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Syntheses of Arnottin I and Arnottin II

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Abstract

Short total syntheses of arnottin I and II were accomplished in 5 and 6 steps, respectively. A sesamol-benzyne cycloaddition with a 3-furyl-benzoate followed by regiospecific lactonization provided rapid, large-scale access to the core of arnottin I. Saponification of arnottin I and hypervalent iodide mediated spirocyclization provided an efficient and direct preparation of racemic arnottin II.

The arnottins (I and II) are coumarin-type natural products isolated from the bark of the *xanthoxylum arnottianum* Maxim (rutaceae) and are surmised to possess antibiotic properties.¹ Syntheses of these interesting metabolites have been reported after the initial isolation and structural determination.² The absolute stereochemical configuration of spirocyclic arnottin II was synthetically determined via asymmetric dihydroxylation of a reduced isomer of arnottin I by Yamaguchi and coworkers.^{2c}

Tandem oxidative dearomatization and spirocyclization³ is capable of converting simple benzocoumarins to chiral spirocyclic lactones that are found in several natural product families. The direct conversion of arnottin I to arnottin II by using this method has not yet been reported. Hypervalent iodide mediated oxidative dearomatization has been employed in the synthesis of various natural products including galanthamine and other *amaryllidaceae* alkaloids.^{4,5} Recent advances have allowed for asymmetric hypervalent iodide oxidative dearomatization;^{6,7} however, few examples exist within total synthesis. In order to study and expand upon current methods for hypervalent iodide mediated spirocyclization, a short and concise synthesis of the arnottins was pursued. The preparation of arnottin I utilized a

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Supporting Information

¹H and ¹³C NMR spectra for all new compounds is provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Notes

The authors declare no competing financial interest.

benzyne cycloaddition, hydrolysis, and oxidative spirocyclization to arnottin II to provide large quantities of the metabolites for testing.

A convergent synthetic path to arnottin I was planned using a benzyne cycloaddition with a 3-furyl benzoate, followed by lactone formation (Scheme 1). Bis-lithiation of 6-bromosessamol,⁸ followed by trimethylsilyl chloride quench and triflation using under Mori's procedure⁹ afforded benzyne precursor **4** in 74% overall yield on 5 gram scale. The furyl coupling partner was prepared from readily available dimethoxybenzoic acid and converted to either the methyl (**5a**) or *tert*-butyl bromoester (**5b**) in 2 steps.^{2c} The bromoester (**5**) was cross-coupled under Suzuki's condition with commercially available 3-furylboronic acid in 82 and 96% yield for the methyl and *tert*-butyl ester, respectively. The benzyne-mediated cycloaddition proved capricious and required the sessamol silyltriflate to be used in excess (1.4 equiv.) with slow generation of the benzyne using weakly soluble CsF in acetonitrile. The *in-situ* cycloaddition produced the arnottin I progenitors (rac-**7a**, rac-**7b**) in 66 and 64% yield, respectively.

Unsaturated bicyclic ethers, such as **7**, can be converted to naphthols under a variety of conditions including Bronsted acids,¹⁰ ruthenium,¹¹ rhodium,¹² and aluminum complexes.¹³ The naphthol regioisomer produced is less predictable and was unknown for structure **7** at the onset of these studies. For the transformation of esters rac-**7a** and rac-**7b** to **1**, several conditions were attempted: Lewis acids such as BF₃-etherate or Sc(OTf)₃ gave complex mixtures and nucleophiles such as NaI and NaBr resulted in degradation. Bronsted acids were most effectual with HCl and TsOH both providing arnottin I for rac-**7a** and rac-**7b** in differing yield. Exposure of methyl ester rac-**7a** to TsOH in methanol led to non-regiospecific naphthol formation resulting in both arnottin I (15%) and the 4-naphthol derivative **8**.¹⁴ Identical reaction conditions were attempted with *tert*-butyl ester rac-**7b** and surprisingly led to clean conversion of arnottin I in 92% yield with no 4-naphthol derivative observed. The synthetically prepared arnottin I displayed spectroscopic and physical properties identical to the natural product.¹ The disparity in reaction yield between rac-**7a** and rac-**7b** to arnottin I and the absent 4-naphthol derivative in the rac-**7b** reaction suggests the mechanism follows different paths for each ester employed. The methyl ester (rac-**7a**) produced both arnottin I and the 4-naphthol derivative suggesting naphthol formation occurred with little regiospecificity. The resultant 1-naphthol produced arnottin I whereas the 4-naphthol was incapable of cyclization. The *tert*-butyl ester (rac-**7b**) cleanly afforded arnottin I suggesting the ester is deprotected prior to naphthol formation. One plausible mechanism is the weakening of a *tert*-butyl ester proton due to carbonyl lone-pair donation into the C-O σ^* of the bicycle, resulting in loss of isobutylene and carboxylate promoted rupture of the allylic ether as shown by intermediate **9** (Figure 1). The resultant benzylic alcohol (**10**) is quickly dehydrated to arnottin I. Furthermore, *in situ* ¹H NMR, showed no *tert*-butanol formation during the course of the reaction discouraging the phenol formation and lactonization scenario. Isobutylene was not observed, however, the volatility would make detection difficult. The fortuitous sequence afforded large quantities of arnottin I and allowed the study of conversion to arnottin II.

Saponification of arnottin I required immediate exposure to spirocyclization conditions due to competitive recyclization and recovery of arnottin I in acid. Careful hydrolysis of arnottin

I was followed by protonation of the carboxylate to a pH of 2–3, which reduced the conversion to arnottin I and retained solubility for the spirocyclization studies.

The saponified phenol acid was immediately exposed to different hypervalent iodide conditions to effect the spirocyclization. The highly reactive bis(trifluoroacetoxy)iodobenzene (PIFA) was necessary to form racemic arnottin II in DCM with cesium carbonate as an additive in 23% yield (Table 1, entry 1). Kita noted substantial increases in yield using fluorinated solvents¹⁰ that were also investigated. Trifluoroethanol (TFE, entry 2, 25%) was inferior as compared to hexafluoroisopropanol (HFIP, entry 3, 40%) as solvent. Blends of DCM and HFIP (entry 4, 28%) did not offer enhanced yields. An intensely colored intermediate was formed over the first twenty minutes of the reaction and persisted throughout the duration of the reaction. Two possible intermediates could exist; a ligand exchanged trapped γ^3 -iodane **11**, or a dissociated cationic complex **12**.^{4b} We reasoned the breakdown of the mixed hypervalent intermediate could occur through liberation of the weaker carboxylate donor using a nucleophilic donor. DMAP (entry 5) was added to the reaction, but did not increase the yield substantially as compared to its absence (entry 3). Perchlorate salts, known to increase yields involving nucleophilic addition to phenoxenium radical cations,¹⁵ also did not improve the reaction and had noted degradation (entry 6). Slow addition of PIFA over one hour provided a boost in yield and generated arnottin II in 56% overall yield over the two steps (entry 7). Attempts at asymmetric spirocyclization using chiral hypervalent iodide sources are planned.

In conclusion, we developed an efficient route from readily available materials to the arnottins using a benzyne cycloaddition and regiospecific ether fragmentation-lactonization cascade. Several other coumarin based natural products can now be accessed more efficiently using this tactic.

EXPERIMENTAL SECTION

tert-Butyl 6-(furan-3-yl)-2,3-dimethoxybenzoate (**6b**)

1.43 g (4.50 mmol, 1.0 eq.) of *tert*-butyl 6-bromo-2,3-dimethoxybenzoate (**5b**),^{2c} 750.0 mg (6.76 mmol, 1.5 eq.) of furan-3-boronic acid, and 1.865 g (13.50 mmol, 3.0 eq.) of K₂CO₃ were dissolved in DMF (30.0 mL). The resulting solution was degassed under argon for 10 minutes. 253.0 mg of Pd(PPh₃)₂Cl₂ (1.06 mmol, 8 mol%) and H₂O (10.0 mL) were then added to the reaction flask, and this solution was stirred at 90 °C for 4 hours. The reaction mixture was run through a Celite plug, diluted with toluene (10.0 mL), and concentrated *en vacuo*. This product was purified by column chromatography (3:1 hexanes/EtOAc, v/v) and dried under vacuum to yield 1.32 g of methyl 6-(furan-3-yl)-2,3-dimethoxybenzoate (**6b**, 96% yield) as a white solid. mp 46–48 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.51 – 7.48 (m, 1H), 7.42 (t, *J* = 1.7 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.50 (dd, *J* = 1.8, 0.9 Hz, 1H), 3.89 (d, *J* = 1.9 Hz, 6H), 3.83 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 13C NMR (101 MHz, CDCl₃) δ 167.0, 151.8, 145.8, 142.8*, 142.7*, 139.7*, 139.6*, 130.4, 124.8, 123.7, 122.5, 113.1, 111.2*, 111.1*, 82.3, 61.5, 56.0, 28.1; IR (neat, cm⁻¹) 2973, 2935, 1715, 1482, 1291, 1265, 1059, 1029, 795; TLC R_f = 0.60 (3:1 hexanes/EtOAc, v/v); HRMS (DART) *m/z* Calc'd for C₁₇H₂₁O₅ (M+H)⁺ : 305.1389, found 305.1375. *denotes rotamers.

Methyl 6-(furan-3-yl)-2,3-dimethoxybenzoate (6a)

2.00g (18.0 mmol) of Methyl 6-bromo-2,3-dimethoxybenzoate (**5a**) yielded 3.53g (12.5 mmol, 82% yield) of 6-(furan-3-yl)-2,3-dimethoxybenzoate (**6a**) according to the above procedure. m.p. 43–45 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.49 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.42 (t, *J* = 1.7 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.50 (dd, *J* = 1.8, 0.9 Hz, 1H), 3.89 (s, 3H), 3.89 (s, 3H), 3.83 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 168.3, 151.6, 145.9, 143.0, 139.1, 128.3, 124.5, 123.8, 122.6, 113.6, 110.3, 61.5, 55.8, 52.3; IR (neat, cm⁻¹) 804, 1258, 1723; TLC R_f = 0.4 (2:1 hexanes/EtOAc, v/v); HRMS (DART) *m/z* Calc'd for C₁₄H₁₄O₅ (M+H)⁺: 262.0841, found 262.0838.

***tert*-butyl 6-(5,8-dihydro-5,8-epoxynaphtho[2,3-d][1,3]dioxol-6-yl)-2,3-dimethoxybenzoate (7b)**

335.0 mg (1.036 mmol, 1.4 eq.) of 6-trimethylsilylbenzo[d][1,3]dioxol-5-yl-trifluoromethanesulfonate (**4**)⁹ and 225.0 mg (0.74 mmol, 1.0 eq.) of *tert*-butyl 6-(furan-3-yl)-2,3-dimethoxybenzoate (**6b**) were dissolved with acetonitrile (10.0 mL) in a flame-dried flask. The solution was charged with argon, then 337.0 mg (2.22 mmol, 3.0 eq.) of CsF was added and the reaction mixture was let stir at 23 °C for 24 hours. The solution was diluted with water (30.0 mL) and extracted with ethyl acetate (3 × 15.0 mL). The combined organic layers were washed with water (30.0 mL) and brine (30.0 mL), dried over MgSO₄, and concentrated under reduced pressure. The product was purified by column chromatography (3:1 hexanes/EtOAc, v/v) to yield 201.6 mg of *tert*-butyl 6-(5,8-dihydro-5,8-epoxynaphtho[2,3-d][1,3]dioxol-6-yl)-2,3-dimethoxybenzoate (**7b**, 64% yield) as an off-white solid. m.p. 150 °C (decomp.); ¹H NMR (400 MHz, CDCl₃) δ 6.98 (d, *J* = 8.5 Hz, 1H), 6.94 (dd, *J* = 1.4, 0.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.83 (t, *J* = 0.5 Hz, 1H), 5.94 (d, *J* = 1.4 Hz, 1H), 5.86 (d, *J* = 1.4 Hz, 1H), 5.79 (t, *J* = 0.8 Hz, 1H), 5.73 (dt, *J* = 1.8, 0.8 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 1.49 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 166.7, 153.3, 152.6, 146.2, 144.8, 144.4, 143.4, 143.0, 136.7, 129.7, 122.9, 122.1, 112.6, 104.0, 103.7, 101.3, 85.0, 84.0, 82.4, 61.5, 56.1, 28.1; IR (neat, cm⁻¹) 2973, 2935, 1715, 1482, 1292, 1265, 1142, 1059, 1029, 795; TLC R_f = 0.31 (3:1 hexanes/EtOAc, v/v); HRMS (DART) *m/z* Calc'd for C₂₀H₁₇O₇ (M-C₄H₈)⁺: 369.0974, found 369.0960.

Methyl 6-(5,8-dihydro-5,8-epoxynaphtho[2,3-d][1,3]dioxol-6-yl)-2,3-dimethoxybenzoate (7a)

780.0 mg (2.23mmol) of methyl 6-(furan-3-yl)-2,3-dimethoxybenzoate (**6a**) yielded 375.0 mg (0.98mmol, 66% yield) of methyl 6-(5,8-dihydro-5,8-epoxynaphtho[2,3-d][1,3]dioxol-6-yl)-2,3-dimethoxybenzoate (**7a**) as per the above procedure. m.p. 56–58 °C (decomp); ¹H NMR (500 MHz, CDCl₃) δ 6.98 (d, *J* = 8.6 Hz, 1H), 6.93 (m, 2H), 6.81 (m, 2H), 5.93 (d, *J* = 1.4 Hz, 1H), 5.87 (d, *J* = 1.4 Hz, 1H), 5.75 (t, *J* = 0.8 Hz, 1H), 5.71 (dt, *J* = 1.8, 0.8 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 167.9, 153.5, 152.4, 146.3, 144.7, 144.3, 143.1, 142.6, 136.5, 127.6, 123.4, 122.0, 113.1, 103.9, 103.5, 101.2, 84.9, 83.9, 61.6, 56.0, 52.5; IR (neat, cm⁻¹) 2941, 1724, 1460, 1254, 1035; TLC R_f = 0.5 (2:1 hexanes/EtOAc v/v); HRMS (DART) *m/z* Calc'd for C₂₁H₁₉O₇ (M+H)⁺: 383.1131, found 383.1129.

Arnottin I (1)

150.0 mg (0.354 mmol, 1.0 eq.) of *tert*-butyl 6-(5,8-dihydro-5,8-epoxynaphtho[2,3-*d*][1,3]dioxol-6-yl)-2,3-dimethoxybenzoate (**7b**) was added to a flame-dried round-bottomed flask and dissolved in anhydrous MeOH (5 mL). 15.2 mg (0.0884 mmol, 0.25 eq.) of *p*-toluenesulfonic acid was then added to this solution and stirred at 50 °C under nitrogen atmosphere for 24 hours. The reaction mixture was then cooled to 0 °C and filtered, and the off-white solid was washed with cold MeOH. This product was dried under vacuum to yield 113.4 mg of arnottin I (**1**, 92% yield). m.p. >250 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, *J* = 8.9 Hz, 1H), 7.85 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.14 (s, 1H), 6.10 (s, 2H), 4.03 (s, 3H), 3.99 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 166.7, 153.2, 152.5, 146.1, 144.8, 144.4, 143.4, 142.9, 136.6, 129.6, 122.8, 122.1, 112.6, 103.9, 103.6, 101.3, 85.0, 83.9, 82.3, 61.5, 56.0, 28.0; IR (neat, cm⁻¹) 3010, 2943, 1734, 1489, 1463, 1276, 1122, 1039, 821; TLC R_f = 0.50 (1:1 hexanes/EtOAc, v/v); HRMS (DART) *m/z* Calc'd for C₂₀H₁₅O₆ (M+H)⁺: 351.0869, found 351.0855.

Arnottin II (2)

Arnottin I (**1**, 12.0 mg, 0.035 mmol) was suspended in 0.5 mL of THF: MeOH:H₂O (3:1:1, v/v/v) and 7.0 mg, (0.17 mmol, 5.0 eq.) of LiOH·H₂O was added. The reaction was heated at 50 °C for 2 hours over which time the solution became red. The flask was cooled to 0 °C and 1M HCl was added dropwise until the solution turned yellow-orange indicating a pH of 2–3. The solution was extracted with Et₂O (2 × 1.0 mL), dried over Na₂SO₄ and concentrated at 23 °C yielding an unstable yellow-orange solid. The flask was cooled to 0 °C and HFIP (0.50 mL) was added. PIFA (17.0 mg, 0.041 mmol, 1.1 eq.) in 0.50 mL of HFIP was added over 1 hour at 0 °C via syringe pump and then the reaction was stirred at 23 °C. After 12 hours the reaction was quenched with 1M HCl (1.0 mL), extracted with CH₂Cl₂ (2 × 1.0 mL), dried over Na₂SO₄ and concentrated. Flash chromatography (2:1 hexanes/EtOAc, v/v) yielded arnottin II (**2**, 7.0 mg, 0.02 mmol, 56% yield) as an off yellow solid. m.p. 206–208 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.37 (s, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.78 (t, *J* = 4.1 Hz, 2H), 6.68 (d, *J* = 9.9 Hz, 1H), 6.09 (m, 4H), 4.17 (d, *J* = 0.8 Hz, 3H), 3.86 (s, 4H); ¹³C NMR (126 MHz, CDCl₃) δ 191.1, 167.6, 154.1, 153.6, 149.1, 148.6, 139.2, 134.6, 130.3, 128.4, 123.2, 119.2, 117.4, 115.6, 108.1, 107.7, 102.6, 84.5, 62.8, 57.0; IR (neat, cm⁻¹) 1682, 1770, 2853, 2921; TLC R_f = 0.45 (1:1 hexanes/EtOAc v/v); HRMS (DART) *m/z* Calc'd for C₂₀H₁₅O₇ (M+H)⁺: 367.0818, found 367.0811.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Proposed carboxylate-assisted lactonization cascade.

Scheme 1.
Preparation of Arnottin I.

Table 1

Screen of hypervalent iodide conditions.

entry	solvent	additive	time (h)	temp (°C)	yield ^a (%)
1	DCM	CsCO ₃	4	-40	23
2	TFE		4	-20	25
3	HFIP		12	0	40
4	DCM/HFIP		12	0	28
5	HFIP	Et ₃ N, DMAP	12	0	35
6 ^b	HFIP/MeCN	MgClO ₄	12	0	25
7 ^b	HFIP		12	0	56

^aYield refers to isolated yields following silica gel chromatography.

^bSyringe pump addition of PIFA over one hour.