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Method for Synthesis of 12H-pyrido[1,2-a:3,4-b']diindoles. Total Synthesis of Homofascaplysin C.

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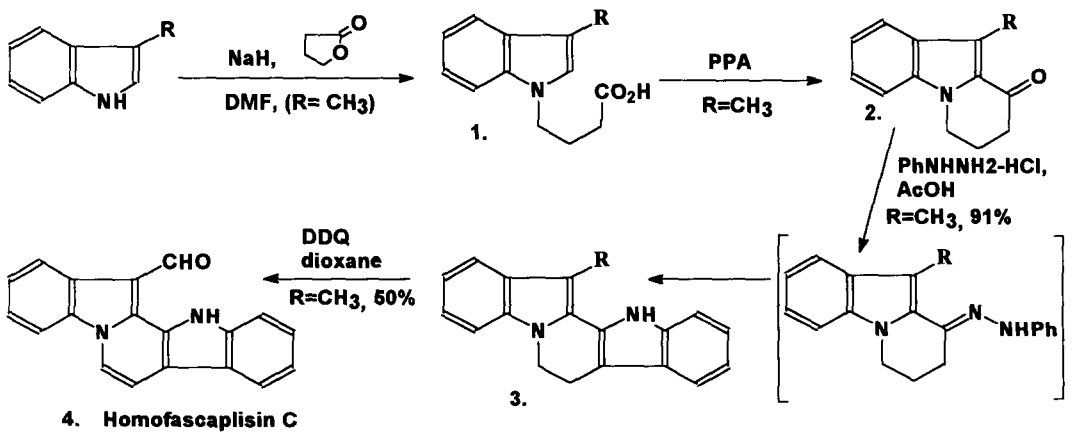
Abstract. An efficient synthesis of a 12H-pyrido[1,2-a:3,4-b']diindole system is proposed. 3-Methylindole has been converted into homofascaplysin C by a four reaction sequence in which the last step is dehydrogenation and oxidation of the methyl- to formyl group at the same time. Copyright © 1996 Elsevier Science Ltd

The first natural 12H-pyrido[1,2-a:3,4-b]diindole was the fascaplysin, which has anti-microbial activity and is cytotoxic against L-1210 mouse leukemia.[1] And later homofascaplysins A, B, C and secofascaplysin A were discovered in the Fijian sponge F. reticulata.[2]

All previous synthetic work relating to these natural products includes the preparation of pyrido-[1,2-a]indole fragment as a late step[3] or by heteroring cross-coupling and cyclisation.[4]

I now describe a short and efficient synthesis of a 12H-pyrido[1,2-a:3,4-b']diindole system and a total synthesis of homofascaplysin C (four steps) starting from 3-methylindole.

4-(3-Methyl-1H-indol-1-yl)butanoic acid (1) and 6,7,8,9-tetrahydro,10-methylpyrido[1,2-a]indol-9-one(2) were prepared using Jirkovsky's method.[5] Treatment of the pyrido[1,2-a]indole (2) with phenylhydrazine hydrochloride in refluxing acetic acid gave 6,7-dihydro-13-methyl-12H-pyrido[1,2-a:3,4-b']di-indole(3) in 91% yield.[6] This route, which depends upon the easy availability of the 3-R-indoles, would appear to have application to the relatively simple synthesis of several other pyrido[1,2-a:3,4-b']diindoles.



Compound (3) underwent oxidative dehydrogenation and oxidation of methyl group to formyl group by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (3 mol, dioxane, reflux, 2 h) to give a homofascaplysin C(4) in

one step. The 50% yield for this stage has not been optimized. The main physical data (IR, ^{1}H-NMR, MS) of 4 are identical to those of the natural product.

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6. Selected spectral data for compound 3.: IR(nujol): 3410 cm (NH); ^{1}H-NMR (250 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.57 (d, 1H), 7.54 (d, 1H), 7.43 (d, 1H), 7.30 (d, 1H) 7.15-7.25 (m, 3H), 7.10 (t, 1H), 4.27 (t, 2H), 3.24 (t, 2H), 2.61 (s, 3H); MS m/z 272 (M^+).

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