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Unexpected domino ring closure: highly stereoselective construction of a tetracyclic indole alkaloid ring system

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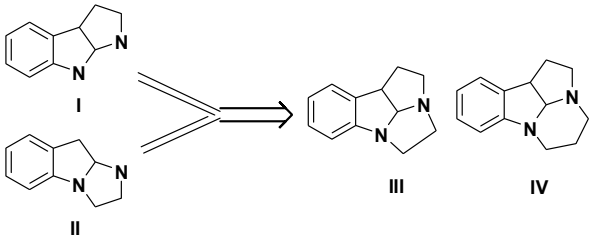
ABSTRACT

An unexpected highly stereoselective domino ring closure gave the tetracyclic indole alkaloid **IV-2** in good yield in one hydrogenation step.

The discovery of an efficient method to construct polycyclic rigid ring systems present in natural products with excellent regioselectivity and diastereoselectivity is an important goal for both academic and industrial researchers.[1] Domino or cascade reactions allow the formation of rigid ring systems in one pot which avoids isolation of intermediates in multistep syntheses of complex molecular targets. However, the development of a highly stereoselective domino reaction for the construction of indole polycyclic rings is still a challenge and remains difficult.[2]

The tetrahydropyrrolo[2,3-*b*]indole skeleton **I** is a key structural component of many indole alkaloids exhibiting a diverse range of biological activity.[3] The tetrahydroimidazo[1,2-*a*]indole system **II** is also found in many natural products such as tryptoquivalines, asperlicins, fiscalins, fumiquinazolines and kapakahines.[4] Tetracyclic [6,5,5,5] ring system **III** can be considered as a combination of tetrahydropyrrolo[2,3-*b*]indole **I** and tetrahydroimidazo[1,2-*a*]indole **II** (Scheme 1). The presence of these heterocyclic systems in natural products stimulates interest in the structural manipulation of these new compounds. As such, the synthesis of tetracyclic [6,5,5,5] ring system **III** and [6,5,5,6] ring system **IV** is of interest, and recently, Herranz reported an acid-promoted cyclization of tryptophan-based α-amino nitriles to synthesize ring system **III**, the structure of which was determined by 2D NMR.[5]



Scheme 1. Tetracyclic ring systems **III** and **IV**.

There is only one example in the literature for the synthesis of a tetracyclic [6,5,5,6] ring system **IV**. Compound **IV-1** was synthesized by phosphoryl chloride-mediated cyclization of the condensation product of tryptamine with diketene; however, **IV-1** could not be functionalized for structural manipulation (Fig. 1).[6]

During the course of our synthetic efforts aimed at developing a novel rigid chiral ligand for asymmetric catalysis, we identified an unexpected domino ring closure process which provided an easy and stereoselective access to the tetracyclic [6,5,5,6] ring system **IV-2**. Herein, we present the synthesis of **IV-2**, the structure of which has been confirmed by X-ray analysis.

Starting from commercially available L-tryptophan methyl ester **1**, initial protection of the ammonium nitrogen atom with benzyl chloroformate in the presence of sodium bicarbonate, followed by acid-catalyzed ring closure afforded the hexahydro[2,3-*b*]pyrroloindole **3** in an overall yield of 60% as an *endo*/*exo* mixture of isomers. Subsequent acetylation of **3** with 5 equiv of acetyl chloride in the presence of Et_3N and DMAP failed to yield the desired acetylation product **5**; however, the unexpected Claisen condensation product **4** was obtained.[7] When 1 and 2 equiv of acetyl chloride were employed, compound **4** was also obtained as the major product in 41% and 71% yields, respectively. Even when we decreased the reaction temperature, slowed down the addition rate and reduced the amount of acetyl chloride, compound **4** was still

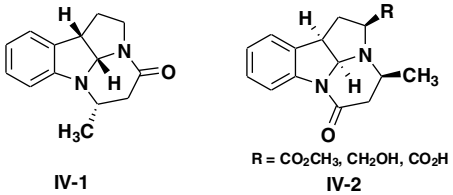


Figure 1. Tetracyclic [6,5,5,6] ring **IV-1** and **IV-2**.

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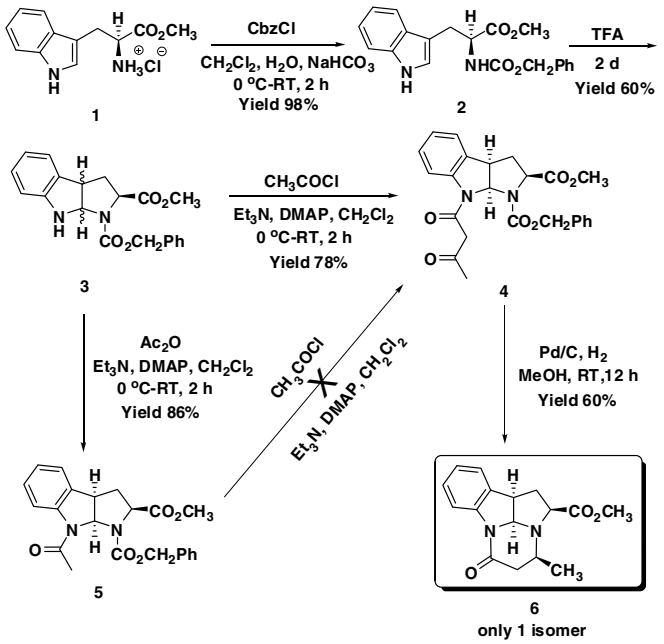


Scheme 2. Synthesis of tetracyclic ring product **6**.

obtained as the major product (Scheme 2). However, compound **5** could be acquired by the use of acetic anhydride and Et_3N. Treatment of **5** with acetyl chloride in the presence of base failed to yield **4**. The ^1H NMR spectrum of **4** was slightly complex due to the existence of rotamers. A single crystal was grown from an ether/hexane (1:1) mixture and its structure was confirmed (Fig. 2).

As demonstrated by the crystal structure, compound **4** adopted an envelope-like conformation. It was clear that the methyl ester group was directly under the phenyl ring, and other orientations were blocked by the bulky benzyloxy group. The rigid and crowded nature could account for the reason why we met with failure when we tried to carry out a Grignard addition to the methyl ester.[8]

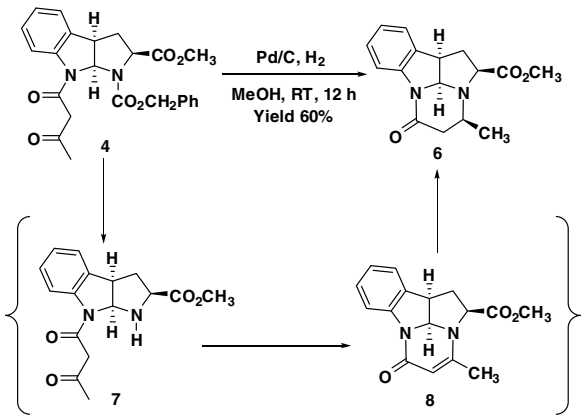
Thus deprotecting the benzyloxy group is essential for the success of this transformation. In the next step, deprotection followed by filtration to remove Pd/C gave a colourless crystalline solid in good yield.[9] The ^1H NMR spectrum showed that the signal of the carbamate CH_3 group protons was shifted significantly from δ 2.33 to δ 1.41 compared to the corresponding signal in **4**. To elucidate its precise structure, a crystal suitable for X-ray analysis was grown by slow evaporation from a mixture of CH_2Cl_2 and hexane. As shown in Figure 1, a new six-membered ring D was formed which was fused to the two heterocyclic rings, A and B. The methyl ester group preferred the *endo*-conformation.

The proposed mechanism for the formation of **6** involved two steps, (1) deprotection of the benzyl carbamate in the presence of Pd/C and H_2 to afford intermediate **7** and (2) reductive amination where the amine attacks the γ-carbonyl group to give **8** which undergoes reduction to afford the final product **6** (Scheme 3).

Chemical functionalization of compound **6** was next explored in order to further manipulate the tetracyclic ring system. An initial attempt to carry out a Grignard addition to the carboxylate group failed due to the rigid scaffold of the ring system. However, reduction of **6** with $LiBH_4$ was performed successfully in THF to yield the chiral alcohol **9** as a single isomer which can be further manipulated (Scheme 4).

To test the generality of this new finding, commercially available N_α-carbobenzyloxy-L-tryptophan **10** was first treated with benzyl alcohol using DCC coupling to afford **11**, which underwent acid-catalyzed ring closure to provide the hexahydro[2,3-*b*]pyrrolo indole **12**. Reaction of **12** with excess acetyl chloride and Et_3N provided **13** in 70% yield. Finally, hydrogenation gave the chiral tetracyclic acid **14** as a single isomer in 78% yield (Scheme 5).

In summary, an unexpected highly stereoselective domino ring closure process led to an easy, clean and efficient synthesis of a tetracyclic indole alkaloid ring system. Structural manipulation of



Scheme 3. Proposed mechanism.

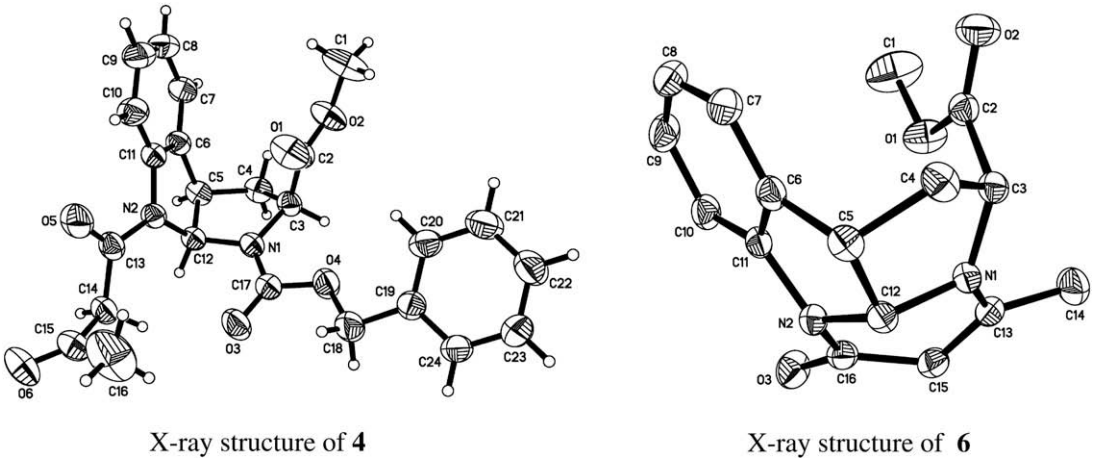
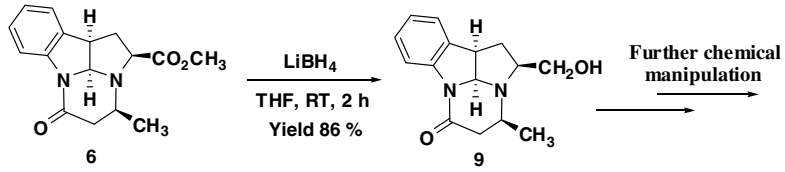
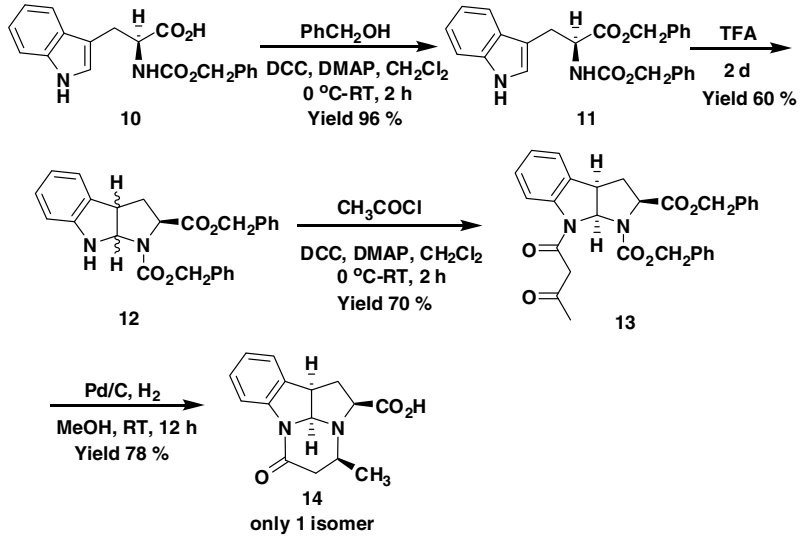


Figure 2. ORTEP drawing of molecule **4** and **6**.



Scheme 4. Chemical manipulation of **6**.



Scheme 5. Synthesis of tetracyclic acid **14**.

these new compounds provided other versatile building blocks. Further modification and application of this reaction to synthesize other ring systems is ongoing in our lab.

Acknowledgements

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7. Compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, 1H, J = 9.8 Hz), 7.43–7.22 (m, 6H), 7.22–7.16 (m, 1H), 7.13–7.04 (m, 1H), 6.15 (d, 1H, J = 9.8 Hz), 5.12 (s, 2H), 4.86(d, 1H, J = 16.0 Hz), 4.58 (d, 1H, J = 12.2 Hz), 4.19-3.99 (m, 2H), 3.06 (s, 3H), 2.75–2.70 (m, 1H), 2.61–2.50 (m, 1H), 2.33 (s, 2H), 2.12–1.95 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.7, 171.3, 167.8, 154.4, 144.2, 142.7, 135.8, 131.3, 128.6, 127.6, 125.1, 123.6, 119.2, 77.9, 67.3, 59.8, 52.4, 45.7, 33.3, 31.0. IR(KBr): cm^{-1} 3032, 2951, 2250, 1712, 1600, 1109, 912, 754, 732, 700; HRMS (m/z) calcd: 436.1629; found: 436.1630 (M^+). Crystal data for **4**: C_{24} H_{24} N_2 O_6, M = 436.45, crystal dimensions 30 × 0.30 × 0.20 mm^3, orthorhombic. space group $P2(1)2(1)2(1)$ a = 10.0800(3) Å, b = 11.1128(3) Å, c = 19.7964(6) Å. V = 2217.53(11) Å^3, Z = 4, D_{calcd} = 1.307 Mg/m^3, independent reflections 6785 ($R_{(int)}$ = 0.0305) $F(000)$ = 920, final R_1 = 0.0420, wR_2 = 0.1094 and R (all data) = 0.0555, Rw = 0.1203, CCDC number 624126.
8. Design and syntheses of a new class of structurally rigid tricyclic chiral ligands and their application for enantioselective reduction of ketones. Xiao, J.; Loh, T.-P., submitted for publication.
9. *General procedure for this domino ring cyclization to synthesize tetracyclic system* ***6:*** (2*S*,3a*R*,8a*R*)-1-Benzyl 2-methyl 8-(3-oxobutanoyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2*H*)-dicarboxylate **4** (300 mg, 0.69 mmol) was dissolved in 2 ml of methanol and 10% Pd/C (75 mg, 0.069 mmol) was added. The mixture was stirred overnight at room temperature under a H_2 balloon. After filtration through Celite and evaporation, the residue was purified by column chromatography to afford product **6** (170 mg, 60%) as a crystalline solid. Compound **6** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, 1H, J = 7.8 Hz), 7.17 (d, 2H, J = 7.8 Hz), 7.03–6.98 (td, 1H, J = 0.9, 7.6 Hz), 5.37 (d, 1H, J = 7.6 Hz), 3.99 (dd, 1H, J = 2.3, 8.4 Hz), 3.90–3.72 (m, 2H), 3.36 (s, 3H), 2.76–2.51 (m, 2H), 2.31–2.12 (m, 2H), 1.41 (d, 3H, J = 1.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 168.6, 142.8, 132.7, 128.1, 124.1, 124.0, 116.6, 83.0, 60.3, 52.1, 48.9, 43.7, 37.8, 37.7, 19.3. IR(KBr): cm^{-1} 2926, 1717, 1655, 1479, 1396, 1252, 1065, 772, 719; HRMS (m/z) calcd: 286.1312; found: 286.1305 (M^+). Crystal Data for **6**: $C_{16}H_{18}N_2O_3$, M = 286.32, colorless prism, 0.45 × 0.30 × 0.20 mm^3, trigonal, space group $P3(2)$, a = 7.62510(10) Å, b = 7.62510(10) Å, c = 20.5405(6) Å, V = 1034.27(4) Å^3, Z = 3, D_{calcd} = 1.379 Mg/m^3, reflections collected 17517, independent reflections 4080 (R_{int} = 0.0244), final R [$I > 2\sigma(I)$] = 0.0317, R (all data) = 0.0332, Rw = 0.0842, CCDC number 671820.