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Synthesis of Decahydropyrrolo[2,1,5-*cd*]indolizine through Consecutive [2 + 3] Cycloadditions and 6-Exo-Trig Cyclization

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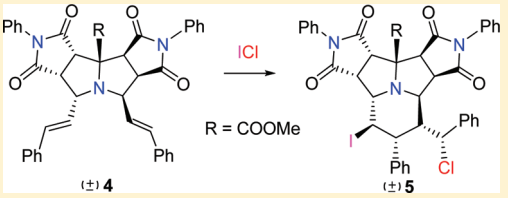
Supporting Information

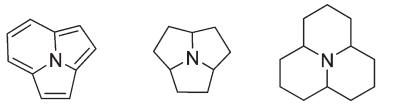
ABSTRACT: Azomethine ylide formed from glycine methyl ester and cinnamaldehyde adds to *N*-phenylmaleimide to form pyrrolidine derivative, further treatment of which with cinnamaldehyde and *N*-phenylmaleimide affords the second [2 + 3] cycloaddition adduct, a pyrrolizine derivative with two styrenyl groups at the 3,5-positions. Addition of ICl to the pyrrolizine derivative results in the 6-*exo*-trig cyclization of the styrenyl groups to form a cycl[3.2.2]azine derivative. The reactions are highly stereoselective affording 11 chiral carbons in three steps. The structure of the cycl[3.2.2]azine derivative was determined by single-crystal X-ray analysis.

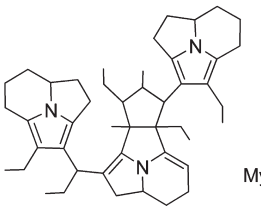


Pyrrolo[2,1,5-*cd*]indolizine or cycl[3.2.2]azine was first synthesized through a two-step cyclization procedure starting from indolizine.[1] The nitrogen-doped aromatic system has attracted much attention. A number of different synthetic methods have been reported for its synthesis.[2−4] These include the [8 + 2]-cycloaddition of indolizine with an electron-deficient acetylene[5−7] and intramolecular condensation of 3-acyl-5-methylindolizines.[8] The cyclazine family has been shown to have a wide range of bioactivities.[9] A partially hydrogenated framework was later found in several natural products such as the myrmicarins, which were isolated from the poison gland of the African ant species *Myrmicaria opaciventris*.[10] Total synthesis of myrmicarin alkaloids is a challenging problem because of its complex stereochemistry and sensitivity to air, silica gel, and alumina. So far, only the simple members have been synthesized.[11−13] In spite of numerous efforts on the synthesis of aromatic and partially hydrogenated pyrrolo[2,1,5-*cd*]indolizine, little is known about the synthesis of fully hydrogenated pyrrolo-[2,1,5-*cd*]indolizine.[14] In contrast, a number of methods have been reported for the synthesis of dodecahydropyrido[2,1,6-*de*]quinolizine or azaphenalene with three six-membered rings[15] and octahydro-1*H*-pyrrolo[2,1,5-*cd*]pyrrolizine or azatriquinane with three five-membered rings.[16] As a continuation of our studies of oligocyclic compounds, in particular, nitrogen-containing cyclic compounds,[17−19] here we report the formation of a fully hydrogenated pyrrolo[2,1,5-*cd*]indolizine derivative.

The synthesis begins with a 1,3-dipole cycloaddition to *N*-phenylmaleimide to form compound **3**.[20] Further treatment of **3** with cinnamaldehyde and *N*-phenylmaleimide yields the tetracyclic compound **4**. Addition of iodochloride to **4** resulted in a 6-exo-trig cyclization process to yield **5** with a decahydrocyclazine core. The reactions were quite stereoselective, affording mainly one stereoisomer. Other unstable isomers may have formed but decomposed into uncharacerizable products.

Formation of compounds **3** and **4** follows the classical 1,3-dipole addition mechanism. The iodochloride-induced cyclization was unexpected. It probably starts from iodium addition to the double bond trans to the ester group to form benzyl cation **A**, which then adds to the other double bond to form another benzyl cation. Finally, addition of chloride to this second cation affords **5**. The steric effect of the ester group may be the key factor differentiating the two styrenyl groups in the first step, i.e., regioselectivity of the ICl addition. The steric effect of the phenyl groups and ring strain of the cycl-[3.2.2]azine framework should be the driving force for the stereoselectivity in the final cyclization step, forming four chiral carbons.





Single-crystal X-ray structure of compound **5** was obtained (shown in Figure 1 in the Supporting Information). The two maleimide moieties are almost planar and trans to each other

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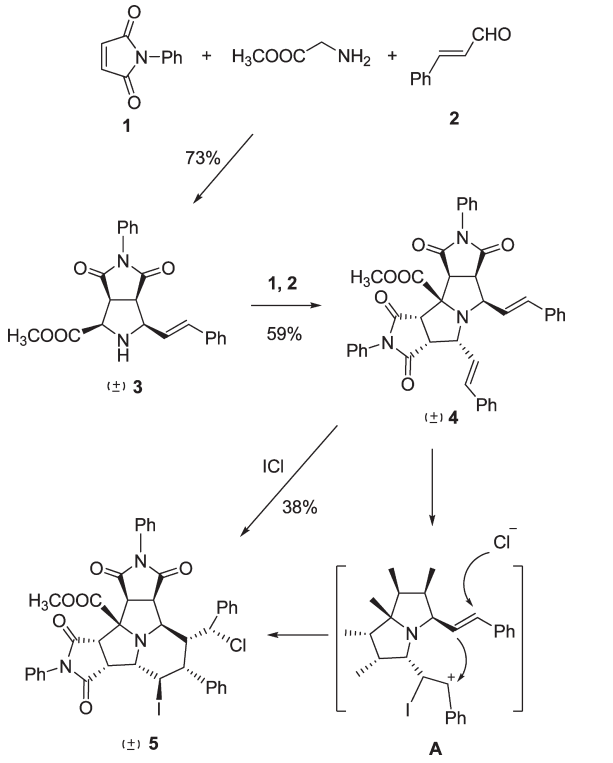
Scheme 1. Stereoselective Synthesis of Decahydropyrrolo-[2,1,5-*cd*]indolizine 5



relative to the cycl[3.2.2]azine ring. The piperidine moiety adopts a twisted-boat conformation. The two hydrogen atoms next to the piperidine nitrogen atom are in a trans configuration, indicating that the precursor **4** should also have the same trans configuration as depicted in Scheme 1. It is unlikely that the two styrenyl groups switch positions in the ICl reaction. The relative geometries of the chloro-, iodo-, and phenyl-bounded chiral carbons are also clearly revealed from the X-ray structure. There are four molecules in the unit cell, two of which are the same as those drawn in Scheme 1. The other two molecules are enantiomeric to the structure drawn for **5** in Scheme 1. Based on the X-ray structure of **5** and spectroscopic data, structures of other compounds can be assigned as shown in Scheme 1. The stereochemistry of compound **3** is in agreement with well established literature results[17,18,20] including the single crystal X-ray structure of an analogous compound prepared by similar method.[17]

In summary, a fully hydrogenated pyrrolo[2,1,5-*cd*]indolizine derivative is prepared through a three-step sequence, two consecutive azomethine ylide cycloadditions, and a ICl-induced 6-exo-trig cyclization. These reactions are highly stereoselective affording 11 chiral centers in the final product. The final key step involves formation and relay of a benzyl cation intermediate. This strategy may be applied to the synthesis of other multicyclic compounds. Further work is in progress to develop efficient cyclization methods.

EXPERIMENTAL SECTION

All reagents were used as received. Dichloromethane (DCM) was distilled over phosphorus pentoxide. Other solvents were used as received. The reactions were carried out in air.

Compound 3. Glycine methyl ester (865 mg, 9.45 mmol) and cinnamaldehyde (1282 mg, 9.71 mmol) were dissolved in DCM (22 mL) and silica gel (1350 mg) was added to the solution. The solution was stirred for 3 h at 0 °C, and then the solution was filtered to remove silica gel, which was washed with DCM (15 mL). The filtrate was combined, and *N*-phenylmaleimide (1.679 mg, 9.71 mmol) and silver acetate (49 mg, 0.29 mmol) were added. The resulting solution was stirred at room temperature for 6 h. The product **3** was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl ester, 3:1 to 1:1 v/v) as a white solid: 2284 mg (73% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.19 (m, 12H),6.73 (d, 1H, J = 15.9 Hz), 6.40 (dd, 1H, *J* = 7.5, 6.9 Hz), 4.09 (d, 2H, *J* = 6.9 Hz), 3.84 (s, 3H), 3.68 (t, 1H, *J* = 7.8 Hz), 3.48 (t, 1H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) all signals represent 1C except noted 175.2, 174.2, 170.3, 136.4, 132.8, 131.7, 129.2 (2C), 128.8, 128.7(2C), 128.1, 126.8 (2C), 126.5 (2C), 125.2, 62.8, 62.7, 52.6, 49.5, 48.9; FT-IR (microscope) 3324, 3060, 3029, 2994, 2950, 2925, 2868, 1745, 1707, 1598, 1500, 1450, 1438, 1390, 1362, 1259, 1208, 1144, 1121, 975, 757, 693 cm^{-1}; ESI-HRMS *m*/*z* calcd for $C_{22}H_{21}N_2O_4$ $[M + H]^+$ 377.1496, found 377.1504.

Compound 4. Compound **3** (1000 mg, 3.01 mmol), *N*-phenylmaleimide (552 mg, 3.19 mmol), and cinnamaldehyde (421 mg, 3.19 mmol) were dissolved in DCM (5 mL) and the solvent was evaporated to dryness. This mixture was irradiated with a household microwave oven (700 W at full power) for 10 min. The residue was dissolved in DCM, and the product **4** was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl ester, 4:1 to 3:1 v/v) as a white solid: 1178 mg (59% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02−7.55 (m, 20H), 6.69 (d, 1H, *J* = 3.8 Hz), 6.66 (d, 1H, *J* = 4.0 Hz), 6.29 (dd, 1H, *J* = 15.4, 10.1 Hz), 6.11 (dd, 1H, *J* = 15.8, 7.4 Hz), 4.75 (d, 1H, *J* = 8.4 Hz), 4.42 (d, 1H, *J* = 8.4 Hz), 4.34 (t, 1H, *J* = 9.2 Hz), 4.22 (t, 1H, *J* = 8.4 Hz), 3.9 (s, 3H, *J* = 8.8 Hz), 3.6 (t, 1H, *J* = 8.8 Hz), 3.6 (t, 1H, *J* = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) all signals represent 1C except noted δ 175.8, 174.5, 174.1, 172.9, 170.2, 136.1, 135.9, 135.8, 133.0, 131.4, 129.5 (3C), 129.1 (4C), 128.8, 128.2 (3C), 128.2 (3C), 128.0, 127.9, 127.7, 126.7 (6C), 126.4 (3C), 125.7 (3C), 122.4, 81.7, 66.9, 64.3, 53.6, 51.7, 50.2, 49.9, 47.5; FT-IR (microscope) 3060, 3026, 2954, 2923, 2851, 1778, 1710, 1598, 1498, 1380, 1192, 1177, 691 cm^{-1}; ESI-HRMS *m*/*z* calcd for $C_{41}H_{34}N_3O_6$ $[M + H]^+$ 664.2442, found 664.2442.

Compound 5. Compound **4** (456 mg, 0.68 mmol) was dissolved in DCM (4 mL), and ICl (237 mg, 1.46 mmol) was added. After the mixture was stirred at room temperature for 10 min, saturated aqueous $Na_2S_2O_3$ was added. The reaction mixture was extracted with DCM and dried over anhydrous Na_2SO_4. The extract was concentrated, and the residue was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl ester, 4:1 v/v) to give compound **5** as a white solid: 216 mg (38% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.14 (m, 20H), 5.46 (dd, 1H, *J* = 12.6, 8.2 Hz), 4.76 (d, 1H, *J* = 8.0 Hz), 4.63 (d, 2H, *J* = 8.7 Hz), 4.37 (t, 1H, *J* = 8.6 Hz), 4.02 (m, 1H), 3.92 (t, 1H, *J* = 5.3 Hz), 3.70 (s, 1H), 3.57(dd, 1H, *J* = 8.3, 6.0 Hz), 2.57 (dd, 1H, *J* = 7.8, 6.0 Hz), 2.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) all signals represent 1C except noted δ 175.8, 173.9 (2C), 173.8, 169.6, 138.9, 138.3, 131.5, 131.4, 129.2 (3C), 129.1 (3C), 129.0, 128.8 (2C), 128.3, 128.2 (2C), 128.1, 127.7, 127.2 (2C), 126.4 (2C), 125.8 (2C), 125.2, 79.5, 72.3, 64.1, 57.7, 54.1, 49.9, 49.7, 48.1, 47.0, 46.8, 45.2, 21.6; FT-IR (microscope) 3064, 3029, 2955, 2855, 1771, 1739, 1712, 1705, 1598; ESI-HRMS *m*/*z* calcd for $C_{41}H_{34}ClIN_3O_6$ $[M + H]^+$ 826.1175, found 826.1171.

Single crystals were obtained from slow evaporation of **5** in DCM/^{i}PrOH. Crystal data for **5**: $C_{42}H_{35}Cl_3IN_3O_6$, M_w = 910.98 g mol^{-1}, *T* = 173(2) K, monoclinic, space group *P*2(1)/*n*, unit cell dimensions *a* = 12.988(3) Å, *b* = 12.188(2) Å, *c* = 23.837(5) Å, β = 98.01(3)°, *V* = 3736.6(13) Å^3, *Z* = 4, ρ_{calcd} = 1.619 Mg m^3, absorption coefficient = 1.126 mm^{-1}. Reflections collected/unique 29664/8533 [*R*(int) = 0.0503]. Final *R* indices [$I > 2\sigma(I)$] R_1 = 0.0482, wR_2 = 0.1116. CCDC-817229.

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■ ASSOCIATED CONTENT

Supporting Information. Spectroscopic data for compounds **3**−**5** and crystallographic data for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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