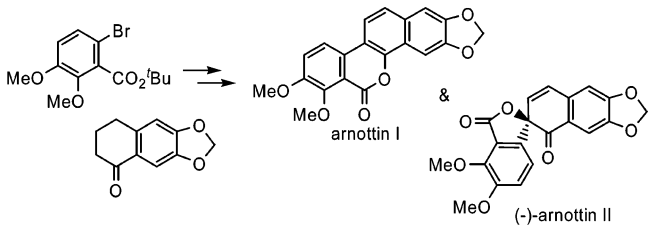

Application of the Buchwald protocol to the coupling of *o*-bromobenzoates and 1-tetralones directly affords benzodihydronaphthopyrones with a fused tetracyclic system. Aromatization of the 7,8-dimethoxy-2,3-methylenedioxy derivative yielded arnottin I, whereas oxidation with dioxirane afforded dihydroarnottin II composed of a spiro phthalide−tetralone system. Sharpless asymmetric dihydroxylation using AD-mix yielded optically active dihydroarnottin II with good enantioselectivity. The absolute stereochemistry of the stereogenic center in the (+)-spiro product was determined to be *R* by X-ray crystallographic analysis of the dibromo derivative. (+)-Dihydroarnottin II was subjected to successive bromination and dehydrobromination to prepare (−)-arnottin II. The *R*-configuration of natural (−)-arnottin II, previously assigned by application of the exciton chirality method to the Cotton effects observed in the CD spectrum, was confirmed by asymmetric synthesis.

Introduction

Arnottin I (**1**) and (−)-arnottin II (**2**) are non-alkaloidal minor components isolated from the bark of *Xanthoxylum arnottianum* Maxim. (Rutaceae).[1] Their structures have been determined to be 7,8-dimethoxy-2,3-methylenedioxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one[2] and 3,4-dehydro-6,7-methylenedioxy-1-tetralone-2-spiro-3′-(6,7-dimethoxyphthalide),[3] respectively, by independent synthetic approaches using a common 2-benzofuranyl-1-tetralone, which was linearly derived from a chalcone. The benzofuranyltetralone was also used as the synthetic intermediate for the preparation of a fully aromatized benzo[*c*]phenanthridine alkaloid, chelerythrine.[4] Thus, the former was found to have the same 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one skeleton as gilvocarcin antibiotics,[5] and the latter is a spiro derivative of 3,4-dehydro-1-tetralone with a phthalide skeleton. The absolute stereochemistry of the spiro carbon in **2** was assigned as *R* using the exciton chirality method to analyze the Cotton effects in the CD spectrum.[6] Herein, we report the concise synthesis of arnottin I (**1**) and (−)-arnottin II (**2**) from dihydroarnottin I (**3**). Dihydroarnottin I was directly prepared by palladium (Pd)-catalyzed coupling of *o*-bromobenzoate **4** and 6,7-methylenedioxy-1-tetralone (**5**) using the Buchwald protocol,[7] by aromatization with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),

[†] Chiba University.
[‡] Tokushima Bunri University.

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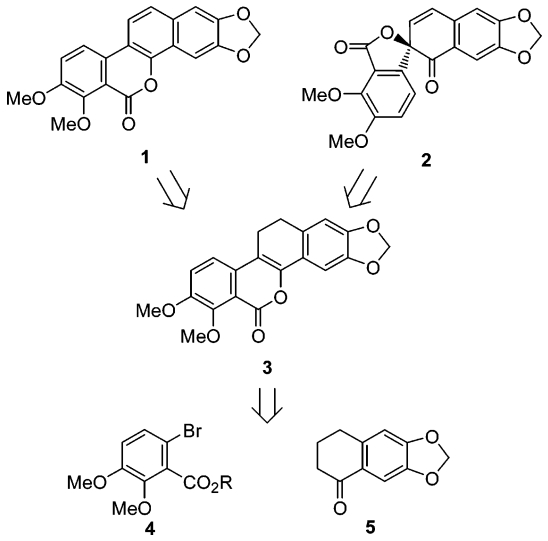
SCHEME 1. Retrosynthesis of Arnottin I (1) and (−)-Arnottin II (2)



and by Sharpless asymmetric dihydroxylation (AD) using AD-mix followed by dehydrogenation. In addition, we determined the absolute stereochemistry of the spiro carbon in **2** by X-ray crystallographic analysis.

Results and Discussion

Our retrosynthetic strategy for arnottin I (**1**) and (−)-arnottin II (**2**) through 7,8-dimethoxy-2,3-methylenedioxy-6*H*-benzo[*d*]-11,12-naphtho[1,2-*b*]pyran-6-one (dihydroarnottin I) (**3**) as a common key intermediate is shown in Scheme 1. Previously, benzodihydronaphthopyrone skeletons have been prepared as synthetic intermediates for benzo[*c*]phenanthridine bases from either 2-(*o*-hydroxycarbonylphenyl)-4-phenylbutyric acid derivatives[8] or 2-aryl-1-tetralone.[9] We designed the direct formation of dihydroarnottin I (**3**) using the Pd-catalyzed coupling of an alkyl 6-bromo-2,3-dimethoxybenzoate (**4**) and 6,7-methylenedioxy-1-tetralone (**5**). Dihydroarnottin I (**3**) itself was also prepared from opianic acid and acetophenone, in seven steps by Bailey and Worthing[8a] 50 years ago; however, a straightforward synthesis has not yet been reported.

Preparation of Benzodihydronaphthopyrone Systems. Several approaches to arylation at the α-position of carbonyl compounds have been reported.[7,10,11] Of these, Pd-catalyzed coupling reactions[7,10] seem to be the most promising routes. The 2-arylation of 1-tetralones using the Pd-catalyzed coupling reaction has also been achieved by Buchwald's[7] and Nolan's groups.[10] A combination of palladium acetate ($Pd(OAc)_2$) or tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) and a biphenyl-type phosphine ligand including 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) was used by the former group,[7] whereas an *N*-heterocyclic carbene−palladium complex catalyst was used by the latter.[10] We expected that the direct formation of benzodihydronaphthopyrones, a basic skeleton of **3**, would result from the easy cyclization of the coupling product, 2-aryl-1-tetralone, due to the presence of an ester function at the ortho position of the 2-aryl group. Therefore, we applied Buchwald's protocol[7] to the reaction of *o*-bromobenzoates and 1-tetralones (e.g., **4** and **5**, respectively). First, we examined the reactions of simpler bromobenzenes **6** and 1-tetralone itself (**7**) in the presence of a Pd-catalyst, ligand, and base in toluene (PhMe) at 80 °C as preliminary model coupling experiments (Table 1).

Treatment of 2-bromotoluene (**6**, X = 2-Me) with **7** under the Buchwald conditions ($Pd(OAc)_2$, with 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl and sodium *tert*-butoxide [^{t}BuONa]) afforded 2-(2-methylphenyl)-1-tetralone (**8**, X = 2-Me)[12] as the coupling product in satisfactory yield (entry 1 in Table 1); however, a complex mixture was formed for 3,4-methylenedioxybromobenzene (**6**, X = 3,4-OCH_2O) (entry 2 in Table 1). Replacement of the ligand and base led to the formation of 2-aryl-1-tetralone **8** (X = 3,4-OCH_2O)[13] but in low yield (entry 3 in Table 1). On the other hand, we found that a combination of $Pd_2(dba)_3$, xantphos, and potassium phosphate (K_3PO_4) gave the best result when methyl 2-bromobenzoate (**6**, X = 2-CO_2Me) was used as an aryl unit, and, as expected, a benzodihydronaphthopyrone system **9**[8b] was directly formed (entries 7 and 8 in Table 1).

Careful examination of the other products in these reaction mixtures suggested the presence of 1-naphthol derived from 1-tetralone (**7**). Therefore, we investigated the effect of sodium disulfite ($Na_2S_2O_5$) as an antioxidant, and we found that it remarkably improved product formation (entry 9 in Table 1). In this last reaction, *tert*-butyl ester was used in place of the methyl ester. We subsequently discovered that the ester unit also affects the coupling reaction (Table 2).

Next, we examined the formation of dihydroarnottin I (**3**) by Pd-coupling reaction of alkyl *o*-bromobenzoates (**4**) and 6,7-methylenedioxy-1-tetralone (**5**) (Table 2). Employing the conditions ($Pd_2(dba)_3$, xantphos, K_3PO_4, and $Na_2S_2O_5$) noted in entry 9 of Table 1, treatment of **4** and **5** afforded the desired product **3**; however, the yield was low (entry 1 in Table 2). A prolonged reaction time led to a slight increase in the yield (entry 2 in Table 2), and promising results were obtained by changing the base from K_3PO_4 to cesium carbonate (Cs_2CO_3) (entry 3 in Table 2). We found that the alkyl function of the ester, the solvent, and the reaction temperature played important roles in the coupling reaction (entries 4−7 in Table 2). Overall, the best conditions for the formation of dihydroarnottin I (**3**) by Pd-coupling reaction were a combination of $Pd_2(dba)_3$, xantphos, Cs_2CO_3, and $Na_2S_2O_5$ in PhMe using *tert*-butyl 6-bromo-2,3-dimethoxybenzoate as an aryl unit (entry 3 in Table 2).

Synthesis of Arnottin I (1) and (−)Arnottin II (2). Arnottin I (**1**) was easily prepared by simple aromatization of dihydroarnottin I (**3**) with DDQ (see Scheme 5).[14] On the other hand, oxidative ring contraction of the six-membered enol lactone unit in dihydroarnottin I (**3**) to the five-membered γ-lactone unit

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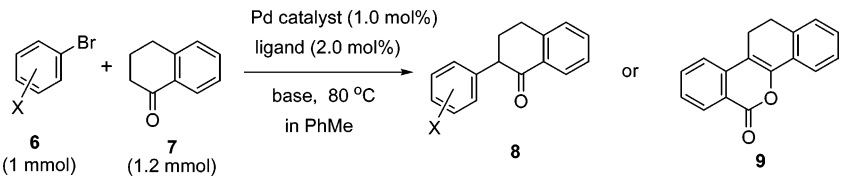
(14) Preparation of arnottin I (**1**) has also been reported (a) by Pd-catalyzed method using 1-naphthyl 2-halobenzoate, see: Harayama, T.; Yasuda, H. *Heterocycles* **1997**, *46*, 61−64. Harayama, T.; Yasuda, H.; Akiyama, T.; Takeuchi, Y.; Abe, H. *Chem. Pharm. Bull*. **2000**, *48*, 861−864. (b) By Ni-catalyzed method, see: Madan, S.; Cheng, C.-H. *J. Org. Chem.* **2006**, *71*, 8312−8315.

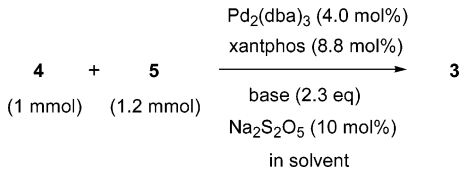
TABLE 1. Preliminary Pd-Coupling Reactions of Bromobenzenes 6 and 1-Tetralone (7)



entry	X in **6**	Pd	ligand[a]	base (equiv)	time (h)	results
1	2-Me	$Pd(OAc)_2$	A	^{t}BuONa (1.3)	20	**8** (X = 2-Me): 76%
2	3,4-OCH_2O	$Pd(OAc)_2$	A	^{t}BuONa (1.3)	15	CM[b]
3	3,4-OCH_2O	$Pd(OAc)_2$	B	K_3PO_4 (2.3)	15	**8** (X = 3,4-OCH_2O): 15%
4	2-CO_2Me	$Pd(OAc)_2$	A	^{t}BuONa (1.3)	20	CM[b]
5	2-CO_2Me	$Pd(OAc)_2$	B	K_3PO_4 (2.3)	20	NR[c]
6	2-CO_2Me	$Pd(OAc)_2$	C	K_3PO_4 (2.3)	20	**9**: 10%
7	2-CO_2Me	$Pd_2(dba)_3$	C	K_3PO_4 (2.3)	20	**9**: 44%
8[d]	2-CO_2Me	$Pd_2(dba)_3$	C	K_3PO_4 (2.3)	15	**9**: 46%
9[e]	2-$CO_2{}^t$Bu	$Pd_2(dba)_3$	C	K_3PO_4 (2.3)	15	**9**: 81%

[a] The following ligands were used: A, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl; B, 2-dicyclohexylphosphino-2′-methylbiphenyl; or C, 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (xantphos). [b] Complex mixture. [c] No reaction. [d] Reaction was carried out at 100 °C using 1.6 mol % of Pd catalyst and 3.6 mol % of ligand. [e] $Na_2S_2O_5$ (10 mol %) was added as an antioxidant.

TABLE 2. Pd-Coupling Reactions of Alkyl *o*-Bromobenzoates 4 and 6,7-Methylenedioxy-1-tetralone (5)



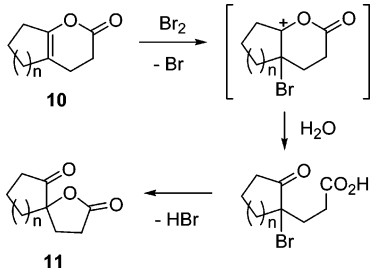
entry	**4**	solvent	base	time (h)	**3** (%)
1[a]	R = ^{t}Bu	PhMe	K_3PO_4	24	18
2[a]	R = ^{t}Bu	PhMe	K_3PO_4	48	37
3[a]	R = ^{t}Bu	PhMe	Cs_2CO_3	48	73
4[a]	R = Me	PhMe	Cs_2CO_3	27	21
5[a]	R = Me	PhMe	Cs_2CO_3	48	30
6[b]	R = ^{t}Bu	*o*-xylene	K_3PO_4	20	22
7[b]	R = ^{t}Bu	*o*-xylene	Cs_2CO_3	20	21

[a] Reaction was carried out at 100−105 °C. [b] Reaction was carried out at 125−130 °C.

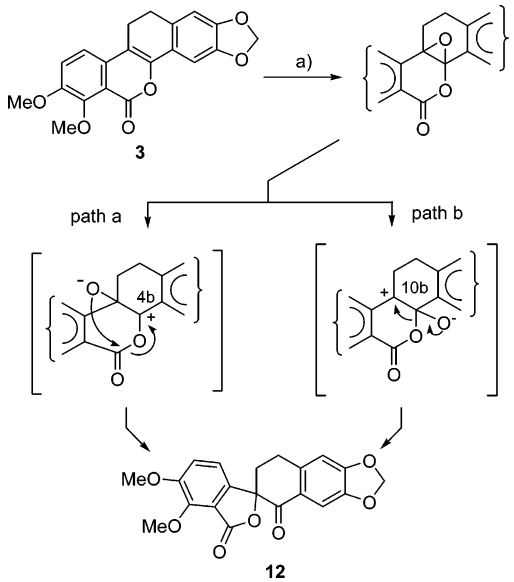
was required for the preparation of (−)-arnottin II (**2**). Such ring contractions can be mediated by either *N*-bromosuccinimide[15] or bromine[16] under basic conditions, and the application of oxidative ring contraction[16c] to bicyclic enol lactone **10** using an aqueous bromine−sodium hydrogen carbonate system yielded cyclic α-spiro(γ-lactonyl)ketone **11** through formal bond migration, wherein inversion of the stereogenic center may have occurred (Scheme 2).

These brominative oxidations, however, cannot be simply applied to the asymmetric synthesis of (−)-arnottin II (**2**) because their use under asymmetric conditions has not been described. Epoxidation (or dihydroxylation) of a bicyclic enol ether, applied under asymmetric conditions, could also yield a spiro lactonylketone after oxidation, followed by spontaneous ring contraction. Epoxidation is illustrated in Scheme 3, wherein two potential pathways exist because of the possible generation of stable benzylic cations at the 4b and 10a positions in pathways

SCHEME 2. Reported Oxidative Ring Contraction of Bicyclic Enol Lactone 10



SCHEME 3. Oxidation of Dihydroarnottin I (3) to Dihydroarnottin II (12) with Dioxirane[a] and Possible Reaction Pathways



[a] Reagents and conditions: (a) 1,1,1-trifluoroacetone, OXONE, $NaHCO_3$, EDTA−Na_2·$2H_2O$ in acetonitrile−$CHCl_3$.

a and b, respectively. Pathway a, in which the stereogenic center is retained, is predicted to be more likely based on the electronics of the system and is supported by the high level of asymmetric induction observed during the subsequent AD reaction (see

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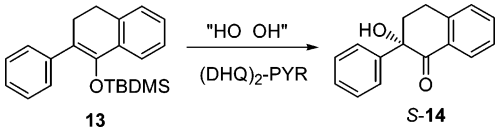
SCHEME 4. Reported AD of 2-Phenyl-1-tetralone *tert*-Butyldimethylsilyl Ether (13)



below). As expected, treatment of **3** with dioxirane using a slight modification of the previous report,[17] 1,1,1-trifluoroacetone in place of acetone, resulted in the formation of dihydroarnottin II (**12**) as the sole isolable product in 47% yield.

Unfortunately, asymmetric epoxidations using chiral dioxirane systems, such as OXONE-trifluoroacetylcamphor[17a] and OXONE-pyranose derivative,[18] or camphorylsulfonyloxaziridine,[19] failed. Therefore, we focused on the Sharpless AD method. Sharpless[20] has reported the catalytic AD of tetrasubstituted olefins, including the enol ether of 2-alkyl (or 2-aryl)-1-tetralones, in which the best ligand partners of dihydroquinine (DHQ) (or dihydroquinidine [DHQD]) are phthalazine (PHAL) and pyrimidine (PYR) and in which high enantioselectivity is observed. In the case of 2-phenyl-1-tetralone *tert*-butyldimethylsilyl ether (**13**),[20b] 2-hydroxy-2-phenyl-1-tetralone (**14**) was obtained in 94−98% yield with 93−97% ee; thus, the combination of $(DHQ)_2$-PYR afforded the (*S*)-hydroxylated product *S*-**14** in 97% ee (Scheme 4). According to their mnemonic device,[20b] it is reasonable that a dihydroxylation product with a (4*bS*,-10*bR*)-configuration is formed by the application of AD using a diastereomeric $(DHQD)_2$-ligand system to benzodihydronaphthopyrones, thereby generating an (*R*)-spiro product, as shown in Figure 1.

We examined AD of dihydroarnottin I (**3**) under the reported standard conditions[20b] (AD-mix in 50% *tert*-BuOH−H_2O), but we observed almost no reaction. We achieved a significant improvement in yield by increasing the amounts of osmium and ligand to 11 and 55 mol %, respectively, and by the addition of dichloromethane (CH_2Cl_2) as a cosolvent (Scheme 5). The combination of AD-mix-*β* and $(DHQD)_2$−PHAL afforded (+)-dihydroarnottin II (+)-**12** in 83% yield and 88% ee, whereas *ent*-(−)-dihydroarnottin II (−)-**12** was obtained in 85% yield and 88% ee when AD-mix-α and $(DHQ)_2$−PHAL were used.

Introduction of a double bond into (+)-dihydroarnottin II (+)-**12** by application of the reported procedure (bromination−dehydrobromination)[3] gave (−)-arnottin II (**2**), which was identical to the natural product except for the specific rotation. The synthetic (−)-arnottin II, obtained in 98% ee after recrystallization, showed an $[\alpha]^{25}_D$ −217 (*c* 0.026, MeOH) ($[\alpha]^{25}_D$ −241 [*c* 0.105, $CHCl_3$]), whereas an $[\alpha]_{589}$ −280 ($c\ 9 \times 10^{-3}$, MeOH) had been reported for the natural compound.[3] Chiral HPLC analysis of the stored natural arnottin II indicated that it was enantiomerically pure (see Supporting Information). Thus, it was concluded that the large discrepancy (Δ 63) in the $[\alpha]_D$ data between synthetic and natural (−)-arnottin II could be due to the limited use of the natural sample for optical rotation dispersion in the previous experiment.

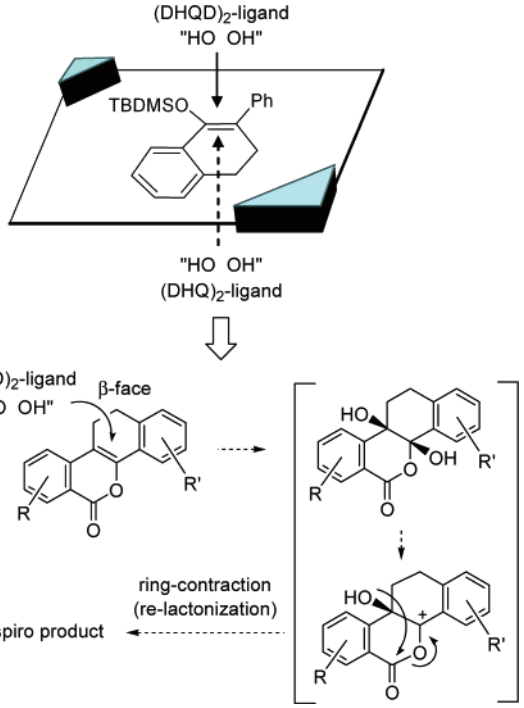
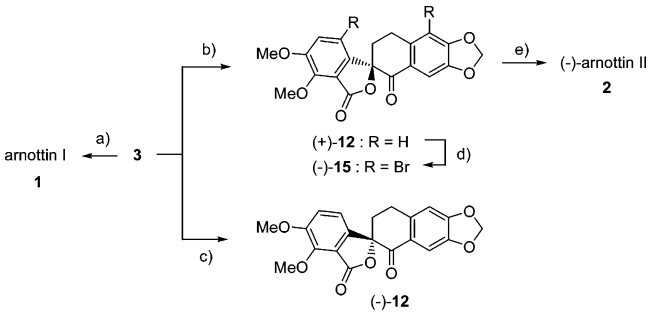


FIGURE 1. Expected asymmetric induction in the AD of benzodihydronaphthopyrones using a $(DHQD)_2$−ligand system.

SCHEME 5. Syntheses of Arnottin I (1) and (−)-Arnottin II (2) from Dihydroarnottin I (3)[a]



[a] Reagents and conditions: (a) DDQ, benzene, 90 °C, 12 h (94% yield). (b) AD-mix-*β*, $(DHQD)_2$−PHAL, $MeSO_2NH_2$, $K_2OsO_2(OH)_4$, 50% *tert*-BuOH−H_2O, CH_2Cl_2, 0 °C, 95 h (83% yield). (c) AD-mix-α, $(DHQ)_2$−PHAL, $MeSO_2NH_2$, $K_2OsO_2(OH)_4$, 50% *tert*-BuOH−H_2O, CH_2Cl_2, 0 °C, 67 h (95% yield). (d) Br_2, $CHCl_3$, room temperature, 30 h (86% yield). (e) (i) NBS, AIBN, benzene, 85 °C, 24 h and 65 °C, 20 h; (ii) DBU, benzene, reflux, 1 h (47% yield).

Among several attempts at derivatizing (+)-**12** to determine the absolute stereochemistry of the stereogenic center, we succeeded in preparing a single crystal of (−)-dibromodihydroarnottin II ((−)-**15**) by treatment with bromine. The stereogenic center of the dibrominated product (−)-**15** was unambiguously established to be of *R*-configuration by X-ray crystallographic analysis.[21] These facts indicated not only that asymmetric induction is reasonable, even with tetrasubstituted enol ethers incorporated into a ring system, but also that the configuration for a natural (−)-arnottin II (**2**) was correctly assigned by applying the exciton chirality rule[6] to the CD spectrum.

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In conclusion, we developed a concise and straightforward synthesis of arnottin I (**1**) and (−)-arnottin II (**2**) by applying Buchwald's protocol for the Pd-coupling arylation of ketones and the Sharpless AD method for the introduction of oxygen. We previously reported the chemical conversion of arnottin II to homochelidonine, a partially hydrogenated benzo[*c*]phenanthridine alkaloid.[22] The current results present another formal asymmetric synthesis of homochelidonine.

Experimental Section

7,8-Dimethoxy-2,3-methylenedioxy-6*H*-benzo[*d*]-3,4-dihydronaphtho[1,2-*b*]pyran-6-one (Dihydroarnottin I) (3): Entry 3 in Table 2. A mixture of methyl *o*-bromobenzoate (**4**) (317 mg, 1 mmol), 6,7-methylenedioxy-1-tetralone (**5**) (285 mg, 1.5 mmol), $Pd_2(dba)_3$ (37 mg, 0.04 mmol), xantphos (51 mg, 0.088 mmol), 98% Cs_2CO_3 (749 mg, 2.3 mmol), and $Na_2S_2O_5$ (19 mg, 0.1 mmol) in PhMe (2 mL) was stirred at 105 °C for 48 h. The mixture was diluted with $CHCl_3$ (20 mL), filtered through a Celite pad, and washed with $CHCl_3$ (15 mL). The combined organic solutions were washed with water (10 mL) and brine (5 mL), dried (Na_2SO_4), and evaporated. The residue was washed with AcOEt (5 mL) to afford **3** (228 mg, 64%) as a yellow solid. The aqueous layer was acidified with 2 N HCl (2 mL) and extracted with $CHCl_3$ (5 mL × 2). The organic solution was dried (Na_2SO_4) and evaporated. The residue (33 mg) was refluxed in benzene (1 mL) with *p*-TsOH·H_2O (2 mg, 0.01 mmol) for 1 h using Dean−Stark apparatus. Additional **3** (32 mg [total 260 mg, 73%]) was given by filtration of separated solid. Recrystallization from CH_2Cl_2 gave yellow prisms, mp 250−251 °C. IR (ATR): ν_{max} 1730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.82 (dif. t, J = 7.3 Hz, 2H), 2.92 (dif. t, J = 7.3 Hz, 2H), 3.95 (s, 3H), 3.99 (s, 3H), 5.98 (s, 2H), 6.71 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.34 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.7, 27.6, 56.7, 61.5, 101.2, 103.5, 107.1, 108.3, 115.3, 117.7, 120.1, 122.8, 130.8, 132.2, 146.7, 146.8, 148.0, 151.8, 152.3, 158.4. Anal. Calcd for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 68.13; H, 4.50.

Arnottin I (7,8-Dimethoxy-2,3-methylenedioxy-6*H*-benzo[*d*]-naphtho[1,2-*b*]pyran-6-one) (1). A suspension of **3** (106 mg, 0.3 mmol) and DDQ (136 mg, 0.6 mmol) in benzene (5 mL) was refluxed for 2 h. After addition of $CHCl_3$ (70 mL), the mixture was successively washed with H_2O (5 mL), 1 N NaOH (3 mL × 5), H_2O (3 mL × 5), and brine (3 mL), dried (Na_2SO_4), and evaporated. Recrystallization of the residue from $CHCl_3$ afforded **1** (99 mg, 94%) as colorless prisms, mp 299−300 °C (lit.[2] mp 293−297 °C). IR (ATR): ν_{max} 1736 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.99 (s, 3H), 4.03 (s, 3H), 6.10 (s, 2H), 7.14 (s, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.85 (s, 1H), 7.88 (d, J = 8.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 56.6, 61.6, 99.1, 101.5, 104.0, 112.1, 115.5, 117.75, 117.83, 119.7, 120.3, 123.2, 129.8, 131.2, 146.1, 148.6, 148.9, 151.9, 153.1, 157.7. Anal. Calcd for $C_{20}H_{14}O_6$: C, 68.57; H, 4.03. Found: C, 68.30; H, 4.02. HREIMS *m*/*z*: 350.0799 (calcd for $C_{20}H_{14}O_6$ (M^+): 350.0790).

(*R*)-(+)-6,7-Methylenedioxy-1-tetralone-2-spiro-3′-(6,7-dimethoxyphthalide) (Dihydroarnottin II) ((+)-12). A mixture of AD-mix-β (1.4 g), $K_2OsO_2(OH)_4$ (7 mg, 10 mol %), $(DHQD)_2$−PHAL (78 mg, 50 mol %), H_2O (5 mL), and *tert*-BuOH (5 mL) was stirred at room temperature for 15 min. To the mixture was added a mixture of methanesulfonamide (29 mg, 0.3 mmol) and **3** (71 mg, 0.2 mmol) in CH_2Cl_2 (10 mL), and the resultant mixture was stirred at 0 °C for 95 h. After addition of sodium sulfite (2 g), the mixture was stirred at room temperature for 1 h and extracted with CH_2Cl_2 (10 mL). The aqueous solution was acidified with 2 N HCl (7 mL) and extracted with AcOEt (5 mL × 2). The combined organic solutions were washed with brine (5 mL), dried (Na_2SO_4), and evaporated. Purification of the residue by column chromatography (AcOEt/hexane = 1:3) followed by recrystallization from AcOEt−hexane gave (+)-dihydroarnottin II ((+)-**12**) (62 mg, 83%) as colorless needles, mp 145−147 °C. IR (ATR): ν_{max} 1753, 1685 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.46 (ddd, J = 13.6, 6.2, 5.4 Hz, 1H), 2.64 (ddd, J = 13.6, 8.2, 5.8 Hz, 1H), 3.20 (ddd, J = 17.4, 8.2, 5.4 Hz, 1H), 3.30 (ddd, J = 17.4, 6.2, 5.4 Hz, 1H), 3.89 (s, 3H), 4.12 (s, 3H), 6.06 (s, 2H), 6.76 (s, 1H), 6.89 (d, J = 8.2 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 7.41 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 26.0, 33.9, 56.8, 62.4, 85.0, 102.0, 107.2, 108.0, 116.7, 118.2, 119.0, 125.6, 140.4, 141.0, 147.6, 148.7, 153.2, 153.3, 166.8, 188.6. Anal. Calcd for $C_{20}H_{16}O_7$: C, 65.22; H, 4.38. Found: C, 65.15; H, 4.41; HRFABMS *m*/*z*: 369.0984 (calcd for $C_{20}H_{17}O_7$ (M^+ + H): 369.0974). $[\alpha]^{22}_D$ +61 (*c* 0.05, $CHCl_3$); 88% ee by chiral HPLC (CHIRALPAK IA, 0.46 cm × 25 cm); *n*-hexane/CH_2Cl_2/EtOH = 15:5:4; flow rate = 0.5 mL/min; detection wavelength = 254 nm; t_R (major) = 14.4 min, t_R (minor) = 21.8 min.

(*R*)-(−)-5-Bromo-6,7-methylenedioxy-1-tetralone-2-spiro-3′-(4-bromo-6,7-dimethoxyphthalide) ((−)-15). A mixture of (+)-dihydroarnottin II (+)-**12** (76 mg, 0.206 mmol) and a solution of 1.37 M solution of Br_2 in $CHCl_3$ (1.5 mL, 2.06 mmol) was stirred at room temperature for 30 h, washed with 5% $Na_2S_2O_3$ aq (2 mL × 3) and brine (2 mL), dried (Na_2SO_4), and evaporated. Purification of the residue (99 mg) by column chromatography (hexane/AcOEt = 4:1−1:1) followed by recrystallization (AcOEt) gave (−)-**15** (93 mg, 86%) as colorless prisms, mp 281−282 °C. IR (ATR): ν_{max} 1757, 1676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.27−2.31 (m, 1H), 3.22−3.36 (m, 3H), 3.94 (s, 3H), 4.10 (s, 3H), 6.15 (d, J = 1.2 Hz, 1H), 6.16 (d, J = 1.2 Hz, 1H), 7.33 (s, 1H), 7.50 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 25.2, 31.3, 57.0, 62.4, 84.7, 102.2, 102.3, 106.6, 109.8, 120.2, 122.9, 126.9, 139.8, 140.0, 147.0, 148.1, 151.6, 154.1, 165.3, 186.2. Anal. Calcd for $C_{20}H_{14}Br_2O_7$: C, 45.66; H, 2.61. Found: C, 45.40; H, 2.68. $[\alpha]^{24}_D$ −121 (*c* 0.08, $CHCl_3$).

Arnottin II (2). A mixture of dihydroarnottin II (+)-**12** (68 mg, 0.185 mmol), NBS (33 mg, 0.185 mmol), and AIBN (3 mg, 0.0185 mmol) in dry benzene (5 mL) was heated under argon. After being stirred at 85 °C for 24 h and then at 65 °C for 20 h, DBU (78 mg, 0.499 mmol) was added to the filtrate. The resultant mixture was refluxed for 1 h under argon, diluted with AcOEt (10 mL), washed with 2 N HCl (2 mL), 10% $NaHSO_3$ (2 mL), sat. $NaHCO_3$ (1 mL), and brine (2 mL), dried (Na_2SO_4), and evaporated. Purification of the residue by column chromatography (benzene/AcOEt = 100:2) afforded arnottin II (**2**) (32 mg, 47%). Recrystallization from CH_2Cl_2–Et_2O afforded pale yellow needles, mp 222−224 °C (lit.[3] mp 225−226 °C). IR (ATR): ν_{max} 1776, 1687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.86 (s, 3H), 4.17 (s, 3H), 6.09 (d, J = 10.0 Hz, 1H), 6.10 (s, 2H), 6.69 (d, J = 10.0 Hz, 1H), 6.78 (s, 1H), 6.78 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 56.9, 62.7, 84.3, 102.4, 107.6, 107.9, 115.5, 117.2, 119.1, 123.0, 128.3, 130.2, 134.4, 139.1, 148.4, 149.0, 153.4, 153.9, 167.5, 191.0. Anal. Calcd for $C_{20}H_{14}O_7$: C, 65.57; H, 3.85. Found: C, 65.31; H, 3.80. $[\alpha]^{25}_D$ −217 (*c* 0.026, MeOH) (lit.[3] $[\alpha]_{589}$ −280 [*c* 9 × 10^{-3}, MeOH]), $[\alpha]^{25}_D$ −240 (*c* 0.105, $CHCl_3$); 98% ee by chiral HPLC (CHIRALPAK IA, 0.46 cm × 25 cm); *n*-hexane/CH_2Cl_2/EtOH = 15:5:4; flow rate = 0.5 mL/min; detection wavelength = 254 nm; t_R (major) = 13.5 min, t_R (minor) = 19.8 min.

(21) X-ray data were collected on a Bruker SMART 1000 CCD detector. The crystal structure was solved by direct methods SHELXS-97 (Sheldrick, 1997) and refined by full-matrix least-squares SHELXL-97 (Sheldrik, 1997). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included at their calculated positions. Crystal data for (−)-**15**: $C_{20}H_{14}Br_2O_7$; M = 526.13 g mol^{-1}, orthorhombic, $P2_12_12_1$, colorless prisma measuring 0.40 × 0.30 × 0.05 mm, T = 150 K, a = 7.3016(10) Å, b = 8.4264(12) Å, c = 30.356(4) Å, V = 1867.7(5) $Å^3$, Z = 4, D_{calcd} = 1.871 Mg m^{-3}, μ = 4.383 mm^{-1}, T_{max} = 0.8106, T_{min} = 0.2731, GOF on F^2 = 1.056, R1 = 0.0551, wR2 = 0.1428 [$I > 2\sigma(I)$], R1 = 0.0693, and wR2 = 0.1547 (all data), absolute structure parameter = 0.000(17). CCDC-611350.

(22) Yoshida, M.; Watanabe, T.; Ishikawa, T. *Tetrahedron Lett.* **2002**, *43*, 6751−6753.

Note Added after ASAP Publication. The incorrect X-ray data for (−)-**15** was cited in ref 21 in the version published ASAP December 7, 2006; the corrected version was published ASAP December 12, 2006.

Supporting Information Available: Preparation of starting bromobenzoates, general experimental procedure in Table 1, spectral data of **8** (X = 2-Me; X = 3,4-OCH_2O) and **9**, synthesis of (±)- and (−)-**12**, NMR charts of **1**, **2**, **3**, (+)- and (−)-**12**, and (−)-**15**, chiral HPLC charts of synthetic and natural **2** and (+)- and (−)-**12**, ORTEP drawing of (−)-**15**, and X-ray data of (−)-**15** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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