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Iminophosphorane-Mediated Syntheses of the Fascaplysin Alkaloid of Marine Origin and Nitramarine.

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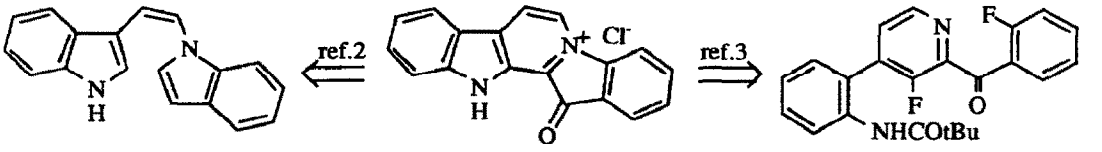
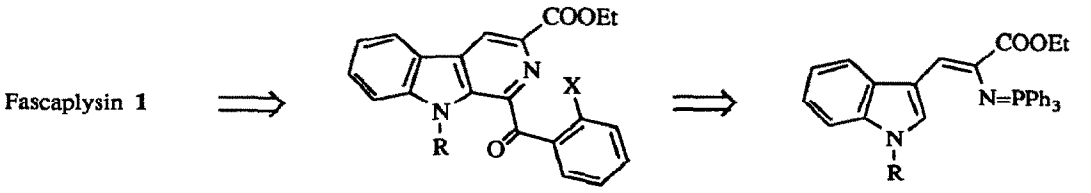
Abstract: *New and efficient syntheses of the fascaplysin alkaloid of marine origin and nitramarine are described. In both syntheses the key step, formation of the β-carboline ring, involve a tandem aza-Wttig/ electrocyclic ring closure process.*

Fascaplysin **1** represents the first naturally occurring member of the pentacyclic ring system 12H-pyrido[1,2-a : 3,4-b']diindole, and might be considered as a member of the alkaloids derived from the β-carboline, which have extra ring annulated across the β-carboline ring C-1 and N-2 positions. The dark red pigment fascaplysin **1**, which shows an antimicrobial and cytotoxic activity against the L-1210 mouse leukemia in vitro, was isolated in 1988 from the Fijian sponge *Fascaplypsinopsis Berquist sp.*[1] Two syntheses for the preparation of the fascaplysin **1** have previously been reported. The first one, which involves seven steps from indole in 65% yield, is based on acid-catalyzed cyclization of the pivotal intermediate diindole **2**, followed by dehydrogenation and finally oxidation.[2]



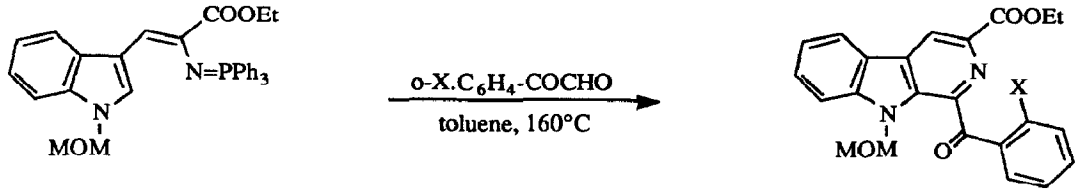
2 **1** **3**

The second approach to the synthesis of **1** is based on the cyclization of the highly substituted 2,4-diarylpyridine **3** obtained from two benzene and one pyridine building blocks via metalation and cross-coupling reaction.[3]



5 **4**

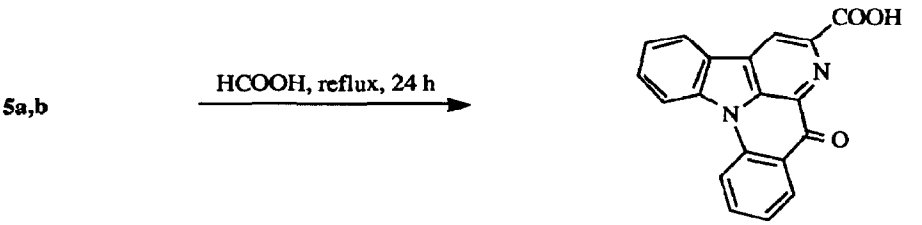
The tandem aza Wittig/electrocyclic ring-closure has been successfully utilized for the synthesis of naturally occurring 1-substituted β-carboline such as eudistomins A and M,[4] and lavendamycin.[5] We wish to report here on the extension of this fruitful methodology to the total synthesis of fascaplysin from a simple indole derivative. A retrosynthetic analysis of fascaplysin **1** suggests that it could be prepared by cyclization of the 1-substituted β-carboline **5**, available from an β-(3-indolyl)vinyl iminophosphorane **4** via an aza Wittig/electrocyclic ring-closure.



4

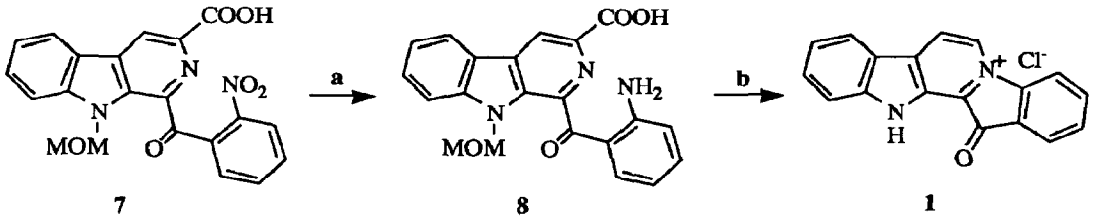
5 a X= Cl
b X= F
c X= NO_2

Thus, we initially required a N-protected-3-formylindole and the protecting group of choice was the methoxymethyl group. Conversion of the N-methoxymethyl-3-formylindole[6] into the key intermediate iminophosphorane **4** was performed by sequential treatment with ethyl azidoacetate and triphenylphosphine.[7] Iminophosphorane **4** reacted with several arylglyoxals[8] in toluene at 160°C in a sealed tube to give 1-aroyl-β-carboline derivatives **5** in 60-65% yields. The conversion **4**→**5** involves initial aza Wittig reaction to give a 2-azahexatriene which subsequently undergoes electrocyclic ring-closure. Further dehydrogenation under the reaction conditions leads to **5**.[9]



6

When compounds **5a** and **5b** were treated either with formic acid or pyridinium hydrochloride at 170°C cyclization took place across the indole nitrogen atom instead of the pyridinic nitrogen to give the previously unreported ring system **6** in excellent yield (90%),[10] and all attempts to promote the thermal cyclization of **5a** to fascaplysin failed. This series of frustating results was finally broken by using **5c** as efficient precursor for the eventual formation of cationic 5-membered ring. Thus, hydrolysis of **5c** with LiOH in THF / H_2O at room temperature provided **7** in near quantitative yield, selective reduction of the nitro group to give **8** was achieved in 80% yield by catalytic hydrogenation in the presence of PtO_2.[11]

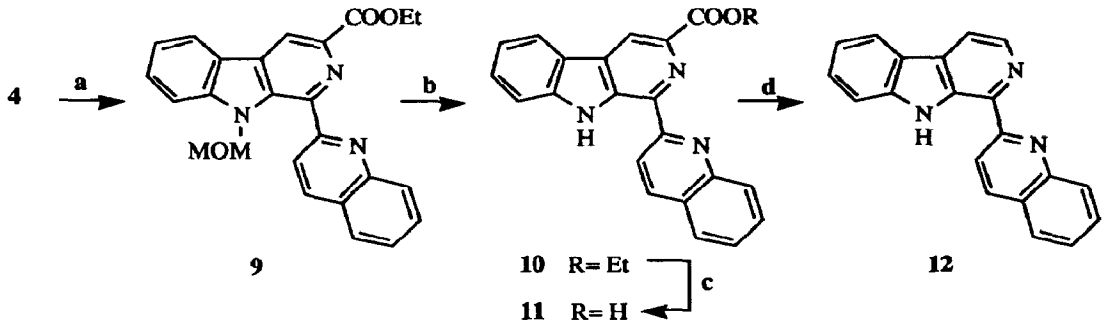


7 **8** **1**

Reagents and conditions: a) H_2, PtO_2, MeOH; b) $NaNO_2$, MeOH-H_2O, HCl O°C→reflux

Direct conversion of **8** into fascaplysin **1**, which involves formation of the cationic 5-membered ring, deprotection and decarboxylation, was performed in 60% yield by diazotization and further heating of the resulting diazonium salt.[12]

The tandem aza Wittig / electrocyclic ring-closure has also been applied to the synthesis of the alkaloid nitramarine **12**, isolated from the aerial parts of *Nitraria Komorovii*,[13] which displays hypotensive and spasmolytic activities. The only synthesis described involves a three-step sequence: a) palladium-catalyzed coupling of 1-chloro-β-carboline with tributyl(1-ethoxyvinyl)stannane, b) hydrolysis to give 1-acetyl-β-carboline and c) condensation with 2-aminobezaldehyde.[14]



Reagents: a) 2-formylquinoline, toluene, 160°C; b) HCOOH, Δ
c) LiOH, THF/H_2O, r.t.; d) Cu, quinoline, 260°C.

Reaction of iminoposphorane **4** with 2-formylquinoline in toluene at 160°C in a sealed tube provided **9** in 65% yield, deprotection of the N-methoxymethyl group with formic acid (99%), hydrolysis of the ester group with LiOH at room temperature (near quantitative yield) and finally decarboxylation with copper/quinoline at 260°C (53%) led to nitramarine **12**. This was identical in all respects (IR, MS, ^1H and ^{13}C m.n.r.) with the natural product.

In conclusion, we have developed a new and efficient four-step synthesis of the alkaloids fascaplysin of marine origin and nitramarine, which involves as key step an aza Wittig/electrocyclic ring-closure process.

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8. The previously unreported *o*-nitro and *o*-fluorophenylglyoxals were prepared in good yields (70-75%) from the corresponding *o*-susbtituted acetophenone by oxidation with selenium dioxide (Nardí, N.; Tajana, A.; Massarani, E. *Ann. Chim (Rome)* **1969**, *59*, 1075.
9. Compound **5a**: 65% yield, m.p. 154-155°C (colorless prisms from ethanol/ethyl acetate); ^1H n.m.r. (300 MHz, $CDCl_3$) δ 1.37 (t, 3H, J=7.2Hz, CH_3CH_2O), 3.02 (s, 3H, CH_3OCH_2), 4.41 (q, 2H, J=7.2Hz, CH_3CH_2O),

5.88 (s, 2H, CH_3OCH_2), 7.38-7.41 (m, 2H, H-6 + aryl), 7.42 (d, 1H, J=7.8Hz, aryl), 7.44 (d, 1H, J=7.8Hz, H-8), 7.65-7.67 (m, 2H, H-7 + aryl), 7.86 (dd, 1H, J=7.8, 1.6Hz, aryl), 8.23 (d, 1H, J=7.8Hz, H-5), 8.97 (s, 1H, H4); ^{13}C n.m.r. (75 MHz, $CDCl_3$) δ 12.3 (CH_3CH_2O), 53.7 (CH_3OCH_2), 59.5 (CH_3CH_2O), 73.3 (CH_3OCH_2), 110.6 (C-8), 119.1 (C-4), 121.5 (C-4a), 121.8 (C-6), 121.9 (C-5), 126.6, 129.7 (C-7), 130.5 (C-4b + C-aryl), 132.7 (2 C-aryl), 134.0 (q), 134.7 (C-9a), 137.1 (C-8a), 137.3 (q), 140.8 (C-3), 142.8 (C-1), 165.3 (COO), 193.2 (CO); m/z (%) 422 (M^+, 8), 387 (100).

Compound **5b**: 60% yield, m.p. 168-169°C (colorless needles from ethanol/ethyl acetate); ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ 1.32 (t, 3H, J=7.2Hz, CH_3CH_2O), 2.81 (s, 3H, CH_3OCH_2), 4.37 (q, 2H, J=7.2Hz, CH_3CH_2O), 5.67 (s, 2H, CH_3OCH_2), 6.98 (dd, 1H, J=8.1, 8.4Hz, aryl), 7.21 (td, 1H, J=7.5, 1.2Hz, aryl), 7.33 (td, 1H, J=8.1, 1.2Hz, H-6), 7.44-7.49 (m, 1H, aryl), 7.52 (d, 1H, J=8.1Hz, H-8), 7.59 (td, 1H, J=8.1, 1.5Hz, H-7), 7.95 (dd, 1H, J=7.8, 5.7Hz, aryl), 8.16 (d, 1H, J=8.1Hz, H-5), 8.9 (s, 1H, H-4); ^{13}C n.m.r. (75 MHz, $CDCl_3$) δ 14.3 (CH_3CH_2O), 55.2 (CH_3OCH_2), 61.5 (CH_3CH_2O), 74.7 (CH_3OCH_2), 110.2 (C-8), 116.3 (d, $^2J_{C\text{-}F}$ =22.1Hz), 118.8 (C-4), 121.4 (C-4a), 121.6 (C-6), 121.8 (C-5), 124.0, 125.6 (d, $^2J_{C\text{-}F}$ =10.6Hz), 129.5 (C-7), 132.2 (d, $^3J_{C\text{-}F}$=7.1Hz), 132.3 (C-4b), 133.4 (C-9a), 134.9 (d, $^3J_{C\text{-}F}$=9.1Hz), 137.2 (C-8a), 141.7 (C-3), 142.6 (C-1), 162.2 (d, $^1J_{C\text{-}F}$=256.0Hz), 165.3 (C=O), 190.7 (C=O); m/z (%) 406 (M^+, 3), 123 (100).

Compound **5c**: 65% yield, m.p. 212-214°C (from ethanol/ethyl acetate 1:1); ^{1}H n.m.r. (200 MHz, DMSO-d_6) δ 1.27 (t, 3H, J=7.2Hz, CH_3CH_2O), 3.13 (s, 3H, CH_3OCH_2), 4.28 (q, 2H, J=7.2Hz, CH_3CH_2O), 6.18 (s, 2H, CH_3OCH_2), 7.45 (td, 1H, J=7.6, 0.7Hz, H-6), 7.70-7.84 (m, 3H, H-8 + 2 aryl), 7.87 (dd, 1H, J=7.9, 1.4Hz, H-7), 7.92 (d, 1H, J=8.2Hz, aryl), 8.13 (dd, 1H, J=8.1, 1.6Hz, aryl), 8.45 (d, 1H, J=7.5Hz, H-5), 9.02 (s, 1H, H-4); ^{13}C n.m.r. (50 MHz, DMSO-d_6) δ 13.4 (CH_3), 54.7 (CH_3), 60.3 (CH_2), 75.9 (CH_2), 111.6 (C-8), 119.3 (C-4), 120.6 (C-4a), 121.6 (C-6), 121.7 (C-5), 123, 129.5 (C-7), 129.7, 130.9, 133.0 (C-4b), 133.3, 134.9 (C-9a), 135.1 (q), 136.4 (C-8a), 137.1 (C-3), 142.7 (C-1),147.7 (q), 163.6 (C=O), 191.4 (C=O); m/z (%) 433 (M^+, 53), 299 (100).

10. Compound **6** : 90% yield, m.p. 280-282°C (yellow prisms from ethanol); ^{1}H n.m.r. (300 MHz, DMSO-d_6) δ 7.41 (td, 1H, J=8.0, 0.9Hz, H-10), 7.57 (d, 1H, J=7.7Hz, H-12), 7.60 (d, 1H, J=8.0Hz, H-1), 7.61 (td, 1H, J=8.1, 0.9Hz, H-3), 7.72 (td, 1H, J=7.9, 1.4Hz, H-2), 7.73 (td, 1H, J=7.7, 1.1Hz, H-11), 7.91 (d, 1H, J=8.1Hz, H-4), 8.50 (d, 1H, J=7.8Hz, H-9), 9.20 (s, 1H, H-5), 12.56 (s, 1H, COOH); ^{13}C n.m.r. (75 MHz, DMSO-d_6) δ 113.5 (C-10), 120.4 (C-4b), 121.2 (C-3), 121.3 (C-5), 122.4 (C-12), 126.7 (C-1), 129.6 (C-2+C-4), 130.7 (q), 130.8 (C-12a), 131.6 (C-11), 131.8 (C-4a), 134.7 (C-7b), 136.3 (C-13a), 137.0 (C-8a), 138.3 (C-6), 142.4 (C-7a), 166.2 (C=O), 195.5 (C=O); m/z (%) 315 (M^+, 39), 111 (100).
11. When the reduction of compound **7** was carried out with the system Zn/EtOH/THF the nitro as well as the carbonyl group were reduced to give the hydroxy-amino derivative of **7**.
12. *Typical Procedure:* To a solution of **8** (90 mg, 0.24 mmol) in methanol (5 ml) were added water (20 ml) and concentrated hydrochloric acid (5ml). The solution was cooled at 0°C and a solution of sodium nitrite (16 mg, 0.24 mmol) in water (5 ml) was added dropwise. The resultant solution was stirred at 0°C for 45 min and then refluxed for 1 h. The red solution was concentrated to dryness and the residue was treated with ethyl acetate and the remaining solid was recrystallized from methanol to give fascaplysin **1** in 60%, m.p. 232-234°C (lit[1] m.p. 233-235°C). The main physical data (IR, MS, ^{1}H and ^{13}C n.m.r.) of **1** are identical to those of the natural product.
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