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Synthetic studies toward the citrinadins: enantioselective preparation of an advanced spirooxindole intermediate

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Abstract

This manuscript describes the enantioselective preparation of a spirooxindole that is suited for advancement to either Citrinadin A or B.

Keywords

Citrinadin; spirooxindole; natural product; synthesis; Heck reaction

1. Introduction

Citrinadins A and B (**1** and **2**, respectively) are structurally complex oxindole-containing alkaloids that were isolated from *Penicillium citrinum* N059 by Kobayashi in the early 2000's.¹ These compounds display modest potential as anticancer agents and were initially assigned the structures illustrated as **1** and **2** in Figure 1. Recent synthetic studies directed toward **1** by Martin, and our own efforts directed toward **2**, independently revealed that the stereochemistry assigned to each stereogenic carbon atom residing within the pentacyclic cores of **1** and **2** was incorrect.² These structures were thus reassigned as illustrated for natural citrinadin B (**3**) in Figure 1.^{3,4}

Our previous synthesis of **3** employs racemic spirooxindole ($\pm$)-(**5**) in a [3+2] cycloaddition with enantioenriched nitron (–)-(**4**) wherein the latter essentially serves as a resolving agent in delivering enantioenriched cycloadduct (+)-**6**. In the course of adapting our synthesis to deliver citrinadin A, we began exploring strategies for the enantioselective preparation of **5**, thereby avoiding its resolution and consequently improving the efficiency of the key cycloaddition reaction. Herein we report the enantioselective preparation of this spirocyclic oxindole.

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2. Results and Discussion

In our completed synthesis of citrinadin B, we employed an intramolecular Heck reaction to convert amide **7** to oxindole **8**, which in turn was transformed into spirocycle **5** (Scheme 2, top).

Thus, an obvious approach for preparing enantioenriched material would be to perform the same Heck reaction with a chiral catalyst. In preliminary studies we were quite successful in applying asymmetric Heck chemistry to the conversion of **9** to its corresponding oxindole (+)-**10** (Scheme 2, middle); however, attempts to advance *o,o*-disubstituted anilines (e.g., **11**) proved problematic and similar catalytic asymmetric conditions failed completely.⁵

Given the failings of the asymmetric Heck route, we began developing an approach to **5** wherein assembly of the cyclopentane component would precede the intramolecular Heck reaction. As illustrated retrosynthetically in Scheme 3, this sequence employs a primary amide (**13**) as the substrate in a diastereoselective Heck reaction, wherein stereocontrol would derive from a resident stereogenic alcohol which, upon β -hydride elimination, is converted to the requisite ketone.⁶ Disconnection of **13** via the amide linkage leads to our points of departure, known compounds **14** and **15**.⁷

In the forward sense, exposure of known ketone **15** to Br₂ furnished dibromide (**16**) which, upon DBU promoted double elimination, delivered the corresponding diene (**17**).

Saponification of **17** to acid **18** set the stage for amide formation, which was accomplished upon exposure of an intermediate acid chloride to dibromoaniline (**14**). The derived amide (**19**) was subjected to catalytic asymmetric reduction under conditions developed by Corey to furnish the desired alcohol (–)-**13** in good yield with adequate levels of stereocontrol.⁸

Initial attempts to advance (–)-**13** to the desired spirocyclic ketone **20**, without first protecting the secondary alcohol, met with limited success. As illustrated in Table 1, a number of standard conditions for the Heck cyclization were explored and found to deliver, at best, a 37% yield of the desired product.

In an effort to improve the cyclization, we explored a variety of alcohol protecting groups and found that converting (–)-**13** to the corresponding TBS-ether (–)-**21** greatly improved the subsequent Heck chemistry (Scheme 5).

As illustrated in Table 2 (entry 3) this reaction performed best at higher dilution and in the presence of 4Å molecular sieves (67% yield, 85% BORSM, 88% ee). Although a higher combined yield and potentially useful in situ enolether cleavage were observed in the absence of molecular sieves (entry 2), the product derived from enol ether cleavage (i.e., **20**) was found to undergo racemization upon exposure to basic conditions and thus its formation was best avoided.⁹

The delicate nature of the enol ether (**22**), coupled with the tendency of its hydrolysis product to undergo racemization, dictated that it be advanced without extensive purification. Thus, a protocol was developed wherein the Heck cyclization was immediately followed by

N-benzylation and then *O*-desilylation of the protected product (**23**, Scheme 6). By employing this strategy, the stereochemical integrity in the desired enone (+)-**5** was successfully maintained.

3. Conclusion

In conclusion, we have developed a strategy for the enantioselective preparation of enone (+)-**5**, an advanced intermediate suited for conversion to the natural enantiomers of citrinadin A and B. Stereogenicity at the quaternary carbon in (+)-**5** is controlled via a diastereoselective intramolecular Heck cyclization. Ongoing efforts to advance (+)-**5** to citrinadin A will be reported in due course.

4. Experimentals

4.1. General

Unless otherwise stated, reactions were magnetically stirred in flame- or oven-dried glassware under an atmosphere of nitrogen. Triethylamine, diisopropylamine, and methanol were dried over calcium hydride and freshly distilled. Benzene, tetrahydrofuran, dichloromethane, toluene, and diethyl ether were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. All other commercially available reagents were used as received.

Unless otherwise stated, all reactions were monitored by thin-layer chromatography (TLC) using Silicycle glass-backed extra hard layer, 60 Å plates (indicator F-254, 250 µm). Column or flash chromatography was performed with the indicated solvents using Silicycle SiliaFlash® P60 (230–400 mesh) silica gel as the stationary phase. All melting points were obtained on a Gallenkamp capillary melting point apparatus (model: MPD350.BM2.1) and are uncorrected. Infrared spectra were obtained using a Nicolet Avatar 320 FTIR or Bruker Tensor 27 FTIR. ¹H and ¹³C NMR spectra were recorded on a Varian Inova 400 or Varian Inova 400 autosampler. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual proton resonance of CDCl₃. Coupling constants (*J*) are reported in Hertz (Hz). High resolution mass spectra were performed at the Central Instrument Facility by Donald L. Dick of Colorado State University.

4.1.1 Dibromide 16—To a solution of ester **15** (850.0 mg, 4.29 mmol) in CCl₄ (8.6 ml) at 0 °C was added bromine (659.0 µl, 12.9 mmol). The reaction mixture was stirred at 0 °C for 2 h, then concentrated *in vacuo* and purified by flash chromatography (20% EtOAc/hexanes) to provide the dibromide **16** as a white semi-solid (940.2 mg, 62% yield). m.p. 46–51 °C, IR (thin film): 2980, 1732, 1214 cm⁻¹; ¹H NMR δ 4.54 (d, *J* = 10.0 Hz, 1H), 4.30 - 4.15 (m, 2H), 3.47 (d, *J* = 9.6 Hz, 1H), 1.67 (s, 3H), 1.41 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.82 (s, 3H); ¹³C NMR δ 202.3, 169.8, 73.1, 61.7, 58.7, 46.3, 41.0, 23.9, 19.8, 19.4, 14.4; HRMS (ESI) Calcd. for C₁₁H₂₀Br₂NO₃ [M+NH₄]⁺: 371.9810. Found: 371.9801.

4.1.2 Ester 17—To a solution of dibromide **16** (940.2 mg, 2.64 mmol) in CH₂Cl₂ (13 ml) at 0 °C was added DBU (987.2 µl, 6.60 mmol). After stirring at 0 °C for 15 min, the reaction mixture was warmed to room temperature for and stirred for 1 h. The reaction was quenched

with saturated NH_4Cl solution (15 ml). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (MgSO_4), concentrated *in vacuo*, and purified by flash chromatography (2% $\rightarrow$ 10% EtOAc/hexanes) to provide the ester **17** as a pale yellow oil (420.2 mg, 82% yield). IR (thin film): 2982, 1708, 1468, 1224 cm^{-1} ; ^1H NMR δ 6.81 (s, 1H), 6.09 (s, 1H), 5.42 (s, 1H), 4.29 (q, $J = 7.2$ Hz, 2H) 1.43 (s, 6H), 1.33 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR δ 195.4, 165.2, 163.8, 153.5, 137.9, 116.8, 61.5, 44.6, 26.2(x2), 14.2; HRMS (ESI) Calcd. for $\text{C}_{11}\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$: 195.1021. Found: 195.1004.

4.1.3 Acid 18—To a solution of ester **17** (11.0 g, 56.1 mmol) in THF (420 ml) and H_2O (140 ml) at room temperature was added lithium hydroxide (4.0 g, 168.2 mmol). The reaction mixture was stirred for 2 h and quenched with a 1M HCl solution (400 ml). The aqueous layer was extracted with EtOAc, and the combined organic layers were dried (MgSO_4), concentrated *in vacuo* and purified by flash chromatography (50% $\rightarrow$ 100% EtOAc/hexanes) to provide the carboxylic acid **18** as a pale yellow solid (8.3 g, 89% yield). m.p. 135–137 $^\circ\text{C}$, IR (thin film): 1684, 1178, 929, 802 cm^{-1} ; ^1H NMR δ 6.98 (s, 1H), 6.17 (s, 1H), 5.49 (s, 1H), 1.49 (s, 6H); ^{13}C NMR δ 195.3, 168.4, 163.9, 153.5, 140.1, 117.7, 44.6, 26.2(x2); HRMS (ESI) Calcd. for $\text{C}_9\text{H}_9\text{O}_3$ $[\text{M}-\text{H}]^-$: 165.0552. Found: 165.0552.

4.1.4 Amide 19—To a solution of carboxylic acid **18** (7.0 g, 42.0 mmol) in 1, 2-dichloroethane (420 ml) at 0 $^\circ\text{C}$ was added DMF (420 μl) and $(\text{COCl})_2$ (4.0 ml, 46.2 mmol). After being stirred at room temperature for 2 h, the reaction mixture was treated with 2,6-dibromoaniline (11.6 g, 46.2 mmol) and pyridine (6.8 ml, 84.0 mmol). The derived reaction mixture was heated to reflux and stirred for 16.5 h, after which the reaction was cooled to room temperature and quenched with 1M HCl (400 ml). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried (MgSO_4), concentrated, *in vacuo* and purified by flash chromatography (10% $\rightarrow$ 50% EtOAc/hexanes) to provide the anilide **19** as a white solid (13.1 g, 78% yield). m.p. 167–169 $^\circ\text{C}$, IR (thin film): 3252, 2967, 2928, 1704, 1505, 726 cm^{-1} ; ^1H NMR δ 7.64 (d, $J = 8.0$ Hz, 2H), 7.36 (s, 1H), 7.11 (t, $J = 8.0$ Hz, 1H), 6.70 (s, 1H), 6.17 (s, 1H), 5.49 (s, 1H), 1.57 (s, 6H); ^{13}C NMR δ 195.7, 169.7, 163.4, 152.7, 133.7, 133.3(x2), 130.2, 124.1(x2), 116.7, 45.7, 26.4(x2); HRMS (ESI) Calcd. for $\text{C}_{15}\text{H}_{14}\text{Br}_2\text{NO}_2$ $[\text{M}+\text{H}]^+$: 397.9391 Found: 397.9397.

4.1.5 Alcohol 13—To a solution of anilide **19** (1.0 g, 2.51 mmol) in THF (13 ml) at -35 $^\circ\text{C}$ was added (*S*)-Me-CBS catalyst (250.0 μl , 0.251 mmol, 1M in THF) and $\text{BH}_3\cdot\text{SMe}_2$ (1.2 ml, 12.5 mmol). The reaction temperature was maintained at -35 $^\circ\text{C}$ and the stirring was continued for 3 days. The reaction was then quenched with MeOH (2 ml) and saturated NH_4Cl (20 ml). The aqueous layer was extracted with EtOAc, and the combined organic layers were concentrated and purified by flash chromatography (30% $\rightarrow$ 75% EtOAc/hexanes) to provide alcohol **13** as a white solid (780 mg, 77% yield). Chiral HPLC condition; CHIRAL PAK IA, Hexane:*i*PrOH=95:5, retention time 19.587, 23.228. $[\alpha]_{\text{D}}^{28} = -29.1$ (c 1.0, CHCl_3): 88% ee. m.p. 61–63 $^\circ\text{C}$, IR (thin film): 3266, 2964, 1674, 1505, 727 cm^{-1} ; ^1H NMR δ 7.57 (d, $J = 8.0$ Hz, 2H), 7.49 (s, 1H), 7.02 (t, $J = 8.0$ Hz, 1H), 6.44 (s, 1H), 5.33 (d, $J = 1.6$ Hz, 1H), 5.19 (s, 1H), 5.18 (s, 1H), 1.43 (s, 3H), 1.40 (s, 3H); ^{13}C NMR δ 164.0, 161.8, 148.8, 134.3, 134.2, 132.4(x2), 129.9, 124.1(x2), 108.4, 76.0, 48.6, 28.6, 27.7; HRMS (ESI) Calcd. for $\text{C}_{15}\text{H}_{14}\text{Br}_2\text{NO}_2$ $[\text{M}-\text{H}]^-$: 397.9391 Found: 397.9382.

4.1.6 Silyl ether 21—To a solution of alcohol **13** (10.4 g, 25.9 mmol) in DMF (130 ml) at room temperature was added imidazole (5.3 g, 77.8 mmol) and TBSCl (11.7 g, 77.8 mmol). After being stirred at room temperature for 2 h, the reaction mixture was quenched with saturated NaCl solution (100ml). The aqueous layer was extracted with the mixture of EtOAc/Hexane = 1/1 and the combined organic layers were washed with H₂O (80 ml x3), dried (MgSO₄), concentrated *in vacuo*, and purified by flash chromatography (5%→20% EtOAc/hexanes) to provide **21** as a white solid (11.8 g, 88% yield). [α]_D²⁸ = -53.0 (c 1.0, CHCl₃); m.p. 190–191 °C, IR (thin film): 3293, 2929, 1655, 1491, 1094, 775 cm⁻¹; ¹H NMR δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.27 (s, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.35 (s, 1H), 5.31 (d, *J* = 2.0 Hz, 1H), 5.19 (s, 1H), 5.18 (s, 1H), 5.11 (d, *J* = 2.4 Hz, 1H), 1.45 (s, 3H), 1.42 (s, 3H), 0.96 (s, 9H), 0.18 (s, 6H); ¹³C NMR δ 164.1, 161.2, 148.0, 134.9(x2), 134.4, 132.4(x2), 129.8, 124.1(x2), 106.7, 76.3, 48.0, 28.8, 26.4, 26.1(x3), 18.5, -4.26; HRMS (ESI) Calcd. for C₂₁H₂₉Br₂NNaO₂Si [M+Na]⁺: 536.0232 Found: 536.0226.

4.1.7 Enone (+)-5—To a solution of silyl ether **21** (21.2 mg, 41.1 μ mol) in DMA (4.1 ml) in a Schlenk flask at room temperature was added PdCl₂(PPh₃)₂ (2.9 mg, 4.1 μ mol), Et₃N (57.3 μ l, 411 μ mol), and activated Molecular Sieves 4Å (5 pellets). The mixture was degassed using a freeze-pump-thaw cycle (X3)) and then heated to 100 °C. After stirring at 100 °C for 15 h, the reaction mixture was cooled to room temperature and quenched with saturated NaCl solution (5ml). The aqueous layer was extracted with a mixture of EtOAc/Hexane = 2/1 and the combined organic layers were washed with H₂O (1 ml x3), dried (MgSO₄), concentrated *in vacuo*, and purified by short flash chromatography (5%→10% EtOAc/hexanes) to provide the inseparable mixture of starting material **21** and TBS enol ether **22** (16.2 mg).

To a solution of the mixture (**21** and **22**) (16.2 mg) in DMF (372 μ l) at 0 °C was added NaH (1.7 mg, 39.2 μ mol). After being stirred at 0 °C for 15 min, the reaction was treated with benzyl bromide (4.8 μ l, 39.2 μ mol) and allowed to warm to room temperature. After stirring for 4 h, the reaction was quenched with H₂O (1 ml). The aqueous layer was extracted with the mixture of EtOAc/Hexane = 1/1 and the combined organic layers were dried (MgSO₄), concentrated *in vacuo*, and purified by flash chromatography (5%→30% EtOAc/hexanes) to provide the benzylated compound **23** as a pale yellow oil (4.6 mg, 21% yield over 2 steps) and desired enone (+)-**5** (7.5 mg, 43% over 2 steps) as white solid and anilide **21** (1.0 mg, 5% over 2 steps). Compound **23**: [α]_D²⁴ = +82.0 (c 1.0, CHCl₃); IR (thin film): 2929, 2857, 1720, 1606, 1341, 1253, 1118, 830 cm⁻¹; ¹H NMR δ 7.35–7.23 (complex m, 6H), 7.07 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 5.37 (dd, *J* = 16.0, 6.8 Hz, 1H), 5.20 (s, 1H), 4.86 (d, *J* = 8.8 Hz, 1H), 4.75 (d, *J* = 1.2 Hz, 1H), 1.18 (s, 3H), 1.03 (s, 3H), 1.00 (s, 9H), 0.22 (d, *J* = 6.0 Hz, 6H); ¹³C NMR δ 179.2, 157.5, 157.1, 140.8, 138.0, 134.2(x2), 128.5(x2), 127.1, 126.8(x2), 125.2, 123.1, 110.6, 102.3, 62.5, 48.5, 44.8, 28.6, 25.9, 25.8(x3), 18.4(x2), -4.5, -4.6; HRMS (ESI) Calcd. for C₂₈H₃₄BrNNaO₂Si [M+Na]⁺: 546.1440 Found: 546.1428.

4.1.8 Enone (+)-5 from 23—To a solution of TBS enol ether **23** (22.2 mg, 42.3 μ mol) in THF (423 μ l) at 0 °C was added HF•pyridine (38.1 μ l, 423 μ mol). After stirring at 0 °C for 30 min, the reaction mixture brought to room temperature and stirred for 1 h before being

quenched with H₂O (1 ml). The aqueous layer was extracted with EtOAc and the combined organic layers were dried (MgSO₄), concentrated, and purified by flash chromatography (10% → 20% EtOAc/hexanes) to provide (+)-**5** as a white solid (12.5 mg, 72% yield). Chiral HPLC condition; CHIRAL PAK IA, Hexane: *i*PrOH=90:10, retention time 9.052, 9.783. 89% ee. $[\alpha]_D^{24} = +39.0$ (c 1.2, CHCl₃) m.p. 114–116 °C; IR (thin film): 2969, 1731, 1451, 1121, 735 cm⁻¹; ¹H NMR δ 7.42 (dd, *J* = 8.4, 0.8 Hz, 1H) 7.34–7.24 (complex m, 5H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.20 (s, 1H), 5.39 (q, *J* = 16.4 Hz, 2H), 5.29 (s, 1H), 2.81 (q, *J* = 18.0 Hz, 2H), 1.17 (d, *J* = 1.2 Hz, 6H); ¹³C NMR δ 202.7, 179.2, 152.6, 141.0, 137.5, 134.8, 132.3, 128.6(x2), 127.3, 126.8(x2), 123.8, 123.6, 116.9, 102.8, 54.8, 48.0, 44.9, 44.8, 26.4, 23.9; HRMS (ESI) Calcd. for C₂₂H₂₁BrNO₂ [M+H]⁺: 410.0755 Found: 410.0756.

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6. In previous studies we had determined that the efficiency of the intramolecular Heck reaction employing *o,o*-disubstituted anilines was greatly improved if the amide remained unprotected. Additionally, in our hands useful levels of stereochemical induction in asymmetric Heck reactions en route to 3,3-disubstituted oxindoles have been observed only when disubstituted amides are employed as substrates. Collectively, these observations led to our abandoning the catalytic asymmetric Heck approach.
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8. The stereochemical outcome of this reaction was assigned as illustrated based on the model developed by Corey. This assignment was supported by reduction of **19** employing the (R)-oxazaborolidine and comparison of the derived enantiomers via their corresponding Mosher Esters, see: Dale JA, Mosher HS. *J Am Chem Soc.* 1973; 95:512.
9. We speculate that epimerization occurs via the intermediacy of **i**; thus, maintaining the integrity of the enolether and/or protection of the oxindole nitrogen is required to preserve stereochemistry. Efforts to prevent racemization via N-protection of the amide prior to cyclization failed. Thus employing a robust silyl ether protecting group proved critical for a successful reaction.

Figure 1.
The Citrinadins: Reported Revised Structures

Scheme 1.
Key Cycloaddition en route to Citrinadin B.

Scheme 2.
Synthesis of Enone ($\pm$)-**8**

Scheme 3.
Retrosynthetic Analysis of (+)-**5**

Scheme 4.
Preparation of Hydroxy Heck Substrate **13**.

Scheme 5.
TBS Protection of Allyl Alcohol (-)-13

Scheme 6.
Completion of (+)-5.

Table 1

Initial Diastereoselective Heck Attempts.

Entry	Reagents	Solvent	Time	Yield
1	Pd(OAc) ₂ , PPh ₃ , Et ₃ N	toluene	12 h	trace
2	Pd(OAc) ₂ , PPh ₃ , Et ₃ N, H ₂ O	toluene	12 h	trace
3	Pd(OAc) ₂ , K ₂ CO ₃ , <i>n</i> -Bu ₄ NCl	DMF	24 h	--
4	PdCl ₂ (PPh ₃) ₂ , Et ₃ N	DMA	24 h	25%
5	PdCl ₂ (PPh ₃) ₂ , Et ₃ N	DMA	14 h	37%
6	Pd ₂ (dba) ₃ ·CHCl ₃ , Ag ₃ PO ₄ , Et ₃ N	DMA	24 h	--

Table 2

Heck Cyclization on Protected Substrate.

Entry	Concentration (M)	Time	Yield 21	Yield 22	Yield 20
1	0.01	12 h	13%	63%	5%
2	0.01	24 h	9%	67%	13%
3 ^a	0.01	12 h	18%	67%	0%
4	0.05	12.5 h	15%	52%	17%

^a 4 ÅMS added