Synthesis of Racemic, N-Benzylated Neoechinulin A and Isoneoechinulin A[1]

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Abstract: Two N-benzylated analogues of the antioxidant, radical scavenging, and neuroprotective alkaloid neoechinulin A were prepared. Since, according to SAR studies, stereochemistry does not play an important role, both analogues were prepared in racemic form, using enaminone chemistry.

Key words: N-benzylated alkaloid analogues, neoechinulin A, diketopiperazines, enaminones, 2-isoprenylated, 2-prenylated indoles

Neoechinulin A is a simple indole alkaloid most abundantly produced by microorganisms of *Aspergillus* sp., such as *A. amstelodami*,[2] *A. ruber*[3] and *A. repens*,[4] others including *Eurotium rubrum*,[5] *Xylaria euglossa*,[6] *Chaetomium globosum*,[7] and plants like *Bridelia ferruginea*.[8] The alkaloid has been isolated from these species by several research groups and also its total synthesis was already accomplished.[9] In the literature there are several reports on the strong antioxidant, radical scavenging, and neuroprotective properties of neoecinulin A. Doi et al. reported antioxidative activities in ferric thiocyanate and thiobarbituric acid tests in which neoechinulin A showed better antioxidative activity than α-tocopherol.[4] Son et al. demonstrated very good free radical scavenging activity of neoechinulin A in a DPPH (1,1-diphenyl-2-picrylhydrazyl) assay;[10] while Arai et al. reported neuronal cell protective properties of neoechinulin A against peroxynitrite, a very potent reactive nitrogen species (RNS) capable of oxidizing biomolecules and nitrating tyrosine residues. Peroxynitrite is formed from nitric oxide and superoxide, endogenous free radicals present in several pathogenic processes including sepsis,[11] Alzheimer's and Parkinson's disorders.[12] Neoechinulin A thus represents an interesting lead compound for the design of new therapeutics for the treatment of peroxynitrite caused disorders.

Recently, we have demonstrated that enaminones can be successfully used in the synthesis of various heterocyclic systems[13] and some simple diketopiperazine-based indole alkaloid analogues with the α,β-unsaturated Trp moiety, such as dipodazine,[14] tryprostatin B,[15] and others like meridianines[16] and aplysinopsines.[17] Based on our previous work and the SAR studies of Arai et al.,[18] we envisaged preparing novel neoechinulin A analogues. As reported earlier, the diketopiperazine structure of neoechinulin A, together with its exocyclic double bond and indole moiety, is crucial for concomitant antioxidative, antinitration, and cytoprotective activity.[18] Though the mechanism of action of neoechinulin A still remains uncertain, it is postulated that the alkaloid's cytoprotective properties are due to its ability to induce antioxidizing enzymes by reacting with biomacromolecules; or that neoechinulin A can directly react with RNS and/or ROS (reactive oxygen species) and alkyl radicals.[18] To clarify this question, additional research has to be conducted involving SAR of novel neoechinulin A analogues. Since the absolute stereochemistry of the center in position 6 of neoechinulin A is not important for biological activity,[18a] we proposed preparing two racemic analogues **1** and **2**, with the *N*-benzyl group in position 1 of the diketopiperazine ring. This would increase lipophilicity of the analogues **1** and **2** compared to neoechinulin A and also reduce the number of hydrogen-bond donors, resulting in additional SAR information. Analogue **1** possesses the isoprenyl group of neoechinulun A at the indole 2-position; whereas analogue **2** features the prenyl group (Figure 1).

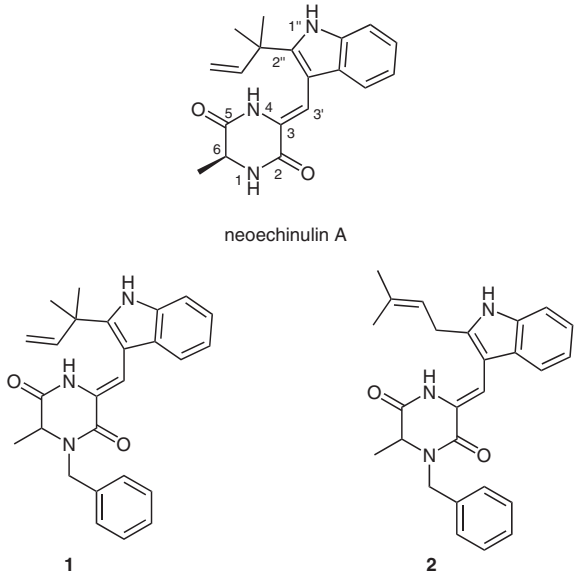

Figure 1 Neoechinulin A and analogues **1** and **2**

The synthesis of both analogues started from the methyl ester of (*R*,*S*)-alanine hydrochloride (**3**), which was reductively N-benzylated with benzaldehyde using sodium cyanoborohydride to give the *N*-benzyl methyl ester of (*R*,*S*)-alanine (**4**). This was then reacted with chloroacetyl chloride to form the methyl ester of (*R*,*S*)-*N*-benzyl-*N*-

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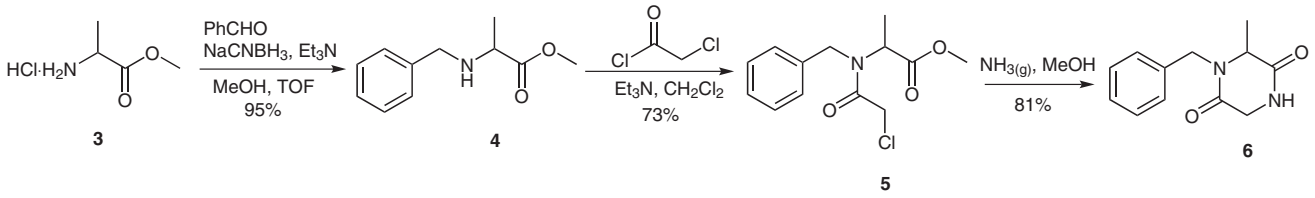
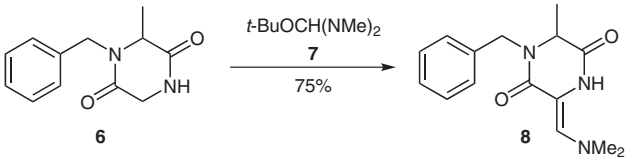


Scheme 1 Synthesis of diketopiperazine precursor **6**

chloroacetyl alanine (**5**) that was cyclized with ammonia in methanol into (*R*,*S*)-1-benzyl-6-methylpiperazine-2,5-dione (**6**, Scheme 1).

Previously we have already reported on compound **6** in the context of its chiral solvating properties[19] and dipodazine analogues synthesis.[14] Diketopiperazine **6** was then reacted with *t*-BuO-bisdimethylaminomethane (Bredereck's reagent, **7**) to furnish (*Z*)-(*R*,*S*)-1-benzyl[(dimethylamino)methylidene]-6-methylpiperazine-2,5-dione (**8**, Scheme 2).

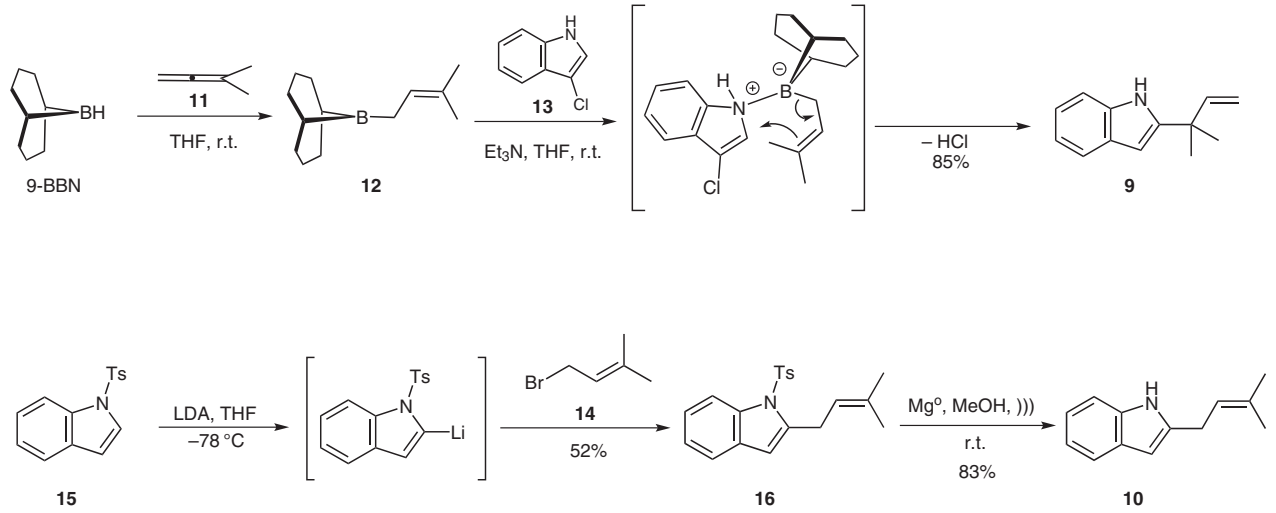


Scheme 2 Synthesis of enaminone **8** for direct coupling with 2-isoprenylindole (**9**) and 2-prenylindole (**10**)

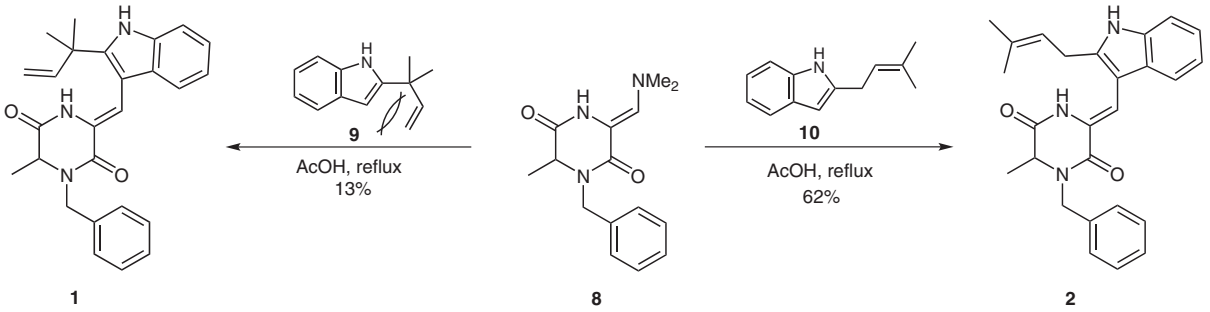
2-Isoprenylindole (**9**) was prepared using a similar procedure to that reported by Danishefsky in his tryprostatin B synthesis (where the analogous 2-isoprenylated tryptophan derivative was prepared[20]) from 9-(3-methylbut-2-enyl)-9-borabicyclo[3.3.1.]nonane (**12**), prepared by modified procedure of Brown,[21] and 3-chloroindole (**13**). We found out that this is a very simple two-step, one-pot synthesis of 2-isoprenylated indole (**9**). 2-Prenylated indole (**10**) was prepared from prenylbromide **14** with the lithiated derivative of *N*-tosylindole (**15**), followed by reductive detosylation of 2-prenylated *N*-tosylindole (**16**) with Mg powder in methanol (Scheme 3).[15b]

Next 2-isoprenylindole (**9**) and 2-prenylindole (**10**) were coupled with the enaminone **8**, affording targets **1** and **2**. In the case of reaction of 2-isoprenylindole (**9**) with enaminone **8**, the reaction yield was much lower in comparison to reaction of 2-prenylated indole (**10**) with enaminone **8**. The reason for this is presumably the greater steric shielding of nucleophilic position 3 of indole derivative **9** than in **10**. We have previously used bulkier substituents at position 2 of indole for similar coupling reactions, 2-phenylindole for example, but the yields were always better than in the case of 2-isoprenylated indole (**9**).[14,15a] In the case of 2-phenylindole the phenyl ring is perpendicular to the indole ring and is thus sterically much less demanding for such coupling reactions than 2-isoprenylated derivative **9**, where the indole core is attached to the quaternary sp^3 carbon of the isoprenyl chain (Scheme 4).

The structures of **1** and **2** were determined spectroscopically (NMR, IR) by MS and in the case of prenylated analogue **2** by elemental analysis. Their spectroscopic data are in agreement with those reported for neoechinulin A.[9] Both compounds were isolated as *Z*-isomers as established by HMBC spectroscopy on the basis of the long-range coupling constant ^3J(C,H) between the methylidene proton $C^{3'}$–H and carbonyl C atom C^2=O determined from the antiphase splitting of the corresponding cross-peak (Figure 2).[22]



Scheme 3 Synthesis of 2-isoprenylindole (**9**) and 2-prenylindole (**10**)



Scheme 4 Coupling of 2-isoprenylindole (**9**) and 2-prenylindole (**10**) with enaminone **8** – synthesis of targets **1** and **2**

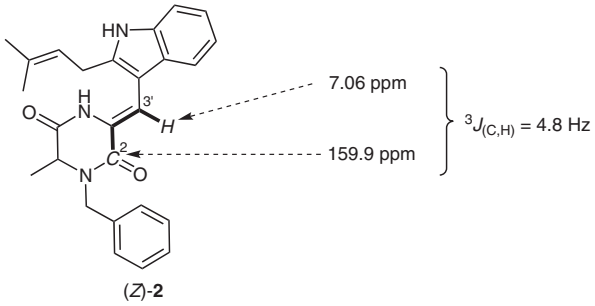


Figure 2 Configuration around exocyclic double bond was determined by using a NMR HMBC experiment

In summary, two N-benzylated analogues **1** and **2** of neoechinulin A have been prepared, using direct coupling of 2-isoprenylated (**9**) and 2-prenylated (**10**) indoles with enaminone **8**. This synthetic methodology represents a viable alternative to Horner–Wadsworth–Emmons olefination, frequently used for synthesis of α,β-unsaturated-α-amino acids. Both analogues **1** and **2** are more lypophilic in comparison to neoechinulin A and represent valuable compounds in additional SAR studies for clarification of its antinitration, antioxidative, and cytoprotective mechanism of action.

3-Chloroindole (13)

Indole (2.93 g, 25 mmol) was disolved in DMF (18 mL) at 0 °C, and NCS (3.67 g, 27.5 mmol) was added. After 15 min at 0 °C, the reaction mixture was stirred at r.t. for an additional 45 min, and then the reaction mixture was poured in 150 mL of ice-cold water and $K_2S_2O_5$ (2.15 mg). The precipitate was filtered, dissolved in CH_2Cl_2 (30 mL) and extracted with H_2O (4 × 30 mL). The organic phase was then dried over Na_2SO_4 and concentrated at 100 mbar and 25 °C. The residual yellowish-green solid of crude 3-chloroindol (**13**) showed spectroscopic data corresponding to the literature data;[23] yield 3.25 g (86%), compound decomposed on heating. IR (KBr): ν_{max} = 3409, 3126, 3051, 1719, 1617, 1519, 1453, 1332, 1289, 1205, 1087, 1000, 929, 810, 740, 596 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 7.05–7.14 (1 H, m, Ar), 7.14–7.23 (1 H, m, Ar), 7.38–7.45 (1 H, m, Ar), 7.45–7.47 (2 H, m, Ar), 11.33 (1 H, s, NH). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.15–7.18 (1 H, m, Ar), 7.19–7.28 (2 H, m, Ar), 7.25–7.39 (1 H, m, Ar), 7.60–7.67 (1 H, m, Ar), 8.05 (1 H, br s, NH). MS (EI): *m/z* = 151 [M^+].

2-(2-Methylbut-3-en-2-yl)-1-*H*-indole (9)

All glass ware was dried in a vacuum oven at 100 °C, for an hour before use. To 9-BBN (29.4 mL, 0.5 M in THF) 3-methylbuta-1,2-diene (**11**) (1.44 mL,14.7 mmol) was added under inert atmosphere, and the reaction mixture was stirred at r.t. for 3.5 h. After that time, Et_3N (1.23 mL, 8.82 mmol) and 3-chloroindole (**13**) (1.11 g, 7.35 mmol) were added, and the reaction mixture was stirred for an additional 17 h. Saturated aq NaCl was poured in the reaction mixture, and THF was removed under vacuum. The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic phases dried over Na_2SO_4 and concentrated under vacuum. The brown oily residue was purified by column chromatography (EtOAc–PE = 1:40), and the product was isolated as yellow oil; yield 1.17 g (85%). IR (KBr): ν_{max} = 3422, 2968, 1637, 1542, 1459, 1406, 1289, 1234, 998, 918, 786, 749, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (6 H, s, 2 × CH_3), 5.12 (1 H, dd, J_1 = 1.1 Hz, J_2 = 17.3 Hz, CH), 5.10 (1 H, dd, J_1 = 1.1 Hz, J_2 = 10.4 Hz, CH), 6.05 (1 H, dd, J_1 = 10.3 Hz, J_2 = 17.6 Hz, CH), 6.51 (1 H, dd, J_1 = 0.9 Hz, J_2 = 2.1 Hz, Ar), 7.06 (1 H, dt, J_1 = 1.2 Hz, J_2 = 6.1 Hz, Ar), 7.12 (1 H, dt, J_1 = 1.2 Hz, J_2 = 7.0 Hz, Ar), 7.25–7.33 (1 H, m, Ar), 7.50–7.60 (1 H, m, Ar), 7.86 (1 H, br s, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.6, 38.4, 98.2, 110.6, 112.4, 119.8, 120.3, 121.5, 128.8, 136.1, 146.0, 146.3. MS (EI): *m/z* = 185 [M^+]. HRMS (EI): m/z calcd for $C_{13}H_{15}N$ [M^+]: 186.1283; found: 186.1279.

(*Z*)-1-Benzyl-3-[(dimethylamino)methylidene]-6-methylpiperazine-2,5-dione (8)

For the experimental data on compound **8** see ref. 13.

(*Z*)-(1)-Benzyl-6-methyl-3-{[2-(2-methylbut-3-ene-2-yl)-1*H*-indol-3-yl]methylidene}-piperazine-2,5-dione (1)

To enaminone **8** (0.547 g, 2 mmol) dissolved in glacial AcOH (4 mL), 2-isoprenylindole (**9**) (0.621 g, 3.35 mmol) was added, and the reaction mixture was refluxed for 7 h. The mixture was then cooled and concentrated under vacuum, and the residue was purified by column chromatography (EtOAc–PE = 1:2). The yellow oil thus obtained was crystallized from CH_2Cl_2 and heptane; yield 0.107 g (13%) of pale yellow solid, mp 249–252 °C. IR (KBr): ν_{max} = 3365, 3328, 2973, 1703, 1657, 1610, 1492, 1449, 1433, 1391, 1340, 1248, 11911149, 995, 917, 878, 751, 702, 609 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.56 (3 H, d, *J* = 6.9 Hz, CH_3), 4.02 (1 H, q, *J* = 6.9 Hz, CH), 4.17 (1 H, d, *J* = 15.0 Hz, CH), 5.20 (1 H, dd, J_1 = 0.7 Hz, J_2 = 17.4 Hz, CH), 5.23 (1 H, dd, J_1 = 0.7 Hz, J_2 = 10.6 Hz, CH), 5.42 (1 H, d, *J* = 15.0 Hz, CH), 6.09 (1 H, dd, J_1 = 10.6 Hz, J_2 = 17.4 Hz, CH), 7.10–7.23 (2 H, m, Ar), 7.30–7.42 (7 H, m, Ar), 8.28 (1 H, br s, NH). ^1H NMR (300 MHz, DMSO-d_6): δ = 1.47 (3 H, d, *J* = 6.3 Hz, CH_3), 1.48 (3 H, s, CH_3), 1.51 (3 H, s, CH_3), 3.94 (1 H, q, *J* = 6.9 Hz, CH), 4.33 (1 H, d, *J* = 14.6 Hz, CH), 5.04 (1 H, d, *J* = 14.8 Hz, CH), 5.06 (1 H, dd, J_1 = 1.1 Hz, J_2 = 17.6 Hz CH), 5.07 (1 H, dd, J_1 = 1.2 Hz, J_2 = 10.2 Hz, CH), 6.09 (1 H, dd, J_1 = 10.9 Hz, J_2 = 16.9 Hz, CH), 6.96–7.20 (4 H, m, 3 H of Ar, CH), 7.26–7.46 (6 H, m, Ar), 9.18 (1 H, s, NH), 11.05 (1 H, s, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 18.5, 27.4, 27.7, 46.9, 56.0, 103.8, 111.5, 111.7, 112.4, 118.9, 119.3, 120.6, 123.8, 126.1, 127.4, 127.9, 128.6, 135.1, 137.2, 144.3, 145.1, 159.6, 166.0. MS (EI): *m/z* = 414 [MH^+]. HRMS (EI): m/z calcd for $C_{26}H_{27}N_3O_2$: 414.2182 [MH^+]; found: 414.2170.

(*Z*)-1-Benzyl-6-methyl-3-{[2-(3-methylbut-2-enyl)-1*H*-indol-3yl]methylene}piperazine-2,5-dione (2)

To enaminone **8** (0.547 g, 2 mmol) dissolved in glacial AcOH (4 mL), 2-prenylindole (**10**) (0.371 g, 2 mmol) was added, and the reaction mixture was refluxed for 2 h. The mixture was then cooled and concentrated under vacuum, and the residue was purified by column chromatography (EtOAc–PE = 1:2). The resultant orange foam was crystallized from MeOH–H_2O; yield 0.514 g (62%) of yellow solid, mp 138–141 °C. IR (KBr): ν_{max} = 3258, 3063, 2976, 1661, 1624, 1539, 1494, 1444, 1406, 1351, 1256, 1164, 1098, 984, 880, 788, 743 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.45 (3 H, d, J = 6.9 Hz, CH_3), 1.72 (6 H, s, 2 × CH_3), 3.42 (1 H, dd, J_1 = 7.0 Hz, J_2 = 16.9 Hz, CH), 3.51 (1 H, dd, J_1 = 7.0 Hz, J_2 = 16.9 Hz, CH), 3.96 (1 H, q, J = 6.9 Hz, CH), 4.30 (1 H, d, J = 15 Hz, CH), 5.07 (1 H, d, J = 15.0 Hz, CH), 5.31 (1 H, dd, J_1 = 7.0 Hz, J_2 = 7.1 Hz, CH), 7.00–7.25 (3 H, m and s, Ar and CH), 7.25–7.43 (7 H, m, Ar), 9.44 (1 H, s, NH), 11.30 (1 H, s, NH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 17.7, 18.3, 25.5, 25.9, 46.9, 56.1, 104.7, 111.0, 111.2, 119.0, 119.5, 120.3, 120.8, 123.2, 126.4, 127.4, 127.8, 128.6, 133.0, 135.9, 137.3, 140.0, 159.9, 166.2. HMBC: δ = 7.06 (CH), 159.9 (CO, J = 4.8 Hz). MS (EI): m/z = 414 [MH^+]. HRMS (EI): m/z calcd for $C_{26}H_{27}N_3O_2$: 414.2182 [MH^+]; found: 414.2171. Anal. Calcd for $C_{26}H_{27}N_3O_2$: C, 75.52; H, 6.58; N, 10.16. Found: C, 75.29; H, 6.39; N, 10.21.

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References and Notes

(1) The term isoneoechinulin A is proposed by authors of this work and refers to the prenyl group replacing the isoprenyl group in neoechinulin A. This nomenclature is used for naming compound **2**.

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