Natural Product Inspired Designing and Synthesis of β-Carboline and γ-Lactones Based Molecular Hybrids

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1.0 Control Experiments:-

To validate the hypothesis that water drives the reaction through dual activation via increasing the electrophilic character of formyl (during allylation) and ester group (during lactonisation) and simultaneously enhancing the nucleophilic potential of hydroxyl group, a control experiments was performed to study the influence of *p*-TSA, TFA and AcOH to catalyze the intramolecular lactonisation. The addition of 100 mol% of *p*-TSA/TFA/AcOH to homoallyl alcohol (afforded from the reaction of **15a** and **B**) does not significantly reduced the reaction time during condensation process which clearly shows that external catalyst had no influence on reaction undoubtedly indicating the assistance by water or some internal catalysis.



Addition of p-TSA/TFA/AcOH (1.0 equiv.) after formation of homoallyl alcohol



Scheme 1. Effect of addition of *p*-TSA, TFA or AcOH after formation of homoallyl alcohol

In order to collect more evidences, we monitored the pH of medium during the whole reaction sequence as presented in Table 1. Initially, pH of medium was 7.05 but it was reduced to 2.96 (Strongly acidic) after 10 min of addition of allyl bromide and indium powder, which indicates the generation of H-Br in reaction mixture. Interestingly, the pH of medium remains acidic throughout the reaction sequence. From this study, it appeared that *in situ* generated H-Br or H_3O^+ (Acidic pH) may be responsible for increasing the electrophilic character of formyl or ester group and water has little role to play.

	$(1, THF/H_2O)$ $(3:2, v/v), rt,$ $(3:2, v/v), $	h Me NR % 15aB	₂Me
Sr. No.	Conditions	Time	pH of medium
1	THF: H ₂ O (3:2), 10 mL, rt	00:00	7.05
2	Indium + allyl bromide (B) in THF: H ₂ O, rt	00:10	2.96

Table 1. Change of pH during the course of reaction under standard conditions

3	Added Aldehyde (15a)	00:11	3.00
	to reaction mixture (indium + allyl bromide in THF:H $_2$ O), rt		
4	Homoallyl alcohol formed, rt	00:26	3.20
5	Homoallyl alcohol + cyclic product, rt	1:26	3.85
6	Lactonisation completed (15aB), rt	4:00	4.26
	(66% yield) Clean reaction		

To verify that acidic pH was the major factor in assisting the reaction, we performed another control experiment (Table 2) where Et₃N (1.0 equiv.) was initially mixed with THF: H₂O (pH = 11.12) and then allyl bromide and indium powder was added to the content and stirred for 10 min (pH = 9.70). Thereafter aldehyde was added to the reaction mixture and stirred the content at room temperature for 4 h. It was observed that even after 4 h neither homoallyl alcohol not cyclic product was observed at room temperature. However, heating the reaction content at 100 °C led to completion of reaction (pH = 9.17) after 6 h and desired product was obtained in 45% yield. Interestingly, the pH of reaction medium remained basic throughout the experiment. This control experiment clearly inferred that pH was not the sole factor that was assisting the reaction as the reaction occurred under acidic as well as basic pH of medium.

All these studies clearly concluded that water was playing the main role during the whole reaction. However, acidic pH might be assisting in allylation reaction as allylation was very fast under acidic pH. Secondly, the assistance of N-2 nitrogen in lactonisation process via polarization of hydroxyl group can't be denied as it has basic nature. Another evidence comes from the fact that in freshly distilled THF, no reaction occurs even after 48 h under refluxing (Table 1, entry 2); however addition of water leads to a fast reaction.

$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \text{In, THF/H}_{2}O \\ \text{CO}_{2}\text{Me} \\ \text{N} \\ \text{N} \\ \text{CHO} \\ 15a \\ \end{array} \\ \begin{array}{c} \text{H} \\ \text{Br} \\ \text{H} \\ \text{CHO} \\ 15a \\ \end{array} \\ \begin{array}{c} \text{H} \\ \text{H} \\ \text{H} \\ \text{H} \\ \text{H} \\ \text{H} \\ 15a \\ \end{array} \\ \begin{array}{c} \text{H} \\ $			
Sr. No.	Conditions	Time	pH of medium
1	THF: H ₂ O (3:2) 10 mL + Et ₃ N (1.0 equiv.), rt	00:00	11.12
2	Indium + allyl bromide (B) in THF: H_2O having Et_3N at room temperature	00:10	9.70
3	Addition of aldehyde (15a) to reaction mixture (indium + allyl bromide in THF:H ₂ O + Et ₃ N) at 100 °C	00:11	9.71

Table 2. Change of pH during the course of reaction after addition of Et₃N

4	Homoallyl alcohol formed at 100 °C	3:26	9.36
5	Homoallyl alcohol + cyclic product at 100 °C	5:30	9.30
6	Lactonisation completed (15aB) at 100 °C,	6:00	9.17
	(45% yield). Not a clean reaction		

Procedure for large scale synthesis of methyl 1-(dimethoxymethyl)-2,3,4,9-tetrahydro-1*H***-pyrido[3,4-***b***]indole-3-carboxylate (4)**^{13a}: To a stirred solution of L-tryptophan methyl ester (30.0 g, 137.6 mmol) in anhydrous dichloromethane (180 mL), 2,2-dimethoxy acetaldehyde (60% aqueous solution in water) (28.6 mL, 165.1 mmol) was added at room temperature. Thereafter a solution of 15 mL TFA (5 % TFA in CH₂Cl₂) in 120 mL dichloromethane was added in small portions and the reaction mixture was further stirred at room temperature for 12 h. After completion of the reaction as confirmed by TLC, the reaction was quenched by slow addition of 10% aqueous NaHCO₃ solution under stirring. After the pH was adjusted to alkaline (ca 7.5), the organic layer was separated and the aqueous layer was further extracted with chloroform (3 × 100 mL). The organic layers were combined and washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to yield the product as yellow oil **4** (35.6 g, 85%; R_f = 0.45 (hexane/EtOAc, 50:50, v/v) which was utilized for the next step without further purification.

Procedure for preparation of methyl 1-(dimethoxymethyl)-9H-pyrido[3,4-b]indole-3carboxylate (7): To a stirred solution of **4** (35.0 g, 115.1 mmol) in dry THF (200 mL), KMnO₄ (105.0 g) was added in small portions over a period of 1 hour and stirred vigorously at room temperature for 15 h. After completion of the reaction as monitored by TLC, the viscous blackish content was filtered through celite bed and washed 7-8 times with chloroform. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to yield the light yellow viscous product which was further triturated with hexane/EtOAc, (90:10, v/v) to yield an analytically pure white solid product, **7** (30.1 g, 87%, R_f = 0.40 (hexane/EtOAc, 50:50, v/v). It deserves attention that KMnO₄ should be added in small portions as the reaction is highly exothermic. When the reaction was performed in freshly distilled dry DMF, it was completed in 2 h. **General Procedure for preparation of methyl 1-formyl-9H-pyrido[3,4-b]indole-3-carboxylate (10):** To a stirred solution of **7** (20.0 g, 66.67 mmol) in glacial AcOH (80 mL); water (120 mL) was added and heated the content at 100 °C for 45 min. A yellow solid precipitated out during this period from the reaction mixture. After 45 minutes, the reaction content was cooled to room temperature and diluted with ice cold water (200 mL). Thereafter, the yellow solid product was filtered under suction and further washed with 10% aqueous NaHCO₃ solution (100 mL). The yellow solid was further air dried and triturated with 5% ethyl acetate: hexane (v/v, 50 mL) to yield the analytically pure yellow solid product, **10** (16.42 g, 99%). It deserves attention here that if during deprotection of acetal (**7**) heating is performed at 100 °C for longer duration (>1 h) or at higher temperature, it results in change in color of compound from yellow to dark brown solid and decrease in yield.

Procedure for preparation of methyl 1-(dimethoxymethyl)-9-methyl-9H-pyrido[3,4-b]indole-3-carboxylate (12a): To a stirred solution of **7** (10.0 g, 33.3 mmol) in dry DMF (50 mL), NaH (60% in paraffin oil) (2.4 g, 60.0 mmol) was added portionwise and stirred the reaction mixture at room temperature for 30 min. Thereafter methyl iodide (3.1 mL, 49.9 mmol) was added drop-wise and the reaction was stirred for additional 1 h at room temperature. On completion of the reaction, as monitored by TLC, the contents were poured into ice cold water (100 mL) under stirring to obtain a solid product. Thereafter the reaction mass was filtered through a buchner funnel to get the solid product which was washed twice with cold water and finally triturated with hexane to yield the yellow solid product, **12a** (10.15 g, 97%, R_f = 0.55 (hexane/EtOAc, 50:50, v/v) which was utilized for the next step.

General Procedure for preparation of methyl 1-formyl-9-methyl-9H-pyrido[3,4-*b*]indole-3carboxylate derivatives (10, 15a) as exemplified for 15a: To a stirred solution of 12a (10.0 g, 31.8 mmol) in glacial AcOH (40 mL); water (60 mL) was added and heated the content at 100°C for 45 min. During this period, yellow solid precipitated out from the reaction mixture. After 45 minutes, the reaction content was cooled to room temperature and diluted with ice cold water (200 mL), yellow solid was filtered under suction and further washed with 10% aqueous NaHCO₃ solution (100 mL). The yellow solid was further air dried and triturated with 5% ethyl acetate: hexane (v/v, 10 mL) to yield the analytically pure yellow solid product, **15a** (7.85 g, 92%). It deserves attention here that if during deprotection of acetal heating is performed at 100 °C for longer duration (>1 h), it results in change in color of compound from yellow to dark brown solid and decrease in yield.

Procedure for preparation of ethyl 1-(dimethoxymethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4*b***]indole-3-carboxylate (5):** To a stirred solution of L-tryptophan ethyl ester (5.00 g, 21.5 mmol) in anhydrous dichloromethane (30 mL), 2,2-dimethoxy acetaldehyde (60% aqueous solution in water) (2.7 mL, 25.8 mmol) was added at room temperature. Thereafter a solution of 2.5 mL TFA (5 % TFA in CH₂Cl₂) in 20 mL dichloromethane was added in small portions and the reaction mixture was further stirred at room temperature for 12 h. After completion of the reaction as confirmed by TLC, the reaction was quenched by slow addition of 10% aqueous NaHCO₃ solution under stirring. After the pH was set to slight alkaline (ca 7.5), the organic layer was pooled and the aqueous layer was further extracted with chloroform (3 × 20 mL). The organic layers were combined and washed with brine (30 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to yield the product as yellow oil **5** (5.49 g, 80%; R_f = 0.50 (hexane/EtOAc, 50:50, v/v) which was utilized for the next step without further purification.

Ethyl 1-(dimethoxymethyl)-2,3,4,9-tetrahydro-1*H*-**pyrido**[**3,4-***b*]**indole-3-carboxylate (5).** Yield: 80% (5.49 g from 5.0 g) as a yellow oil, $R_f = 0.50$ (hexane/EtOAc, 50:50, v/v); IR (Neat): $v_{max} =$ 1731 (CO₂Et); ¹H NMR (400 MHz, CDCl₃) (diasteromeric mixture, 1:1) $\delta =$ 1.26 (t, *J* = 7.1 Hz, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H), 2.83-2.91 (m, 1 H), 3.08-3.19 (m, 3 H), 3.50 (s, 3 H), 3. 54 (s, 3 H), 3.56 (s, 3 H), 3.63 (s, 3 H), 3.76-3.80 (m, 1 H), 3.84 (s, 1 H), 4.02 (t, *J* = 5.6 Hz, 1 H), 4.11-4.23 (m, 2 H), 4.27-4.32 (m, 3 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 4.50 (d, *J* = 6.4 Hz, 1 H), 7.10 (t, *J* = 7.6 Hz, 2 H), 7.17 (t, *J* = 7.5 Hz, 2 H), 7.33-7.36 (m, 2 H), 7.49-7.53 (m, 2 H), 8.40 (s, 1 H), 8.58 (s, 1 H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 14.3, 14.4, 24.5, 25.7, 51.3, 53.4, 54.2, 54.7, 55.3, 55.7, 56.2, 56.5, 61.1, 61.3, 106.6, 107.2, 108.2, 108.9, 110.9, 111.1, 118.1, 118.2, 119.2, 119.4, 121.8, 121.9, 126.9, 130.8, 131.5, 131.6, 135.9, 136.0, 173.1, 173.7 ppm; MS (ES): *m/z* (%) = 319.1 (100) [M+1]⁺; C₁₇H₂₂N₂O₄ (318.1580): calcd. for C 64.13, H 6.97, N 8.80; found C 64.18, H 7.02, N 8.85.

Procedure for preparation of ethyl 1-(dimethoxymethyl)-9H-pyrido[3,4-b]indole-3carboxylate (8) : To a stirred solution of **5** (5.00 g, 15.7 mmol) in dry DMF (40 mL), KMnO₄ (15.0 g) was added in small portions over a period of 20 min and stirred vigorously at room temperature for 2 h. After completion of the reaction as monitored by TLC, the viscous blackish content was poured in ice cold water and extracted with ethyl acetate (4 x 30 mL). The organic layer was further washed with 10% aq. NaHCO₃ solution (30 mL) and subsequently by brine (30 mL). The organic layer was concentrated *in vacuo* to yield the light yellow viscous product which was further triturated with hexane: EtOAc, (90:10, v/v) to obtain a pure white solid product, **8** (4.60 g, 93%, $R_f = 0.45$ (hexane: EtOAc, 50:50, v/v). It deserves attention that KMnO₄ must be added in small portions as the reaction is highly exothermic.

Ethyl 1-(dimethoxymethyl)-9H-pyrido[3,4-b]indole-3-carboxylate (8). Yield: 93% (4.60 g from 5.00 g) as a brown solid, m.p. 114-115 °C, $R_f = 0.45$ (hexane/EtOAc, 50:50, v/v); IR (Neat): $v_{max} = 1711$ (CO₂Et); ¹H NMR (400 MHz, CDCl₃) $\delta = 1.47$ (t, J = 7.0 Hz, 3 H), 3.51 (s, 6 H), 4.52 (q, J = 7.0 Hz, 2 H), 5.76 (s, 1 H), 7.33 (d, J = 4.5 Hz, 1 H), 7.56 (s, 2 H), 8.17 (d, J = 7.7 Hz, 1 H), 8.86 (s, 1 H), 9.55 (s, 1 H) ppm; ¹³C NMR (100 MHz, CDCl₃) $\delta = 14.6$, 55.1, 61.6, 107.1, 112.1, 118.1, 120.8, 121.4, 121.8, 129.1, 130.1, 134.9, 137.1, 140.7, 166.1 ppm; MS (ES): m/z (%) = 315.3 (100) [M+1]⁺, 353.2 (100) [M+39]⁺; C₁₇H₁₈N₂O₄ (314.1267): calcd. for C 64.96, H 5.77, N 8.91; found C 65.18, H 5.90, N 9.07.

General Procedure for preparation of ethyl 1-(dimethoxymethyl)-9-methyl-9H-pyrido[3,4b]indole-3-carboxylate (13a and 13c) derivatives as exemplified by 13a: To a stirred solution of 8 (2.0 g, 6.4 mmol) in dry DMF (20 mL), Cs_2CO_3 (3.0 g, 9.6 mmol) was added and stirred the reaction mixture at room temperature for 15 min. Thereafter methyl iodide (0.6 mL, 9.6 mmol) was added drop-wise and the reaction was stirred for additional 1 h at room temperature. On completion of the reaction, as monitored by TLC, the contents were poured into ice cold water (50 mL) under stirring. Thereafter the reaction mass was filtered through sintered funnel to get the solid product which was washed twice with cold water and finally washed with hexane to yield the yellow solid product, **13a** (1.92 g, 92%, $R_f = 0.60$ (hexane/EtOAc, 50:50, v/v) which was utilized for the next step without further purification. Similarly *N*-benzyl derivatives **13c** were prepared by using benzyl bromide in presence of Cs_2CO_3 in dry DMF. It is worth mentioning here that if NaH is used as a base, trans esterified product is also formed with normal product.

Ethyl 1-(dimethoxymethyl)-9-methyl-9H-pyrido[**3,4-***b*]**indole-3-carboxylate (13a).** Yield: 92% (1.92 g from 2 g) as a brown solid, m.p. 109-110 °C, $R_f = 0.60$ (hexane/EtOAc, 50:50, v/v); IR (Neat): $v_{max} = 1711$ (CO₂Et); ¹H NMR (400 MHz, DMSO-*d*₆) $\delta = 1.39$ (t, *J* = 7.2 Hz, 3 H), 3.50 (s, 6 H), 4.19 (s, 3 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 5.67 (s, 1 H), 7.38 (t, *J* = 7.2 Hz, 1 H), 7.70 (t, *J* = 8.0 Hz, 1 H), 7.77 (d, *J* = 8.4 Hz, 1 H), 8.46 (d, *J* = 7.6 Hz, 1 H), 8.99 (s, 1 H) ppm; ¹³C NMR (100 MHz, CDCl₃) $\delta = 14.6$, 33.8, 56.0, 61.5, 110.4, 110.7, 118.2, 120.6, 121.3, 121.5, 128.9, 130.9, 135.5,

136.1, 141.2, 143.2, 166.0 ppm; MS (ES): *m/z* (%) = 329.2 (100) [M+1]⁺; C₁₈H₂₀N₂O₄ (328.1423): calcd. for C 65.84, H 6.14, N 8.53; found C 65.98, H 6.40, N 8.76.

Ethyl 9-benzyl-1-(dimethoxymethyl)-9H-pyrido[**3**,**4**-*b*]indole-**3**-carboxylate (**13**c). Yield: 75% (1.93 g from 2.00 g) as a yelllow solid, m.p. 118-119 °C, $R_f = 0.70$ (hexane/EtOAc, 50:50, v/v); IR (Neat): $v_{max} = 1719$ (CO₂Et); ¹H NMR (400 MHz, DMSO-*d*6) $\delta = 1.39$ (t, J = 6.8 Hz, 3 H), 3.34 (s, 6 H), 4.41 (d, J = 7.1 Hz, 2 H), 5.59 (s, 1 H), 6.13 (s, 2 H), 6.92 (d, J = 6.8 Hz, 2 H), 7.16-7.22 (m, 3 H), 7.36 (t, J = 7.1 Hz, 1 H), 7.44 (d, J = 8.0 Hz, 1 H), 7.56 (t, J = 7.5 Hz, 1 H), 8.49 (d, J = 7.6 Hz, 1 H), 9.05 (s, 1 H) ppm; ¹³C NMR (100 MHz, CDCl₃) $\delta = 14.6$, 50.0, 55.5, 61.6, 109.5, 111.6, 118.3, 121.0, 121.3, 121.8, 125.9, 126.7, 128.4, 129.1, 131.2, 136.0, 136.2, 138.2, 141.3, 142.7, 165.9 ppm; MS (ES): m/z (%) = 405.3 (100) [M+1]⁺; C₂₄H₂₄N₂O₄ (404.1736): calcd. for C 71.27, H 5.98, N 6.93; found C 71.48, H 6.12, N 7.16.

1-(Dimethoxymethyl)-9-methyl-9H-pyrido[3,4-*b***]indole (14a). Yield: 90% (1.91 g from 2.0 g) as a yellow solid, m.p. 106-107 °C, R_f = 0.50 (hexane/EtOAc, 70:30, v/v); IR (Neat): v_{max} = 1064 (C-O); ¹H NMR (400 MHz, CDCl₃) \delta = 3.52 (s, 6 H), 4.19 (s, 3 H), 5.76 (s, 1 H), 7.26-7.30 (m, 1 H), 7.49 (d, J = 8.4 Hz, 1 H), 7.59-7.63 (m, 1 H), 7.99 (d, J = 5.1 Hz, 1 H), 8.11-8.14 (m, 1 H), 8.38 (d, J = 5.1 Hz, 1 H) ppm; ¹³C NMR (100 MHz, CDCl₃) \delta = 33.3, 55.3, 109.1, 109.9, 115.4, 119.8, 121.1, 121.2, 128.6, 131.0, 134.7, 136.7, 140.8, 142.8 ppm; MS (ES): m/z (%) = 257.1 (100) [M+1]⁺; C₁₅H₁₆N₂O₂ (256.1212): calcd. for C 70.29, H 6.29, N 10.93; found C 70.52, H 6.45, N 1.06.**

General Procedure for preparation of ethyl 1-formyl-9-methyl-9H-pyrido[3,4-b]indole-3carboxylate derivatives (16a and 16c) as exemplified for 16a: To a stirred solution of **13a** (1.0 g, 3.05 mmol) in glacial AcOH (4 mL); water (6 mL) was added and heated the content at 100 °C for 45 min. During this period, yellow solid is precipitated out from the reaction mixture. After 45 minutes, the reaction content was further diluted with ice cold water (20 mL) and yellow solid product was filtered under suction and further washed with 10% aqueous NaHCO₃ solution (20 mL). The product was further air dried and triturated with ethyl acetate: hexane (5:95, v/v, 10 mL) to yield the analytically pure yellow solid product, **16a** (0.76 g, 89%). It deserves attention here that if during deprotection of acetal heating is performed at 100 °C for longer duration (>1 h), it results in change in color of compound from yellow to dark brown solid and decrease in yield.

Ethyl 1-formyl-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (16a). Yield: 89% (0.765 g from 1 g) as a brown solid, m.p. 142-143 °C, $R_f = 0.55$ (hexane/EtOAc, 70:30, v/v); IR (Neat): $v_{max} =$

1626 (CHO), 1697 (CO₂Et); ¹H NMR (400 MHz, CDCl₃) δ =1.52 (t, *J* = 7.1 Hz, 3 H), 4.30 (s, 3 H), 4.58 (q, *J* = 7.1 Hz, 2 H), 7.44 (t, *J* = 7.4 Hz, 1 H), 7.59 (d, *J* = 8.3 Hz, 1 H), 7.72 (t, *J* = 7.8 Hz, 1 H), 8.23 (d, *J* = 7.9 Hz, 1 H), 9.02 (s, 1 H), 10.40 (s, 1 H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 14.6, 34.9, 62.0, 110.7, 120.6, 121.1, 121.6, 121.8, 130.0, 132.9, 136.9, 137.2, 137.3, 143.7, 165.3, 193.5 ppm; MS (ES): *m/z* (%) = 283.1 (100) [M+1]⁺; C₁₆H₁₄N₂O₃ (282.1004): calcd. for C 68.07, H 5.00, N 9.92; found C 68.28, H 5.29, N 10.15.

Ethyl 9-benzyl-1-formyl-9H-pyrido[3,4-b]indole-3-carboxylate (16c). Yield: 96% (0.85 g from 1.0 g) as a brown solid, m.p. 156-157 °C, $R_f = 0.60$ (hexane/EtOAc, 70:30, v/v); IR (Neat): $v_{max} = 1624$ (CHO), 1696 (CO₂Et); ¹H NMR (400 MHz, CDCl₃) $\delta = 1.51$ (t, J = 7.1 Hz, 3 H), 4.57 (q, J = 7.1 Hz, 2 H), 6.17 (s, 2 H), 6.88-6.90 m, 2 H), 7.15-7.17 (m, 3 H), 7.42 (t, J = 7.6 Hz, 1 H), 7.54 (d, J = 8.4 Hz, 1 H), 7.64 (t, J = 7.9 Hz, 1 H), 8.23 (d, J = 7.8 Hz, 1 H), 9.03 (s, 1 H), 10.27 (s, 1 H) ppm; ¹³C NMR (100 MHz, CDCl₃) $\delta = 14.2$, 49.9, 61.5, 99.1, 112.7, 117.8, 123.3, 124.9, 125.6, 126.9, 128.2, 128.9, 129.0, 130.1, 142.3, 162.7, 166.6, 171.1 ppm; MS (ES): m/z (%) = 359.2 (100) [M+1]⁺; C₂₂H₁₈N₂O₃ (358.1317): calcd. for C 73.73, H 5.06, N 7.82; found C 73.98, H 5.19, N 7.97.

9-Methyl-9H-pyrido[**3**,**4**-*b*]**indole-1-carbaldehyde (17a).** Yield: 67% (1.1 g from 2.0 g) a light yellow solid, m.p. 130-131 °C, $R_f = 0.60$ (hexane/EtOAc, 80:20, v/v); IR (Neat): $v_{max} = 1695$ (CHO); ¹H NMR (400 MHz, CDCl₃) $\delta = 4.26$ (s, 3 H), 7.38 (t, J = 7.6 Hz, 1 H), 7.55 (d, J = 8.4 Hz, 1 H), 7.67-7.71 (m, 1 H), 8.17 (d, J = 7.8 Hz, 1 H), 8.19 (d, J = 4.9 Hz, 1 H), 8.65 (d, J = 4.8 Hz, 1 H), 10.36 (s, 1 H) ppm; ¹³C NMR (100 MHz, CDCl₃) $\delta = 34.7$, 110.4, 118.7, 120.7, 121.0, 121.5, 129.6, 132.6, 137.7, 138.4, 143.5, 193.7 ppm; MS (ES): m/z (%) = 211.2 (100) [M+1]⁺; C₁₃H₁₀N₂O (210.0793): calcd. for C 74.27, H 4.79, N 13.33; found C 74.48, H 5.13, N 13.56.



Figure S-1: ¹H-NMR spectrum of ethyl 1-(dimethoxymethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*] indole-3-carboxylate (*Diastereomeric mixture*, 1:1) (5).



Figure S-2: ¹³C-NMR spectrum of ethyl 1-(dimethoxymethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*] indole-3-carboxylate (*Diastereomeric mixture*, 1:1) (5).



Figure S-3: ¹H-NMR spectrum of ethyl 1-(dimethoxymethyl)-9H-pyrido[3,4-b]indole-3-carboxylate (8).



Figure S-4: ¹³C-NMR spectrum of ethyl 1-(dimethoxymethyl)-9H-pyrido[3,4-b]indole-3-carboxylate (8).



Figure S-5: ¹H-NMR spectrum of ethyl 1-(dimethoxymethyl)-9-methyl-9H-pyrido[3,4-b]indole-3-carboxylate (13a).



Figure S-6: ¹³C-NMR spectrum of ethyl 1-(dimethoxymethyl)-9-methyl-9H-pyrido[3,4-b]indole-3-carboxylate (13a).



Figure S-7: ¹H-NMR spectrum of ethyl 9-benzyl-1-(dimethoxymethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (13c).



Figure S-8: ¹³C-NMR of ethyl 9-benzyl-1-(dimethoxymethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (13c).



Figure S-10: ¹³C-NMR spectrum of 1-(dimethoxymethyl)-9-methyl-9*H*-pyrido[3,4-*b*]indole (14a).



Figure S-12: ¹³C-NMR spectrum of ethyl 1-formyl-9-methyl-9H-pyrido[3,4-b]indole-3-carboxylate (16a).



Figure S-14: ¹³C-NMR spectrum of ethyl 9-benzyl-1-formyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (16c).



Figure S-15: ¹H-NMR spectrum of 9-methyl-9*H*-pyrido[3,4-*b*]indole-1-carbaldehyde (17a).



Figure S-16: ¹³C-NMR spectrum of 9-methyl-9*H*-pyrido[3,4-*b*]indole-1-carbaldehyde (17a).



Figure S-17: ¹H-NMR spectrum of methyl 1-((2*R*, 3*R*)-4-methylene-5-oxo-3-phenyltetrahydrofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(10A)**.



Figure S-18: ¹³C-NMR spectrum of methyl 1-((2*R*, 3*R*)-4-methylene-5-oxo-3-phenyltetrahydrofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(10A)**.



Figure S-19: X-ray crystallographic analysis of methyl 1-((2*R*, 3*R*)-4-methylene-5-oxo-3-phenyltetrahydrofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**10A**).



Figure S-20: NOESY-NMR spectrum of methyl 1-((2R, 3R)-4-methylene-5-oxo-3-phenyltetrahydrofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**10A**) in CDCl₃.



Figure S-21: ¹H-NMR spectrum of methyl 1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(10B)**.



Figure S-22: ¹³C-NMR spectrum of methyl 1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(10B).**



Figure S-23: ¹H-NMR spectrum of methyl 1-((2R, 3S)-3-(2-bromophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-



Figure S-24: ¹³C-NMR spectrum of methyl 1-((2R, 3S)-3-(2-bromophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9H-pyrido[3,4-b]indole-3-carboxylate (10G).



Figure S-25: ¹H-NMR spectrum of (4*R*, 5*R*)-3-methylene-4-phenyl-5-(9*H*-pyrido[3,4-*b*]indol-1-yl)dihydro furan-2(3*H*)-one **(11A).**

Z:\\DB-02-VOL C13 e single pulse decouplee gated NOE	141.418 138.762 138.562 138.562 138.5723 135.532 135.532 125.5366 122.9000 122.4763 122.8983 122.8983 122.8983 122.8983 122.8983 122.8983 122.8983 122.8983 122.8983 122.8983 122.4762 123.7774 122.7774 122.7774 122.7774 122.7774 122.7774 122.7774 122.7774 122.7774 122.7774 122.7774 122.7774 123.77755 1	—83.9707 77.4774 77.1600 77.1599 76.8412	50.2635	-31.0934
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Figure S-26: ¹³C-NMR spectrum of (4*R*, 5*R*)-3-methylene-4-phenyl-5-(9*H*-pyrido[3,4-*b*]indol-1-yl)di hydrofuran-2(3*H*)-one **(11A).**



Figure S-27: ¹H-NMR spectrum of methyl 9-methyl-1-((2*R*, 3*R*)-4-methylene-5-oxo-3-phenyltetrahydro furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15aA).**



Figure S-28: ¹³C-NMR spectrum of methyl 9-methyl-1-((2*R*, 3*R*)-4-methylene-5-oxo-3-phenyltetrahydro furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15aA).**



Figure S-29: ¹H-NMR spectrum of methyl 1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15aB).**



Figure S-30: ¹³C-NMR spectrum of methyl 1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15aB).**



Figure S-31: ¹H-NMR spectrum of methyl 9-methyl-1-((2*R*, 3*R*)-4-methylene-5-oxo-3-(*p*-tolyl)tetrahyd-rofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15aC).**



Figure S-32: ¹³C-NMR spectrum of methyl 9-methyl-1-((2*R*, 3*R*)-4-methylene-5-oxo-3-(*p*-tolyl)tetrahyd-rofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**15aC**).



Figure S-33: ¹H-NMR spectrum of methyl 1-((2*R*, 3*S*)-3-(4-bromophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15aD).**



e S-34: ¹³C-NMR spectrum of methyl 1-((2*R*, 3*R*)-3-(4-bromophenyl)-4-methylene-5-oxotetra hydrofuran-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15aD).**



Figure S-35: ¹H-NMR spectrum of methyl 1-((2*R*, 3*R*)-3-(4-fluorophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15aE).**



Figure S-36: ¹³C-NMR spectrum of methyl 1-((2*R*, 3*R*)-3-(4-fluorophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15aE).**





Figure S-37: ¹H-NMR spectrum of methyl 1-((2*R*, 3*R*)-3-(4-methoxyphenyl)-4-methylene-5-oxotetrahy-drofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15aF)**.

Figure S-38: ¹³C-NMR spectrum of methyl 1-((2*R*, 3*R*)-3-(4-methoxyphenyl)-4-methylene-5-oxotetrahy-drofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15aF)**.



Figure S-39: ¹H-NMR spectrum of methyl 1-((2*R*, 3*S*)-3-(2-bromophenyl)-4-methylene-5-oxotetra hydrofuran-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15aG)**.



Figure S-40: ¹³C-NMR spectrum of methyl 1-((2*R*, 3*S*)-3-(2-bromophenyl)-4-methylene-5-oxotetra hydrofuran-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15aG)**.



Figure S-41: ¹H-NMR spectrum of methyl 1-((2*R*, 3*S*)-3-(2-chlorophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate in DMSO- d_6 (**15aH**).



Figure S-42: ¹H-NMR spectrum of methyl 1-((2*R*, 3*R*)-3-(3-chlorophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15al)**.



Figure S-43: ¹³C-NMR spectrum of methyl 1-((2*R*, 3*R*)-3-(3-chlorophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15al).**

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Figure S-44: ¹H-NMR spectrum of methyl 9-allyl-1-((2*R*, 3*R*)-4-methylene-5-oxo-3-phenyltetrahydro furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15bA).**



Figure S-45: ¹H-NMR spectrum of methyl 9-allyl-1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxo tetrahydrofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15bB).**



Figure S-46: ¹³C-NMR spectrum of methyl 9-allyl-1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxo tetrahydrofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15bB).**



Figure S-47: DEPT-135 NMR spectrum of methyl 9-allyl-1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxo tetrahydrofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15bB)**.



Figure S-48: ¹H-NMR spectrum of methyl 9-allyl-1-((2*R*, 3*R*)-4-methylene-5-oxo-3-(*p*-tolyl)tetrahydro furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15bC)**.



Figure S-49: ¹³C-NMR spectrum of methyl 9-allyl-1-((2*R*, 3*R*)-4-methylene-5-oxo-3-(*p*-tolyl)tetrahydro furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15bC).**



Figure S-50: ¹H-NMR spectrum of methyl 9-allyl-1-((2*R*, 3*R*)-3-(4-fluorophenyl)-4-methylene-5-oxo tetrahydrofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15bE)**.



Figure S-51: ¹³C-NMR spectrum of methyl 9-allyl-1-((2*R*, 3*R*)-3-(4-fluorophenyl)-4-methylene-5-oxo tetrahydrofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15bE).**



tetrahydrofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (15bF).



Figure S-54: ¹H-NMR spectrum of methyl 9-benzyl-1-((2*R*, 3*R*)-4-methylene-5-oxo-3-phenyltetrahydro furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15cA)**.



gure S-55: ¹³C-NMR spectrum of methyl 9-benzyl-1-((2*R*, 3*R*)-4-methylene-5-oxo-3-phenyltetrahydro furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15cA)**.



Figure S-56: ¹H-NMR spectrum of methyl 9-benzyl-1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxote trahydrofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15cB).**



Figure S-57: ¹³C-NMR spectrum of methyl 9-benzyl-1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxote trahydrofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15cB)**.



Figure S-58: ¹H-NMR spectrum of methyl 9-benzyl-1-((2*R*, 3*R*)-4-methylene-5-oxo-3-(*p*-tolyl)tetrahyd rofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15cC)**.



Figure S-59: ¹³C-NMR spectrum of methyl 9-benzyl-1-((2*R*, 3R)-4-methylene-5-oxo-3-(*p*-tolyl)tetrahyd rofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15cC)**.



Figure S-60: ¹H-NMR spectrum of methyl 1-((2*R*, 3*R*)-4-methylene-5-oxo-3-phenyltetrahydrofuran-2-yl) -9-(prop-2-yn-1-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15dA)**.



Figure S-61: ¹³C-NMR spectrum of methyl 1-((2*R*, 3*R*)-4-methylene-5-oxo-3-phenyltetrahydrofuran-2-yl) -9-(prop-2-yn-1-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(15dA)**.



Figure S-62: ¹H-NMR spectrum of methyl 1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-(prop-2-yn-1-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**15dB**).



Figure S-63: ¹³C-NMR spectrum of methyl 1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-(prop-2-yn-1-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**15dB**).



Figure S-64: ¹H-NMR spectrum of ethyl 1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(16aB).**



Figure S-65: ¹³C-NMR spectrum of ethyl 1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(16aB).**



Figure S-66: ¹H-NMR spectrum of ethyl 1-((2*R*,3*S*)-3-(2-bromophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(16aG)**.



Figure S-67: ¹³C-NMR spectrum of ethyl 1-((2*R*, 3*S*)-3-(2-bromophenyl)-4-methylene-5-oxotetrahydro furan-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(16aG).**



Figure S-68: ¹H-NMR spectrum of ethyl 9-benzyl-1-((2*R*, 3*R*)-4-methylene-5-oxo-3-phenyltetrahydro furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**16cA**).



Figure S-69: ¹³C-NMR spectrum of ethyl 9-benzyl-1-((2*R*, 3*R*)-4-methylene-5-oxo-3-phenyltetrahydro furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(16cA).**



Figure S-70: ¹H-NMR spectrum of ethyl 9-benzyl-1-((2*R*, 3*R*)-3-(4-chlorophenyl)-4-methylene-5-oxotetr-ahydrofuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate in CDCl₃ (16cB).



phenyldihydrofuran-2(3H)-one (17aA).



Figure S-73: Expansion of ¹H-NMR spectrum of (4*R*, 5*R*)-5-(9-methyl-9*H*-pyrido[3,4-*b*]indol-1-yl)-3-methylene-4-phenyldihydrofuran-2(3*H*)-one (**17aA**).

