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A Straightforward and Practical Formal Synthesis of Lavendamycin Ethyl Ester.

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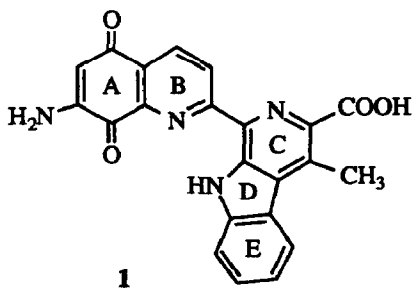
Abstract. *Aza Wittig reaction of iminophosphorane derived from ethyl α-azido-β-(3-indolyl)butyrate and 8-benzyloxy-7-bromo-2-formylquinoline is the key step in a new synthesis of lavendamycin ethyl ester.*

Lavendamycin **1**, isolated in 1981 from the fermentation broths of *Streptomyces lavendulae*,[1] displays an important antimicrobial activity, inhibitory activity for the lysogenic strain of *E. coli* and more importantly antitumor[2] activity against P-388 and L-1210 and is an inhibitor of the HIV reverse transcriptase.[3] Consequently, this target molecule has been the focus of synthetic efforts since its initial structural identification. Synthetic approaches towards **1** involve either Bichler-Napieralski reaction between β-methyltryptophan and quinaldic acid derivatives[4] or Pictet-Spengler cyclization reaction between β-methyltryptophan and 8-benzyloxy-2-formylquinoline[5] to build the ring C. The Boger approach[6] is based on the formation of the ring B by Friedlander cyclization between an *ortho*-aminobenzaldehyde possessing suitable functionalities and a 1-acetyl-β-carboline derivative, available by regioselective inverse electron demand [4+2] cycloaddition reaction of electron deficient 1,2,4-triazine with α-arylenamine, followed by palladium (0)-mediated β-carboline synthesis. A recent formal synthesis of lavendamycin methyl ester involves a modified Knoevenagel-Stobbe pyridine formation and further ring D construction by thermolytic nitrene insertion.[7]



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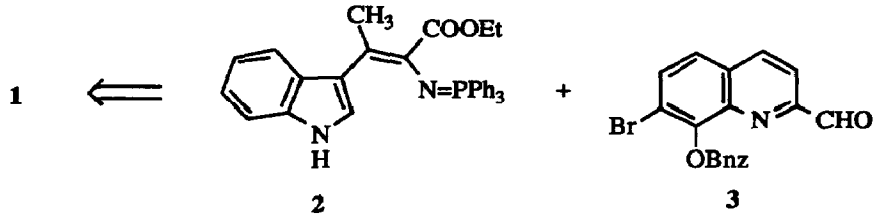
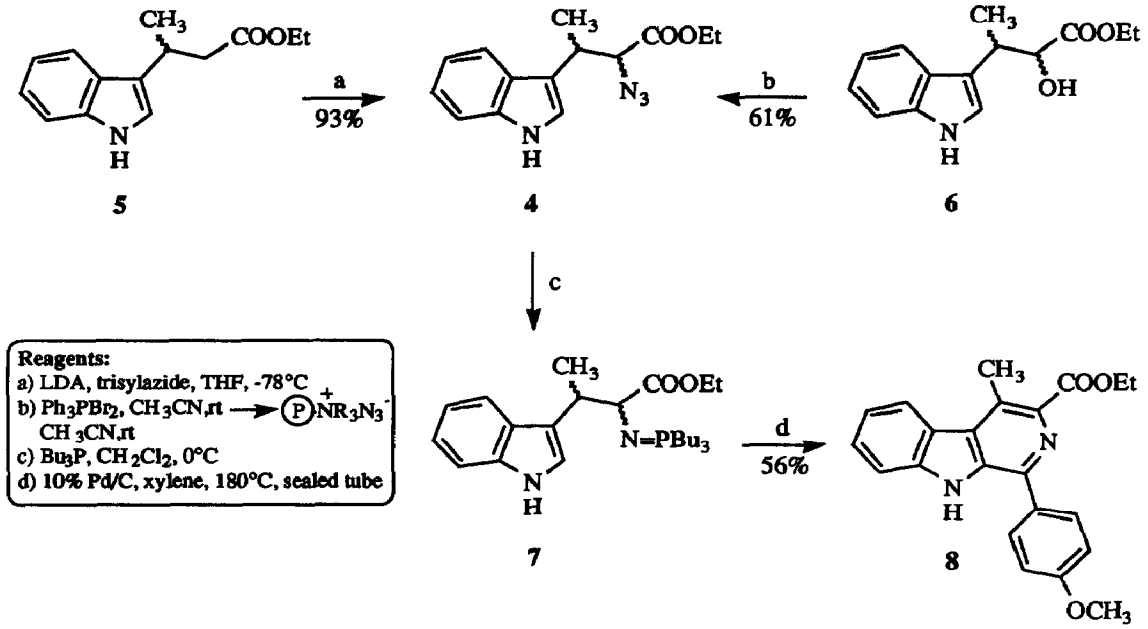
The tandem aza Wittig/electrocyclic ring-closure has been successfully utilized for the synthesis of several types of carboline derivatives.[8] Model studies starting from the iminophosphorane derived from the ethyl α-azido-β-(3-indolyl)propenoate resulted in the formation of 1-(2-quinolyl)-β-carbolines with contain the gross ring system of lavendamycin.[9] We now report a slight modification of this strategy in the form of an efficient and practical formal synthesis of lavendamycin ethyl ester. At first the iminophosphorane **2** was selected in order to incorporate in the β-carboline ring the functionalities necessary for preparation of the natural product into the cyclization step. Unfortunatly, attempts to prepare **2** : condensation of 3-acetylindole with ethyl azidoacetate in the presence of different bases and dehydratation agents; Michael-addition of indole on ethyl α-azidobutenoate and Heck reaction of 3-iodoindole with ethyl α-azidobutenoate in the presence of palladium reagents, were unsuccessful. Keeping this mind, we turned our attention to the preparation of the dihydroderivative ethyl α-azido-β-(3-indolyl)butyrate **4**. This compound was prepared by two ways[10] a) starting from the readily available ethyl 3-(3-indolyl)butyrate[11] **5** by the imide-enolate azidation procedure described by Evans and co-



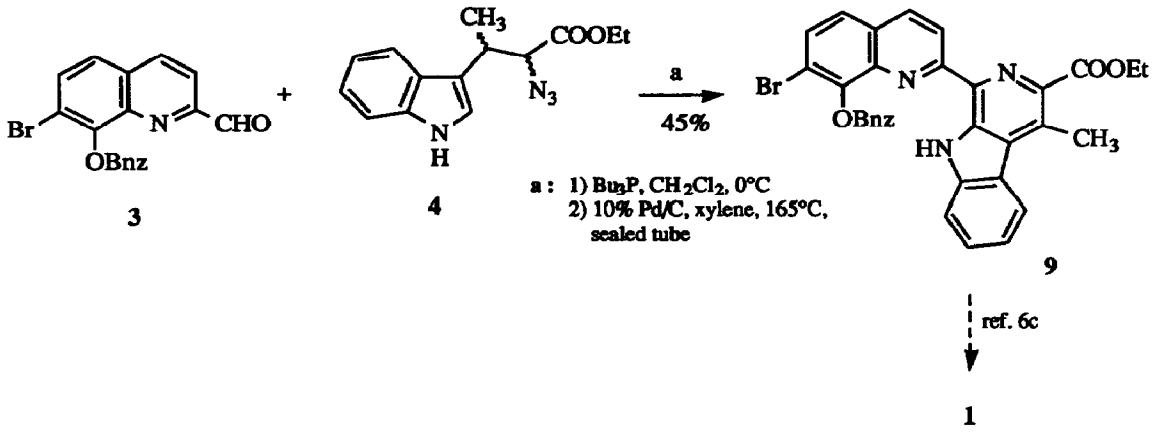
workers[12] using LDA/2,4,6-triisopropylbenzenesulfonyl azide[13] (trisyl azide) or b) starting from 2-hydroxy-3-(3-indolyl)butyrate **6**, available from indole and ethyl 2,3-epoxybutyrate,[14] by sequential treatment with triphenylphosphine dibromide and polymeric quaternary ammonium azide.[15]

The azide **4** does not convert to the corresponding iminophosphorane by treatment with triphenylphosphine even after an extended reaction time (10h). However, treatment of **4** in dichloromethane at 0°C with tributylphosphine under nitrogen produces the iminophosphorane **7**, which could be isolated as a viscous oil in almost quantitative yield. In a model study this iminophosphorane reacted with aromatic aldehydes, namely 4-methoxy benzaldehyde to give the β-carboline derivative **8**, possessing suitable functionalities in the pyridine ring. Best results were obtained when the reaction was carried out in xylene in a sealed tube at 180°C in the presence of Pd/C.



The next step was the preparation of the aldehyde **3** which possesses suitable functionality for conversion to the 7-aminoquinoline-5,8-quinone, AB ring of lavendamycin; This compounds was easily prepared in high yield by a two-step sequence starting from 2-amino-3-benzyloxy-4-bromobenzaldehyde[6b]: a) Friedlander condensation with acetone provided 8-benzyloxy-7-bromo-3-methylquinoline in 78%, b) oxidation with selenium dioxide afforded **3** (mp 79-81°C) in 82% yield.[16] Reaction of the aldehyde **3** with the iminophosphorane **7**, generated in situ from **4** and tributylphosphine, in a sealed tube at 165°C in the presence of Pd/C provided **9** in 45% yield.[17]

This constitutes a formal total synthesis of lavendamycin ethyl ester, since **9** is the ethyl ester of the Boger lavendamycin intermediate,[6c] and it may be converted into the final product in a straightforward manner.



Acknowledgements:
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References and notes:

1. Doyle, T.W.; Balitz, R.E.; Nettletone, D.E.: Gould, S.J.: Tann, C.H.: Moews, A.E. *Tetrahedron Lett.* **1981**, 4595.
2. Balitz, D.M.; Bush, J.A.; Bradner, W.T.; Doyle, T.W.; O'Herron, F.A.; Nettleton, D.E. *J. Antibiotic.* **1982**, *35*, 259; Erickson, W.R.; Gould, S.J. *J. Am. Chem. Soc.* **1985**, *107*, 5831.
3. Hafuri, Y.; Takemori, E.; Oogose, K.; Nakamura, S.; Kitahara, Y.; Nakahara, S.: Kubo, A. *J. Antibiotic.* **1988**, *41*, 1471.
4. Kende, A.S.; Ebetino, F.H. *Tetrahedron Lett.* **1984**, 923; Kende, A.S.; Ebetino, F.H.; Battista, R.; Boatman, R.J.; Lorah, D.P.; Lodge, E. *Heterocycles* **1984**, *21*, 91; Rao, A.V.R.; Chavan, S.P.; Sivadasan, L. *Tetra hedron* **1986**, *42*, 5065.
5. Hibino, S.; Okazaki, M.; Sato, K.; Morita, I.; Ichikawa, M. *Heterocycles* **1983**, *20*, 1957; Hibino, S.; Okazaki, M.; Ichikawa, M.; Sato, K.; Ishizu, T. *Heterocycles* **1985**, *23*, 261.
6. a) Boger, D.L.; Paneck, J.S. *Tetrahedron Lett.* **1984**, 3175; b) Boger, D.L.; Duff, S.R.; Panek, J.S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782; c) Boger, D.L.; Duff, S.R.; Panek, J.S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790.
7. Ciufolini, M.A.; Bishop, M.J. *J. Chem. Soc. Chem. Commun.* **1993**, 1463.
8. Molina, P.; Fresneda, P.M. *J. Chem. Soc. Perkin Trans 1* **1988**, 1819; Molina, P.; Alajarín, M.; Vidal, A.; Sanchez-Andrada, P. *J. Org. Chem.* **1992**, *57*, 929; Molina, P.; Almendros, P.; Fresneda, P.M. *Tetrahedron Lett.* **1993**, 4701.
9. Molina, P.; Fresneda, P.M.; Cánovas, M. *Tetrahedron Lett.* **1992**, 2891.
10. *Typical procedure*: To a solution of diisopropylamine (0.082 g, 8.1 mmol) in dry THF (30 ml), was added dropwise n-butyllithium (2M, 3.9 ml, 7.8 mmol). The solution was stirred at -78°C under dry N_2 for 45 min. A solution of ethyl 3-(3-indolyl)butyrate 5 (0.3 g, 1.3 mmol) in THF (15 ml) was added in one portion, and the resultant solution was warmed to -30°C for 15 min and was then recooled to -78°C. Hexamethylphosphoric triamide (HMPA) (3.5 ml, 20 mmol) was added and to the above enolate solution was added a pre-

cooled (-78°C) solution of trisylazide (1.6 g, 5.2 mmol) in dry THF (20 ml). The reaction mixture was stirred at -78°C for 1 h, and then was quenched with glacial acetic acid (1.7 ml, 29.7 mmol). The resulting mixture was allowed to warm to room temperature, stirred for 12h, treated with a saturated solution of $NaHCO_3$ (100 ml) and extracted with dichloromethane (3x40 ml). The organic extracts were combined, washed with a so lution of sodium chloride (1x10 ml), dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed on a silica gel columm using Et_2O/hexane (1:1) as eluent to afford **4** in 93% yield. ^1H n.m.r. (300 MHz, $CDCl_3$) δ 1.14 (t, 3H, ^3J= 7.1 Hz), 1.43 (d, 3H, ^3J= 6.9 Hz), 3.73 (quintuplet, 1H, J= 6.9 Hz, H-β), 4.12 (q, 2H, ^3J= 7.1 Hz), 4.21 (d, 1H, J=5.7 Hz, H-α), 7.1 (d, 1H, J= 2.4 Hz, H-2), 7.1-7.3 (m, 2H, H-5 + H-6), 7.36 (dd, 1H, J= 8.1 and 0.8 Hz, H-7), 7.64 (dd, 1H, J= 7.7 and 0.8 Hz, H-4), 8.2 (s, 1H, NH). ^{13}C n.m.r. (75 MHz, $CDCl_3$) δ 13.9 (CH_3), 16.1 (CH_3), 33.4 (C-β), 61.6 (CH_2), 67.2 (C-α), 111.3 (C-7), 116.6 (C-3), 118.7 (C-4), 119.5 (C-5), 122.0 (C-6), 122.2 (C-2), 126.2 (C-3a), 136.2 (C-7a), 169.0 (C=O).

11. Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. *Tetrahedron Lett.* **1978**, 1759.
12. The direct azide transfer methodology has been succesfully applied to the asymmetric synthesis of vancomycin-related α-azidoarylglycines: Evans, D.A.; Britton, T.C.; Dorow, R.L.; Dellaria, J.F. *Tetrahedron* **1988**, *44*, 5525; Evans, D.A.; Ellman, J.A.; Dorow, R.l. *J. Am. Chem. Soc.* **1990**, *112*, 4011; Evans,; Devries, K.M. *Tetrahedron Lett.* **1992**, 1189.
13. Harmon, R.E.; Wellman, G.; Gupta, S.K. *J. Org. Chem.* **1973**, *38*, 11.
14. Von Wittenan, M.S.; Els, H. *J. Am. Chem. Soc.* **1963**, *85*, 3425.
15. Hassner, A.; Stern, M. *Angew. Chem. Int. Ed. Eng.* **1986**, *25*, 478.
16. **3**: (82%). ^1H n.m.r. (300 MHz, $CDCl_3$) δ 5.56 (s, 2H, $PhCH_2O$), 7.5-7.3 (m, 3H, $2H_m + H_p$), 7.51 (d, 1H, J= 8.7 Hz, H-5), 7.67 (dd, 2H, J=7.4, 1.5 Hz, $2H_o$), 7.79 (d, 1H, J= 8.7 Hz, H-6), 8.04 (d, 1H, J= 8.4 Hz, H-4), 8.28 (d, 1H, J=8.4 Hz, H-3), 10.23 (s, CHO); ^{13}C n.m.r. (75 MHz, $CDCl_3$) δ 76.8 ($PhCH_2O$), 117.5 (C-3), 118.0 (C-7), 123.8 (C-6), 128.2 (C_p), 128.3 ($2C_o$), 128.6 ($2C_m$), 130.7 (C-4a), 133.5 (C-5), 137.0 (C-8a), 137.8 (C-4), 143.1 (C_i), 151.9 (C-8), 153.0 (C-2), 193.3 (CHO).
17. *Typical Procedure*: To a cooled at 0°C solution of tributylphosphine (0.35 g, 1.7 mmol) in dry dichloromethane (25 ml), was added a solution of **4** (0.47 g, 17 mmol) in the same solvent (20 ml). The mixture was stirred at 0°C under nitrogen for 6 h.The solvent was removed under vacuo and to the residual iminophosphorane **7** were added o-xylene (20 ml), 10% Pd/C (0.051 g), and 8-benzyloxy-7-bromo-2-formyl quinoline **3** (0.6 g, 1.7 mmol). The resultant mixture was treated in a sealed tube at 165°C for 20 h. After cooling, the solution was filtered and the filtrate was concentrated to dryness. The residue was chromatographed on a silica gel columm using ethyl acetate/hexane as eluent to give **9** (45%, yellow prisms, m.p. 186-188°C, from dichloromethane/diethyl ether). ^1H n.m.r. (300 MHz, $CDCl_3$) δ 1.55 (t, 3H, J= 7.2 Hz, CH_3CH_2OCO), 3.10 (s, 3H, CH_3), 4.55 (q, 2H, J= 7.2 Hz, CH_3CH_2OCO), 5.25 (s, 2H, $PhCH_2O$), 6.27 (d, 1H, J=7.7 Hz, H-8), 7.3-7.2 (m, 2H, H-7 + H-6), 7.4-7.3 (m, 3H, $2H_m+H_p$), 7.44 (d, 1H, J= 8.7 Hz, H-5'), 7.62-7.58 (dd, 2H, J= 7.2, 1.8 Hz, $2H_o$), 7.62 (d, 1H, J= 8.7 Hz, H-6'), 8.16 (d, 1H, J= 8.7 Hz, H-4'), 8.18 (d, 1H, J= 7.5 Hz, H-5), 8.77 (d, 1H, J= 8.7 Hz, H-3'), 11.65 (s, 1H, NH); ^{13}C n.m.r. (75 MHz, $CDCl_3$) δ 14.6 (qt, ^1J= 126.9, ^2J= 2.6 Hz, CH_3CH_2OCO), 16.8 (q, ^1J= 128.5 Hz, CH_3), 61.3 (tq, ^1J= 147.5, ^2J= 4.5 Hz, CH_3CH_2OCO), 75.4 (tt, ^1J= 146.1, ^3J= 4 Hz, $PhCH_2O$), 112.7 (dd, ^1J= 163.0, ^3J= 7.3 Hz, C-8), 117.5 (d, ^2J= 12.5 Hz, C-7'), 119.7 (d, ^1J=169.2 Hz, C-3'), 120.4 (dd, ^1J= 160.6, ^3J= 7.1 Hz, C-6), 121.9 (q, ^3J= 5.9 Hz, C-4a), 123.4 (dd, ^1J= 159.9, ^3J= 7.5 Hz, C-6), 124.6 (dd, ^1J= 164.7, ^2J= 4.6 Hz, C-5'), 127.6 (d, ^1J= 159.1 Hz, C_p), 127.8 (d, ^1J= 161.2 Hz, $2C_o$), 128.2 (t, ^2J= 8.3 Hz, C-4'a), 128.3 (dt, ^1J= 160.1, ^2J= 7.5 Hz, C-7), 128.9 (dd, 1J= 160.1, ^2J= 6.6 Hz, $2C_m$), 129.9 (d, ^2J= 7 Hz, C-4b), 130.7 (d, ^1J= 168.1 Hz, C-6'), 132.0 (q, ^2J= 6.2 Hz, C-4), 134.4 (s. C-8'a), 135.4 (s, C-9a), 136.6 (dd, ^1J=163.2, ^2J= 4.5 Hz, C-4'), 137.1 (m, C-8a), 137.3 (m, C_i), 140.6 (q, ^3J= 6 Hz, C-3), 142.3 (t, ^3J= 6 Hz, C-1), 151.6 (d, ^3J= 7 Hz, C-8'), 157.5 (d, ^2J= 7.5 Hz, C-2'), 167.6 (s, C=O).

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