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A short synthesis of de-'prenyl'-ardeemin

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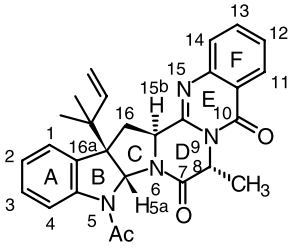
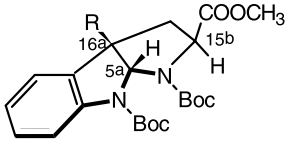
Abstract—A four-step synthesis of the ardeemin framework by starting from *N*-2-aminobenzoyl-α-amino esters is described. In the last step, the acid promoted cyclization of the 1,4-*anti*-4-alkyl-1-(3-indolylmethyl)-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones occurs irreversible and stereocontrolled. © 2003 Elsevier Science Ltd. All rights reserved.

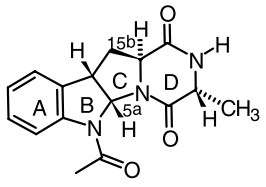
The ability of *N*-acetylardeemin (**1**), a metabolite of the fungus *Aspergillus fischerii* (var. brasiliensis), to restore vinblastine sensitivity to a previously resistant tumour cell line[1,2] led to its inclusion in the great variety of synthetic and naturally occurring MDR reversal agents.[3] The up to now unique total synthesis of **1**, which was developed by Danishefsky (nine steps and 12.5% overall yield),[4,5] involved as the key step the preliminary construction of the pyrroloindole **2a** through a kinetically controlled process followed by introduction of the reverse prenyl group (**2b**). We have shown that precursors of de-'prenyl'-5-acetylardeemin (**5a**), may be obtained as diastereomeric mixtures by acid-promoted cyclization and subsequent acylation of



5-Acetylardeemin (**1**)



2a, R= SePh
(ardeemin numbering)
2b, R= 1,1-dimethylallyl



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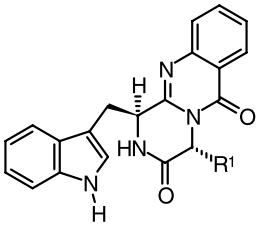
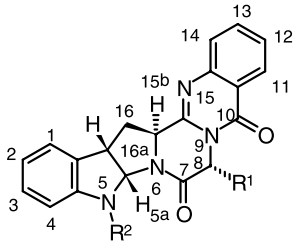


(-)-**4b** R^1= Me
(-)-**4c** R^1= *i*Pr



(-)-**5a** R^1= Me, R^2= Ac
(-)-**5b** R^1= Me, R^2= H
(-)-**5c** R^1= *i*Pr, R^2= H

Figure 1.

Keywords: ardeemins; quinazolinediones; pyrroloindole; acid-promoted cyclizations.

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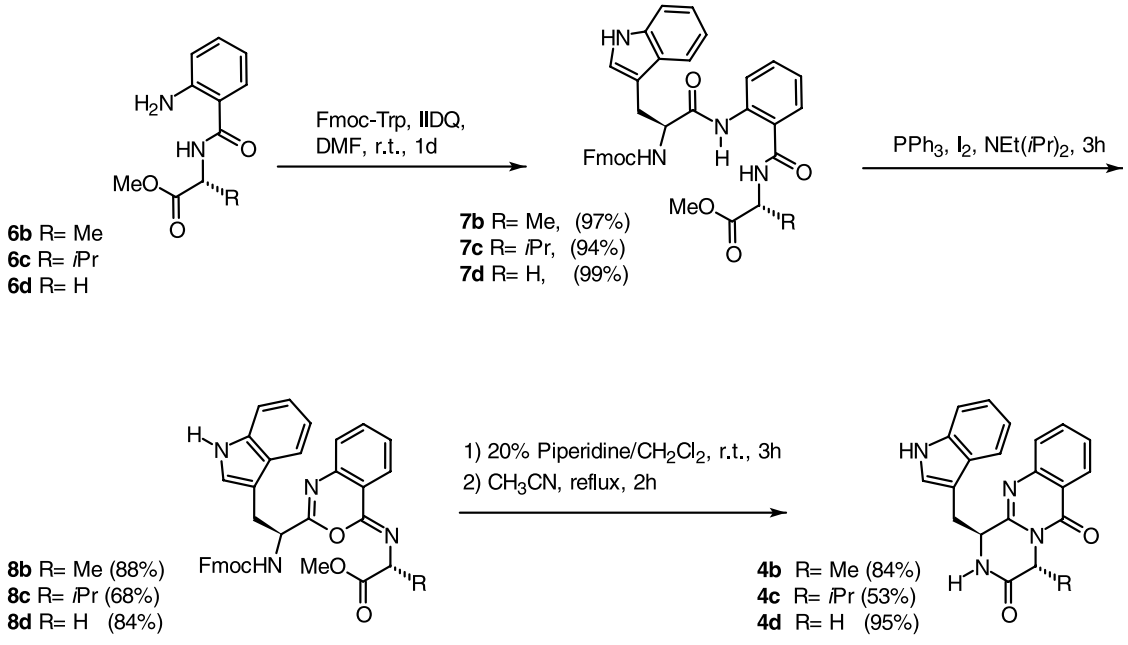
tryptophan *cyclo*-dipeptides.[6] Thus, *cyclo*-(L-Trp-D-Ala) afforded compound **3**, a in 72% d.e.[7] In this paper we report a short and much more efficient protocol to de-'prenyl'- ardeemin (**5b**) and its *iso*-propyl analogue (**5c**) in which the construction of ring C was undertaken in the last stage of the process (Fig. 1).

Scheme 1 outlines the general synthesis of compounds **4**. Acylation of the D-α-amino esters with *o*-nitrobenzoyl chloride under Schotten–Baumann conditions, followed by catalytic hydrogenation of the nitro group (10% Pd/C, 1.5 atm), afforded the aryl amides **6** in 80% overall yield. Reaction of **6** with Fmoc-L-Trp in DMF, using 1-isobutoxycarbonyl-2-isobutoxy-1,2-dihydroquinoline (IIDQ) as coupling reagent,[8] gave compounds **7** in nearly quantitative yields. Cyclization of **7** to benzoxazines **8** was accomplished in 68–88% yield by using triphenylphosphine–iodine and Huning's base in dry dichloromethane.[9,10] Treatment of **8** with 20% piperidine in dichloromethane produced the corresponding piperidine amidine,[11] which was refluxed in acetonitrile (2 h) rearranging[12–14] to the expected 1-(3-indolylmethyl)pyrazino[2,1-*b*]quinazoline-3,6-diones **4** in good overall yields.

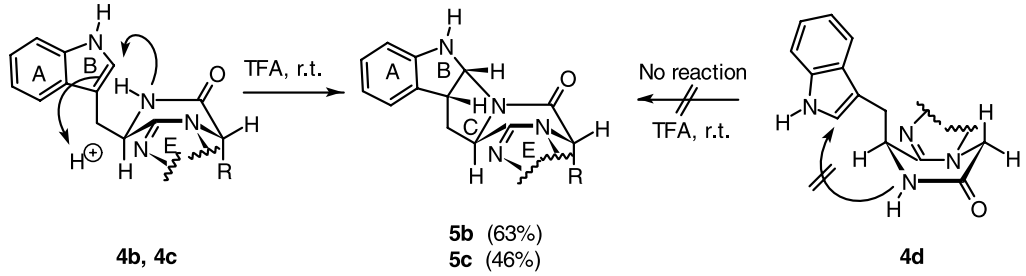
The acid-promoted cyclizations of compounds **4b**,**c** in which the H(5a) and H(15b)-protons (ardeemin numbering) are in an *anti* relationship, were performed in neat trifluoroacetic acid affording the stable compounds (–)-**5b** (63%) and (–)-**5c** (46%) as the only reaction products.[15] The relative configuration of **5** was established unequivocally by NOESY experiments, where the *syn* relationship between the methyl or isopropyl substituent at C(8) and the H(15b)-proton was observed.[16]

When **4d** was submitted to acid promoted cyclization only starting material was recovered,[17] in spite of the different reaction conditions assayed. This failure may be due to an inadequate conformation of the indole ring, which is pseudoaxial in this compound instead of pseudoequatorial as in **4b**,**c** (Scheme 2). This pseudoaxial disposition was confirmed by NOESY experiments (NOE between H-4_{ax} and H-2′ of the indolyl moiety) and by the chemical shift of the C-1 carbon atom.[18]

In summary, the ardeemin framework can be approached stereoselectively by acid promoted cyclization of 1,4-*anti*-4-alkyl-1-(3-indolylmethyl)pyrazino[2,1-*b*]quinazoline-3,6-diones. De-'prenyl' ardeemin (–)-**5b**



Scheme 1.



Scheme 2.

was obtained in four steps and 45% overall yield starting from *N*-2-aminobenzoyl-D-Ala methyl ester.

Acknowledgements

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15. *General procedure for cyclization to de-'prenyl' ardeemin*: The corresponding 1-(3-indolylmethyl) derivative **4b**,**c** (0.207 mmol) was added in one portion to TFA (5 mL). The solution was stirred for 20 min (compound **4b**) or 2.30 h (compounds **4c**) and was poured onto an externally ice-cooled, vigorously stirred, two-phase system of CH_2Cl_2 (20 mL) and 20% aqueous K_2CO_3 (20 mL). The pH of the aqueous layer was adjusted to 7 and was extracted with $CHCl_3$. The organic layers were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography (ethyl acetate/petroleum ether, (8:2 for **5b**) and (6:4 for **5c**)). **5b**: mp 208–209°C; $[\alpha]_D^{25}$ −218.1 (*c* 0.16, $CHCl_3$); IR (NaCl) 3336, 1676, 1605, 1469 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25 (dd, 1H, $J=1.3$ and 8.1 Hz, H-11), 7.75 (ddd, 1H, $J=1.3$, 7.1 and 8.3 Hz, H-13), 7.64 (dd, 1H, $J=1.2$ and 8.3 Hz, H-14), 7.48 (ddd, 1H, $J=1.2$, 7.1 and 8.1 Hz, H-12), 7.22 (d, 1H, $J=7.7$ Hz, H-1), 7.11 (dt, 1H, $J=0.8$ and 7.7 Hz, H-3), 6.80 (dt, 1H, $J=0.8$ and 7.7 Hz, H-2), 6.65 (d, 1H, $J=7.7$ Hz, H-4), 5.79 (d, 1H, $J=6.8$ Hz, H-5a), 5.46 (q, 1H, $J=7.2$ Hz, H-8), 5.19 (br s, 1H, N-H^i), 4.61 (dd, 1H, $J=6.3$ and 10.5 Hz, H-15b), 4.13 (t, 1H, $J=7.0$ Hz, H-16a), 3.08 (dd, 1H, $J=6.3$ and 13.2 Hz, H-16), 2.75 (ddd, 1H, $J=7.2$, 10.5 and 13.2 Hz, H-16), 1.51 (d, 3H, $J=7.2$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.7, 159.9, 150.7, 149.0, 147.0, 134.6, 128.7, 127.3, 127.2, 127.1, 126.8, 124.2, 120.4, 119.4, 109.3, 75.9, 57.2, 53.3, 44.5, 35.8, 16.7. Anal. calcd for $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 15.63. Found: C, 69.97; H, 5.46; N, 15,47.
16. The enantiomeric purity was measured by chiral HPLC using a Chiracel OD column (26 cm×0.25 cm), UV-detection at 254 nm, employing hexane/2-propanol 9/1.
17. **4d**: ^1H NMR (500 MHz, $CDCl_3/CD_3OD$) δ 8.02 (dd, 1H, $J=1.5$ and 8.1 Hz, H-7), 7.76 (ddd, 1H, $J=1.5$, 7.0 and 8.3 Hz, H-9), 7.68 (dd, 1H, $J=1.4$ and 8.3 Hz, H-10), 7.42 (ddd, 1H, $J=1.4$, 7.0 and 8.1 Hz, H-8), 7.22 (d, 1H, $J=8.0$ Hz, H-4′), 6.92 (dt, 1H, $J=0.8$ and 8.0 Hz, H-6′), 6.88 (s, 1H, H-2′), 6.78 (d, 1H, $J=8.0$ Hz, H-7′), 6.51 (dt, 1H, $J=0.8$ and 8.0 Hz, H-5′), 4.83 (t, 1H, $J=4.3$ Hz, H-1), 4.24 (d, 1H, $J=18.8$ Hz, H-4), 3.49 (dd, 1H, $J=4.6$ and 14.6 Hz, $\underline{CH_2}$-Ar), 3.26 (dd, 1H, $J=4.0$ and 14.6 Hz, $\underline{CH_2}$-Ar), 2.54 (d, 1H, $J=18.8$ Hz, H-4); ^{13}C NMR (125 MHz, $CDCl_3/CD_3OD$) δ 167.1 (C3), 160.8 (C6), 151.7 (C11a), 147.3 (C10a), 136.6 (C7′a), 135.4 (C9), 127.6 (C8), 127.0 (C3′a), 126.9 (C10), 126.8 (C7), 125.5 (C2′), 122.3 (C6′), 119.7 (C5′), 117.6 (C7′), 111.9 (C4′), 107.3 (C3′), 57.1 (C1), 44.5 (C4), 33.7 (CH_2Ar).
18. In 1,4-dialkylated pyrazino[2,1-*b*]quinazoline-3,6-diones the piperazine ring adopts for both diastereoisomers a flat boat conformation, being the C(4)-substituent always pseudoaxial despite of its relative size.[19] In monoalkylated pyrazino[2,1-*b*]quinazoline-3,6-diones, both alternatives, C(1) as well as C(4)-substitution, always adopt a pseudoaxial disposition.[20] The chemical shift values of the C-1 carbon atom are higher in these compounds compared to the 1,4-*anti* isomers, where the C-1 substituent is pseudoequatorial ($\delta \sim 52$).
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