Pergamon

Tetrahedron Letters, Vol. 36, No. 39, pp. 7085-7088, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01462-4

New Syntheses of the Marine Alkaloids Eudistomins D and U.

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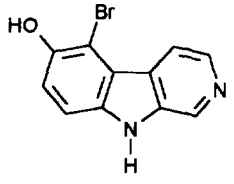
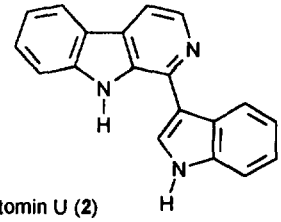
Abstract: *Short and convergent syntheses of eudistomins U and D are reported. The approach is based on a convergent methodology which involves such reactions as metalation and heteroring cross-coupling.*

Eudistomins, originally isolated and studied by Rinehart *et al*,[1] are natural marine alkaloids which show very interesting biological properties.[2] Most of them, as eudistomin D (**1**) which has significant antiviral and antimicrobial activities, are found to be active against HSV-1. They have been isolated from the Caribbean tunicate *Eudistoma olivaceum*. Last year, Francisco *et al*[3] isolated, from the Caribbean ascidian *Lissoclinum fragile*, a new β-carboline with a 3-indolyl substituent at C-1, eudistomin U (**2**). This alkaloid was found to be capable of binding to DNA and showed a strong antibacterial activity. The first described synthesis[2] of eudistomin D was by bromination of 6-methoxy-β-carboline and subsequent demethylation. This year, Molina *et al*[4] described the first total synthesis of eudistomin U in a four-step sequence involving a tandem aza Wittig/electrocyclic ring closure process. This last paper prompted us to describe our first results in the total synthesis of eudistomins.

Earlier, we have described a new general synthesis of the 4-parent carbolines[5] and α-substituted-β-carbolines.[6] More recently, we have described an original synthesis of 6-hydroxyharman[7] as well as a new synthesis of eudistomin T.[8] We wish to report here on the extension of this fruitful strategy to the total synthesis of eudistomins D and U starting from simple benzene and pyridine derivatives (scheme 1).



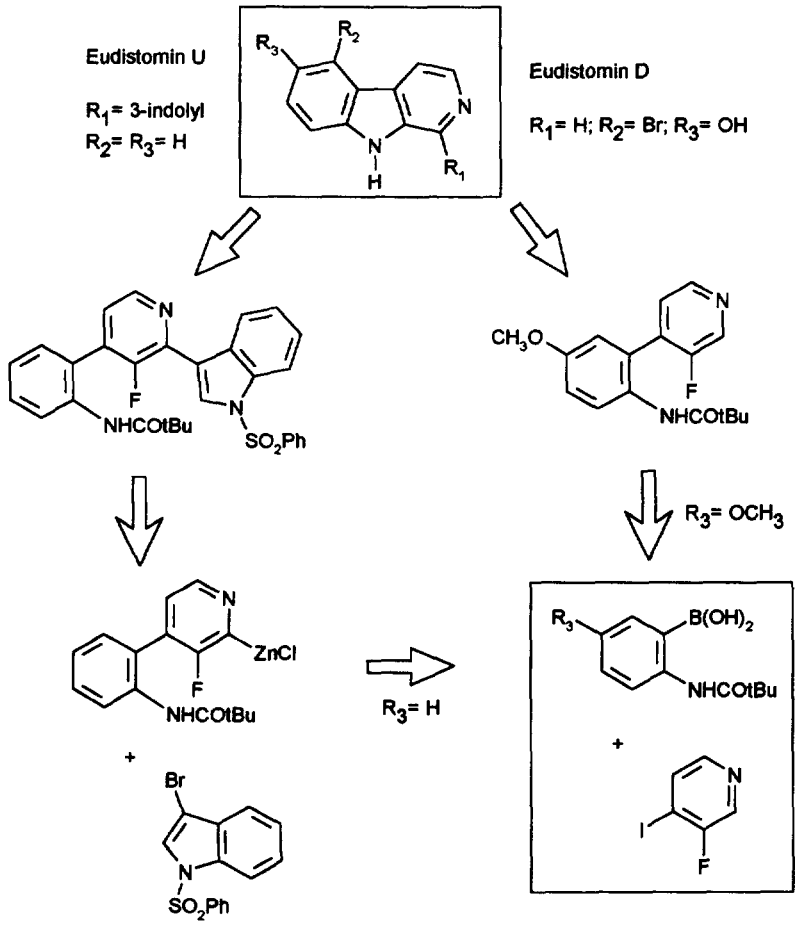
Eudistomin D (**1**)



Eudistomin U (**2**)

Scheme 1

A retrosynthetic analysis (scheme 2) of these eudistomins suggests that they could be prepared from one benzene and one pyridine building blocks via metalation[9] and cross-coupling[10] reactions.

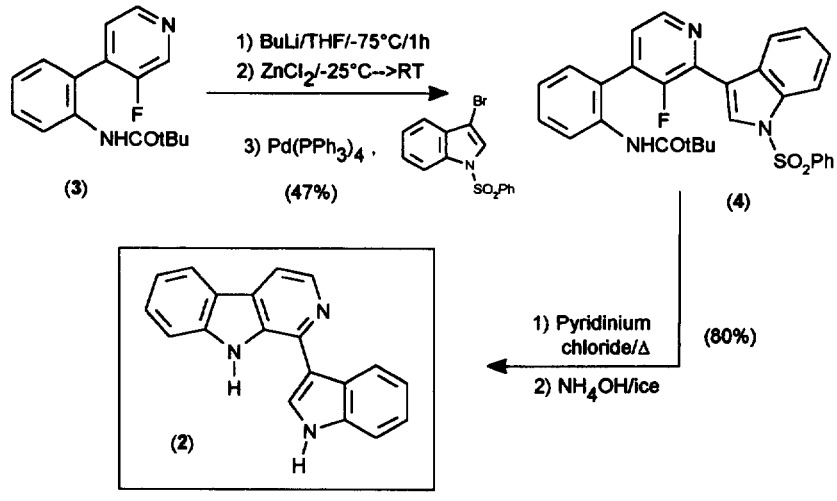


Scheme 2

Eudistomin U.

Regioselective metalation of **3**[5] by n-butyllithium in THF at -75°C was followed by a transmetalation of the resulting lithio species with zinc chloride.[11] Subsequently, 3-bromo-1-(phenylsulfonyl)indole[12] and a catalytic amount of tetrakis(triphenylphosphine)palladium[0] were added and the mixture refluxed for 36 hours to afford the corresponding trisubstituted pyridine **4** in 47% yield. The resulting trisubstituted pyridine **4** was finally cyclized[5] to eudistomin U[16] (**2**) by treatment with boiling pyridinium chloride followed by a basic

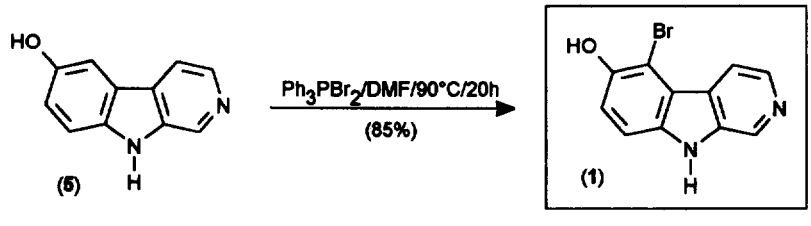
workup (scheme 3). The crude product was purified by flash chromatography on silica with a mixture of ethyl acetate and cyclohexane (5:5) as eluent.



Scheme 3

Eudistomin D.

As part of our research in the field of substituted β-carbolines, we have previously described an original synthesis of 6-hydroxynorharman (**5**).[7,13] We have now decided to take the synthesis a step further by describing the successful bromination of this compound to afford another naturally occuring brominated β-carboline. Bromination of **5** by triphenylphosphine dibromide in DMF according to Levy *et al*[14] procedure gave eudistomin D[15] (**1**) in good yield (scheme 4). This compound was purified, after basic workup, by flash chromatography on silica, using methanol/chloroform (1:5) as eluent.



Scheme 4

The reported syntheses of eudistomins D and U rely on such key steps as metalation and cross-coupling. The strategy is fully convergent, regioselective and allows interesting 85% (1 step) and 38% (2 steps) overall yields respectively. We have shown that, in contrast with the synthetic route to compound **1**, it is similarly possible to demethylate prior to bromination and vice versa,[2] leading to substitution at same C-5 of the respective precursor molecules with comparable yields. With respect to eudistomin U (**2**), we have been able to obtain an overall yield slightly higher than the previous described synthesis[4] and the proposed method is quite convergent. The present work is currently being extended to the preparation of related eudistomins.

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15. Compound 1: main physical data of this product are: yellow amorphous solid; m.p.: >260°C; IR (KBr) 3360, 2919, 2355, 1619, 1560, 1443, 1313, 1249, 1094, 800, 796 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ (ppm) 7.32 (d, 1H, H-8, J= 8.6 Hz), 7.55 (d, 1H, H-7, J= 8.6 Hz), 8.39 (d, 1H, H-4, J= 5.5 Hz), 8.63 (d, 1H, H-3, J= 5.5 Hz), 9.04 (s, 1H, H-1), 10.02 (s, 1H, OH), 10.85 (s, 1H, NH). Anal. Calcd for $C_{11}H_7BrN_2O$ (263.096): C, 50.22; H, 2.68; N, 10.65. Found: C, 50.13; H, 2.72; N, 10.74.
16. Compound 2: main physical data of this product are: yellow foam; m.p.: 92°C; IR (KBr) 3210, 2921, 2854, 2368, 1624, 1560, 1458, 1420, 1236, 1107, 931, 815 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.29-7.35 (m, 3H, H-5' + H-6' + H-7'), 7.37 (d, 1H, H-4', J= 8.0 Hz), 7.52-7.58 (m, 2H, H-6 + H-7), 7.77 (d, 1H, H-8, J= 8.6 Hz), 7.96 (d, 1H, H-4, J= 5.3 Hz), 8.02 (s, 1H, H-2'), 8.22 (d, 1H, H-5, J= 7.9 Hz), 8.48 (s, 1H, NH), 8.62 (d, 1H, H-3, J= 5.3 Hz), 8.98 (s, 1H, NH). Anal. Calcd for $C_{19}H_{13}N_3$ (283.336): C, 80.54; H, 4.62; N, 14.83. Found: C, 80.43; H, 4.78; N, 14.75.

(*Received in France* 29 *June* 1995; *accepted* 29 *July* 1995)