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A straightforward synthesis of didehydro analogues of *N*-acetylardeemin

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Abstract

The didehydro analogue of *N*-acetylardeemin **1b** was synthesised in a seven step process that started with tryptamine. A regioselective oxidation of the 2-substituted precursor **3b**, followed by a diastereoselective *anti*-cyclization reaction involving an acyliminium intermediate formed from the unisolated tosylate **2b**, is the key-step of this strategy. Application of this procedure to **3a** afforded, instead of the cyclization product, the *cis*-1-hydroxy derivative **2c** which, after acid treatment, gave a 6/4 mixture of *trans*- and *cis*-isomers of the hexacyclic compound **1a**.

Keywords: asymmetric induction; arylation; hypervalent iodine; iminium salts.

The reactivity of 2,4-substituted 2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones as glycine templates is currently being investigated[1] in our group because this system contains three rings of the hexacyclic fungal metabolite *N*-acetylardeemin, which is one of the most potent known inhibitors of multidrug resistance (MDR) to antitumour agents.[2] According to its peptidomimetic structure, the first total synthesis of *N*-acetylardeemin was performed by Danishefsky using L-tryptophan, D-alanine and *o*-azidobenzoyl chloride (a synthetic equivalent of anthranilic acid), as starting materials. A tandem-nucleophilic–electrophilic addition to the C(2)=C(3) indole bond of tryptophan was used to form ring *C* in a first step.[3] A similar cyclization on *cyclo*-L-Trp-L-Ala was used in the preparation of simpler analogues,[4] while in the synthesis of *C-homo*-didehydro analogues, a Pictet–Spengler cyclization on L-TrpOMe was used to form ring *C* in a first step.[5] Here we report a concise procedure to form ring *C* of the new didehydro analogues **1** in the last step, by using compounds **2** as precursors of acyliminium intermediates (Fig. 1). The foregoing precursors can be generated by a new regioselective oxidation of compounds **3**.

Synthesis of **3a** from **4a** has been previously reported.[6] Compound **3b** (Scheme 1), was obtained by a similar route from **4b**, which was readily available by alkylation of tryptamine with ethyl bromoacetate. All steps gave good yields except the condensations of the lactim ethers derived from **5** with anthranilic

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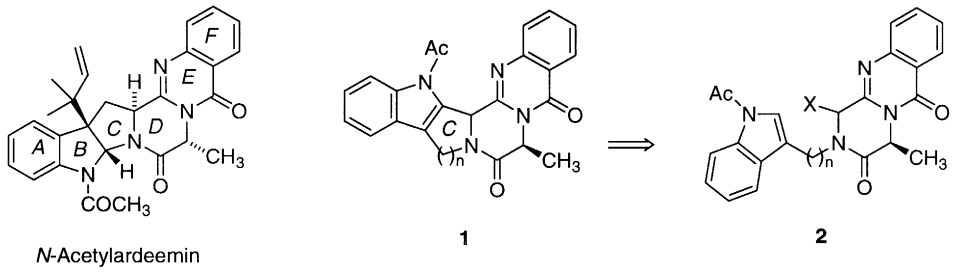
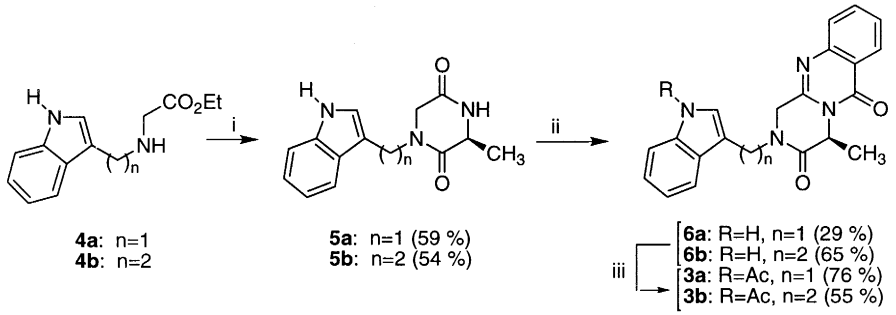


Fig. 1.

acid that yielded only about 30% of the tricyclic compounds **6**. Other attempted alternative strategies to overcome this limitation, such as direct condensation of **5** in the presence of thionyl chloride[7] or its *N*-acylation with *o*-azidobenzoyl chloride followed by an aza-Wittig reaction,[8] were less satisfactory.



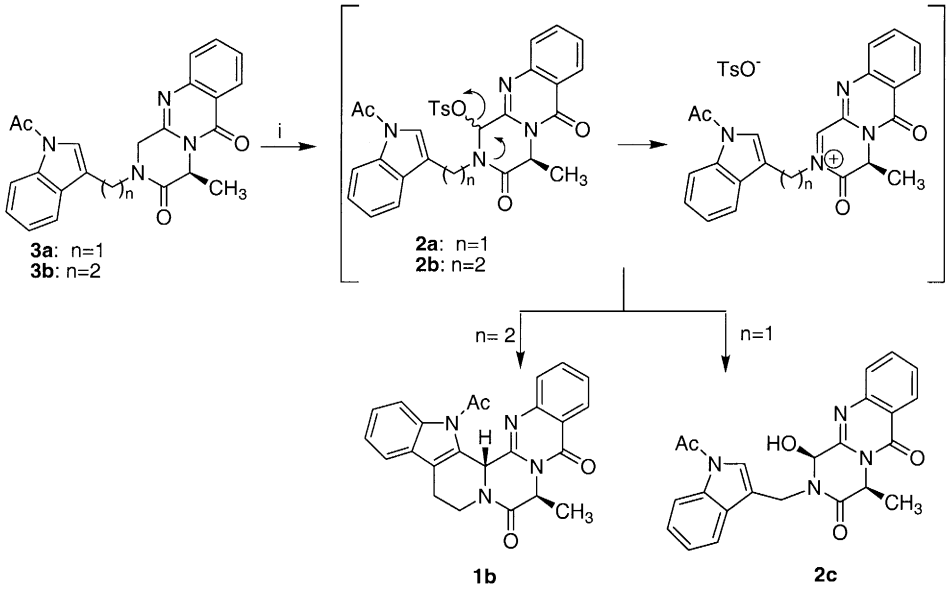
Scheme 1. Reagents and conditions: (i) (a) Cbz-L-Ala, EDC, CH_2Cl_2, rt, 24 h. (b) H_2/Pd–C, MeOH, 20 psi, rt, 3 h. (ii) (a) Et_3OBF_4, CH_2Cl_2, Na_2CO_3, rt, 24 h. (b) Anthranilic acid, 140°C, 2 h. (iii) Ac_2O, pyridine, 140°C, 3 h

We have shown, by using (4*S*)-2,4-dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione as a model compound, that [hydroxy(tosyloxy)iodo]benzene (which is a very efficient reagent for oxidation of ketones to their α-tosyloxy derivatives)[9] leads to the corresponding 1-tosyloxy derivative, and that this compound behaves as an efficient electrophilic glycine template.[10] When this strategy was applied to **3b** (Scheme 2), compound **1b** was isolated directly in 48% yield, after purification of the product by column chromatography. This spontaneous and diastereoselective cyclization presumably involves the acyliminium species[11] generated by elimination of tosylate in the non-isolated oxidation compound **2b**.

The *trans* structure of **1b** was assigned by NMR in combination with NOE difference spectroscopy, where a small enhancement of the methyl signal (1.78 ppm) was observed when the ring junction proton (6.83 ppm) was irradiated. This suggests a pseudoaxial disposition for the methyl group, and consequently, the attached proton must be nearly coplanar between the two carbonyl groups and thus deshielded (q, 5.64 ppm). The diastereoselectivity of this cyclization reflects the effect of the methyl group directing the approach of the π-nucleophile to the opposite less hindered face. In addition, MM2 calculations predict greater stability of the *trans*-isomer by 4.16 Kcal/mol.

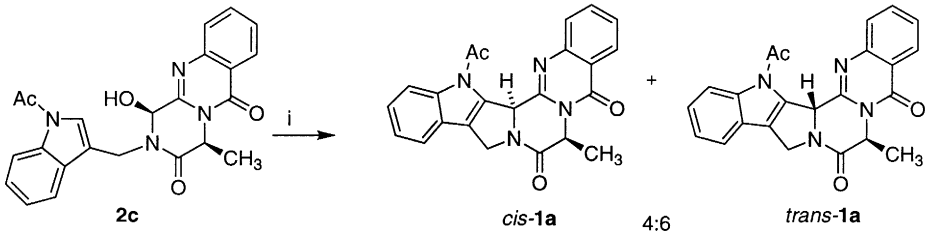
When the same procedure was applied to **3a**, crude tosylate **2a** was isolated but, after column chromatography, was transformed into the *cis*-hydroxy derivative **2c**, formed by addition of water to the acyliminium species originating from **2a**. The *cis* configuration of **2c** was deduced from the absence of NOEs between the methyl group and H-1 proton and is in accordance with previous results of our group.[10]

Drastic conditions were required to promote cyclization of alcohol **2c**. Thus, treatment of **2c** with concentrated sulfuric acid gave a 67% yield of an, up to now, inseparable mixture of the hexacylic



Scheme 2. Reagents and conditions: (i) $(PhI^{+}OH)^{-}OTs$, EtOAc, reflux, 8 h

compounds *trans*-**1a** and *cis*-**1a** in a 6/4 ratio determined by integration of the ring junction proton signals (Scheme 3). The *trans*-isomer was identified due to the analogy of the methyl group (1.91 ppm) and ring junction proton (6.47 ppm) signals with those of *trans*-**1b**. In the *cis*-isomer, the methyl protons resonate at lower chemical shift (1.50 ppm) because of the shielding effect of the indole ring; the ring junction proton signal is displaced significantly to 5.83 ppm. The diastereomeric ratio observed is also in accordance to the calculated relative stability of both isomers.



Scheme 3. Reagents and conditions: (i) concd H_2SO_4, 0°C, 4–8 h

Some experimental data of representative new compounds are shown in Table 1.

Current efforts are directed toward applying this intramolecular cyclization to other aromatic π-nucleophiles, and the results of these investigations will be reported in due course.

Acknowledgements

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Table 1
Representative experimental data of new compounds

Compound	yield (%)	m.p. (°C)	$[\alpha]_D^{25a}$
1b	48	*b*	+84.0 (0.10)
2c	67	*b*	+72.2 (0.10)
3b	55	*b*	+16.0 (0.25)
4b	48	*b*	-
5b	97	180-82	+10.0 (0.30)
6b	65	>230	+24.0 (0.48)

[a] solvent: dichloromethane.[b] not solid

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