Synthesis of a Benzannulated Pyrrolizidine by a Copper-Catalyzed Intramolecular α-Arylation Reaction

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A synthetic route to the pyrrolo[1,2-*a*]indole ring system (benzannulated pyrrolizidine) involving a base-induced intramolecular aza-*Michael* reaction as the key C–N bond-forming penultimate step, followed by a Cu-catalyzed intramolecular α-arylation reaction, to provide the tricyclic framework over six steps is described.

Introduction. – Tricyclic heterocycles are pervasive structural frameworks in nature and have a broad profile of biological features, such as antibiotic, anthelmintic, antifungal, antitumor, antiviral, anti-inflammatory, and cytotoxic activities. Examples of natural products with O- or N-containing tricyclic structures include gynunone, neuchromenin, citreoindole, and fumiquinazoline (*Fig. 1*) [1–3].

Their biological activities render this family of organic compounds interesting structural scaffolds for the development of new drug candidates. Notably, these structural motifs are rarely reported in medicinal-chemistry publications, indicating that there still exists a need to develop more efficient procedures, particularly those that allow the synthesis of complex azapolycyclic ring systems.

Heterocyclic structures pertinent to this communication involve the pyrrolo[1,2-*a*]indole ring system which has been employed in the stereocontrolled synthesis of the mitosane skeleton (*Fig. 2*) [4].

As part of our research program aimed at developing new methodologies for the synthesis of heterocyclic compounds [5], we directed our focus towards preparation of

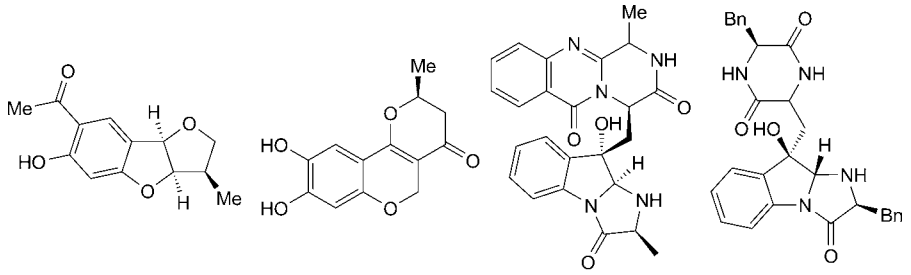


Fig. 1. *Examples of O- or N-containing natural products*

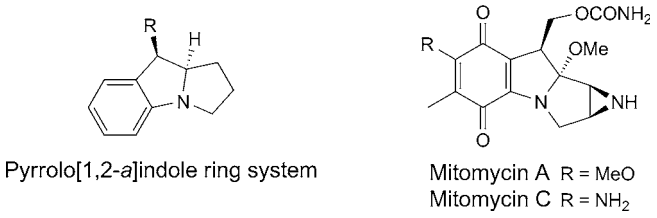
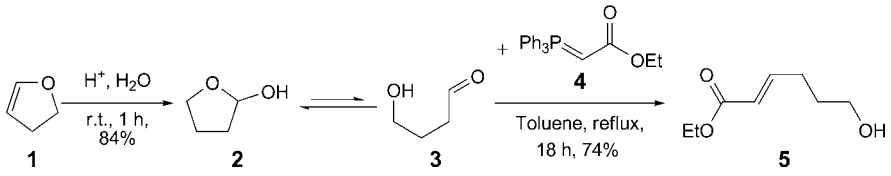


Fig. 2. *Pyrrolo[1,2-*a*]indole ring system and mitosane*

tricyclic structures for future applications in total syntheses. Herein, we report an efficient and simple synthetic route to a 'benzannulated pyrrolizidine' derivative *via* a base-induced intramolecular aza-*Michael* reaction as the key C–N bond forming step, followed by a Cu-catalyzed intramolecular α-arylation.

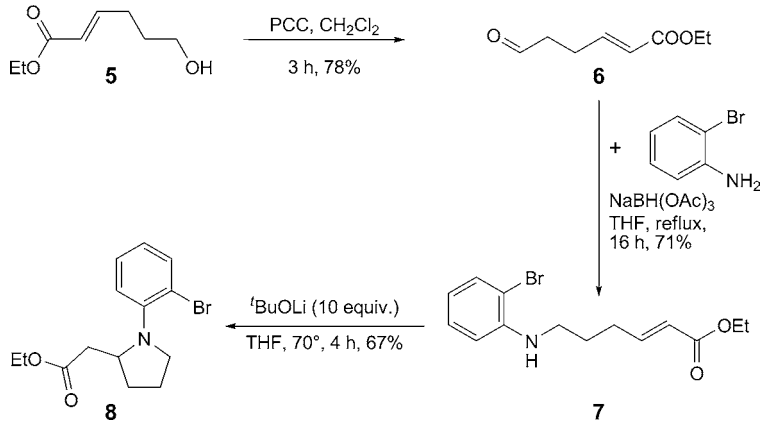
Results and Discussion. – Synthesis of the target tricyclic molecule started with tetrahydrofuran-2-ol (**2**), which was obtained by an acid-catalysed hydrolysis of 2,3-dihydrofuran **1** [6]. Tetrahydrofuran-2-ol (**2**) exists in a tautomeric equilibrium with 4-hydroxybutanal **3** and thus enables the synthesis of a α,β-unsaturated ester substrate *via* a *Horner–Wadsworth–Emmons* (HWE) reaction with the appropriate phosphonium ylide **4** (*Scheme 1*). Synthesis of **5** proceeded smoothly to afford the hydroxy α,β-unsaturated ester **5** in good yield and with predominately (E)-selectivity (> 96%) as determined by ^{1}H-NMR spectroscopy: evidenced by the presence of two signals exhibiting a splitting pattern of double *triplet*s at 6.95 ($J = 7.2$ and 15.6) and 5.85 ppm ($J = 1.6$ and 15.6) . All ^{1}H- and ^{13}C-NMR signals were unambiguously assigned and correlated well with literature values [7][8].

Scheme 1. *Synthesis of Hydroxy α,β-Unsaturated Ester* **5**



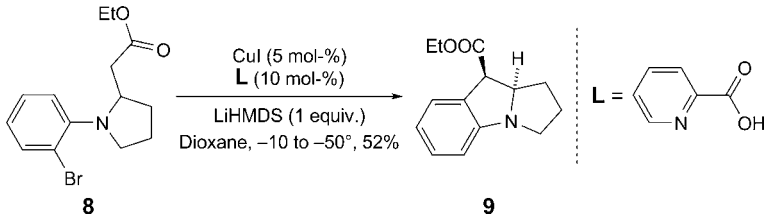
The hydroxy ester **5** was converted to the corresponding formyl ester **6** by pyridinium chlorochromate (PCC) oxidation in good yields. Compound **6** was used immediately in the next step (*Scheme 2*). We envisaged a base-induced intramolecular aza-*Michael* reaction to install the pyrrolidine moiety. Hence, to prepare target molecule **8**, a reductive amination was carried out between **6** and 2-bromoaniline with $NaBH(OAc)_3$ as reducing agent. The expected product **7** was obtained in good yield, with the incorporation of Br that could be exploited in the last key bond-forming step of the synthesis. After extensive optimizations studies, we found that the intramolcular aza-*Michael* reaction could be effected in the presence of a strong base, such as ^{t}BuOLi, to afford the *N*-substituted pyrrolidine derivative **8** in good yield.

Scheme 2. *Synthesis of Pyrrolidine Derivative* **8**



So, with compound **8** in hand, the stage for the evaluation of the intramolecular Cu-catalyzed α-arylation reaction was set (*Scheme 3*). Precedence for this type of cyclization had been established in a similar substrate in which CuI catalyzed a remote amide-assisted intramolecular arylation, followed by alkylation, in the synthesis of hexahydropyrroloindole alkaloids [9]. We applied a modification of the intermolecular protocol reported by *Kwong* and co-workers in 2007 [10]; employing a catalytic amount of 2-picolinic acid (**L**) and CuI, and 1 equiv. of lithium bis(trimethylsilyl)amide (LiHMDS) as base was successful in providing the target molecule **9** in modest yield. Interestingly, the formation of the *trans*-isomer of **9** was favored which we were able to isolate by column chromatography, and the *cis*-isomer was not detected during purification. Of the *trans*-isomer, the N–CH H-atom in the ^{1}H-NMR spectrum displayed a characteristic *ddd* signal at *ca.* 3.9 ppm and coupling constants indicative of a *trans*-isomer.

Scheme 3. *Synthesis of Pyrrolidine* **9**



Conclusions. – In summary, we have developed a synthetic protocol for the preparation of a pyrrolo[1,2-*a*]indole ring system, utilizing a Cu-catalyzed intramolecular α-arylation reaction as the key C–C bond-forming step, to afford the target molecule in 15.4% overall yield over six steps.

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Experimental Part

General. All commercial reagents were used as received. Anh. THF and 1,4-dioxane were purchased from *Sigma–Aldrich*. Column chromatography (CC): silica gel (200–400 mesh). TLC: silica-gel plates, UV light (254 nm) or vanillin soln. for visualization. M.p.: uncorrected. IR Spectra: either a liquid film between NaCl plates, or pressed in to KBr discs. NMR spectra: in δ [ppm] referenced to residual ^{1}H- and ^{13}C-signals in $CDCl_3$; the coupling constants (J) expressed in Hz. HR-EI-MS: in m/z.

Ethyl (2E)-6-Hydroxyhex-2-enoate (**5**). Ethyl(triphenylphosphonyliden)acetate (22.2 mmol) and tetrahydrofuran-2-ol (17.1 mmol), were refluxed in toluene for 18 h. Upon completion, the mixture was cooled to r.t., washed with brine, extracted three times with CH_2Cl_2, and worked up in the usual way to provide an oily residue, which was purified by CC by afford **5** (74%). Transparent oil. R_f (hexane/AcOEt 3:2) 0.2. IR: 3384, 2939, 1710, 1656, 1445, 1369, 1274, 1197, 1097, 1044, 981, 917, 711. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.97 (*dt*, J = 7.2, 15.6, 1 H), 5.88 (*dt*, J = 1.6, 15, 1 H); 4.23 (*q*, J = 6.8, 2 H); 3.70 (*t*, J = 6.0, 2 H); 2.34 (*q*, J = 7.2, 2 H); 1.74–1.79 (br. *m*, 3 H); 1.32 (*t*, J = 6.8, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.7; 148.5; 121.8; 61.9; 60.2; 30.9; 28.5; 14.3. NMR data were in accordance with those reported in [7].

Ethyl (2E)-6-Oxohex-2-enoate (**6**). To a soln. of **5** (10 mmol) in 100 ml of dry CH_2Cl_2 was added PCC (12 mmol). The resulting mixture was stirred at r.t. for 3 h and dried ($MgSO_4$). The filtrate was concentrated under reduced pressure, and the residual material was purified by CC to give **6** (78%). Transparent oil. R_f (CH_2Cl_2) 0.2. IR: 2982, 2938, 1720, 1654, 1312, 1268, 1193, 1043, 984, 852. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.78 (*s*, 1 H); 6.95 (*dt*, J = 7.2, 15.6, 1 H); 5.85 (*dt*, J = 1.6, 15.6, 1 H); 4.21 (*q*, J = 6.8, 2 H); 2.51 (*t*, J = 7.2, 2 H); 2.28 (*q*, J = 7.2, 2 H); 1.84 (*quint.*, J = 7.2, 2 H); 1.30 (*t*, J = 6.8, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 201.6; 166.4; 147.5; 122.3; 60.2; 43.2; 31.2; 20.3; 14.2 (OCH_2Me). NMR Data are in accordance with those reported in [11].

Ethyl (2E)-6-[(2-Bromophenyl)amino]hex-2-enoate (**7**). In a two-neck 150-ml round-bottom flask, equipped with stirring bar and reflux condenser, 2-bromoaniline (8 mmol), **6** (4 mmol) and $MgSO_4$ (5 g) were dissolved in THF (80 ml), and the mixture was stirred at r.t. for 1.0 h. $NaBH(OAc)_3$ (5.5 mmol) was added, and the mixture was heated to 65° for 20 h. Upon completion of the reaction, the solvent was removed under reduced pressure, and the residue was dissolved in 1M HCl (50 ml), and then carefully neutralized with aq. sat. $NaHCO_3$ soln., and finally extracted with AcOEt (3 × 40 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield **7** (71%). Transparent oil. R_f (hexane/CH_2Cl_2 3:2) 0.2. IR: 3404, 2933, 2861, 1720, 1656, 1593, 1511, 1459, 1317, 1273, 1201, 1169, 1042, 1018, 980, 743, 657. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.44 (*t*, J = 8.0, 2 H); 7.23 (*dt*, J = 1.2, 8.4, 1 H); 7.03 (*dt*, J = 6.8, 15.6, 1 H); 6.64 (*d*, J = 8.4, 2 H); 6.61 (*dt*, J = 1.6, 8.0, 1 H); 5.89 (*dt*, J = 1.6, 15.6, 1 H); 4.30 (br. *s*, 1 H); 4.24 (*q*, J = 6.8, 2 H); 3.23 (br. *m*, 2 H); 2.40 (*q*, J = 6.8, 2 H); 1.90 (*quint.*, J = 7.2, 2 H); 1.33 (*t*, J = 6.8, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.5; 148.2; 144.8; 132.4; 128.5; 122.2; 117.7; 111.2; 109.7; 60.3; 43.1; 29.6; 27.6; 14.3. HR-EI-MS: 311.0525 ($C_{14}H_{18}BrNO_2^+$; calc. 311.0521).

Ethyl 2-[1-(2-Bromophenyl)pyrrolidin-2-yl]acetate (**8**). An oven-dried *Schlenk* tube containing a stirring bar and a rubber septum was evacuated and filled with N_2 four times. A soln. of **7** (2 mmol in anh. THF (4 ml)) was placed in the tube *via* syringe, and the soln. was cooled to −10° using an ice-salt bath. ^{t}BuOLi (1.0M soln. in THF, 20 mmol) was added to the soln., which was left to stir for 1 h. The mixture was then allowed to warm to r.t., the reaction was quenched with sat. NH_4Cl (aq.; 2 ml), and the mixture was extracted with CH_2Cl_2 (2 × 10 ml). The org. extract was dried (Na_2SO_4), concentrated under vacuum, and the residue was purified by CC to afford **9** (67%). Pale-yellow oil. R_f (hexane/CH_2Cl_2, 6:4) 0.1. IR: 3376, 3060, 2975, 2874, 2360, 1897, 1731, 1585, 1474, 1436, 1372, 1314, 1245, 1193, 1155, 1101, 1026, 976, 849, 752, 720, 669. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.56 (*d*, J = 8.4, 1 H); 7.26 (*t*, J = 6.8, 1 H); 7.08 (*d*, J = 8.4, 1 H); 6.87 (*t*, J = 6.8, 1 H); 4.22–4.25 (*m*, 1 H); 4.10 (*q*, J = 7.2, 2 H); 3.88 (*dd*, J = 1.6, 6.4, 1 H); 2.89–2.90 (*m*, 1 H); 2.59 (*dd*, J = 4.0, 15.2, 1 H); 2.31–2.33 (*m*, 1 H); 2.23 (*dd*, J = 9.2, 15.2, 1 H); 1.98–2.02 (*m*, 1 H); 1.88–1.91 (*m*, 1 H); 1.72–1.73 (*m*, 1 H); 1.24 (*t*, J = 7.2, 3 H). ^{13}C-NMR (100 MHz,

$CDCl_3$): 172.5; 147.4; 134.2; 127.8; 123.2; 120.9; 118.5; 60.3; 56.4; 53.0; 38.8; 31.6; 23.8; 14.2. HR-EI-MS: 311.0517 ($C_{14}H_{18}BrNO_2^+$; calc. 311.0521).

*Ethyl 2,3,9,9a-Tetrahydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate* (**9**). A *Schlenk* tube equipped with magnetic stirring bar was charged with CuI (5.0 mol-%) and 2-picolinic acid (10.0 mol-%). The tube was evacuated and filled with N_2 (3 cycles). Next, a soln. of **8** (0.80 mmol) in anh. 1,4-dioxane (1.0 ml) was added by syringe, followed by LiHMDS (1 equiv., 1.0M soln. in THF) at $-10°$. This mixture was stirred at $-10°$ for 10 min, then the resulting soln. was allowed to warm to r.t. and heated to 50° for 3 h. The mixture was cooled to r.t., and the reaction was quenched with sat. aq. NH_4Cl (1.0 ml). H_2O (10.0 ml) was added, and the resulting mixture was extracted with AcOEt (2×10 ml). The combined extracts were washed with brine (10 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by CC to afford **9** (52%). Pale-yellow oil. R_f (hexane/CH_2Cl_2, 6 :4) 0.2. IR: 2984.5, 1741.4, 1731, 1585, 1474, 1436, 1373.7, 1239.8, 1047.1. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.10 (*t*, $J = 8.5$, 1 H); 7.05 (*d*, $J = 7.9$, 1 H); 6.74 (*d*, $J = 7.9$, 1 H); 6.53 (*d*, $J = 7.9$, 1 H); 4.12 (*q*, $J = 7.2$, 2 H); 3.96 (*ddd*, $J = 9.7$, 8.4, 5.3, 1 H); 3.70 (*ddd*, $J = 9.6$, 8.5, 6.1, 1 H); 3.45 (*ddd*, $J = 10.7$, 8.8, 3.7, 1 H); 3.10 (*ddd*, $J = 10.5$, 8.5, 7.6, 1 H); 1.80–1.96 (*m*, 2 H); 1.68 (*m*, 1 H); 1.36–1.30 (*m*, 1 H); 1.24 (*t*, $J = 7.2$, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.5; 154.81; 128.98; 128;41; 124.03; 119.35; 110.76; 68.6; 60.3; 51.8; 44.6; 27.2; 25.1; 14.2. HR-EI-MS: 231.1265 ($C_{14}H_{17}NO_2^+$; calc. 231.1259).

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