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Total Synthesis of a Pyrroloindoloquinazoline Alkaloid

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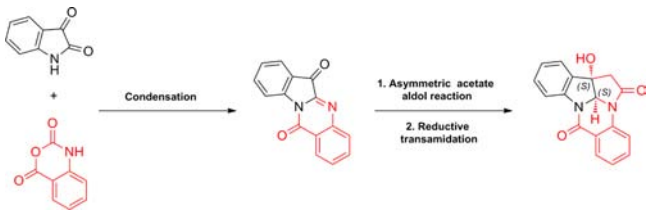
ABSTRACT



A highly concise stereoselective synthesis of a newly identified alkaloid with a pyrroloindoloquinazoline skeleton has been achieved. To this end, a chiral auxiliary mediated asymmetric acetate aldol reaction on tryptanthrin was explored and the resulting adduct was converted to the product by a novel one-pot reductive cyclization/transamidation using $NiCl_2 \cdot 6H_2O/NaBH_4$ in methanol.

Nature is replete with plants and fungi containing indole alkaloids, one of the largest classes of alkaloids encompassing over thousands of compounds.[1] Many of these compounds possess significant physiological activity, and some of them are used in medicine. Among the various plant sources, *Isatis indigotica* (Cruciferae family), a biennial herbaceous plant widely distributed in China, has been extensively focused upon lately due to the diverse structures of chemical constituents isolated and their significant biological profiles.[2] Phytochemical studies of this plant resulted in the isolation of indigotin, indirubin, epigotrin, 2-hydroxy-3-butenyl thiocyanate, 3-(2′-hydroxyphenyl)-4(3*H*)-quinazolinone, purin, isaindigotidione, isatisine, organic acids, and many amino acids.[3−7] Shi et al. has recently reported the isolation of 17 new alkaloids and 14 known analogues from the aqueous extract of the roots of *Isatis indigotica*.[8] Some of these compounds have shown promising antiviral activity against influenza virus A/Hanfang/359/95(H3N2) and an inhibitory effect over Coxsackie virus B3 replication. One among the newly identified natural products was a racemic mixture of alkaloid **4** with a pyrrolo[2,3-*b*]indolo[5,5a,6-*b*,*a*]quinazoline skeleton (Figure 1). This structure represents a fusion between the widely distributed hexahydropyrroloindole (HPI) alkaloids and the relatively scarce indoloquinazoline alkaloids. Both these scaffolds have been independently known to possess a wide array of biological properties.[9] On similar lines, the pyrroloindoloquinazoline skeleton is also expected to show interesting biological properties. Isolation of more natural products containing such an intriguing skeleton is anticipated in the near future and hence arises the need to develop a highly efficient strategy for its stereoselective synthesis.

A decade prior to the isolation of this compound from *Isatis indigotica*, Bremner et al. had observed the formation of pyrroloindoloquinazoline skeleton, while investigating the photoinduced cyclization of *N*-(2-(1-indolylmethyl)-phenyl)chloroacetamide to yield indole fused medium sized heterocyclic scaffolds.[10] However this strategy

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(6) Shi, X.; Ni, Y.; Liu, Y. H. *Chin. Hosp. Pharm. J.* **2006**, *26*, 1397.
(7) Wu, X. Y.; Qin, G. W. *Tetrahedron* **1997**, *53*, 13323.
(8) (a) Chen, M.; Gan, L.; Lin, S.; Wang, X.; Li, L.; Li, Y.; Zhu, C.; Wang, Y.; Jiang, B.; Jiang, J.; Yang, Y.; Shi, J. *J. Nat. Prod.* **2012**, *75*, 1167. (b) Optical rotation of (+)-**4**: natural compound $[\alpha]^{20}_D$ +194.2 (*c* 0.2, MeOH); synthetic compound $[\alpha]^{20}_D$ +192.1 (*c* 0.2, MeOH).
(9) (a) Sanchis, P. R.; Savina, S. A.; Albericio, F.; Alvarez, M. *Chem.—Eur. J.* **2011**, *17*, 1388. (b) Shoji, N.; Umeyama, A.; Saito, N.; Arihara, S. *J. Nat. Prod.* **1989**, *52*, 1160.
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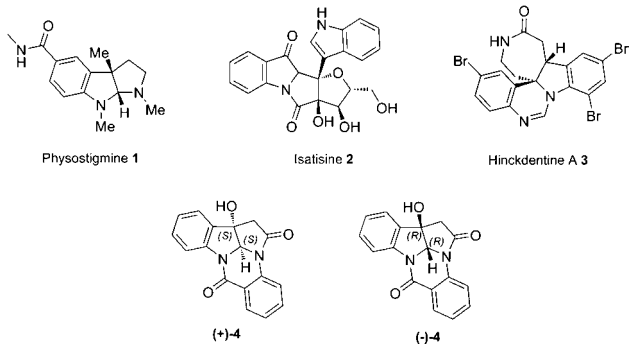
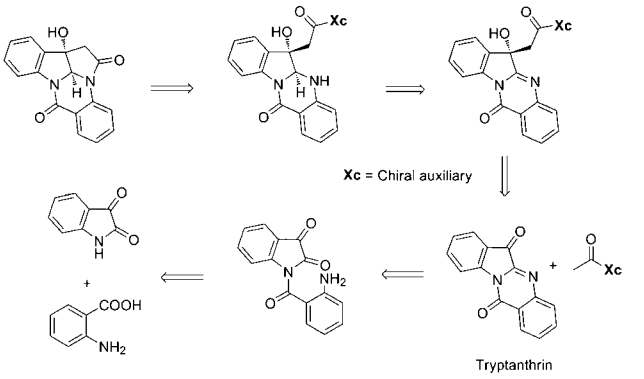


Figure 1. A few natural products with indole fused heterocyclic ring skeleton.

afforded low yields, no stereoselectivity, and other fused heterocycles in significant amounts, and to date no other reports are available. Based on our interests in the asymmetric synthesis[11] of β-hydroxy carbonyl functionality containing natural products, we found compound (+)-**4**, (2a*S*,2a^1*S*)-2a-hydroxy-2,2a-dihydro-1*H*-6b,11b-diazabenzo[*b*]cyclopenta[*lm*]fluorene-1,7-(2a^1*H*)-dione, as a suitable target to further explore our current research on chiral auxiliary mediated aldol reactions.[12] Our efforts resulted in a highly concise stereoselective synthesis of this molecule. This method encompasses a chiral auxiliary mediated diastereoselective acetate aldol reaction on tryptanthrin, followed by a novel one-pot reductive cyclization procedure using the $NiCl_2 \cdot 6H_2O/NaBH_4$ system in methanol which proceeds through a transamidation mechanism. The retrosynthetic analysis of compound (+)-**4** is illustrated in Scheme 1. Taking further strides from the asymmetric acetate aldol reactions of the imidazolidin-2-one chiral auxiliary that we had recently reported,[11b,12a] the reaction on tryptanthrin was conceptualized to suit our design. We envisioned that a dicarbonyl compound or its synthetic equivalent could serve as a suitable starting material to generate the first asymmetric center by an aldol reaction. The aldol substrate could be further modified by functional group transformations and then cyclized to yield the desired product.

Synthesis of (+)-**4** was achieved using two overlapping yet distinct strategies as illustrated in Scheme 2. Tryptanthrin **7** was synthesized by reacting commercially available isatoic anhydride **6** and isatin **5** in the presence of triethylamine.[13] Though several methods are available

Scheme 1. Retrosynthetic Strategy for Pyrroloindoloquinazoline



for the synthesis of tryptanthrin, this procedure was chosen on the basis of operational simplicity, environmental implications, and easily available starting materials, while the other methods employed corrosive reagents such as thionyl chloride or phosphorus oxychloride.[14] The key step in our synthesis is an aldol reaction between tryptanthrin and the acetylated auxiliary, *N*-acetyl-(*S*)-4-isopropyl-1-[(*R*)-1-phenylethyl]imidazolidin-2-one **8**. The distinct advantage of high selectivity in acetate aldol reactions with no endocyclic cleavage made this auxiliary a preferred option. The lithium enolate of **8** was generated using LiHMDS in anhydrous THF at −78 °C and subsequently reacted with tryptanthrin to obtain the aldol adduct **9**. A highly appreciable *syn* acetate aldol selectivity of 98:2 was observed as ascertained from the ^{1}H NMR spectra of the crude product. The stereoselectivity witnessed can be explained on the basis of transition state models depicted in Scheme 3. The front side of the lithium enolate E-1 is shielded by the bulky isopropyl group of the auxiliary which disfavors the approach of the electrophile. In contrast, the rear side is less hindered and hence more accessible. Tryptanthrin has a highly planar geometry owing to the sp^2 imine linkage between the rings B and C. As a virtue of this planar geometry, the electrophile can adopt two spatial arrangements as depicted by the transition states TS-A and TS-B. In both transition states, lithium coordinates with the oxygen atom of the electrophilic carbonyl group. In TS-A, due to the close proximity of the phenyl group of the auxiliary to the rings C and D of the electrophile, the transition state is sterically hindered and this disfavors the formation of the aldol with the (*R*) configuration. In TS-B, lesser crowding between the A ring and the phenyl group minimizes repulsions favoring the formation of the aldol with the (*S*) configuration.

The cyclization of **9** to the desired final product (+)-**4** was achieved by two different methods. Reduction of the imine **9** using $NaBH_4$ in acetic acid afforded **10** stereoselectively. The chemoselective reduction of the imine bond in tryptanthrin using this reagent had been reported.[15]

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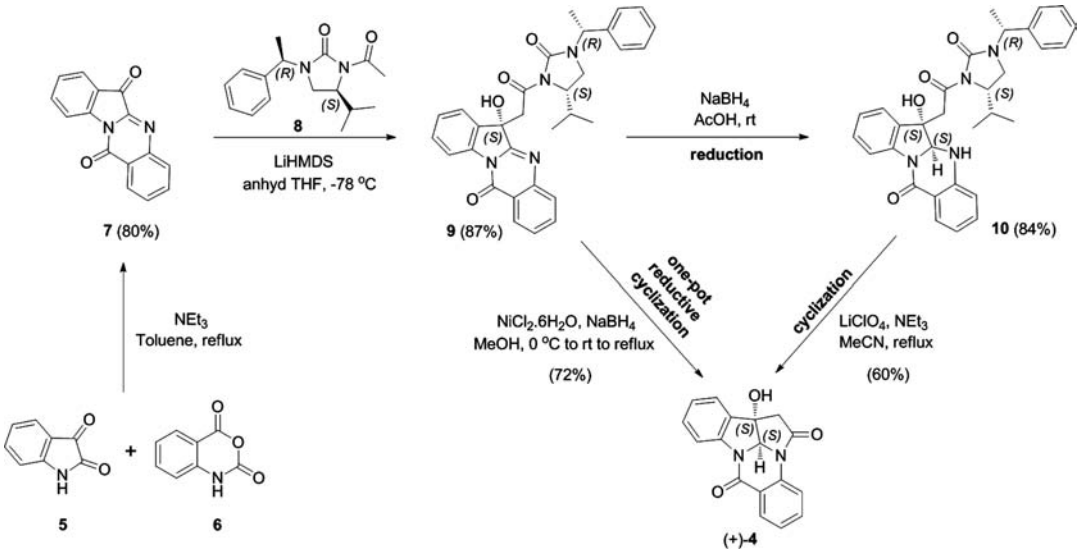
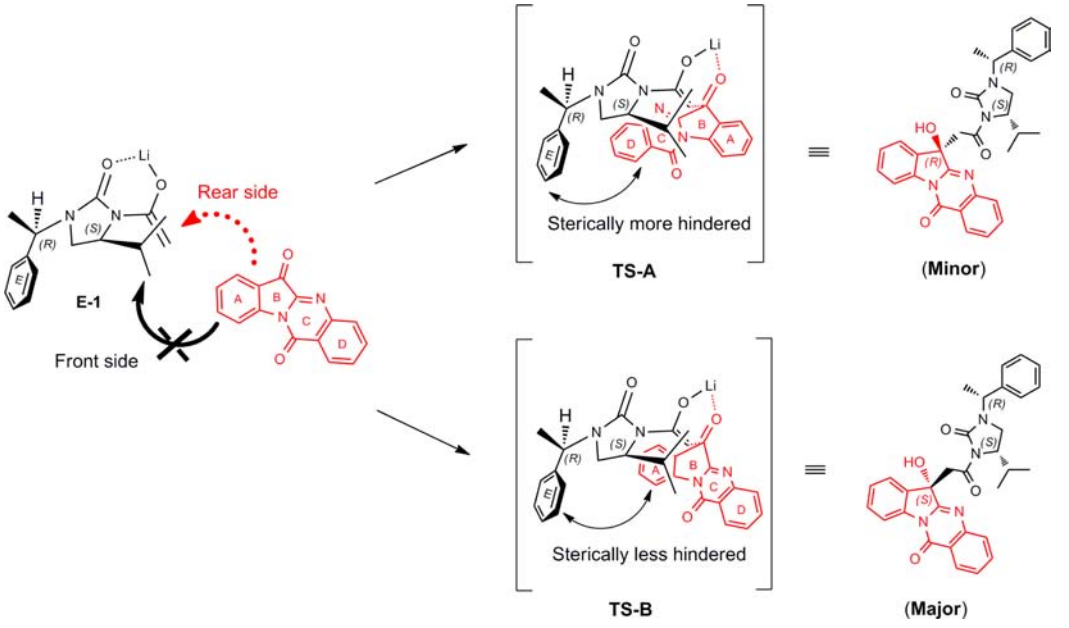
Scheme 2. Synthesis of a Pyrrolo[2,3-*b*]indolo[5,5a,6-*b*,*a*]quinazoline



Scheme 3. Plausible Mechanism for Stereoselectivity in Acetate Aldol Reaction on Tryptanthrin



It was then cyclized by an electrophilic activation mechanism[16] using lithium perchlorate and triethylamine in acetonitrile to obtain the target molecule. However, in order to further simplify the process and improve the yield we envisaged a different approach. Using a combination of $NiCl_2 \cdot 6H_2O/NaBH_4$ in methanol provided a novel one-pot alternative to the reduction and subsequent cyclization of the aldol intermediate. Although this catalytic system is known for effecting the reduction of imines and isoxazolines,[17] there are no reports available on the reductive transamidation of imines. Quite interestingly, following the stereoselective reduction, the transition metal also promoted the cyclization/transamidation in a one-pot process. Noteworthy is the fact that reductive cyclization took place stereoselectively in the substrate controlled asymmetric induction.

A plausible mechanism for the reductive cyclization is demonstrated in Scheme 4. It is expected that nickel forms

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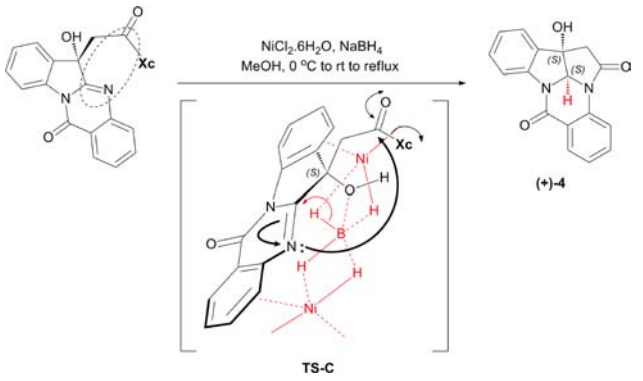
Scheme 4. Plausible Mechanism for Reductive Cyclization



a chelate complex[18] with the π-electron cloud of the aromatic ring which suitably stacks the nickel−borohydride complex below the plane of the ring. This facilitates the interaction between the hydroxyl oxygen and the oxophilic boron, and consequently a hydride transfer occurs from the nickel−boron complex to the electrophilic imine carbon in a stereoselective fashion. Generation of the nitrogen nucleophile, stabilized by the Lewis acidic boron, results in the attack at the carbonyl carbon and a solvent assisted auxiliary cleavage in a single step. The polar protic medium stabilizes the partial charges of the transition state, favoring the forward reaction kinetics. The spectral data of the final compound (+)-**4** were found to be in good agreement with those of the natural product.[8a] The absolute configuration was confirmed by comparing the optical rotation data with the reported values.[8b] A similar procedure using the *N*-acetyl-(*R*)-4-isopropyl-1-[(*S*)-1-phenylethyl]imidazolidin-2-one auxiliary for aldol reaction with tryptanthrin can be adopted for the synthesis of (−)-**4**.

In conclusion, the total synthesis of a recently isolated pyrrolo[2,3-*b*]indolo[5,5a,6-*b*,*a*]quinazoline alkaloid was successfully achieved. The highly concise synthetic strategy involves (i) a chiral auxiliary mediated asymmetric acetate aldol reaction on tryptanthrin and (ii) a reductive cyclization/transamidation using $NiCl_2 \cdot 6H_2O/NaBH_4$ in methanol. We anticipate that the present work opens the door to the systematic synthesis of pyrroloindoloquinazoline alkaloids in an efficient manner.

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Supporting Information Available. Experimental procedures, ^{1}H NMR, ^{13}C NMR, and HRMS (ESI) data of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.