Synthetic Approaches to Hexahydropyrrolo[1,2-*b*]isoquinolones

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Synthetic routes to 1,2,3,5,10,10a-hexahydropyrrolo[1,2,-*b*]isoquinolin-5-ones functionalized at C-10 were investigated. Attempts to prepare the ketone **2**, and subsequently introduce the desired C-10 hydroxymethylene group were unsuccessful due to the failure of **6** to cyclize and the unreactivity of **9** to relevant nucleophiles. Compound **1** was prepared by the condensation of 1-pyrroline with 7-methoxyisobenzopyran-1,3,-(4*H*)-dione to give **12** in quantitative yield. Acyl halide formation and subsequent reduction gave the desired compound **1**.

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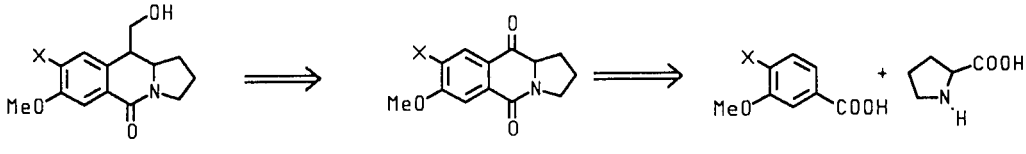
As part of an effort directed at the synthesis of ring contracted deazaanthramycin derivatives, it became necessary to develop suitably functionalized pyrroloisoquinolones. Specifically future transformations would require the presence of a 7-methoxyl group and a 10-hydroxymethylene function (**1**, Scheme I) Retrosynthetic analysis led to the 7-methoxy-10-oxo-1,2,3,4,10,10a-hexahydropyrrolo-[1,2-*b*]isoquinolin-5-one **2** as a reasonable direct precursor. The condensation of *meta*-anisic acid **3** with proline **4** appeared to be an attractive route for the formation of intermediate **2**. Furthermore this method would allow for stereochemical control at the 10a position if racemization could be prevented in the subsequent cyclization step. Simple extension of such a route to a protected hydroxyproline would then allow for functionalization of the pyrrolo ring.

Reaction of 3,4-dimethoxybenzoyl chloride **5** with L-proline gave the amide **6** in good yield (Scheme II). Attempts to cyclize **6** to the pyrroloisoquinolinone tricycle under a number of conditions however, were unsuccessful. Attempted cyclization in concentrated sulfuric acid resulted only in the recovery of amide hydrolysis products after quenching, while attempted thermal cyclizations (diphenyl ether) yielded primarily decomposition products. Similarly cyclization under Freidel-Crafts (F-C) conditions with PPA failed to give the desired product. Reasoning that the electron withdrawing effects of the amide moiety may hinder the cyclization, an alternative approach was investigated in which the F-C acylation was carried out first, leaving cyclization from the proline nitrogen to the aromatic ring for a latter step. Such an approach was shown to be successful in the preparation of hexahydro-

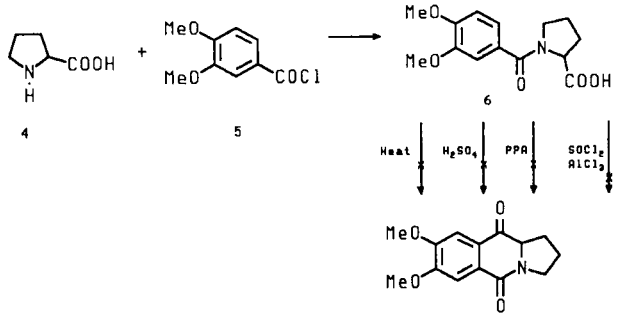
Scheme I



1 2 3 4

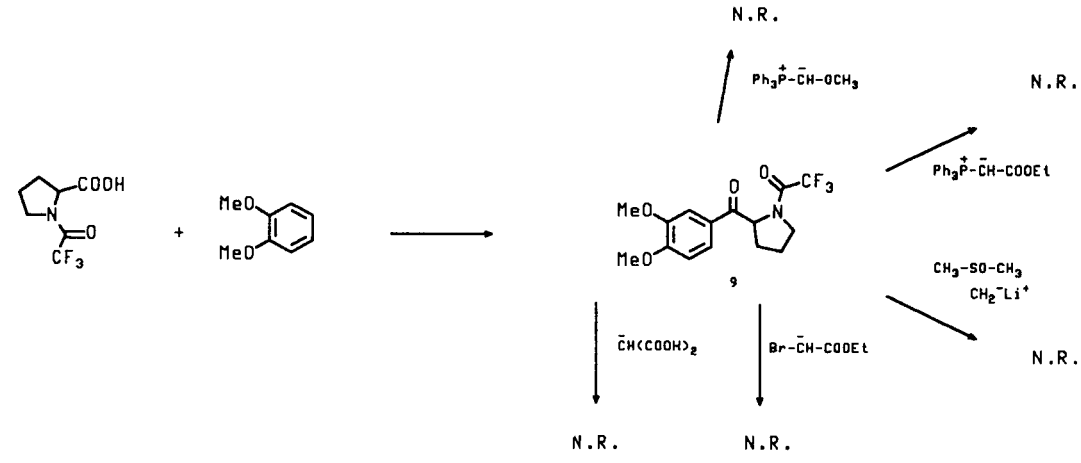
X = H-, CH_3-O-

Scheme II

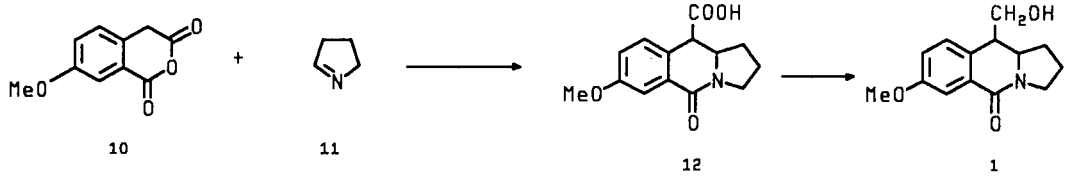


4 5

Scheme III



Scheme IV



pyrrolo[1,2-*b*]isoquinolones by Norlander *et al.* [1]. Proline was protected as the *N*-trifluoroacetyl derivative and then converted to the acyl chloride **7** (oxalyl chloride) (Scheme III). Treatment of **7** with veratrole under F-C conditions gave the ketone **9** in good yield.

Attention at this point was turned toward introduction of functionality which could be transformed to the desired hydroxymethylene group. One approach which was explored involved Wittig reaction of the ketone with methoxymethyltriphenylphosphonium ylide to provide the intermediate enol ether which could be hydrolyzed to the aldehyde [2]. Reaction of ketone **9** with the ylide resulted only in recovery of starting ketone. Changing the base and solvent from sodium hydride, DMF to *n*-butylithium, THF offered no advantage [3]. Other workers have commented on the difficulty of performing Wittig reactions on aryl ketones containing acidic protons [4]. Reactions of ketone **9** with numerous other nucleophiles including sodio diethyl malonate, dimethyloxosulfonium methylide, Ph_3P-*C*H-COOEt, and sodio ethyl bromoacetate were also unsuccessful.

Evidence that the ketone of **10** was unusually unreactive was also demonstrated by its inability to form a hydrazone with DNP. The non-reactivity appears to be due in part to the methoxy substituent *para* to the ketone carbonyl since the unsubstituted ketone readily forms the hydrazone derivative upon exposure to DNP; however, even the ring unsubstituted ketone fails to undergo addition in the presence of other nucleophiles. Failure of the aforementioned synthesis led to the necessity of an alternative approach which would not require introduction of functionality at C-10 by nucleophilic reactions. Haimova *et al.* reported that condensation of 1,3-isochromanediones with azomethines led to the production of 4-carboxy-1,2,3,4-isoquinolin-1-ones [5]. Extension of the condensation to the cyclic azomethines 1-pyrroline **11** gave the 10-carboxypyrroloisoquinolinone **12** in quantitative yield as a mixture of *cis* and *trans* isomers (Scheme IV) [6]. Analysis (hplc) of the two diastereomers revealed a 50/50 mixture of diastereomers, indicating no stereoselection in the cyclization. Stirring in 1 *N* sodium hydroxide had no effect on this ratio. Others have suggested that epimerization may occur under these conditions to give the more stable *trans* product [7]. The *cis* isomer was obtained by recrystallization and stereochemistry was assigned on the basis of the gamma desheilding (−3.0 ppm) of the carboxyl group on the C_1 carbon in the ^{13}C spectrum relative to the *trans* isomer. The requiste hydroxymethylene function was then introduced *via* formation of the acyl halide and subsequent reduction with sodium borohydride to give **1**. Analysis (hplc) of the purified product indicated the presence of two products present in a 10/1 ratio. The ^{13}C nmr spectra identified both products as the two diastereomers and indicated that the major product was the more stable *trans* isomer. Evidently equilibration occurred during the formation of

the acid chloride to give the thermodynamically more stable *trans* isomer.

EXPERIMENTAL

Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded with a Bechamn 4230 spectrophotometer and ^1H and ^{13}C nmr spectra were recorded on a Bruker (400 MHz) NMR spectrometer with tetramethylsilane as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia and are within 0.4% of the theroretical percentages. Reverse-phase hplc analyses were carried out with a Waters Model 60000A Liquid Chromatograph equipped with a Hypersil 5 C-18 column (150 x 4.6 mm) and a Waters Model 440 absorbance detector set at 254 nm, using a 65/35.0.1:-water/methanol/sulfuric acid mobile phase. Common reagent-grade chemicals were purchased from Aldrich Chemical Company. Tetrahydrofuran was distilled from sodium/benzophenone.

N-(3,4-Dimethoxybenzoyl)proline, (**6**).

3,4-Dimethoxybenzoyl chloride (12.0 g, 60 mmoles) was added portionwise over a period of 30 minutes to a vigorously stirred solution of proline (8.18 g, 71 mmoles) in 75 ml of water containing sodium hydroxide (5.2 g, 130 mmoles) cooled to 5°. During the addition, 15% sodium hydroxide solution was added dropwise to maintain a basic *p*H. After the addition was complete, the reaction mixture was stirred at room temperature for 3 hours. Acidification with concentrated HCl yielded a brown gummy oil which was extracted into dichloromethane (3 x 100 ml) and the combined dichloromethane extracts were washed with saturated sodium chloride followed by water. The organic layer was removed, dried (sodium sulfate), filtered and evaporated to give an off-white foam which solidified under vacuum to give 16.8 g (85%) of **6**, mp 154-156°; ^1H nmr (deuteriochloroform): 2.0-2.4 (m, 4H), 3.8-3.95 (m, 2H), 3.98 (s, 6H), 4.8 (t, 1H), 6.8-7.4 (m, 3H).

N-(Trifluoroacetyl)-3,4-dimethoxyprolylbenzene, (**9**).

Compound **9** was prepared by the method of Norlander *et al.* [1], mp 124-125° (lit mp 122-123°).

1-Pyrroline (**11**).

Compound **11** was prepared by the decomposition of the 1-pyrroline trimer upon co-distillation with THF as described by Poisel [8]. The trimer was prepared by the method of Nomura *et al.* [6]. The trimer had bp 7 mm 130-150° (lit bp 12 mm 140-160°).

7-Methoxy-10-carboxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]-isoquinolin-5-one (**12**).

In 30 ml of benzene was placed 2.0 g (10.4 mmoles) of 7-methoxy-1,3-isochromanedione, (**10**) [9,10]. The resulting suspension was heated slightly until a clear solution resulted. To this was added *via* distillation 790 mg (11.4 mmoles, 1.1 equivalents) of 1-pyrroline in 20 ml of dry THF. After the addition was complete the reaction was stirred at reflux for 1½ hours during which time a precipitate began to form. Stirring was continued for 10 hours at room temperature. The precipitate was collected to give 2.62 g (96%) of the *cis* and *trans* isomers of **10**. Recrystallization from methanol/ether gave the pure *cis* isomer. mp 243-245; ir (film): 1740 (COOH), 1620 (amide C=O); m/e 261; ^1H nmr (DMSO-d_6): 1.8-1.9 (m, 2H), 2.0-2.1 (m, 2H), 3.25-3.35 (m, 2H), 3.85 (s, 3H), 3.9 (d, 1H, J = 4.8 Hz), 4.1 (m, 1H), 7.04 (dd, 1H, J = 2.8 Hz, 8.2 Hz), 7.27 (d, 1H, J = 8.2 Hz), 7.35 (d, 1H, J = 2.8 Hz); ^{13}C nmr: 171, s (COOH), 161, s (amide C=O), 159, s (C7), 132, s (C5a), 129, s (C9a), 128, d (C9), 117, d (C8), 111, d (C6), 57, d (C10a), 55, q (CH_3O-), 46, d (C10), 45, t (C3), 29, t (C1), 22, t (C2); *trans* isomer 172, s (COOH), 161, s (amide C=O), 159, s (C7), 132, s (C5a), 129, s (C9a), 128, d (C9), 117, d (C8), 111, d (C6), 58, d (C10a), 55, q (CH_3O-), 46, d (C10), 45, t (C3), 32, t (C1), 22, t (C2).

Anal. Calcd. for $C_{14}H_{14}NO_4$: C, 64.60; H, 5.42; N, 5.38. Found: C, 64.25; H, 5.81; N, 5.29.

7-Methoxy-10-hydroxymethylene-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (**1**).

In 5 ml of benzene was placed the acid (100 mg, 0.38 mmole), and to this added 6 drops of thionyl chloride. The reaction was allowed to stir at reflux for 18 hours. The benzene was removed under reduced pressure and the residue immediately redissolved in dioxane. To this solution was added 40 mg of sodium borohydride and the raction allowed to stir for 2 hours at room temperature. The dioxane was removed under reduced pressure and the residue extracted with ethyl acetate (20 ml) and washed with saturated sodium chloride (3 x 5 ml). The aqueous layers were combined and any remaining product was extracted with 3 x 10 ml of ethyl acetate. The combined organic layers were dried (sodium sulfate) and evaporated to give the crude product which was purified by flash chromatography (silica gel: chloroform/ethanol, 20/1) to give 65 mg (70%) of **1** as a mixture of diastereomers. Separation of the diastereomers by hplc (Hypersil C-18: water/methanol, 65/35) revealed a 10/1 *trans*/*cis* ratio; ir (film): 3200 (OH), 1620 (C=O), m/z = 247, 216; ^1H nmr (deuteriochloroform): 1.77 (m, 2H), 2.13 (m, 2H), 3.0 (m, 1H), 3.4-3.7 (m, 2H), 3.8-3.9 (m, 5H), 4.0 (m, 1H), 7.0 (dd, 1H, J = 2.6, 8.2 Hz), 7.1 (d, 1H, J = 8.2 Hz), 7.5 (d, 1H, J = 2.6 Hz): ^{13}C nmr 161, s (amide C=O), 159, s (C7), 132, s (C5a), 131, s (C9a), 125, d (C9), 118, d (C8), 112, d (C6), 60, t (-CH_2-OH), 59, d (C10a), 55, q (CH_3-O), 45 overlapping t and d (C10, C3), 33, t (C1), 23 t (C2); *cis* isomer 161, s (amide C=O), 159, s (C7), 132, s (C5a), 131, s (C9a), 125, d (C9), 118, d (C8), 112, d (C6), 60, t (-CH_2-OH), 59, d (C10), 55, q (CH_3-O), 45, t (C3), 43, d (C10a), 29, t (C1), 23, t (C2).

Anal. Calcd. for $C_{14}H_{17}NO_3 \cdot 0.3H_2O$: C, 66.54; H, 7.02; N, 5.54. Found: C, 66.44; H, 7.02; N, 5.32.

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