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Convergent Synthesis of Streptonigrin and Lavendamycin Analogues

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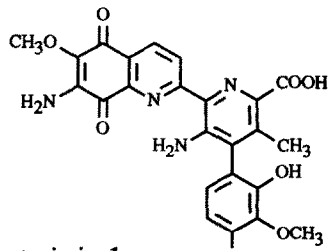
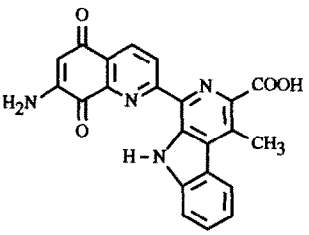
Key Words: *Alkaloid, Cross-coupling, Lavendamycin, Metalation, Oxidative demethylation, Palladium, Streptonigrin.*

Abstract: *A convergent synthesis of streptonigrin and lavendamycin analogues incorporating a quinoline-5,8-dione structure is reported. The approach is based on our synthetic methodology which involves such reactions as metalation, heteroring cross-coupling and oxidative demethylation.*

Streptonigrin (**1**)[1] and *Lavendamycin* (**2**)[2] were isolated and characterized in 1959 and 1981 respectively (Scheme 1). Their structures incorporate a highly substituted 2-(2-pyridyl)quinoline-5,8-dione.[3] Several multi-step syntheses of these antitumor antibiotics or analogues have been reported[4] which often suffered from allow poor overall yields. Our group recently published new and more convergent routes to the streptonigrin[5] and lavendamycin[6] skeletons using palladium catalyzed heteroring cross-coupling between simple benzene, quinoline and pyridine moieties. We report here on the extension of this fruitful strategy to more functionalized streptonigrin and lavendamycin analogues incorporating a quinoline-5,8-dione structure.



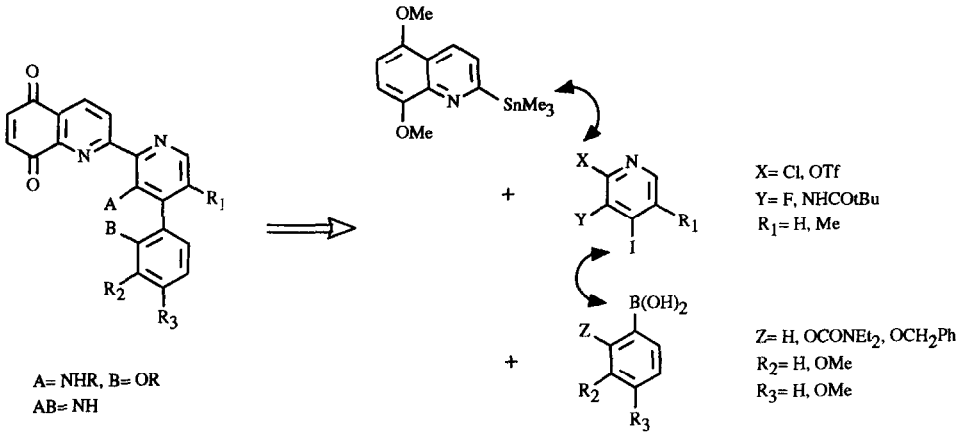
Streptonigrin **1**



Lavendamycin **2**

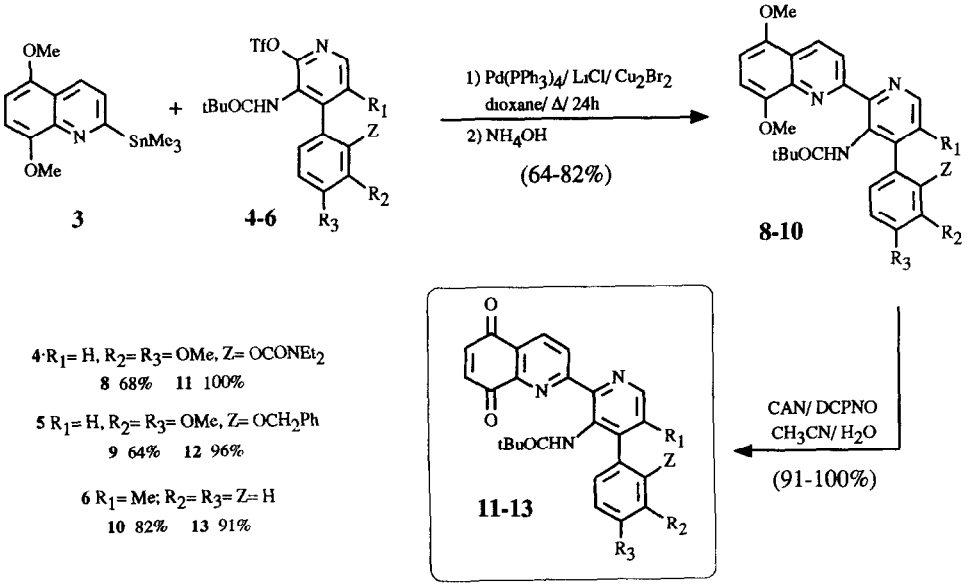
Scheme 1

A retrosynthetic analysis suggests that these structures could be obtained from benzene, pyridine and quinoline building blocks in three or four key-steps: oxidation of the 5,8-dimethoxyquinoline moiety, two heteroring cross-couplings and an indole cyclization in the case of the lavendamycin structure (Scheme 2). This has been conveniently achieved starting from the required aromatics previously obtained by directed ortho metalation.[7]



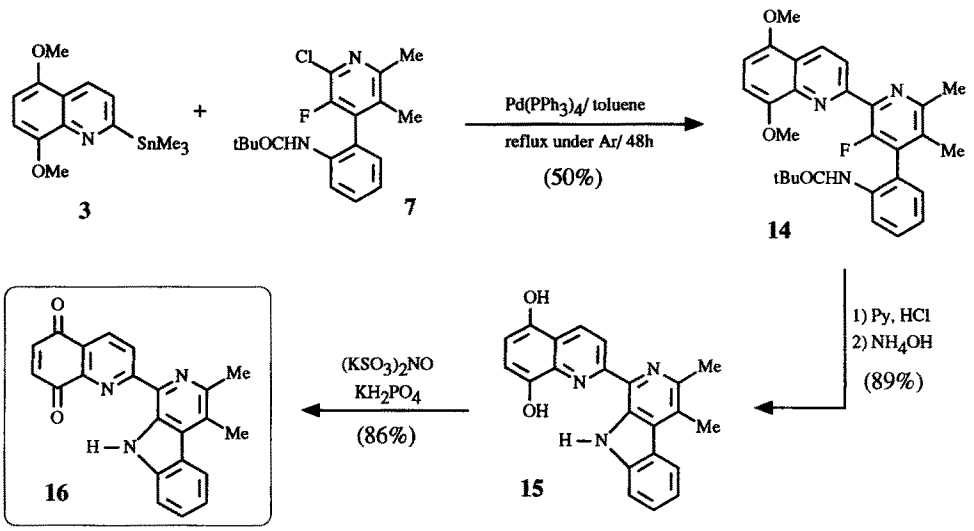
Scheme 2

Palladium-catalyzed cross-coupling between arylstannane **3** and aryltriflates **4**,[5] **5**,[8] **6**[9] using Stille's procedure[12] afforded the polyaryls **8-10** in good yields (2-(5,8-dimethoxyquinolyl)trimethyl stannane **3** was prepared in 85% yield from the corresponding 2-bromoquinoline[11] by bromine-lithium exchange with butyllithium at low temperature, followed by transmetalation with chlorotrimethyltin[10]). Direct oxidative demethylation of compounds **8-10** was carried out with cerium ammonium nitrate (CAN) in the presence of 2,6-pyridinedicarboxylic acid N-oxide (DCPNO) in a mixture of acetonitrile and water.[13] Thus, 2-substituted quinoline-5,8-diones **11-13** (yellow products) were obtained in high yields (Scheme 3).



Scheme 3

Similarly, reaction of stannane **3** with chloropyridine **7**[6] in presence of a catalytic amount of $Pd(PPh_3)_4$ in refluxing toluene led to the polysubstituted triaryl **14** in 50% yield. Cyclization of this compound to the corresponding β-carboline **15** (dark green product) was best achieved by treatment with boiling pyridinium chloride at 215°C.[14] Under these conditions, hydrolysis of the two methoxy groups occurs. Ultimately, oxidation of the β-carboline **15** with Fremy's salt[15] afforded the quinoline-5,8-dione **16** (red product) in very good yield (Scheme 4).



Scheme 4

In conclusion, models **11**,[16] **12**, **13** and **16**[17] were synthesized in 68%, 61%, 74% and 39% overall yields, respectively from stannane **3** and biaryls **4-7**. This general and convergent pathway is currently being extended to the synthesis of *Streptonigrin* and *Lavendamycin* themselves and other analogues as well.

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16. Compound **11**: main physical data of this product are: mp: 171-172°C; IR (KBr) 3300, 3060, 2960, 2920, 1715, 1675, 1600, 1585, 1500, 1470, 1460, 1440, 1410 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.97 (m, 12H, tBu et CH_3); 1.18 (m, 3H, CH_3); 3.19 (m, 4H, 2 CH_2); 3.89 (s, 3H, OMe); 3.91 (s, 3H, OMe); 6.93 (d, 1H, H_5'', J= 8.7 Hz); 7.09 (d, 1H, H_6, J= 10.5 Hz); 7.13 (d, 1H, H_6'', J= 8.7 Hz); 7.16 (d, 1H, H_7, J= 10.5 Hz); 7.39 (d, 1H, H_5', J= 4.8 Hz); 8.56 (d, 1H, H_4, J= 8.3 Hz); 8.58 (d, 1H, H_6', J= 4.8 Hz); 8.68 (d, 1H, H_3, J= 8.3 Hz); 10.1 (s, 1H, NH). Anal. Calcd for $C_{32}H_{34}N_4O_7$ (586.65): C, 65.51; H, 5.84; N, 9.55. Found: C, 65.85; H, 5.88; N, 9.31.
17. Compound **16**: main physical data of this product are: mp: >260°C; IR (KBr) 3320, 3060, 2928, 1662, 1585 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ (ppm) 2.75 (s, 3H, CH_3); 2.88 (s, 3H, CH_3); 7.20 (d, 1H, H_6', J= 10.0 Hz); 7.29 (d, 1H, H_7', J= 10.0 Hz); 7.34 (comp., 1H, H_6); 7.60 to 7.80 (m, 2H); 8.36 (d, 1H, J= 8.0 Hz); 8.51 (d, 1H, H_3', J= 8.3 Hz); 8.92 (d, 1H, H_4',J= 8.3 Hz) and NH signal not detected. Anal. Calcd for $C_{22}H_{15}N_3O_2$ (353.38): C, 74.78; H, 4.28; N, 11.89. Found: C, 74.65; H, 4.39; N, 11.75.

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