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Synthesis of an analogue of lavendamycin and of conformationally restricted derivatives by cyclization via a hemiaminal intermediate

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Abstract—Quinoline **12** was obtained by a Friedländer reaction from 2-aminobenzaldehyde and methyl acetoacetate. Reduction, silylation then oxidation provided compound **8a**. A Pictet–Spengler reaction between the latter and tryptophan methyl ester yielded compound **14**, then compound **7** by desilylation. Numerous attempts to prepare a cyclized derivative of this analogue of lavendamycin **7** by conventional ways failed. Fortunately, a good result was obtained via a hemiaminal intermediate and compound **21** was thus obtained in satisfactory yield. A conjugate addition occurred in the course of its reduction which led to compound **22**. Biological tests were carried out with compound **7** and the conformationally restricted analogues **21** and **22**.

1. Introduction

Lavendamycin **1**,[1] (Fig. 1) a natural product from *Streptomyces lavendulae*, showed antimicrobial and cytotoxic properties[2] and displayed a significant activity against topoisomerases I (MIC = 0.1 μg/mL).[3] However, its biological interest is limited by its toxicity that may be linked to the presence of the quinone moiety. Numerous syntheses of this interesting compound, or of ester derivatives, were carried out[4] as well as the ones of various analogues.[5] Structure–activity relationships have been discussed.

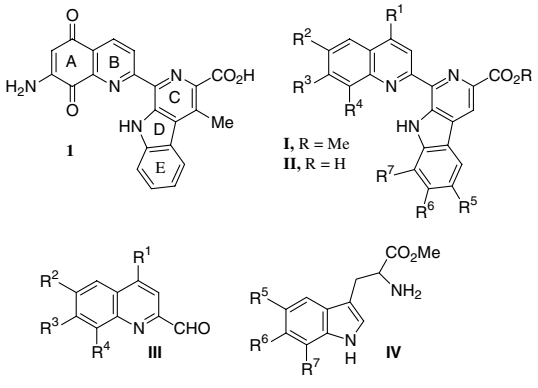

Figure 1.

In a previous work of our group in this area[5h] we prepared several esters **I** and acids **II** without the aminoquinone moiety and the methyl group of C cycle, and with various substituents R^1–R^7. These syntheses were based on a Pictet–Spengler type reaction carried out in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate, starting from **III** and **IV**. We thus obtained the desired esters **I**, and then acids **II** by saponification. The biological tests showed that these compounds maintained a part of the biological properties of the parent molecule. We also observed that unsubstituted product **II** with R^1 to R^7 = H, and the derived compound bearing a C cycle substituted by a methyl group, as in lavendamycin, had the same activities.

When comparing structures of compounds **I** and **II** and the ones of the most important known inhibitor of topoisomerases I, camptothecin itself, **2**[6] and analogues, and also of some other inhibitors such as azaIQD **3**,[3] nitidine **4**, and isofagaridine **5**,[7] it appears that all of them have a rigid structure (Fig. 2). With the hope to obtain products more interesting than **I** and **II**, we then envisioned to synthesize the conformationally restricted analogue **6**, or related compounds. We thought that this

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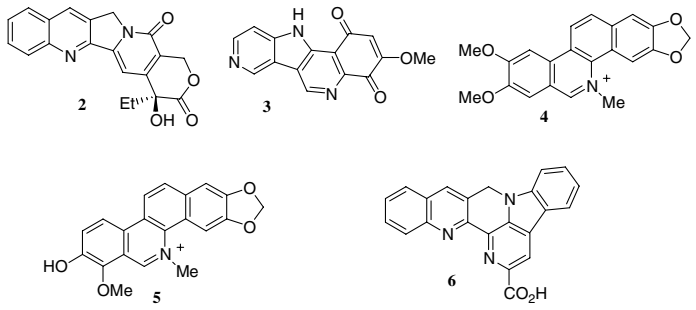


Figure 2.

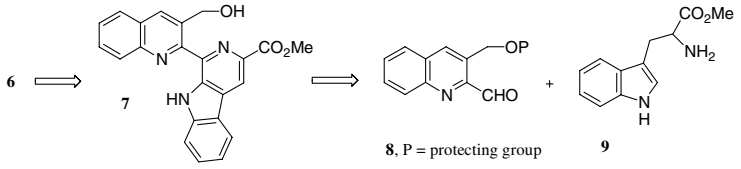
aim could be attained by carrying out a cyclization reaction between the pyrrole nitrogen and a suitable substituent on the B cycle.

2. Results and discussion

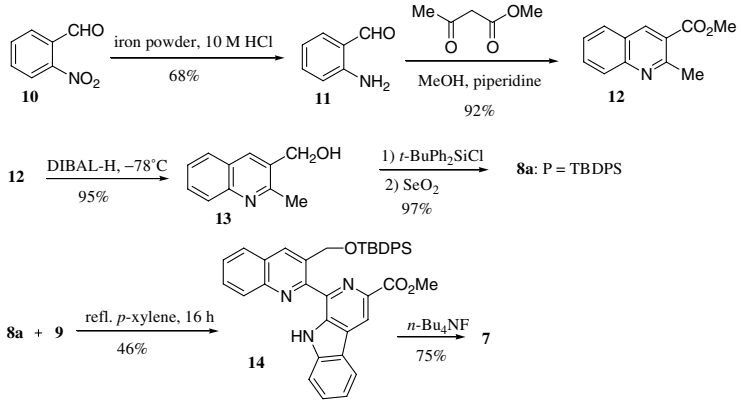
Our strategy to prepare compound **6** or related products was to carry out an intramolecular cyclization from intermediate **7** or a derivative (Scheme 1). This compound would be available by a Pictet–Spengler reaction[5h] from a substituted quinoline **8** and tryptophan methyl ester **9**.

Friedländer reaction between 2-aminobenzaldehyde **11**[8] obtained by reduction of 2-nitrobenzaldehyde **10** with iron powder in acidic medium[9] and methyl acetoacetate led to product **12**.[10] The best result (Scheme 2) for reduction to alcohol **13** was obtained with DIBAL-H. When this alcohol was oxidized by selenium dioxide,[5h] the corresponding aldehyde was not obtained likely due to reactions such as lactol formation. Protection of the hydroxyl group was necessary and then oxidation to aldehydes **8a** (P = TBDPS), **8b** (P = Bn) and **8c** (P = Ac) gave good results. Numerous reactions between **8a** or **8b** or **8c** and tryptophan methyl ester **9** were then carried out with or without a catalyst.[11] The best result was obtained from **8a** at high temperature and without a catalyst. Compound **14** was thus obtained in a reasonable yield (46%) and desilylation provided the desired hydroxyester **7**.

We then tried to find efficient conditions to prepare the target molecule **6**, or other cyclized products, from compound **7** by an intramolecular reaction. One of the difficulties was the poor solubility of this alcohol in most of the organic solvents, even in dimethylsulfoxide. However, an acceptable solubility was observed in *N*-methylpyrrolidinone (NMP). We then tried to carry out the Mitsunobu reaction from compound **7**, under different conditions, and particularly in NMP. It failed to give the desired product and led to recovering of the starting material. This failure may be due to an inappropriate pK_a of the nucleophile.[12]



Scheme 1.

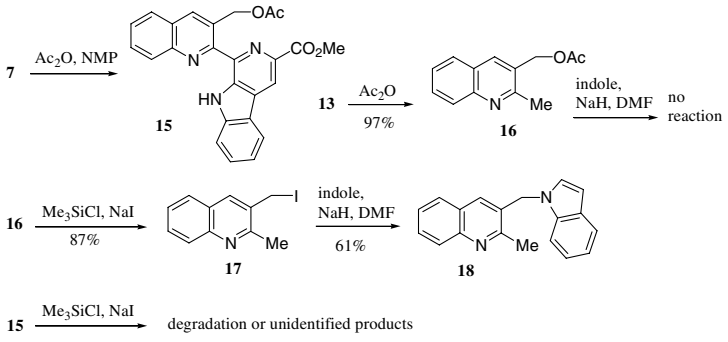


Scheme 2.

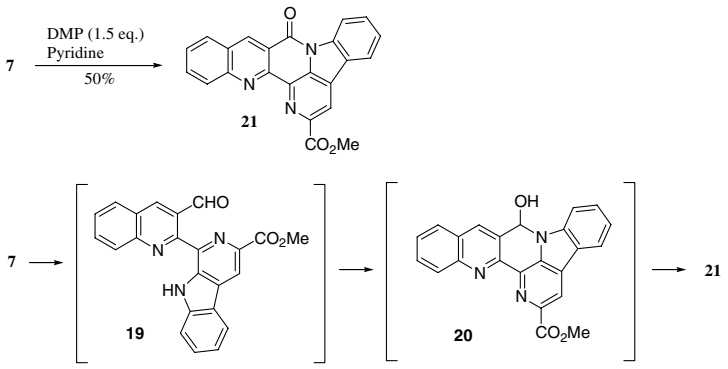
Another possibility was to replace the hydroxyl group by a leaving group to make possible the nucleophilic attack of the pyrrole nitrogen. Numerous attempts to obtain mesylate, tosylate, triflate or halides were unsuccessful and led either to recovery of the starting material or to degradation of products. In contrast, another attempt with acetic anhydride gave the corresponding acetate **15** (86%) (Scheme 3). We then tested the possibility of nucleophilic substitution in a more simple case, from acetate **16**[13] derived from alcohol **13** and indole. However the reaction did not work, but replacement of this poor leaving group by iodide led to the expected product **18**. This good result led us to try to prepare the iodide derivative of **7** from **15** under the same experimental conditions. Unfortunately the reaction led either to unidentified products or to degradation depending on temperature, solvent or reaction time. Another attempt to prepare a bromide derivative from the silylated compound **14** under various conditions also failed. Finally we tested another possibility involving the introduction of the leaving group early in the synthesis and we carried out a Pictet–Spengler reaction between 3-bromomethylquinoline-2-carbaldehyde and tryptophan methyl ester. Once more, only degradation occurred.

As the first two routes failed, we envisioned a less classical possibility. We planned to oxidize compound **7** to replace the hydroxymethyl group by a formyl group, with the hope that a subsequent nucleophilic attack of the pyrrole moiety would work. In a first experiment with manganese dioxide, we were pleased to directly obtain compound **21** without detecting the intermediate aldehyde (Scheme 4). However, this experiment needed a large excess of oxidant and a long reaction time (12 days). Moreover the yield was low (19%). We then examined other conditions, and the Dess-Martin periodinane (DMP)[14] (1.5 equiv) gave the best result. Compound **21** was thus obtained in an acceptable yield of 50% for the three steps (oxidation, cyclization, new oxidation). This formation of compound **21** likely involves the intermediate formation of aldehyde **19** that is sufficiently reactive to give hemiaminal **20**. The latter is not stable under these experimental conditions and is oxidized to compound **21**. Using an excess of reagent (2.1 equiv) resulted in a slight lowering of the yield (45%). Stability of hemiaminals is usually low, except in particular cases such as when intramolecular hydrogen bonding interactions are involved[15] or when the compound is included in a metallocycle.[16] In the case of intermediate **20** an oxidation to compound **21** occurs. In principle the amount of oxidant used (1.5 equiv) is not sufficient for both oxidations, but the overall yield is moderate. Therefore, the possibility of oxidation of **20** by DMP cannot be rejected. However, this oxidation may also occur by air oxygen as it was observed in similar cases.[17]

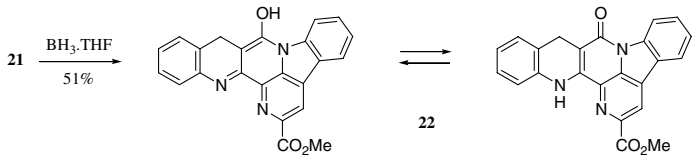
Our objective of preparing a conformationally restricted analogue of lavendamycin was thus achieved but we also examined if preparation of the reduced product **6** would be possible from compound **21**. We choose BH_3·THF in view of reducing only the amide function.[18] As a matter



Scheme 3.



Scheme 4.



Scheme 5.

of fact we were surprised to obtain a product **22**, which might exist in two tautomeric forms, and resulting from a conjugate reduction (Scheme 5). Purification and identification of this compound **22**, as the ones of compounds **7** and **21**, were complicated by its low solubility. It was identified thanks to NMR spectra that revealed, in particular, the presence of a ^{13}C signal of a methylene group in the ^{13}C DEPT 135 experiment, at 26 ppm, and to HRMS which confirmed the presence of an oxygen more with respect to the structure of the expected product (**6**). Some dearomatizations of a pyridinic cycle in the case of reduction of quinoline systems have already been observed.[19] Concerning the both possible tautomeric forms of compound **22**, it is not easy to determinate which one is predominant, however IR data are more consistent with a preference for the lactam form.[20]

3. Conclusions

Finally, we obtained the simplified analogue of lavendamycin **7** by a short way. Thanks to the presence of the hydroxymethyl group on the B cycle several possibilities of cyclization were conceivable. The more classical ways failed, but a good result was obtained for preparation of compound **21** via a hemiaminal. Conjugate reduction provided compound **22**.

Biological tests in cell culture with 60 different tumour cells were carried out for compounds **7**, **21** and **22** by the National Cancer Institute. Unfortunately, they only showed a moderate activity.[21] However their poor solubility in all the solvents is not a favourable point. It should be interesting to apply this strategy to synthesize substituted related compounds which could be probably more soluble.

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20. *Selected preparation procedures and data. Compound* **14**: Compound **8a** (65 mg, 0.153 mmol) was added under nitrogen to a stirred solution of tryptophan methyl ester (50 mg, 0.230 mmol) in anhydrous *p*-xylene (2.5 mL). After 16 h of stirring at reflux, cooling, evaporation and column chromatography on silica gel (cyclohexane/AcOEt, 95:5) provided **14** (44 mg, 46%) as a yellow solid. Mp 220–221 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.68$ (br s, 1H, NH), 9.03 (s, 1H), 8.86 (s, 1H), 8.27 (d, $J = 8.1$ Hz, 1H), 8.21 (d, $J = 7.9$ Hz, 1H), 7.99 (d, $J = 8.1$ Hz, 1H), 7.83–7.77 (m, 5H), 7.69–7.60 (m, 3H), 7.42–7.33 (m, 7H), 5.93 (s, 2H, CH_2), 3.53 (s, 3H, CH_3), 1.21 (s, 9H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.0$ (C=O), 154.2, 145.4, 140.5, 139.2, 136.9, 136.1, 135.8, 135.5, 134.6, 133.8, 130.3, 129.6, 129.3, 128.8, 128.4, 128,0, 127.7 (2C), 127.1, 121.8, 121.7, 120.8, 117.7, 112.2, 64.6 (CH_2), 51.9 (CH_3), 27.1 (C(*C*H_3)$_3$); 19.5 (*C*(CH_3)$_3$) ppm. Anal. Calcd for $C_{39}H_{35}N_3O_3Si$: C, 75.33; H, 5.67; N, 6.76. Found: C, 75.31; H, 5.73; N, 6.74. *Compound* **7**: Glacial CH_3CO_2H (0.6 mL) and a 1 M solution of *n*-Bu_4NF in THF (4.8 mL, 4.8 mmol) were added under nitrogen to a stirred solution of compound **14** (998 mg, 1.61 mmol) in THF (11 mL). After 12 h of stirring at room temp. then evaporation, a mixture of petroleum ether/AcOEt, 1:4 (20 mL) was added. Stirring and heating of the mixture, filtration with heating and recuperation of the solid provided pure **7** (460 mg, 75%) as a yellow solid. Mp 260–262 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.67$ (br s, 1H, NH), 8,93 (s, 1H, arom H), 8.26–8.23 (m, 3H, arom H), 7.88 (dd, $J = 1.2$, 8.1 Hz, 1H, arom H), 7.81 (ddd, $J = 1.5$, 6.9, 8.4 Hz, 1H, arom H), 7.73–7.61 (m, 3H, arom H), 7.42 (ddd, $J = 1.0$, 6.9, 7.9 Hz, 1H, arom H), 6.94 (t, $J = 8.0$ Hz, 1H, OH), 4.97 (d, $J = 8.0$ Hz, 2H, CH_2), 4.10 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $C_2D_2Cl_4$, 60 °C): $\delta = 166.0$ (C=O), 156.4, 146.2, 141.0, 139.4, 138.9, 137.2, 135.8, 134.7, 130.9, 130.1, 129.3, 128.6, 127.7, 127.6 (2C), 121.9, 121.6, 121.3, 117.8, 112.5, 64.5 (CH_2), 52.5 (CH_3) ppm. Anal. Calcd for $C_{23}H_{17}N_3O_3$, 0.3 H_2O: C, 71.05; H, 4.56; N, 10.81. Found: C, 71.00; H, 4.48; N, 10.63. *Compound* **21**: Anhydrous pyridine (0.5 mL) and Dess-Martin periodinane (364 mg, 0.858 mmol) were added under nitrogen to a stirred solution of compound **7** (219 mg, 0.572 mg) in anhydrous NMP (3.9 mL). The reaction mixture was stirred at room temp. for 2d, then CH_2Cl_2 (15 mL) was added. The heterogeneous organic phase was successively washed with a 1:1 mixture (12 mL) of 5% $Na_2S_2O_3$ solution and of a saturated solution of $NaHCO_3$, a saturated solution of $NaHCO_3$ (6 mL), 1 M HCl (6 mL) and then brine (6 mL). The resulting suspension was evaporated without drying. Adding of MeOH (15 mL), heating (~55 °C), filtration with heating and recuperation of the solid provided **21** (108 mg, 50%) as a yellow solid. Mp 304–306 °C. ^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 60 °C): $\delta = 9.46$ (s, 1H), 8.85 (s, 1H), 8.75 (d, $J = 8.1$ Hz, 1H), 8.51 (d, $J = 8.5$ Hz, 1H), 8.17 (d, $J = 7.7$ Hz, 1H), 8.09 (d, $J = 8.5$ Hz, 1H), 7.96 (ddd, $J = 1.3$, 7.2, 8.3 Hz, 1H), 7.77–7.68 (m, 2H), 7.56 (ddd, $J = 0.6$, 7.2, 7.8 Hz, 1H), 4.10 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $C_2D_2Cl_4$, 60 °C): $\delta = 165.8$ (C=O, ester), 159.1, 150.3 (C=O, amide), 148.8, 144.6, 140.2, 139.3, 136.1, 134.5, 133.3, 131.9, 131.4, 130.4, 129.4, 128.5, 127.5, 126.1, 124.7, 123.6, 122.7, 118.5, 117.5, 53.0 (CH_3) ppm. HRMS Calcd for $C_{23}H_{13}N_3O_3$: 379.0957. Found: 379.0957. *Compound* **22**: A 1 M solution of $BH_3{\cdot}THF$ (0.65 mL, 0.632 mmol) was added under nitrogen to a stirred suspension of compound **21** (60 mg, 0.158 mmol) in anhydrous THF (1.8 mL). The heterogeneous mixture was heated at reflux for 5 h, then it was cooled, and a 6 M solution of HCl was added (80 μL). The resulting suspension was evaporated and the crude product was heated (~55 °C) with MeOH (5 mL). A filtration with heating and recuperation of the solid provided **22** (31 mg, 51%) as a yellow solid. Mp 295–297 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.80$ (s, 1H, H-3), 8.65 (d, $J = 8.2$ Hz, 1H), 8.20 (br s, 1H, OH), 8.12 (d, $J = 7.7$ Hz, 1 H), 7.71 (ddd, $J = 1.0$, 8.2, 8.3 Hz, 1H), 7.50 (ddd, $J = 0.7$, 7.8, 7.9 Hz, 1H), 7.20–7.15 (m, 2H), 7.01 (ddd, $J = 0.9$, 7.2, 7.5 Hz, 1H), 6.97 (d, $J = 7.8$ Hz, 1H), 4.17 (s, 2H, CH_2), 4.11 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $C_2D_2Cl_4$, 67 °C): $\delta = 165.4$ (C=O), 159.4, 142.6, 142.4, 140.4, 135.9, 132.2, 131.2, 130.5, 129.7, 129.4, 127.6, 124.9, 123.9, 122.7, 120.3, 118.3, 118.2, 116.9, 115.6, 104.9, 52.8 (CH_3), 26.0 (CH_2) ppm. HRMS Calcd for $C_{23}H_{15}N_3O_3$: 381.1113. Found: 381.1129.
21. For instance, for leukemia CCRF-CEM cells, the GI50 were 2.55×10^{-5}, $>1.00 \times 10^{-4}$, 2.19×10^{-6} M, for compounds **7**, **21**, **22**, respectively, and the LC50 were $>1.00 \times 10^{-4}$ M for the three compounds.