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A synthesis of the tetracyclic carboskeleton of isaindigotidione

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Abstract—An efficient synthesis of the unique indolizino[7,6-*c*]quinoline carboskeleton of isaindigotidione has been achieved. This strategy employed L-proline and isatin as the main building blocks in the construction of the framework. Four transformations occurred in a one-pot operation to furnish the tetracyclic nucleus.
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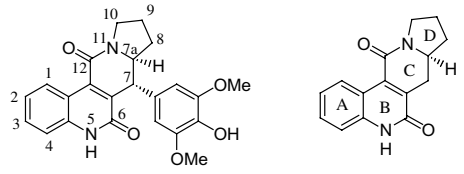
The root of *Isatis indigotica Fort.*, an herbaceous biennial plant found in the Changjiang river valley, is a traditional Chinese medicinal herbal drug named *banlangen*, commonly used to treat ailments such as influenza,[1] and even prescribed recently in Hong Kong for bolstering immunity against the SARS virus. Indirubin, one of the compounds extracted from this root, has proven to be an anticancer agent, which has been used in the clinic for chronic granulocytic leukemia.[2]

Isolated along with indirubin is another interesting alkaloid, isaindigotidione **1**, a novel derivative of indolizino[7,6-*c*]quinoline **2**, which has been found in natural products for the first time (Fig. 1).[1] The biological effects of isaindigotidione **1** have not been ascertained, but the butanol fractions of the root ethanolic extracts, from which isaindigotidione was obtained, were found to be effective in anti-endotoxic tests.[1] To our knowledge, no synthetic studies of this compound or its derivatives have yet been reported. Thus, we have undertaken a synthetic study of isaindigotidione and its analogues. Herein, we report an efficient approach toward the novel tetracyclic skeleton of isaindigotidione **2**, which may be amenable for generating analogues with variation at C7.

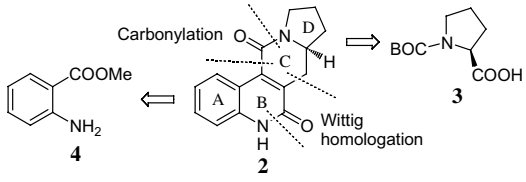


1 2

Figure 1. Isaindigotidione **1** and indolizino[7,6-*c*]quinoline **2**.

Our initial retrosynthesis is shown in Scheme 1. In this route toward the tetracyclic framework of isaindigotidione, ring D would originate from L-proline derivative **3**, and ring A would be provided by methyl anthranilate **4**. The intervening ring B was envisioned to arise from a Dieckmann type cyclization and ring C was to be constructed by the carbonylation of an enol triflate intermediate, followed by intramolecular amide formation.

The synthetic approach as outlined in Scheme 1 was successful up to a point. Boc-L-proline **3** was converted to Boc-L-prolinal by borane reduction and PDC oxidation (Scheme 2).[3] Homologation using the stabilized Wittig reagent carbomethoxymethylenetriphenylphosphorane gave enoate **5** in good yield. Catalytic hydrogenation produced saturated ester **6**.[4] Hydrolysis afforded acid **7**, which was condensed with methyl anthranilate **4**. Acylations of aryl amines are known to be rather sluggish,[5] and our attempts to optimize the



4 2 3

Scheme 1. Initial retrosynthesis of indolizino[7,6-*c*]quinoline **2**.

Keywords: Alkaloid; Indolizine; Quinoline.
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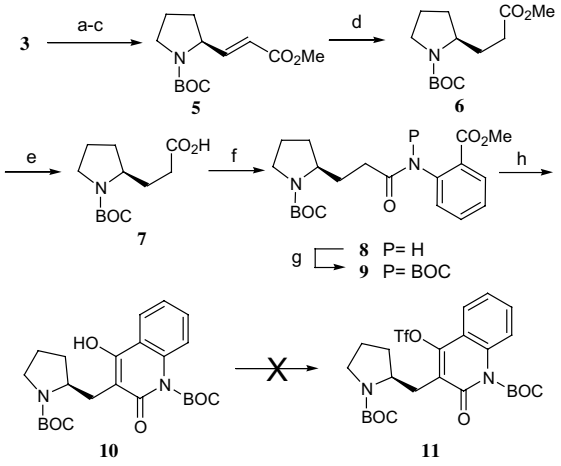
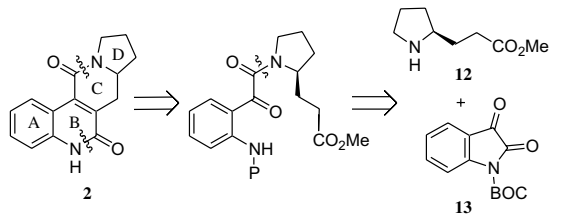


Scheme 2. Reagents and conditions: (a) BH_3–THF, (b) PDC 92% over two steps, (c) $MeO_2CCH{=}PPh_3$, CH_2Cl_2, 96%, (d) H_2, Pd–C, 100%, (e) NaOH, MeOH, 90%, (f) BOP, Et_3N, CH_2Cl_2, **4**, 67%, (g) $(Boc)_2O$, 95%, (h) LDA, THF, 68%.

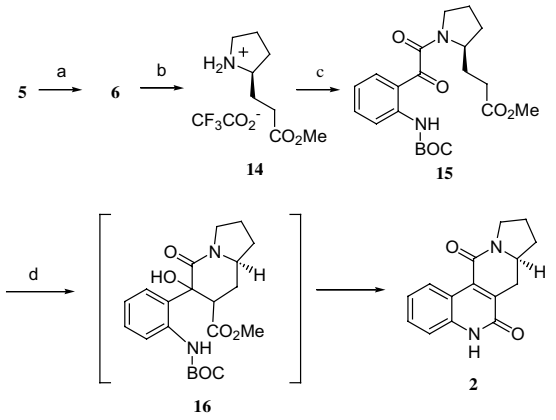
conditions of this coupling did not result in significant improvements in the yield. The use of either BOP or DCC to promote amide formation with methyl anthranilate **4** generated aryl amide **8** in moderate yields. Protection of the amide by $(Boc)_2O$ afforded substrate **9** for the construction of ring B. The Dieckmann-type condensation between the enolate of the amide and the aryl ester proceeded to give β-ketoamide **10**, which existed predominantly in its enol form.

Compound **10** was to be carbonylated via its enol triflate **11**. Triflation using conventional reagents such as Tf_2O/Et_3N,[6] Ph_2NTf/Et_3N,[7] and Comins' reagent[8] were tried, but none of these conditions were successful, in most cases returning only starting material after reaction. It may be that substrate **10** is too sterically congested for triflation to proceed efficiently.

Since the carbonylation step proved problematic, we considered another synthetic strategy, which would avoid the need for carbonylation at this critical stage. We identified isatin as a carbonylated analogue of anthranilate **4**. The retroanalysis toward the tetracyclic skeleton of **2** was redesigned as shown in Scheme 3. Ring C could be furnished by the ring opening reaction of isatin with proline derivative **12**,[9] followed by intramolecular aldol cyclization. Ring B could be formed via a more facile intramolecular version of the previous lactamization. This approach hinged on the effective coupling between proline ester **12** and a protected isatin derivative **13**.



Scheme 3. Second retrosynthetic plan toward quinolone **2**.



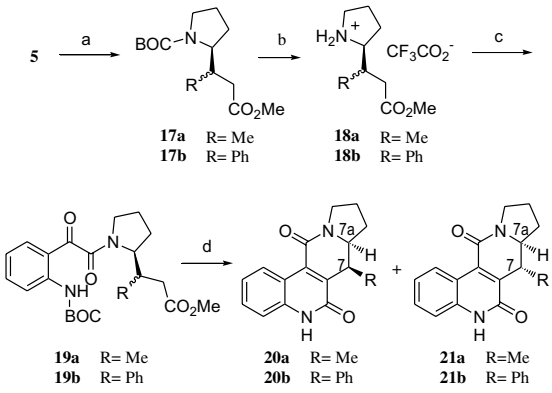
Scheme 4. Reagents and conditions: (a) H_2, Pd–C, MeOH, (b) TFA, CH_2Cl_2, 96% over two steps, (c) **13**, *i*-Pr_2NEt, THF, 90%, (d) NaOMe, MeOH, 96%.

Thus ester **5** was reduced to **6** and deprotected to give proline derivative **12** as its trifluoroacetate salt **14** (Scheme 4). The crude salt was treated with Boc-protected isatin **13**[10] in the presence of excess Hünig's base to give compound **15** in excellent yield. The coupling occurred at room temperature and was surprisingly facile compared to previous acylations of isatin, which required refluxing conditions.[9]

The intramolecular aldol of substrate **15** was only marginally successful upon treatment with excess LDA. The condensation product was formed as a mixture of diastereomeric aldols **16** with large amounts of recovered **15**. Treatment with sodium methoxide in methanol at room temperature generated aldol and dehydrated aldol products, along with tetracyclic compounds in which the final ring closure had also occurred spontaneously. Finally, under refluxing conditions, quinolone **2** was isolated in 96% yield after 5 h.[11] Notably, a total of four transformations, that is, aldol cyclization, dehydration, acylation, and Boc-deprotection occurred in a one-pot operation with great efficiency.

The structure of tetracyclic quinolone **2** was confirmed by standard analytical methods including ^1H, ^{13}C 1-D, and 2-D NMR, IR, and HRMS.[12]

Derivatives of **2**, including isaindigotidione **1**, having the skeletal framework of **2** and bearing substituents at C7, should be accessible through substituted analogues of **6**. Thus a methylated analogue was synthesized in a similar manner based on the strategy for the assembly of **2** (Scheme 5). Methylation via the addition of the Gilman reagent afforded **17a** in excellent yield, as a 2:1 mixture of diastereomers.[13] The mixture of **17a** was deprotected to give **18a**, and treated with isatin **13** as done previously to afford intermediate **19a**. Bis-cyclization using base afforded the methylated derivatives **20a** and **21a** as a 3:1 mixture of diastereomers under more vigorous conditions (8 h).



Scheme 5. Reagents and conditions: (a) Me_2CuLi, 96% for **17a**; PhBr, cat. $Pd(PPh_3)_4$, then H_2/Pd/C, 57% over two steps for **17b**, (b) TFA, quantitative for **18a** and **18b**, (c) **13**, *i*-Pr_2NEt, 86% for **19a**, 85% for **19b**, (d) NaOMe, MeOH reflux, 92% for **20a/21a**, 90% for **20b/21b**.

The structures of the major and minor tetracyclic isomers were deduced as follows. Comparing the coupling constants of the protons at C7 for both diastereomeric products, J_{H7-H7a} in the minor isomer was 12.0 Hz, while that in the major isomer was smaller, with a value of 4.2 Hz. Structures **20a** and **21a** were both optimized computationally by DFT calculations using the B3LYP/6-31G(d) model. In the minimum energy conformation of **21a**, the dihedral angle defined by H7a–C7a–C7–H7 was found to be 167°, that is, nearly *anti*, while that in the major isomer **20a** was 45°. Thus a larger value for J_{H7-H7a} was expected for the isomer with structure **21a**. This stereochemical assignment was further confirmed by J_{H7-H7a} in the natural product **1**, which also has a value of 12.0 Hz.[1] Therefore the minor isomer **21a** possessed the same relative stereochemistry as isaindigotidione **1**.

Since the ratio of diastereomers changed from 2:1 in **17a**, to 3:1 in **20a/21a**, the bis-cyclization reaction conditions were obviously equilibrating. This was also confirmed by the DFT calculations, which showed that the minimized structure of **20a** to be 5.8 kcal/mol more stable than isomer **21a**. Thus **20a** predominated under these reaction conditions because it is the thermodynamically more stable epimer.

The synthesis of the phenylated analogue of **2**, which possesses the full pentacyclic framework of **1**, was also synthesized in a similar manner. Although the addition of methyl cuprate to proline ester derivative **5** was facile, addition of Ph_2CuLi, $Ph_2CuCNLi_2$, PhMgBr, and PhMgBr/CuI gave only 10–20% yield of **17b**.[14] Thus the phenyl group was appended by an alternative two-step strategy. A palladium-catalyzed Heck arylation of ester **5** generated the phenylated alkenoate, which was then reduced by catalytic hydrogenation. The reduction was nonselective and a 1:1 ratio of diastereomers of **17b** was obtained. The mixture of the diastereomers of **17b** was carried forward using the same strategy of deprotection to give **18b**, and acylation to afford **19b** without incident. Base-induced cyclization required over 12 h for complete reaction, and afforded pentacyclic products **20b/21b** in 11:1 ratio in 90% overall yield. The structures of the diastereomeric products were determined again by the value of the coupling constant J_{H7-H7a}, being 4.0 Hz for **20b**, and 12.3 Hz for **21b**. The DFT calculations of diastereomers **20b** and **21b** also showed that the thermo- dynamically more stable isomer was **20b** by about 3.3 kcal/mol. Attempts to invert the stereochemistry of isomer **20b** at C7 by a low-temperature, kinetic protonation were as yet unsuccessful.

We herein disclose an efficient strategy toward the synthesis of the unique tetracyclic and pentacyclic framework of isaindigotidione **1**. We are continuing our investigations to append the final ring to compound **2**, as well as other strategies, to complete the total synthesis of **1**.

Acknowledgements

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References and notes

1. Wu, X.; Qin, G.; Cheung, K. K.; Cheng, K. F. *Tetrahedron* **1997**, *53*, 13323–13328.
2. Hoessel, R.; Leclerc, S.; Endicott, J. A.; Nobel, M. E. M.; Lawire, A.; Tunnah, P.; Leost, M.; Damiens, E.; Marie, D.; Marko, D.; Niederberger, E.; Tang, W.; Eisenbrand, G.; Meijer, L. *Nat. Cell Biol.* **1999**, *1*, 60–67.
3. Trybulski, E. J.; Kramass, R. H. M.; Rusinko, A. *J. Med. Chem.* **1990**, *33*, 3190–3198.
4. Priepke, H.; Brueckner, R.; Harms, K. *Chem. Ber.* **1990**, *123*, 555–563.
5. Miyazawa, T.; Otomatsu, T.; Yamada, T.; Kuwata, S. *Tetrahedron Lett.* **1984**, *25*, 771–772.
6. Bennasar, M. L.; Jiménez, J. M.; Vidal, B.; Sufi, B. A.; Bosch, J. *J. Org. Chem.* **1999**, *64*, 9605–9612.
7. Tilley, J. W.; Sarabu, R.; Wagner, R.; Mulkerins, K. *J. Org. Chem.* **1990**, *55*, 906–910.
8. Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302.
9. Albrecht, F. *Liebigs Ann. Chem.* **1982**, 794–807.
10. Wille, G.; Steglich, W. *Synthesis* **2001**, 759–762.
11. *Preparation of* **2**. To a solution of **15** (44.5 mg, 0.11 mmol) in MeOH (2 mL) was added NaOMe (35.6 mg, 0.66 mmol). The mixture was heated to a gentle reflux for 5 h under Ar until the reaction was deemed complete by TLC. After removal of volatiles, the residue was suspended in water, and extracted with EtOAc. The organics were separated, dried (anhydrous Na_2SO_4), and

concentrated in vacuo. The crude material was purified by flash chromatography (35% EtOAc/hexane) to afford **2** (26.8 mg, 96%) as a milky white solid.

12. *Characterization of* **2**. Mp 231 °C; $[\alpha]_{20}^{D} + 53.6$ (*c* 0.43, $CHCl_3$); IR ($CHCl_3$): 3023, 3017, 2888, 2350, 1645, 1448, 789, 760, 733, 728 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.78–1.85 (m, 1H), 1.88–1.96 (m, 1H), 2.13–2.17 (m, 1H), 2.38 (m, 1H), 2.45 (dd, $J = 16.8$, 13.8 Hz, 1H), 3.52 (dd, $J = 16.80$, 4.2 Hz, 1H), 3.69–3.75 (m, 1H), 3.77–3.86 (m, 2H), 7.29 (t, $J = 7.7$ Hz, 1H), 7.35 (d, $J = 8.1$ Hz, 1H), 7.51 (t, $J = 7.6$ Hz, 1H), 9.02 (d, $J = 8.3$ Hz, 1H), 11.49 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.4, 28.8, 33.7, 45.4, 55.9, 115.7, 117.7, 123.4, 127.8, 130.2, 131.6, 136.3, 137.4, 161.8, 162.2; HRMS-EI (*m*/*z*): M^+ calcd for $C_{15}H_{14}N_2O_2$, 254.1055; found, 254.1053.
13. Le Coz, S.; Mann, A.; Thareau, F.; Taddei, M. *Heterocycles* **1993**, *36*, 2073–2080.
14. Most alkylations of proline derivatives at this site were intramolecular, see: (a) Moriwake, T.; Hamano, S.; Saito, S. *Heterocycles* **1988**, *27*, 1135–1139; (b) Exceptions: Ref. 13, also: Hanessian, S.; Buckle, R.; Bayrakdarian, M. *J. Org. Chem.* **2002**, *67*, 3387–3397; (c) However, Ph_2CuLi added to the closely related ester derived from Garner aldehyde with good diastereoselectivity but diminished yield: Jako, I.; Uiber, P.; Mann, A.; Taddei, M.; Wermuth, C. G. *Tetrahedron Lett.* **1990**, *31*, 1011–1014.