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TOTAL SYNTHESIS OF (±)-NEOECHINULIN A, AN INDOLE ALKALOID CONTAINING OXIDIZED DIKETOPIPERAZINE[1]

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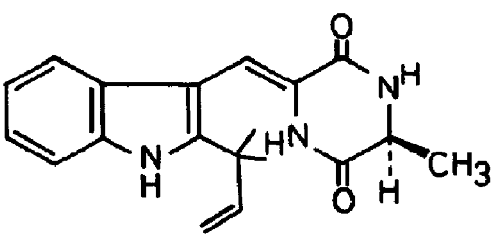
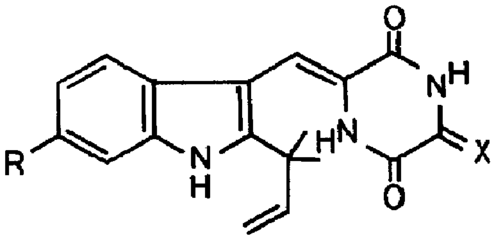
Protected neoechinulin A (*Z* isomer) and its *E* isomer were synthesized by condensation of N-bis(methylthiomethyl)cyclo(Ala-Gly) with 2-(1,1-dimethyl-2-propenyl)-1-methoxymethylindole-3-aldehyde; deprotection of both isomers gave neoechinulin A, whose *Z* configuration was rigorously established. A novel cyclization of the protected neoechinulin A into a seven-membered cyclic compound was reported.

Neoechinulin A has been isolated from *Aspergillus ruber*[2,3] and *Aspergillus amstelodami*.[4] The structure was elucidated as 1; *Z* configuration of the 8,9-double bond being assumed, without rigorous establishment, from the chemical shift,[4] solvent effects[4] and ^{13}C nmr signal[5] of the vinyl proton. Inoue et al.[6] synthesized neoechinulin (2a), and neoechinulin B (2b) and C (2c), but their method could not be applied for the synthesis of neoechinulin A (1). Recently Yonemitsu et al.[7] achieved an elegant one-step synthesis of neoechinulin A by oxidation of a cyclo(Try-Ala) derivative with DDQ. This method, however, diminishes its value in its low yield (25%) and in necessity of a multi-step synthsis to obtain the starting



Neoechinulin A (1)



Neoechinulin (2a) R=$CH_2CH=C(CH_3)_2$, X=O
Neoechinulin B (2b) R=H, X=CH_2
Neoechinulin C (2c) R=$CH_2CH=C(CH_3)_2$, X=CH

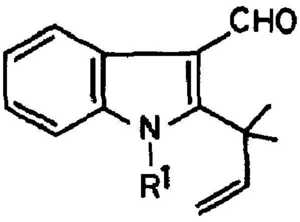
2-(1,1-dimethyl-2-propenyl)tryptophan from 2-(1,1-dimethyl-2-propenyl)indole. Our synthetic strategy of neoechinulin A is the regiospecific aldol condensation[8] of protected cyclo(Ala-Gly (**6**) with easily accessible 2-(1,1-dimethyl-2-propenyl)indole-3-aldehyde (**3**).

The indole-aldehyde[9] **3** was treated with sodium hydride and chloromethyl methyl ether in dimethylformamide at room temp to give the methoxymethyl derivative **4** (75%), mp 60-61°C. Cyclo(L-Ala-Gly) (**5**)was also protected by treatment of sodium hydride and chloromethyl methyl thioether in dimethylformamide at room temp to afford the (racemic)[10] bis(methylthiomethyl) derivative **6** (70%), mp 86-87°C.

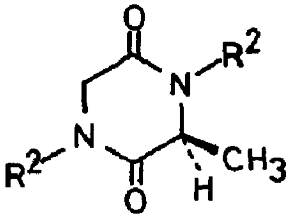
Regiospecific aldol condensation between **4** and **6** was achieved as follows: lithium diisopropylamide (1.2 eq) in tetrahydrofuran (THF) was added dropwise to the solution of **6** in THF at -78°C, followed by addition of THF solution of **4**, and the mixture was warmed up to 0°C. After the addition of methanesulfonyl chloride (1.2 eq) the reaction mixture was allowed to stand at room temp for 1 h. The usual work-up and column chromatography on silica gel gave the _Z_ isomer (**7**_Z_) (55%), mp 152-3°C, and _E_ isomer (**7**_E_) (5%), mp 165-6°C, of the protected neoechinulin A. Stereochemistry of **7**_Z_ and **7**_E_ was rigorously established chemically; by the following reaction **7**_Z_, but not **7**_E_, afforded the novel cyclic compound **9**.[13]

7_Z_ was treated with CH$_3$I in the presence of NaHCO$_3$ in aq acetone at 40°C for 3 days. The reaction mixture was filtered and dried up _in vacuo_.[16] The residue was dissolved in dioxan and heated at 100°C for 1 h. Chromatography on silica gel gave 1-methoxymethyl-neoechinulin A (**8**_Z_), mp 223-4°C (60%) [nmr (CDCl$_3$) 7.22 ppm (1H, s, H-8)], and the cyclic compound **9** (32%), amorphous. The structure of **9** was confirmed by acid hydrolysis with aq formic acid (1:1) to crystalline **10** (72%), mp 131-3°C (sealed tube) [m/e 335 (M$^+$); nmr (CD$_3$OD) ppm 1.33 (3H, d, J=7 Hz), 1.60 (6H, s), 4.02 (1H, q, J=7), 4.80 (1H, d, J=15), 4.86 (1H, d, J=15), 5.05-5.25 (2H, m), 6.15 (1H, dd, J=10 and 18), 6.88 (1H, br.d, J=7), 7.63 (1H, s)]. In the same reaction condition **7**_E_ gave only **8**_E_ (70%), glass [nmr (CDCl$_3$) 6.30 ppm (1H, s, H-8)], and **9** was not detected in the reaction mixture.

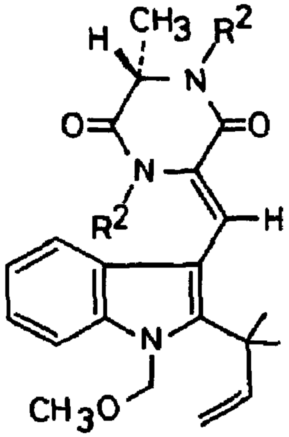
Hydrolysis of both **8**_Z_ and **8**_E_ with aq formic acid (1:1) at room temp for 2 h afforded the same (±)-neoechinulin A (**1**) (90% from both isomers), mp 260°C (sealed tube, decomp.);[18] the _E_ isomer of neoechinulin A was not detected even under irradiation of visible light. The spectral data (nmr, uv, and ir) as well as mp of the synthetic **1** are identical with those of natural neoechinulin A.[3, 17] The stereochemistry of the double bond in **1** was confirmed by



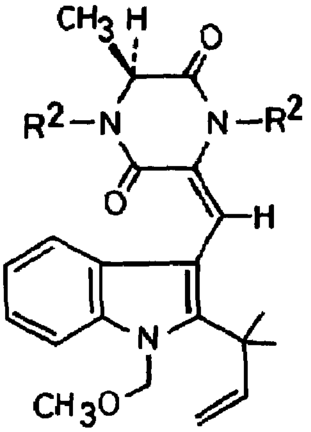
3 R^1=H
4 R^1=CH_2OCH_3



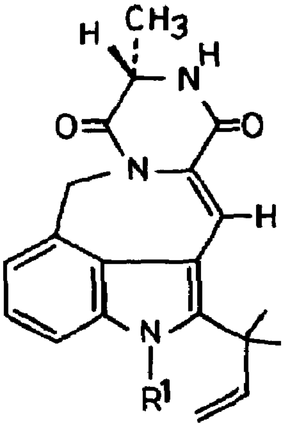
5 R^2=H
6 R^2=CH_2SCH_3



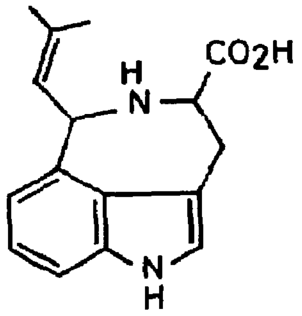
7Z R^2=CH_2SCH_3
8Z R^2=H



7E R^2=CH_2SCH_3
8E R^2=H



9 R^1=CH_2OCH_3
10 R^1=H



Clavicipitic acid (**11**)

comparison of the chemical shift of the vinyl proton with that of Z and E isomers of **8** [**1**: 7.15 ppm; **8Z**: 7.22 ppm; **8E**: 6.30 ppm (solvent: $CDCl_3$)].

Interestingly, compound **9** and **10** are closely related to clavicipitic acid (**11**)[19] produced by Claviceps fusiformis.

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9. K. Tomita, A. Terada and R. Tachikawa, Heterocycles, 4, 733 (1976).
10. Racemization occurred during the protection as determined by nmr using $Eu(d\text{-}TFC)_3$.
11. **7Z**: nmr ($CDCl_3$) ppm 1.74 (6H, s). 1.79 (3H, d, J=7Hz), 1.99, 2.15, 3.36 (each 3H, s), 3.77 (1H, d, J=14). 4.13 (1H, d, J=14), 4.51 (1H, q, J=7). 5.02 (1H, d, J=14), 4.95-5.20 (2H, m) 5.21 (1H, d, J=14), 5.49 (2H, s), 6.22 (1H, dd, J=11 and 18), 7.00-7.45 (4H, m), 7.75 (1H, s); λ_{max} (MeOH) nm (logε) 223 (4.52), 283 (sh), 293 (sh), 322 (4.12).
12. **7E**: nmr ($CDCl_3$) ppm 1.65 (6H, s), 1.74 (3H, d, J=7Hz), 1.96, 2.28, 3.30 (each 3H, s), 4.18 (1H, d, J=14), 4.33 (1H, q, J=7), 4.68 (1H, d, J=14), 4.80 (1H, d, J=14), 5.00-5.16 (2H, m), 5.10 (1H, d, J=14), 5.42 (1H, d, J=11), 5.46 (1H, d, J=11), 6.22 (1H, dd, J=10 and 18), 6.97 (1H, s), 7.0-7.4 (4H, m); λ_{max} (MeOH) nm (logε) 226 (4.59), 267 (4.14), 330 (3.82).
13. NOE experiment [10% NOE was observed on one of the $N\text{-}C\underline{H_2}SCH_3$ of **7E** by irradiation at the vinyl proton (H-8)] and the deshielding effect[14] of the carbonyl group on the vinyl proton of **7Z** also support this conclusion. Exposure of the solution of **7Z** in CH_2Cl_2 to visible light (500W tungusten lamp) at room temp for 24 h gave ca 3:1 mixture of **7Z** and **7E**:[15] the same reaction mixture was also obtained from **7E**.
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15. Recently a similar isomerization was reported in roquefortin [P. M. Scott, J. Polonsky and M. A. Merrien, J. Agric. Food Chem., 27, 201 (1979)].
16. The products were N-monohydroxymethyl derivatives of **8Z** and **9** in this stage.
17. Some physical data of **1** reported in Ref. 2 and 4 differ from those in Ref. 3; the former data may be erroneous.
18. **1**: m/e 323, 254: ν_{max} (KBr) cm^{-1} 3460, 1685, 1635; λ_{max} (MeOH) nm (logε) 223 (4.48), 283 (3.94), 289 (3.93), 335 (4.02); nmr ($DMSO\text{-}d_6$) ppm 1.38 (3H, d, J=7Hz), 1.49 (6H, s), 4.13 (1H, q, J=7), 4.89-5.02 (2H, m), 6.02 (1H, dd, J=10 and 18), 6.84 (1H, s), 6.9-7.4 (4H, m), 8.24, 8.54, 10.94 (each 1H, br.s).
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