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Synthesis of the Indolizino[7,6-*c*]quinoline Alkaloid Isaindigotidione

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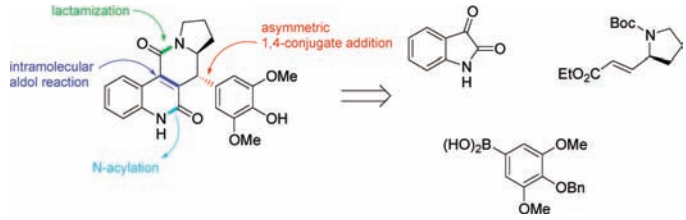
ABSTRACT



The first synthesis of isaindigotidione has been developed utilizing a reaction sequence including an asymmetric rhodium-catalyzed 1,4-conjugate addition, an intramolecular aldol reaction, and a lactamization.

Isaindigotidione (**1**) is a indolizino[7,6-*c*]quinoline alkaloid isolated from the roots of herbaceous *Isatis indigotica* indigenous to China's Changjiang river valley used in traditional Chinese medicine for treating a wide variety of ailments, including influenza and encephalitis. Furthermore, the ethanolic extracts of this plant, from which **1** was obtained, were found to exhibit effective antiendotoxin activity.[1]

Alkaloid **1** appears to be the first reported indolizino[7,6-*c*]quinoline found in nature.[2] A synthesis of the tetracyclic carboskeleton has recently been reported using a bis-cyclization strategy under basic conditions (NaOMe in MeOH).[3] However, the (*S*,*S*) diastereoisomer, which is found in the natural product, was only obtained as the minor isomer (<10%). The authors attributed this result to equilibration to the more thermodynamically stable (*S*,*R*) diastereoisomer in agreement with density functional theory calculations.

Herein we report the first synthesis of **1** along with several analogues. On the basis of the observations of Poon and Chiu,[3] a strategy was sought that would avoid strong basic conditions during the final stage of tetracyclic carboskeleton formation. The approach we employed utilizes an asymmetric rhodium-catalyzed 1,4-conjugate addition of arylboronic acids to construct a key chiral intermediate, an intramolecular aldol reaction to obtain the substituted quinolin-2(1*H*)-one, and a lactamization to generate the indolizino[7,6-*c*]quinoline (Scheme 1).

Rhodium-catalyzed 1,4-conjugate addition of organometallic reagents is a convenient means for the stereoselective construction of C−C bonds.[4] This methodology has been successfully applied to a variety of electron-deficient olefins, including α,β-unsaturated ketones,[5] esters,[6] and amides.[7] In particular, Frost and co-workers recently used this approach with pyrrolidine substrates for a stereoselective route to

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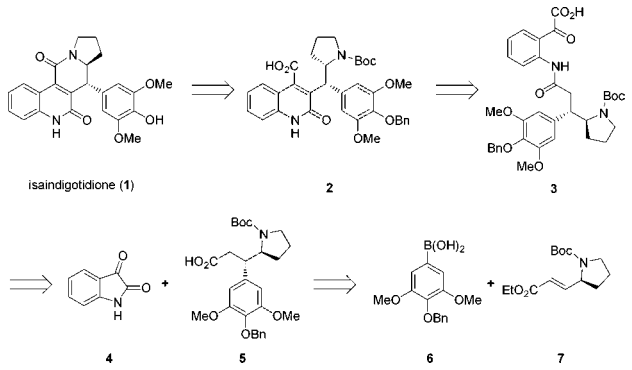
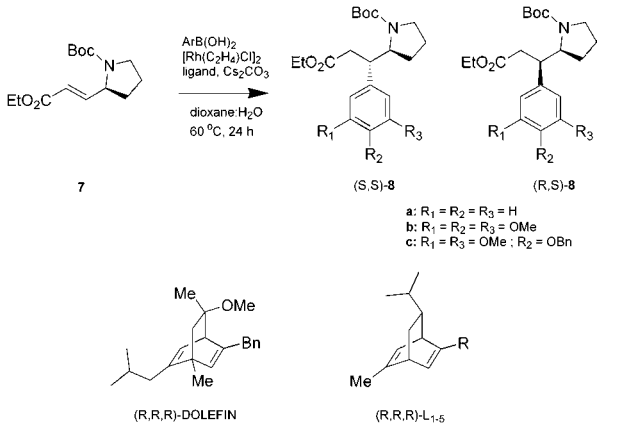
Scheme 1. Synthetic Strategy



functionalized pyrrolizidinones.[8] Our synthesis of **1** likewise takes advantages of the versatility of the rhodium-catalyzed 1,4-conjugate addition for the diastereoselective construction of diversely substituted indolizino[7,6-*c*]quinolines.

Initial efforts focused on synthesizing the chiral amino ester **8** (Table 1). The optimal reaction conditions, using

Table 1. Asymmetric 1,4-Conjugate Addition of Boronic Acids to Pyrrolidine **7**



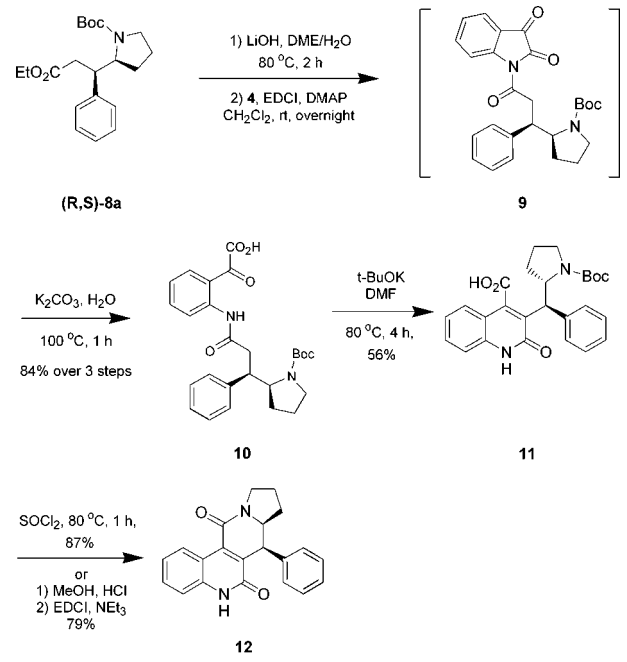
entry	ligand	yield (%)	dr (*S*,*S*):(*R*,*S*)	product
1	dppp	92	6:94	(*R*,*S*)-**8a**
2	(*S*)-BINAP	97	5:95	(*R*,*S*)-**8a**
3	(*R*)-BINAP	66	87:13	(*S*,*S*)-**8a**
4	(*R*,*R*,*R*)-DOLEFIN	90	90:10	(*S*,*S*)-**8a**
5	L_1, R = CO_2Me	51[b]	70:30	(*S*,*S*)-**8a**
6	L_2, R = CH_2OH	22[b]	55:45	(*S*,*S*)-**8a**
7	L_3, R = CH_2OMe	34[b]	63:37	(*S*,*S*)-**8a**
8	L_4, R= CMe_2OH	<10[b]	nd[c]	(*S*,*S*)-**8a**
9	L_5, R= CMe_2OMe	<10[b]	nd[c]	(*S*,*S*)-**8a**
10	(*R*)-BINAP	46	91:9	(*S*,*S*)-**8b**
11	(*R*,*R*,*R*)-DOLEFIN	71	92:8	(*S*,*S*)-**8b**
12	(*R*)-BINAP	39	90:10	(*S*,*S*)-**8c**
13	(*R*,*R*,*R*)-DOLEFIN	70	93:7	(*S*,*S*)-**8c**

[a] Reaction conditions: **7** (1.0 equiv), $ArB(OH)_2$ (4.0 equiv), $Rh(C_2H_4)_2Cl]_2$ (3 mol %), ligand (7 mol %), Cs_2CO_3 (1.0 equiv), 1,4-dioxane/H_2O (10:1), 60 °C, 24 h. [b] Conversion based on ^1H NMR of the crude product. [c] Not determined.

$[Rh(C_2H_4)_2Cl]_2$ as catalyst (3 mol %), a ligand (7 mol %), Cs_2CO_3 (1 equiv), and a phenylboronic acid (4 equiv) in a mixture of 1,4-dioxane:H_2O (10:1) at 60 °C for 24 h, were very similar to those previously reported.[8] The diastereoselectivity of the reaction was dependent on the chirality of the substrate and the ligand. For example, (*S*)-BINAP as well as dppp afforded the (*R*,*S*)-diastereoisomer in excellent yield and high diastereoselectivity (entries 1 and 2). However, (*R*)-BINAP gave (*S*,*S*)-**8a** (the required isomer for **1**) in both lower yield and diastereoselectivity (entry 3). Interestingly, chiral dienes have been reported to be superior to other types of chiral ligands, such as bisphosphines, in terms of both catalytic activity and enantioselectivity for rhodium-catalyzed asymmetric 1,4-conjugate additions.[9,10] (*R*,*R*,*R*)-DOLEFIN, a commercially available chiral diene developed by Carreira and co-workers, was found to improve both the yield of (*S*,*S*)-**8a** to 90% and the diastereoselectivity to 90:10 (entry 4).[11] This ligand proved superior in terms of conversion and selectivity compared to several other chiral diene ligands (entries 5−9).[10c] Next, this reaction was extended to phenylboronic acids containing electron-donating substituents. As expected, (*R*,*R*,*R*)-DOLEFIN was again more efficient than (*R*)-BINAP (entries 10−13). Importantly for the synthesis of **1**, the presence of the 4-benzyloxy did not adversely affect the yield or selectivity of the reaction. (*S*,*S*)-**8c** was obtained in 70% yield and 93:7 diastereoselectivity (entry 13).

Transformation of (*R*,*S*)-**8a** to indolizino[7,6-*c*]quinolines using methodology recently developed by our group was explored (Scheme 2).[12] After quantitative ester hydrolysis

Scheme 2

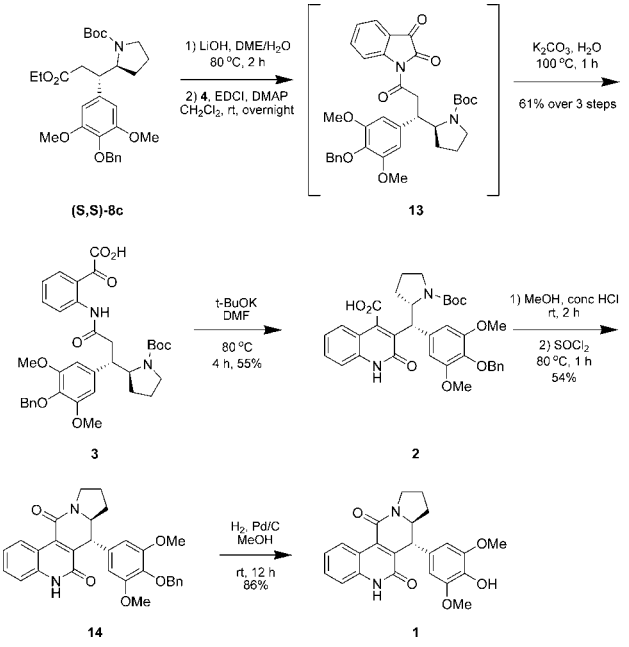


of (*R*,*S*)-**8a**, N-acylation of isatin was accomplished using EDCI. The N-acylated isatin **9**, which is unstable and used without purification, was hydrolyzed in alkaline conditions to give the α-oxoacetic acid **10** in 84% yield over three steps. This material was then subjected to an intramolecular aldol

reaction to give 2-quinolinone **11** in 56% yield. Either direct treatment of this material with $SOCl_2$ or a two-step process (Boc deprotection with HCl/MeOH followed by EDCI-mediated coupling) produced indolizino[7,6-*c*]quinoline **12** in good yields.

Attempts were then made to extend this strategy to the synthesis of **1** (Scheme 3). Ester hydrolysis of (*S*,*S*)-**8c**

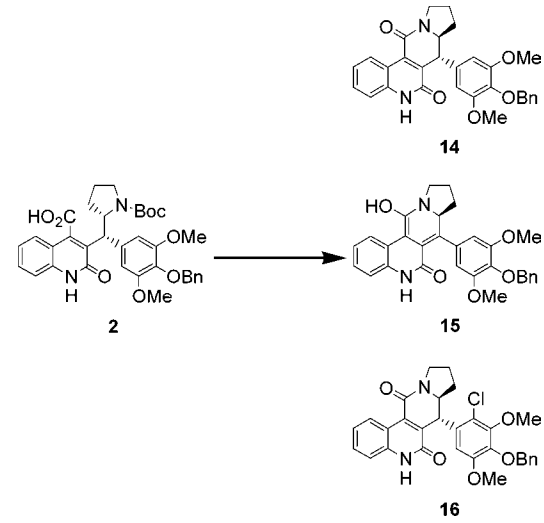
Scheme 3



followed by N-acylation of **4** and ring opening of N-acylated isatin **13** gave the expected product **3** in 61% yield over three steps. The intramolecular aldol reaction was performed in 55% yield generating **2**. However, deprotection and lactamization of **2** was problematic and required optimization.

Initial attempts to remove the Boc protecting group and to induce lactam formation with either EDCI or HBTU gave only minor amounts of the desired product **14** along with **15** as the major product (Table 2, entries 1 and 2). Surprisingly, tautomerization was not observed with the (*R*,*S*) diastereoisomer **11**. However, the same type of byproduct was observed when (*S*,*S*)-**11** was subjected to identical deprotection/coupling conditions. These observations suggest

Table 2. Optimization of the Lactamization



entry	conditions[a]	ratio **14/15/16**	yield (%)
1	A	39/61/0	83
2	B	12/88/0	90
3	C	35/0/65	80
4	D	-	0
5	E	100/0/0	21
6	F	100/0/0	54

[a] Reaction conditions. Condition A: (1) MeOH, HCl, rt, 2 h; (2) EDCI, NEt_3, DMF, rt, 24 h. Condition B: (1) MeOH, HCl, rt, 2 h; (2) HBTU, DIEA, DMF, rt, 24 h. Condition C: $SOCl_2$, 80 °C, 1 h. Condition D: $SOCl_2$ (1.1 equiv), toluene, 100 °C, 24 h. Condition E: $SOCl_2$ (2.2 equiv), toluene, 100 °C, 24 h. Condition F: (1) MeOH, HCl, rt, 2 h; (2) $SOCl_2$ (2.2 equiv), toluene, 80 °C, 2 h.

that the relative stereochemistry influences formation of the tautomeric product and not the presence of the electron-donating substituents in **2**. Parenthetically, it appears that the stereochemistry of the intermediate deprotected 2-quinolinone most likely is responsible for formation of the tautomeric product and not intermediacy of the indolizino[7,6-*c*]quinoline.[13]

Given the difficulties encountered with the initial deprotection/lactamization method, the direct conversion of **2** in the presence of neat $SOCl_2$ was investigated. The desired cyclization was observed, but concomitant chlorination of the electron-rich pendent aromatic ring also occurred leading to **16** as the major product (entry 3).[14] When the reaction was conducted with only 1.1 equiv of $SOCl_2$ in toluene, no

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(13) Indolizino[7,6-*c*]quinolines (*S*,*S*)- or (*R*,*S*)-**12** in DMF in the presence of NEt_3 (2 equiv) were stirred at room temperature for 24 h. No tautomeric product was observed.

cyclization was observed due to lack of Boc deprotection (entry 4). However, **14** was obtained in 21% yield with no detectable production of **16** when 2.2 equiv of $SOCl_2$ was used (entry 5). Encouraged by these results, a two-step sequence was explored. Deprotection of the Boc with HCl in MeOH followed by cyclization in the presence of $SOCl_2$ (2.2 equiv) produced indolizino[7,6-*c*]quinoline **14** in 54% yield over two steps with no observed formation of **15** or **16** (entry 6). Finally, removal of the benzyloxy protecting group from **14** using standard hydrogenation conditions furnished **1** in 86% yield. The ^{1}H and ^{13}C NMR spectral data and optical rotation for the synthetic material were in agreement with those previously reported for the isolated natural product.[1]

In summary, a synthesis of isaindigotidione (**1**) from the enantiopure pyrrolidine **7** using a concise route involving an asymmetric rhodium-catalyzed 1,4-conjugate addition of an arylboronic acid, an intramolecular aldol reaction, and lactamization has been achieved. In addition, this synthetic route provides diastereoselective access to indolizino[7,6-*c*]quinolines.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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