

THE SYNTHESIS OF A POTENTIAL INTERMEDIATE TO APOMITOMYCIN

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Abstract — Condensation of methyl α -bromo-(2-bromo-4,5-dimethoxyphenyl)acetate (10) with 2-thiopyrrolidone (11) and with trans-3-acetoxy-4-(N-ethoxycarbonyl-N-methylamino)-2-thiopyrrolidone (14) gave in high yields methyl (Z)- α -(2-bromo-4,5-dimethoxyphenyl)- α -pyrrolidine-2-ylideneacetate (12), and methyl α -[3-acetoxy-4-(N-ethoxycarbonyl-N-methylamino)pyrrolidine-2-ylidene]acetates (15) and (16), respectively. Treatment of compounds 12 and 15 or 16 with sodium hydride and cuprous bromide in dimethylformamide afforded, again in good yields, methyl 6,7-dimethoxy-1H-pyrrolo[1,2-a]indole-9-carboxylate (13) and methyl trans-1-acetoxy-2-[N-ethoxycarbonyl-N-methylamino]-6,7-dimethoxy-1H-pyrrolo[1,2-a]indole-9-carboxylate (17), respectively.

During the course of synthetic studies directed towards mitomycin derivatives,¹⁻³ we reported a facile synthesis of 3-benzyl-6-methyl-2-oxo-3,6-diazabicyclo[3.1.0]hexane (2) from trans-1-benzyl-3-hydroxy-4-methylamino-2-oxopyrrolidine (1).⁴ The compound 3 is thus readily available⁴ and we now wish to report its use in an effective method for the synthesis of pyrrolo[1,2-a]indoles with functional groups at positions C₁ and C₂. Such functionality is a prerequisite for further conversion to apomitomycin.

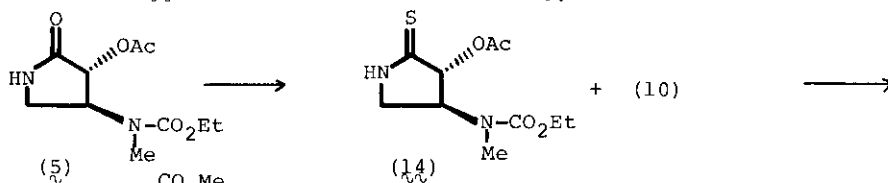
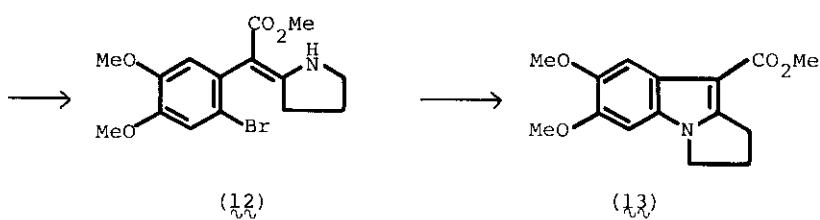
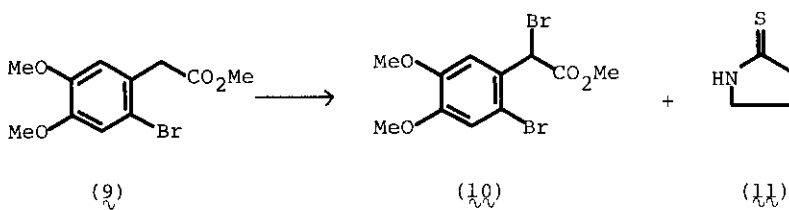
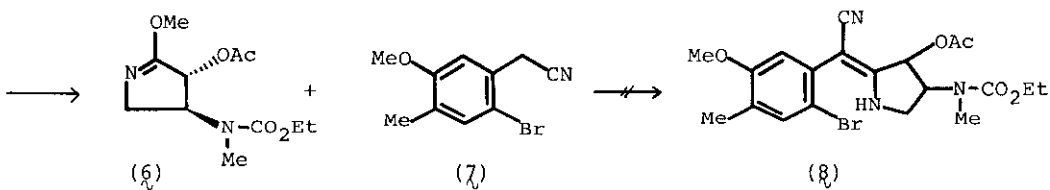
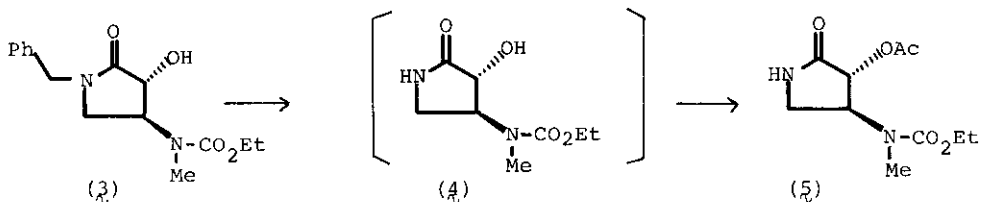
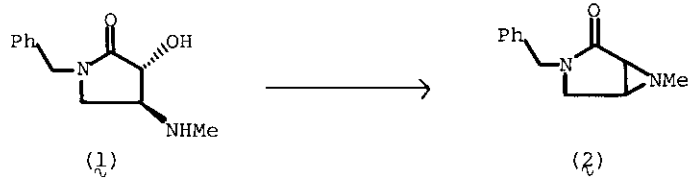
Firstly, condensation of the nitrile¹ 7 with the O-methylpyrrolidone (8) was examined in an attempt to obtain the compound 8. trans-3-Acetoxy-4-(N-ethoxycarbonyl-N-methylamino)-2-oxopyrrolidine (5) was prepared as follows. Reduction of (+)-trans-1-benzyl-4-(N-ethoxycarbonyl-N-methylamino)-3-hydroxy-2-oxopyrrolidine⁴ (3) with sodium in liquid ammonia at -33° in the presence of sodium hydride gave

the debenzylated compound 4 , which was acetylated with acetic anhydride in pyridine at 0° to afford the acetate 5 , mp 108° [nmr (CDCl_3) δ : 2.15 (3H, s, COCH_3), 5.66 (1H, d, $J = 9.3$ Hz, $\text{C}_3\text{-H}$); ir $\nu_{\text{max}}^{\text{CHCl}_3}$ 3460 (NH), 1720 and 1690 cm^{-1} (C=O); m/e 244 (M^+)], in 55 % overall yield. The acetate 5 was treated with trimethyloxonium-fluoroborate⁵ to give the O-methylpyrrolidone 6 [nmr (CDCl_3) δ : 3.87 (3H, s, OCH_3); ir $\nu_{\text{max}}^{\text{CHCl}_3}$ 1740, 1685 (C=O), and 1655 cm^{-1} (C=N); m/e 258 (M^+)] in 94 % yield. It was then attempted to condense the compound 6 with the nitrile 7 under basic conditions involving the use of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), and although the product remains undefined, it was shown not to be the expected condensation product 8 . Since pyrroloindoles have been formed in this type of condensation with unsubstituted O-methylpyrrolidone¹, failure to form compound 8 in the above case may be due to steric hindrance caused by the substituents on the pyrrolidine ring of 6 . Bearing this in mind, we decided to explore the sulfide condensation method developed by Eschenmoser and coworkers⁶⁻⁹ and Felner and Schenker¹⁰

Thus, the dibromide 10 [nmr (CDCl_3) δ : 5.87 (1H, s, $\text{C}_\alpha\text{-H}$); ir $\nu_{\text{max}}^{\text{CHCl}_3}$ 1750 cm^{-1} (C=O); m/e 366 (M^+) and 370 ($\text{M}^+ + 4$)], which was obtained in 82 % yield from the ester 9 ¹¹ with N-bromosuccinimide, was treated with thiopyrrolidone (11)¹² in dry chloroform at room temperature and then the reaction mixture was heated with DBU to afford the pyrrolidinylideneacetate 12 [nmr (CDCl_3) δ : 2.32 (2H, t, $J = 6$ Hz, $\text{N}-\overset{\text{H}}{\text{C}}-\text{CH}_2$); ir $\nu_{\text{max}}^{\text{CHCl}_3}$ 3400 (NH) and 1655 cm^{-1} (C=O); m/e 355 (M^+) and 357 ($\text{M}^+ + 2$)] in 97 % yield.

Cyclisation of compound 12 was effected by using sodium hydride and cuprous bromide¹ in dry dimethylformamide to give the pyrroloindole 13 , mp 162° [nmr (CDCl_3) δ : 2.53 - 2.87 (2H, m, $\text{C}_2\text{-H}_2$), 3.27 (2H, t, $J = 6.8$ Hz, $\text{C}_1\text{-H}_2$), 3.89, 3.92 and 3.98 (each 3H, each s, $3 \times \text{OCH}_3$), 6.74 and 7.67 (each 1H, each s, $2 \times \text{ArH}$); ir $\nu_{\text{max}}^{\text{CHCl}_3}$ 1685 cm^{-1} (C=O); m/e 275 (M^+)] in 95 % yield.

Next, the thiopyrrolidone 14 , mp $115 - 116^\circ$ [nmr (CDCl_3) δ : 2.16 (3H, s, COCH_3), 5.83 (1H, d, $J = 8.7$ Hz, $\text{C}_3\text{-H}$); ir $\nu_{\text{max}}^{\text{CHCl}_3}$ 3440 (NH), 1745, 1705 and 1690 cm^{-1} (C=O); m/e 260 (M^+)], which was obtained in 80 % yield by treatment of the pyrrolidone 5 with phosphorous pentasulfide in benzene, and the dibromide 10 on standing in tetrahydrofuran in the presence of DBU and molecular sieves for one month afforded the pyrrolidinylideneacetates 15 and 16 as a diastereoisomeric mixture [nmr (CDCl_3) δ : 1.73 and 1.66 (3H, each s, COCH_3), 6.05 and 5.75 (1H, each d, $J = 5.6$ Hz and 4.8 Hz, respectively, $\text{N}-\overset{\text{H}}{\text{C}}-\text{CH}$); ir $\nu_{\text{max}}^{\text{CHCl}_3}$ 3390 (NH), 1750, 1695 and 1672 cm^{-1}



(C=O); m/e 514 (M^+) and 516 ($M^+ + 2$)] in 79 % yield.¹³⁾ In the nmr spectrum of **15** and **16**, signals due to the acetoxy groups protons were located at abnormally high field, at 1.73 and 1.66 ppm, suggesting that the acetoxy and aromatic groups were in a cis arrangement of the double bond so that the acetoxy groups were shielded by the aromatic ring. The ratio of the two sets of acetoxy protons was found to be approximately 1 : 1, as was the ratio of the methine protons of C₃ whose resonance signals appeared at 6.05 and 5.75 ppm. Thus the compounds **15** and **16** were shown to be a 1 : 1 mixture of trans-**15** and cis-**16** as Z-form isomers. As separation of **15** and **16** was not successful the mixture was subjected to the same cyclisation reaction conditions as described for the compound **12**, and afforded the compound **17**, mp 171.5 - 172.5° [nmr (CDCl₃) δ : 1.20 (3H, t, J = 7.2 Hz, CH₂CH₃), 2.15 (3H, s, COCH₃), 2.96 (3H, s, NCH₃), 3.88, 3.97 and 4.06 (each 3H, each s, 3xOCH₃), 5.0 - 5.4 (1H, m, C₂-H), 6.75 (1H, d, J = 3.7 Hz, C₁-H), 6.84 and 7.77 (each 1H, each s, 2xArH); ir $\nu_{\text{max}}^{\text{CHCl}_3}$ 1740 and 1690 (C=O); m/e 434 (M^+)] as a single compound in 99 % yield. This showed that the cis-isomer was epimerised to the thermodynamically more stable trans-isomer **17** under the reaction conditions. Thus we have developed a novel method for the synthesis of a 1,2-disubstituted 1H-pyrrolo[1,2-a]indole which is a potential intermediate en route to apomitomycin.

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- 13) In this case, when the compound 14 was refluxed with the dibromide 10 in the presence of molecular sieves in toluene for 30 h, the yield of 15 and 16 was 48.5 % and on using DBU in toluene for 24 h, the yield was 45.5 %.

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