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

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This manuscript is dedicated to Professor Sarah E. Reisman on the occasion of her receiving the Tetrahedron Young Investigator Award

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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.

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 2000s.[1] These compounds display modest potential as anticancer agents and were initially assigned the structures illustrated as **1** and **2** in Fig. 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 Fig. 1.[3,4]

Our previous synthesis of **3** employs racemic spirooxindole (±)-(**5**) in a [3+2] cylcoaddition with enantioenriched nitrone (−)-(**4**) wherein the latter essentially serves as a resolving agent in delivering enantioenriched cycloadduct (+)-**6** (Scheme 1). 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.

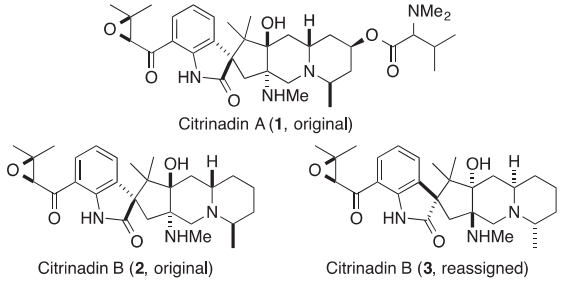

Fig. 1. The citrinadins: reported revised structures.

2. Results and discussion

In our completed synthesis of citrinadin B, we employed an intramolecular Heck reaction to convert amide **7** to oxindole **8**,

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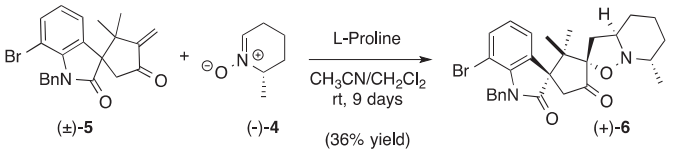
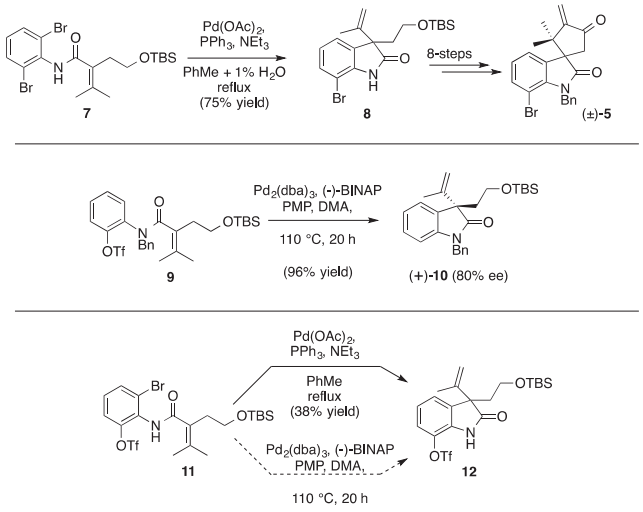


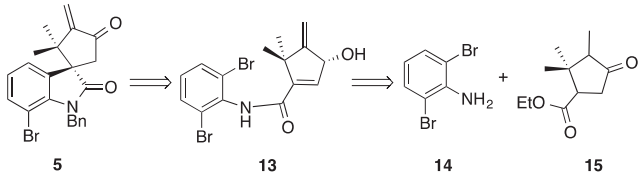
Scheme 1. Key cycloaddition en route to citrinadin B.

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]



Scheme 2. Synthesis of enone (±)-**8**.

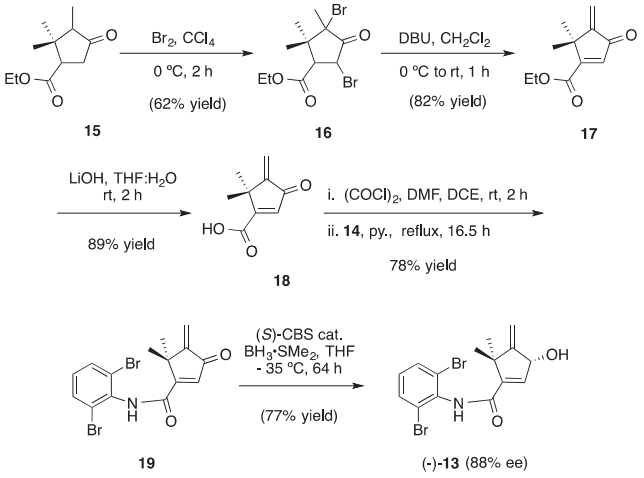
Given the failings of the asymmetric Heck route, we began developing an approach to **5** wherein assembly of the cyclopentane component would precede the intramolecular Heck reaction. As illustrated retrosynthetically in Scheme 3, this sequence employs a primary amide (**13**) as the substrate in a 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]



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

In the forward sense, exposure of known ketone **15** to Br_2 furnished dibromide (**16**), which, upon DBU promoted double elimination, delivered the corresponding diene (**17**) (Scheme 4).

Saponification of **17** to acid **18** set the stage for amide formation, which was accomplished upon exposure of an intermediate acid

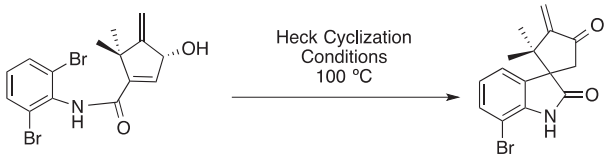


Scheme 4. Preparation of hydroxy heck substrate **13**.

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]

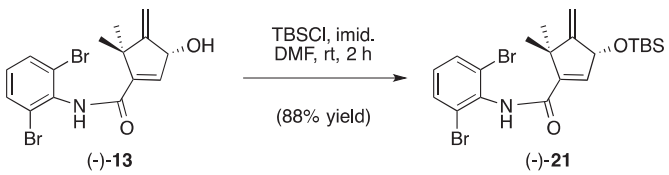
Initial attempts to advance (−)-**13** to the desired spirocyclic ketone **20**, without first protecting the secondary alcohol, met with limited success. As illustrated in Table 1, a number of standard conditions for the Heck cyclization were explored and found to deliver, at best, a 37% yield of the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

Table 1
Initial diastereoselective Heck attempts



Entry	Reagents	Solvent	Time (h)	Yield (%)
1	$Pd(OAc)_2$, PPh_3, Et_3N	Toluene	12	Trace
2	$Pd(OAc)_2$, PPh_3, Et_3N, H_2O	Toluene	12	Trace
3	$Pd(OAc)_2$, K_2CO_3, *n*-Bu_4NCl	DMF	24	—
4	$PdCl_2(PPh_3)_2$, Et_3N	DMA	24	25
5	$PdCl_2(PPh_3)_2$, Et_3N	DMA	14	37
6	$Pd_2(dba)_3 \cdot CHCl_3$, Ag_3PO_4, Et_3N	DMA	24	—

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).



Scheme 5. TBS protection of allyl alcohol (−)-**13**.

As illustrated in Table 2 (entry 3) this reaction performed best at higher dilution and in the presence of 4 Å molecular sieves (67% yield, 85% BORSM, 88% ee). Although a higher combined yield and potentially useful in situ enolether cleavage were observed in the

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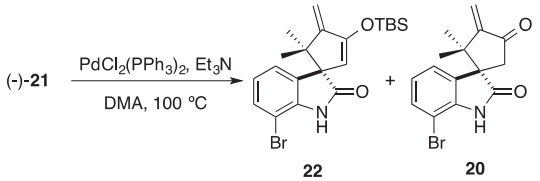
Table 2
Heck cyclization on protected substrate

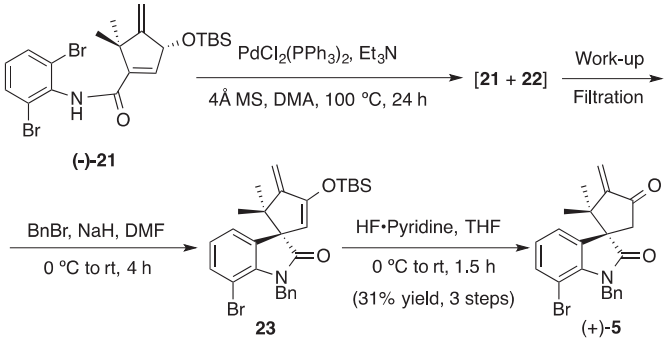


Entry	Concentration (M)	Time (h)	Yield **21** (%)	Yield **22** (%)	Yield **20** (%)
1	0.01	12	13	63	5
2	0.01	24	9	67	13
3[a]	0.01	12	18	67	0
4	0.05	12.5	15	52	17

[a] MS (4 Å) added.

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.



Scheme 6. Completion of (+)-**5**.

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. ^{1}H and ^{13}C 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 $CDCl_3$. 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.

4.2. Dibromide 16

To a solution of ester **15** (850.0 mg, 4.29 mmol) in CCl_4 (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). Mp 46–51 °C. IR (thin film): 2980, 1732, 1214 cm^{-1}; ^{1}H 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); ^{13}C 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 $C_{11}H_{20}Br_2NO_3$ [M+NH$_4$]$^+$: 371.9810. Found: 371.9801.

4.3. Ester 17

To a solution of dibromide **16** (940.2 mg, 2.64 mmol) in CH_2Cl_2 (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%→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}; ^{1}H 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 (×2), 14.2; HRMS (ESI) calcd for $C_{11}H_{15}O_3$ [M+H]$^+$: 195.1021. Found: 195.1004.

4.4. 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 1 M 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%→100% EtOAc/hexanes) to provide the carboxylic acid **18** as a pale yellow solid (8.3 g, 89% yield). Mp 135–137 °C. IR (thin film): 1684, 1178, 929, 802 cm^{-1}; ^{1}H 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 (×2); HRMS (ESI) calcd for $C_9H_9O_3$ [M−H]$^-$: 165.0552. Found: 165.0552.

4.5. Amide 19

To a solution of carboxylic acid **18** (7.0 g, 42.0 mmol) in 1,2-dichloroethane (420 ml) at 0 °C were added DMF (420 μl) and $(COCl)_2$ (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,

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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 mixture was cooled to room temperature and quenched with 1 M 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%→50% EtOAc/hexanes) to provide the anilide **19** as a white solid (13.1 g, 78% yield). Mp 167–169 °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 (×2), 130.2, 124.1 (×2), 116.7, 45.7, 26.4 (×2); HRMS (ESI) calcd for $C_{15}H_{14}Br_2NO_2$ $[M+H]^+$: 397.9391. Found: 397.9397.

4.6. Alcohol 13

To a solution of anilide **19** (1.0 g, 2.51 mmol) in THF (13 ml) at −35 °C were added (*S*)-Me-CBS catalyst (250.0 μl, 0.251 mmol, 1 M in THF) and $BH_3 \cdot SMe_2$ (1.2 ml, 12.5 mmol). The reaction temperature was maintained at −35 °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%→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 (min) 19.587, 23.228. $[\alpha]_D^{28}$ −29.1 (*c* 1.0, $CHCl_3$): 88% ee. Mp 61–63 °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 (×2), 129.9, 124.1 (×2), 108.4, 76.0, 48.6, 28.6, 27.7; HRMS (ESI) calcd for $C_{15}H_{14}Br_2NO_2$ $[M-H]^-$: 397.9391. Found: 397.9382.

4.7. Silyl ether 21

To a solution of alcohol **13** (10.4 g, 25.9 mmol) in DMF (130 ml) at room temperature were 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 (100 ml). The aqueous layer was extracted with the mixture of EtOAc/hexane=1:1 and the combined organic layers were washed with H_2O (80 ml×3), dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography (5%→20% EtOAc/hexanes) to provide **21** as a white solid (11.8 g, 88% yield). $[\alpha]_D^{28}$ −53.0 (*c* 1.0, $CHCl_3$). Mp 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); ^{13}C NMR δ 164.1, 161.2, 148.0, 134.9 (×2), 134.4, 132.4 (×2), 129.8, 124.1 (×2), 106.7, 76.3, 48.0, 28.8, 26.4, 26.1 (×3), 18.5, −4.26; HRMS (ESI) calcd for $C_{21}H_{29}Br_2NNaO_2Si$ $[M+Na]^+$: 536.0232. Found: 536.0226.

4.8. Enone (+)-5

To a solution of silyl ether **21** (21.2 mg, 41.1 μmol) in DMA (4.1 ml) in a Schlenk flask at room temperature were added $PdCl_2(PPh_3)_2$ (2.9 mg, 4.1 μmol), Et_3N (57.3 μl, 411 μmol), and activated molecular sieves 4 Å (5 pellets). The mixture was degassed using a freeze–pump–thaw cycle (×3) 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 (5 ml). The aqueous layer was extracted with a mixture of EtOAc/hexane=2:1 and the combined organic layers were washed with H_2O (1 ml×3), dried ($MgSO_4$), 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 μl) at 0 °C was added NaH (1.7 mg, 39.2 μmol). After being stirred at 0 °C for 15 min, the reaction mixture was treated with benzyl bromide (4.8 μl, 39.2 μmol) and allowed to warm to room temperature. After stirring for 4 h, the reaction was quenched with H_2O (1 ml). The aqueous layer was extracted with the mixture of EtOAc/hexane=1:1 and the combined organic layers were dried ($MgSO_4$), 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 two steps) and desired enone (+)-**5** (7.5 mg, 43% over two steps) as white solid and anilide **21** (1.0 mg, 5% over two steps). Compound **23**: $[\alpha]_D^{24}$ +82.0 (*c* 1.0, $CHCl_3$). 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); ^{13}C NMR δ 179.2, 157.5, 157.1, 140.8, 138.0, 134.2 (×2), 128.5 (×2), 127.1, 126.8 (×2), 125.2, 123.1, 110.6, 102.3, 62.5, 48.5, 44.8, 28.6, 25.9, 25.8 (×3), 18.4 (×2), −4.5, −4.6; HRMS (ESI) calcd for $C_{28}H_{34}BrNNaO_2Si$ $[M+Na]^+$: 546.1440. Found: 546.1428.

4.9. Enone (+)-5 from 23

To a solution of TBS enol ether **23** (22.2 mg, 42.3 μmol) in THF (423 μl) at 0 °C was added HF·pyridine (38.1 μl, 423 μmol). After stirring at 0 °C for 30 min, the reaction mixture brought to room temperature and stirred for 1 h before being quenched with H_2O (1 ml). The aqueous layer was extracted with EtOAc and the combined organic layers were dried ($MgSO_4$), 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 (min) 9.052, 9.783. $[\alpha]_D^{24}$ +39.0 (*c* 1.2, $CHCl_3$): 89% ee. Mp 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); ^{13}C NMR δ 202.7, 179.2, 152.6, 141.0, 137.5, 134.8, 132.3, 128.6 (×2), 127.3, 126.8 (×2), 123.8, 123.6, 116.9, 102.8, 54.8, 48.0, 44.9, 44.8, 26.4, 23.9; HRMS (ESI) calcd for $C_{22}H_{21}BrNO_2$ $[M+H]^+$: 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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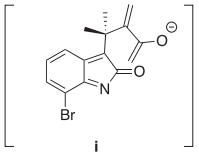
8. The stereochemical outcome of this reaction was assigned as illustrated based on the model developed by Corey. This assignment was supported by reduction of **19** employing the (*R*)-oxazaborolidine and comparison of the derived enantiomers via their corresponding Mosher esters, see: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
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.



i

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