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Total Synthesis of Isatindigotindoline C

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Abstract

Total synthesis of isatindigotindoline C, a 3,3'-spiropyrrolidine oxindole alkaloid, is achieved in two steps using an *exo*-selective decarboxylative [3+2]-dipolar cycloaddition as the key step. The synthesis verifies the originally assigned relative *anti*-stereochemistry for the *bis*-oxindole core of isatindigotindoline C.

Introduction

Isatindigotindolines are a structurally unique family of 3,3'-spiropyrrolidine oxindole alkaloids isolated by Huang and Song *et. al.* in 2018 from the leaves of *Isatis indigotica* plant used in traditional and folk medicine in Asia.[1] The isatindigotindolines caught our attention as potential synthesis targets due to our continued interest in the synthesis of bioactive nitrogenous compounds.[2] During the isolation studies, several isatindigotindolines were shown to inhibit β-amyloid aggregation.[1] Alongside with their potential use in biology, the isatindigotindoline alkaloids are the first examples of secondary metabolites with a 3,3'-spiropyrrolidine oxindole core (Figure 1B), this is a sharp contrast to the abundance of alkaloids with the isomeric 2,3'-spiropyrrolidine oxindole structure (Figure 1A). In addition, the isatindigotindolines constitute a rare example of an entire alkaloid family occurring naturally as racemates.[3]

The structurally most complex member of this alkaloid family, (±)-isatindigotindoline C (**1**), has a *bis*-oxindole core. The relative stereochemistry of the *bis*-oxindole core proved non-trivial to assign during the original isolation and structure determination studies of **1**. Correlating experimental ^{13}C shifts with computed values gave very similar regressions for both *anti* and *syn* bisoxindole diastereomers of **1** (R^2 = 0.9989 vs. R^2 = 0.9984 respectively). The NMR shift correlations, in combination with comparisons to calculated ECD curves allowed the relative configuration to be assigned *anti* (Figure 1C).[1] In order to verify this computation-assisted stereochemistry assignment, and to gain synthetic access to the chemically and

biologically intriguing family of isatindigotindolines, we embarked on the total synthesis of the proposed structure of **1**.

Overall isatindigotindoline C (**1**) displays a formidable synthetic challenge with four contiguous stereogenic centers, including a quaternary all-carbon stereogenic center, and six rings all compacted around a central pyrrolidine ring C (Figure 1D). As a corollary, retrosynthetically disconnecting the principal ring C of **1** through a 1,3-dipolar cycloaddition would result in marked overall simplification in complexity (Scheme 1D). The resulting azomethine ylide **3** can be formed by a decarboxylative condensation between isatin (**4**) and proline (**5**).[4] The chosen approach is also in line with the proposed biosynthetic route, and agrees with the general tendency of racemic natural products to arise from the facile cyclizations of achiral precursors.[1,3]

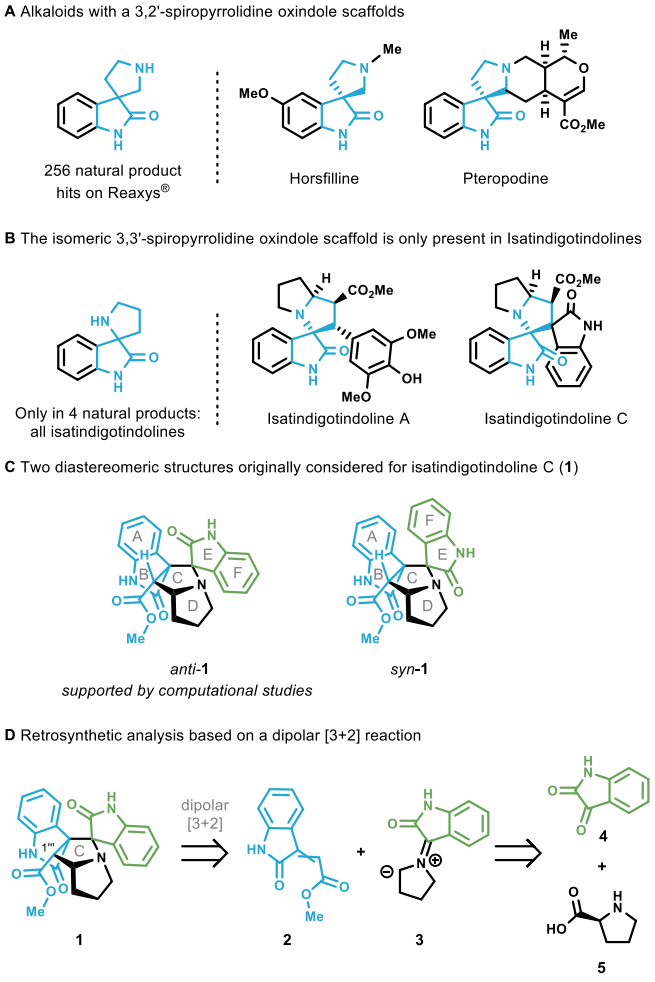


Figure 1. A: The 3,2'-spiropyrrolidine oxindole scaffold is a common motif in many alkaloids (256 hits on Reaxys database). B: The isomeric 3,3'-spiropyrrolidine oxindole scaffold is present only in the 4 solitary

isatindigotindoline alkaloids. C: Two diastereomeric structures originally considered for isatindigotindoline C (*anti*-**1** and *syn*-**1**) differ in the relative configuration of the bisoxindole unit.[1] D: Retrosynthesis of the proposed structure of **1** based on a 1,3-dipolar cycloaddition.

Results and Discussion

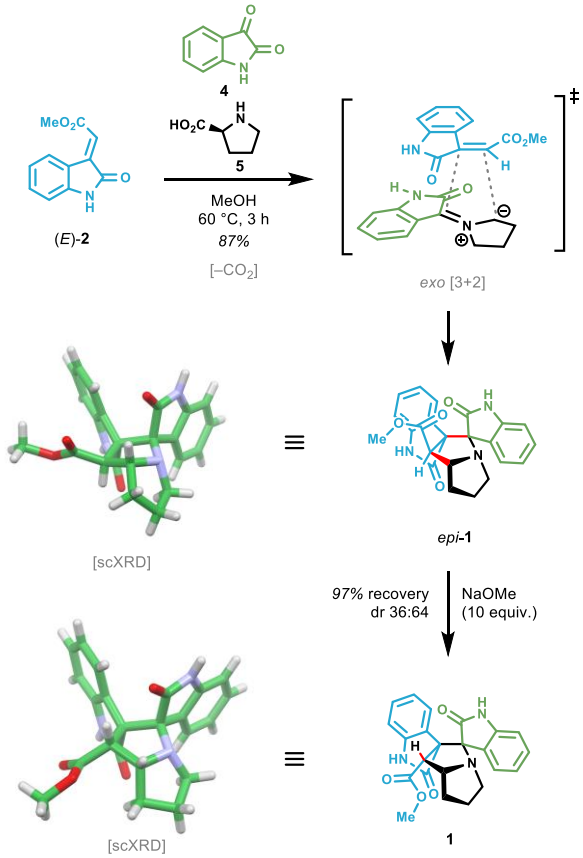
With this plan at hand, we prepared the α,β-unsaturated methyleneindoline dipolarophile (*E*)-**2** from isatin (**2**) and methyl (triphenylphosphoranylidene)acetate according to a previously reported literature procedure.[7] In order to clear the methyl ester α-stereogenic center (C1’’’) of isatindigotindoline C (**1**), the (*E*)-methyleneindoline ester dipolarophile (*E*)-**2** would have to be isomerized to (*Z*)-**2** prior to the key cycloaddition step. However, attempts at isomerizing (*E*)-**2** to (*Z*)-**2** in a Michael–retro-Michael reaction with phenol, thiophenol, or pyridine as nucleophiles led to severe decomposition with (*Z*)-**2** isolatable only in low yields (<5%).[5]

As we could not prepare synthetically useful quantities of (*Z*)-**2**, we envisioned that a *exo*-1,3-dipolar cycloaddition between (*E*)-**2** and the azomethine ylide **3** would furnish 1’’’-*epi*-**1**, which could be late-stage epimerized to natural Isatindigotindoline C (**1**) with a suitable base.[6] The late-stage epimerization was also supported by a short computational study at B97D3/DEF2TZVP-level. Isatindigotindoline C (**1**) lies 1.9 kcal/mol lower than 1’’’-*epi*-isatindigotindoline (1’’’-*epi*-**1**) for minimum energy conformers (See SI for details).

The three-component reaction between (*E*)-**2**, proline (**5**) and isatin (**4**) (1:1:1 molar ratio) readily precipitated the desired *exo* cycloaddition product 1’’’-*epi*-isatindigotindoline C (1’’’-*epi*-**1**) as a white flocculent solid. The reaction was readily scalable, allowing us to produce 1.7 g (87%) of 1’’’-*epi*-**1**. The relative *anti* stereochemistry of the bisoxindole core, and the configuration of the methyl ester α-stereogenic center of the thus formed 1’’’-*epi*-**1** were both reliably established from single crystal x-ray data (Scheme 2).[7]

The late-stage epimerization was then addressed. 1’’’-*epi*-**1** was only partially epimerized with K_2CO_3 (96:4) and NaH (92:8) at rt in THF. Under the same conditions KO*t*Bu and KHMDS led to decomposition of 1’’’-*epi*-**1**. With NaOMe in MeOH, a synthetically viable dr (36:64, favoring **1**) was obtained with 97% mass recovery. Careful flash chromatographic purification of the diastereomeric mixture furnished an analytically pure sample of **1**. The ^{1}H and ^{13}C NMR data of synthetic Isatindigotindoline C (**1**) were in full agreement with those reported for the natural product (see SI).[1] Furthermore, synthetic

isatindigotindoline C (**1**) could be crystallized and the relative *anti*-stereochemistry of the *bis*-oxindole core unambiguously verified by single crystal x-ray analysis.



Scheme 1: Total Synthesis of Isatindigotindoline C (**1**) and 1'''-*epi*-Isatingigotindoline C (1'''-*epi*-**1**). Reagents and conditions: a) methyleneidonoline ester **2** (1.0 equiv.), proline (**5**) (1.0 equiv.), isatin (**4**) (1.0 equiv.), MeOH, 60 °C, 3 h, 87% b) NaOMe (10 equiv.), MeOH, 97% recovery, dr 36:64 (*epi*-**1** to **1**). Crystalline water is omitted from the single-crystal x-ray diffraction structure of **1** for clarity.

Conclusions

In summary, we have achieved the first total synthesis of 3,3'-spiropyrrolidine oxindole alkaloid isatindigotindoline C (**1**) in two steps from the known ester **2**. The single crystal x-ray structure and NMR data of our synthetic material corroborates the original computation-assisted *anti* stereochemistry assignment of the bisoxindole core of **1**. The synthetic route also supports the postulated biosynthetic pathway, and suggests that the key dipolar cycloaddition forging the isatindigotindoline core takes place in an *exo* fashion. The approach discussed herein is readily applicable to the preparation of other members of the isatindigotindoline family as well. Also, considering the ease at which the key dipolar cycloaddition

proceeds, it is likely that additional secondary metabolites containing the elusive 3,3‘-spiropyrrolidine oxindole scaffold remain to be discovered in Nature.

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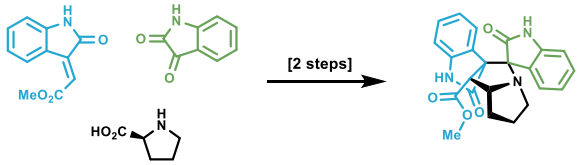

Isatindigotindoline C

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