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Total Synthesis of (+)-Porothramycin B

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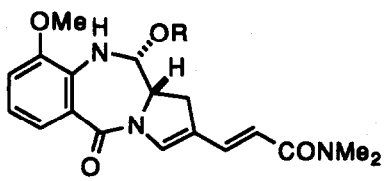
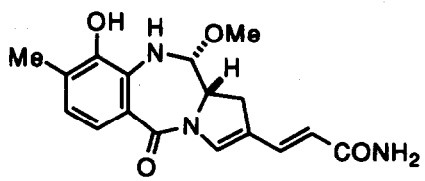
Abstract: *The first total synthesis of (+)-porothramycin B (**1b**) is described. Our synthetic pathway can be readily applied to the synthesis of other members of the pyrrolo[1,4]benzodiazepine antibiotics.*

Porothramycin (**1**) has been recently isolated from a culture broth of *Streptomyces albus* by Tsunakawa and co-workers and has been shown to exhibit potent antitumor activities.[1] Natural porothramycin A (**1a**) could be readily converted to crystalline porothramycin B (**1b**) by treatment with methanol. Porothramycin B (**1b**), whose structure was determined by extensive spectroscopic studies, bears a striking resemblance to anthramycin (**2**), a well-known member of pyrrolo[1,4]benzodiazepine antibiotics.[2,3] In this communication we report the first total synthesis of porothramycin B in an optically pure form. Our synthetic pathway is amenable to a large-scale operation and generally applicable to the synthesis of the anthramycin family antibiotics and their analogs.



1a: R = H
1b: R = Me



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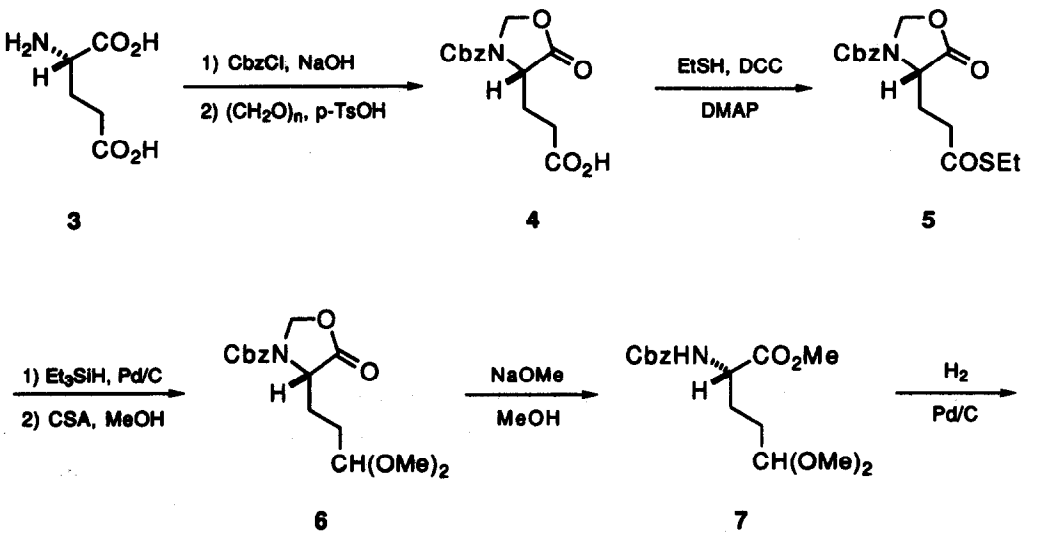
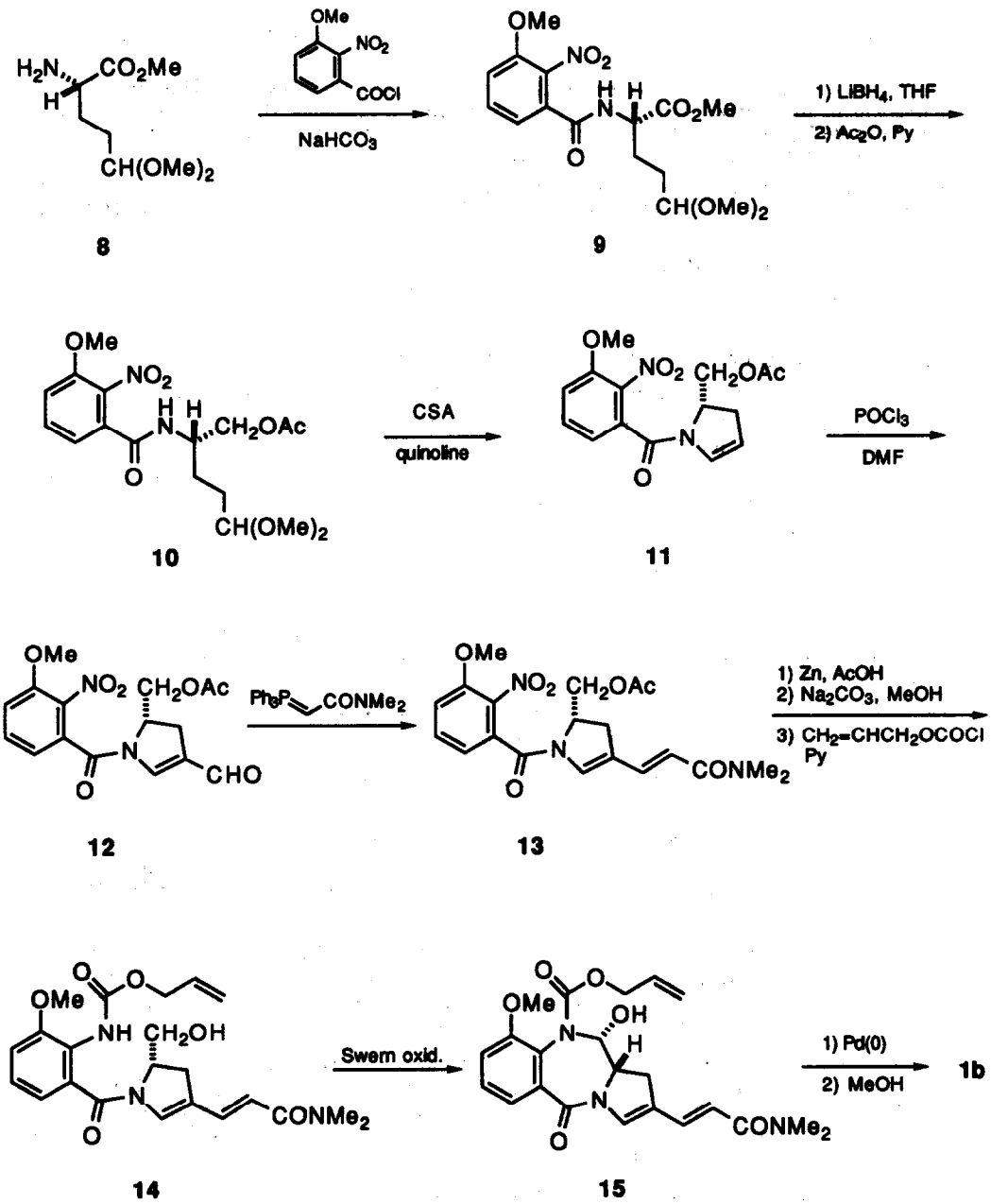
L-Glutamic acid (**3**) was transformed to the known oxazolidinone **4**[4] in a two-step sequence in 88% yield ((1) BnOCOCl, NaOH, 0-23 °C, 2 h. (2) $(CH_2O)_n$, p-TsOH, PhH, reflux (Dean-Stark trap), 30 min). The free carboxylic acid **4** was converted to ethyl thiolester **5** in 87% yield according to the Steglich's procedure[5] (EtSH, DCC, DMAP, CH_3CN, 0 °C, 20 min). Upon treatment with triethylsilane, thiolester **5** underwent smooth reduction to give the desired aldehyde without appreciable hydrogenolysis of the Cbz group (Et_3SiH, 10% Pd/C, acetone, 23 °C, 40 min).[6] The crude aldehyde was immediately protected as the dimethyl acetal **6**, which was subsequently treated with sodium methoxide to give *N*-Cbz-amino ester **7** in 70% yield from **5** ((1) CSA, $CH(OMe)_3$, MeOH, 23 °C, 40 min. (2) NaOMe, MeOH, 23 °C, 70 min). Hydrogenolysis

of the Cbz group of **7** provided the highly versatile amino ester **8** in a quantitative yield (H_2 (1 atm), 10% Pd/C, EtOH, 23 °C, 3 h). Acylation of the amine **8** with 3-methoxy-2-nitrobenzoyl chloride was performed by a two-phase reaction to give the amide **9** in 95% yield (satd. $NaHCO_3$, CH_2Cl_2, 23 °C). Selective reduction of the methyl ester **9** with lithium borohydride in the presence of a trace of $LiBEt_3H$[7] furnished a primary alcohol, which was isolated as the corresponding acetate **10** ((1) $LiBH_4$, cat. $LiBEt_3H$, THF, 23 °C, 80 min. (2) Ac_2O, Py, 23 °C, 15 min). The amidoacetal **10** was subjected to a facile cyclization-elimination reaction by treatment with quinolinium camphorsulfonate (QCS),[8] giving the enamide **11** in 79% yield from **9** (CSA, quinoline, PhH, reflux through an alumina column, 1.5 h). Conversion of the electron-rich enamide **11** to the aldehyde **12** was effected by the conventional Vilsmeier reaction ($POCl_3$ (10 equiv), DMF (20 equiv), 100 °C, 45 min; then NaOAc (45 equiv), H_2O, 100 °C, 15 min).[9,10] After acetylation of the minor, partially deacetylated alcohol, the aldehyde **12** was converted to the conjugated amide **13** by treatment with the stabilized ylide, $Ph_3P{=}CHCONMe_2$,[11] in 74% yield from **11** (PhH, reflux, 2.5 h). Reduction of the nitro group with zinc, hydrolysis of the acetate, and subsequent acylation with allyl chloroformate provided the allyl urethane **14** in 64% yield in a three-step sequence ((1) Zn, AcOH, CH_2Cl_2, 23 °C, 1.5 h. (2) satd. Na_2CO_3, MeOH, 23 °C, 40 min. (3) $ClCO_2CH_2CH{=}CH_2$, Py, CH_2Cl_2, 0 °C, 20 min). Swern oxidation of **14** caused the spontaneous cyclization to give a single stereoisomer of the protected porothramycin A **15** in 72% yield.[12] Deprotection of the allyl urethane **15** was best achieved according to the Deziel's procedure[13] to give unstable, non-crystalline porothramycin A (**1a**) in 67% yield after quick purification by flash chromatography ($Pd(PPh_3)_4$, Pyrrolidine, CH_2Cl_2, 0 °C, 10 min). Crystallization from MeOH-EtOAc (1:20) provided pure porothramycin B (**1b**), which was identical in all respects to the natural porothramycin B by comparison of the spectroscopic data (^1H NMR, ^{13}C NMR, MS, and $[\alpha]_D$).[14,15]





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14. We were unable to perform a direct comparison because an authentic sample of porothramycin B, kindly provided by Bristol-Myers Squibb Research Institute, Tokyo, had completely decomposed when we received it by mail.
15. Satisfactory spectroscopic data were obtained for all new compounds. ^{1}H NMR spectra (250 MHz, $CDCl_3$) and $[\alpha]_D$ of the key intermediates are as follows:

8: $[\alpha]^{25}_D$ = +9.6° (c 0.48, $CHCl_3$); ^{1}H NMR δ 4.38 (t, J = 5.2 Hz, 1H), 3.73 (s, 3H), 3.47 (t, J = 5.9 Hz, 1H), 3.32 (s, 6H), 1.83-1.59 (m, 6H).

11: $[\alpha]^{25}_D$ = -211° (c 0.56, $CHCl_3$); ^{1}H NMR δ 7.52 (t, J = 8.3 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 7.3 Hz, 1H), 6.14 (t, J = 2.0 Hz, 1H), 5.16 (m, 1H), 4.84 (m, 1H), 4.44 (dd, J = 11, 7.2 Hz, 1H), 4.22 (dd, J = 11, 4.4 Hz, 1H), 3.95 (s, 3H), 2.91 (ddt, J = 14.5, 10.3, 2.5 Hz, 1H), 2.50 (dt, J = 14.5, 3.2 Hz, 1H), 2.09 (s, 3H).

13: $[\alpha]^{25}_D$ = -182.8° (c 0.61, $CHCl_3$); ^{1}H NMR δ 7.56 (t, J = 8.3 Hz, 1H), 7.31 (d, J = 15 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.00 (d, J = 7.3 Hz, 1H), 6.49 (s, 1H), 6.13 (d, J = 15 Hz, 1H), 4.92 (m, 1H), 4.52 (dd, J = 11.4, 4.8 Hz, 1H), 4.26 (dd, J = 11,4, 3.7 Hz, 1H), 3.97 (s, 3H), 3.10 (s, 3H), 3.02(s, 3H), 3.1-3.0 (1H), 2.62 (dd, J = 15.8, 3.7 Hz, 1H), 2.08 (s, 3H).

15: $[\alpha]^{25}_D$ = +280° (c 0.50, $CHCl_3$); ^{1}H NMR δ 7.52 (d, J = 15 Hz, 1H), 7.37 (t, J = 8.2 Hz, 1H), 7.36 (s, 1H), 7.30 (d, J = 7.4 Hz, 1H), 7.07 (dd, J = 7.4, 1.8 Hz, 1H), 6.13 (d, J = 15 Hz, 1H), 5.9-5.7 (m, 1H), 5.72 (d, J = 10.8 Hz, 1H), 5.13-5.04 (m, 2H), 4.64 (dd, J = 13.3, 5.5 Hz, 1H), 4.43 (dd, J = 13.3, 5.5 Hz, 1H), 4.0-3.9 (m, 1H), 3.84 (s, 3H), 3.14 (dd, J = 16, 6.8 Hz, 1H), 3.10 (s, 3H), 3.04 (s, 3H), 2.87 (dd, J = 16, 3.0 Hz, 1H).

Synthetic **1b:** mp 162-7 °C (dec.); $[\alpha]^{25}_D$ = +670° (c 0.45, $CHCl_3$); ^{1}H NMR δ 7.64 (dd, J = 8.1, 1.6 Hz, 1H), 7.52 (s, 1H), 7.51 (d, J = 15.0 Hz, 1H), 6.90 (dd, J = 7.7, 1.3 Hz, 1H), 6.78(t, J = 7.9 Hz, 1H), 6.18 (d, J = 6.2 Hz, 1H), 6.06 (d, J = 15.0 Hz, 1H), 4.68 (d, J = 6.4 Hz, 1H), 4.26 (dd, J = 11.2, 5.3 Hz, 1H), 3.90 (s, 3H), 3.35 (s, 3H), 3.17 (dd, J = 15.6, 4.1 Hz, 1H), 3.10 (s, 3H), 3.03 (s, 3H), 2.86 (dd, 15.6, 5.4 Hz, 1H).

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