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# Enantioselective Synthesis of (+) Porothramycin B and its 9-Demethoxy Analogue

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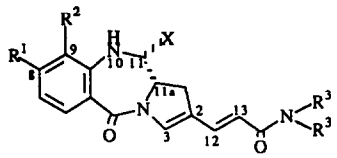
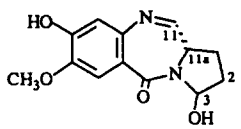
***Abstract.*** *(+) 9-Demethoxyporothramycin B 3a and (+) porothramycin B 3b were synthesized from (S) pyroglutamic acid through a versatile and efficient route.*[1]

Pyrrolo[2,1-c][1,4]benzodiazepines of the anthramycin 1[2] group are antitumor antibiotics produced by various *Streptomyces* which mediate their activities by covalent binding with DNA.[3] Their 11*aS* absolute configuration is important for their antitumor properties. Indeed, this configuration provides these compounds with a twist along the molecule which allows their interaction with DNA.[4]

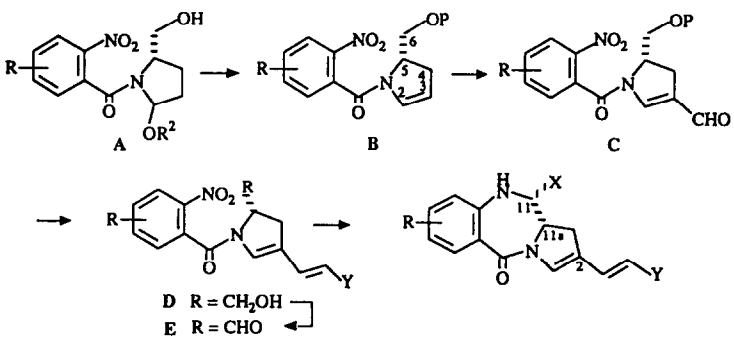




**1** $R^1 = CH_3$, $R^2 = OH$, $R^3 = H$, X= OH
**3a** $R^1 = R^2 = H$, $R^3 = CH_3$, X= $OCH_3$
**3b** $R^1 = H$, $R^2 = X = OCH_3$, $R^3 = CH_3$

**2**

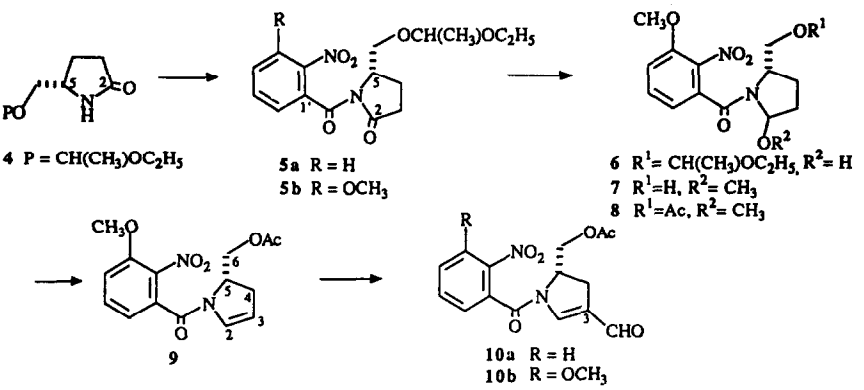
(S) Pyroglutamic acid is a convenient chiral starting material to synthesize natural enantiomers of this family of antitumor compounds, as first exemplified some years ago by the synthesis of neothramycins **2** and analogues.[5] The (5*S*) *N*-2 nitrobenzoyl-5-hydroxymethyl-2-methoxy pyrrolidines of general formula **A** used in this work were shown to be also versatile intermediates in the synthesis of other pyrrolo [2,1-c][1,4]benzodiazepines including a dihydropyrrole ring and a conjugated double bond in a side chain attached to C-2, as outlined in general Scheme 1.



Scheme 1

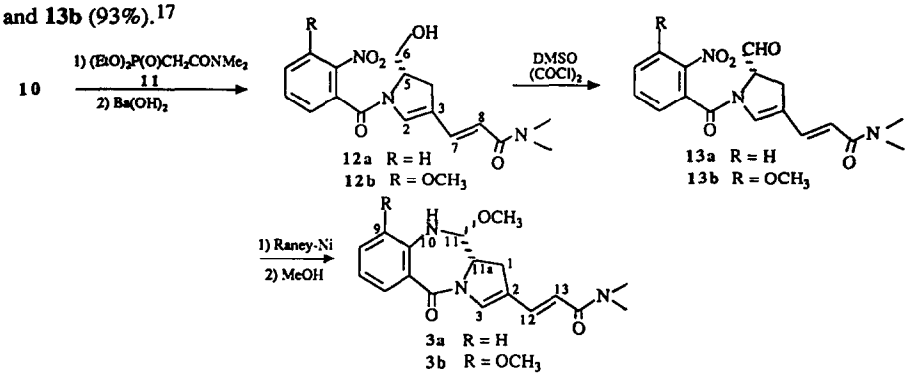
This synthetic strategy involves the preparation of the enamidoaldehydes **C** which allow the introduction of the unsaturated side chain *via* Wittig-type reactions to **D**.[1,6] The recently reported synthesis of porothramycin B **3b**[7] using the same type of intermediate[8] prompts us to disclose our own results in the same area,[1a] and we describe here the short total syntheses of 9-demethoxy porothramycin B **3a** and porothramycin B **3b**.

The imide **5b**, prepared (95% yield)[9] from 3-methoxy-2-nitrobenzoyl chloride and (5*S*) 5-ethoxyethoxymethyl-2-pyrrolidone **4** , as previously described for **5a**[5], was reduced by DIBAL-H. The addition of a hexane solution of DIBAL-H to a THF solution of **5b** was required in this case to lead to a partial regioselective reduction to **6** (68%). These compounds were converted[5] to 9-methoxy *ortho*nitrobenzamides **7** (83%)[10] which was quantitatively acetylated to **8** (Scheme 2). Elimination reaction by heating a toluene solution of **8** in the presence of quinolinium camphorsulfonate (QCS)[6] provided the enamide **9**[11] in 87% yield. The formyl group was introduced at C-3 through a Vilsmeier-Haack reaction affording the key enamidoaldehyde intermediate **10b** (87%).[12]




Scheme 2

The *N,N*-dimethylacrylamide side chain, common to the target molecules **3a** and **3b** was elaborated through a Wittig-Horner reaction with the suitably functionalized diethylphosphonate **11**[13] (Scheme 3). The products of these reactions could be directly saponified with 1N $Ba(OH)_2$, respectively to the alcohols **12a** (97% from **10a**) and **12b** (non optimized 78% yield from **10b**)[14]. Swern oxidation[15] of these primary alcohols **12** required the use of diisopropylethylamine as a base[16] to avoid partial racemization of the aldehydes **13a** (96%) and **13b** (93%).[17]




Scheme 3

The reduction of the aromatic nitro group with an excess of Raney-nickel at room temperature and cyclization to the pyrrolo[2,1-c][1,4]benzodiazepine skeleton were directly followed by treatment with a very diluted solution of trifluoroacetic acid (0.002%) in $CH_2Cl_2$-MeOH (9:1)[18], providing respectively 9-demethoxyporothramycin B **3a** (65%), and porothramycin B **3b** (non optimized 45%).[19]

These results show the versatility of our synthetic strategy to prepare antitumor antibiotics of the anthramycin group as well as 11*aS* enantiomers of structural analogues, the biological activities of which will be reported elsewhere.

**Acknowledgments** : We thank the Ligue Nationale Française contre le Cancer and the Association de la Recherche sur le Cancer for financial support.

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9. **5b** : IR (ν $cm^{-1}$) : 3000, 1750, 1680 ; $^1H$ NMR (200MHz, $CDCl_3$, δ=0 : TMS, J Hz) : 7.52 (dd, 1H, $J_{4',5'}$ = $J_{5',6'}$ = 7.5, C-5'-H), 7.15 and 6.91 (d + m, 2H, $J_{4',5'} = J_{5',6'}$ = 7.5, C-4'-H and C-6'-H), 4.74 (m, 1H, OCHO), 4.62 (m, 1H, C-5-H), 3.96 (s, 3H, C-3'-$OCH_3$), 3.87-3.52 (m, 4H, C-6-$H_2$ and $OCH_2$), 2.8-2.3 (m, 4H, C-4-$H_2$ and C-3-$H_2$), 1.32 (d, 3H, $CHCH_3$), 1.22 (m, 3H, $CH_2CH_3$) ; MS (CI, isobutane, m/z) : 367 ($MH^+$), 321 (100%), 295, 277 ; HRMS (m/z) : ($M^{+\cdot}$) 320.1507, calcd. for $C_{17}H_{22}NO_5$ : 320.1498 .
10. **7b** (major diast.) : $[\alpha]_D$ = -282 (c = 0.39, $CHCl_3$) ; IR : 3420, 2940, 1650, 1580, 1535 ; $^1H$ NMR (250MHz) : 7.55 (dd, 1H, $J_{4',5'} = J_{5',6'}$ = 8, C-5'-H), 7.15 (m, 2H, C-4'-H and C-6'-H), 4.68 (d, 1H, $J_{2,3}$ = 3.8, C-2-H), 4.35 (m, 1H, C-5-H), 3.96 (s, 3H and m, 1H, C-3'-$OCH_3$ and C-6-Ha), 3.70 (m, 1H, C-6-Hb), 3.07 (s, 3H, C-2-$OCH_3$), 2.3-1.7 (m, 4H, C-3-$H_2$ and C-4-$H_2$) ; MS (m/z) : 310 ($M^{+\cdot}$), 309, 292, 291, 279, 278, 197, 180 (100%) ; Analysis : $C_{14}H_{18}N_2O_6$, calcd.% : C = 54.19, H = 5.85, N = 9.03, found : C = 54.01, H = 5.60, N = 8.99.
11. **9** : $[\alpha]_D$ = -222 (c = 0.48,$CHCl_3$, lit[8].= -211, c = 0.56). ; IR : 2940, 1740, 1650, 1535 ; $^1H$ NMR (200 MHz) : 7.54 (dd, 1H, $J_{4',5'} = J_{5',6'}$ = 7, C-5'-H), 7.16 and 7.02 (2d, 2H, $J_{4',5'} = J_{5',6'}$ = 7, C-4'-H and C-6'-H), 6.17 (m ,1H, C-2-H), 5.19 (m, 1H, C-3-H), 4.85 (m, 1H, C-5-H), 4.43 (dd, 1H, $J_{5,6a}$ = 5, $J_{6a,6b}$ = 12, C-6-Ha), 4.22 (dd, 1H, $J_{5,6b}$ = 4 and $J_{6a,6b}$ = 12, C-6-Hb), 3.97 (s, 3H, C-3'-$OCH_3$), 2.93 (m, 1H, $J_{4a,4b}$ = 16, C-4-Ha), 2.50 (dd, 1H, $J_{4a,4b}$ = 16, C-4-Hb), 2.11 (s, 3H, $OCOCH_3$) ; MS : 320 ($M^{+\cdot}$), 279, 180 (100%), 106, 80, 76 ; Analysis : $C_{15}H_{16}N_2O_6$, calcd.% : C = 56.25, H = 5.04, N = 8.75 , found : C = 56.18, H = 5.07, N = 8.57.
12. **10b** : $[\alpha]_D$ = -254 (c = 0.35, $CHCl_3$) ; IR : 3400, 2950, 1750, 1655, 1610. ; $^1H$ NMR(200 MHz) : 9.53 (s, 1H, CHO), 7.61 (dd, 1H, C-5'-H), 7.25 (d, 1H, C-6'-H ou C-4'-H), 7.04 (d, 2H, C-4'-H ou C-6'-H and C-2-H), 4.94 (m, 1H, C-5-H), 4.55 (bd , 1H, $J_{6a,6b}$ = 12, C-6-Ha), 4.19 (dd, 1H, $J_{6a,6b}$ = 12 et $J_{5,6b}$ = 4, C-6-Hb), 3.98 (s, 1H, C-3'-$OCH_3$), 3.08 (dd, 1H, $J_{4a,4b}$ = 16.5, $J_{4a,5}$ = 10, C-4-Ha), 2.77 (dd, 1H, $J_{4a,4b}$ = 16.5,

$J_{5,4b}$ = 4.5, C-4-Hb), 2.08 (s, 3H, $OCOCH_3$) ; $^{13}C$ NMR (50 MHz) : 185.8 (CHO),170.8 (OCO), 163.8 (NCO), 152.3 (C-3'), 145.0 (C-2), 142.7 (C-3), 133.0 (C-5'), 130.3 and 127.0 (C-1' and C-2') ; 119.1 and 115.7 (C-4' and C-6'), 63.5 (C-6), 58.2 and 56.9 ($ArOCH_3$ and C-5), 28.8 (C-4), 20.6 ($COCH_3$) ; MS : 348 ($M^{+\cdot}$), 279, 265, 180 (100%), 164, 133, 106, 78, 76 ; HRMS : ($M^{+\cdot}$) 348.0957, calcd.for $C_{16}H_{16}N_2O_7$ : 348.0958.

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14. a)**12a** : $[\alpha]_D$ = -114 (c = 0.66, $CHCl_3$) ; IR : 3390, 2930, 1635, 1605 ; $^1H$ NMR (200MHz) : 8.26 (d, 1H, $J_{3',4'}$ = 8, C-3'-H), 7.80 and 7.68 (2dd, 2H, C-4'-H and C-5'-H), 7.50 (d, 1H, $J_{5',6'}$ = 8, C-6'-H), 7.22 (d, 1H, $J_{7,8}$ = 15, C-7-H), 6.21 (s, 1H, C-2-H), 6.14 (d, 1H, $J_{7,8}$ = 15, C-8-H), 4.86 (m, 1H, C-5-H), 4.0 (m, 2H, C-6-$H_2$), 3.10 (bs, 1H, OH), 3.01 (s + m, 7H, $N(CH_3)_2$ and C-4-Ha), 2.65 (dd, 1H, $J_{4a,4b}$ = 15, $J_{4b,5}$ = 4.5, C-4-Hb) ; SM : 345 ($M^{+\cdot}$), 327, 280, 269, 208, 150 (100%), 120, 72 ; HRMS : ($M^{+\cdot}$) 345.1308, calcd for $C_{17}H_{19}N_3O_5$ : 345.1317. b)**12b** : $[\alpha]_D$ = -111 (c = 0.76, $CHCl_3$) ; IR : 3390, 2925, 1635, 1600, 1580, 1530 ; $^1H$ NMR(200 MHz) : 7.59 (dd, 1H, $J_{4',5'} = J_{5',6'}$ = 7.5, C-5'-H), 7.29 (d, 1H, $J_{7,8}$ = 15, C-7-H) ; 7.21 and 7.02 (2d, 2H, $J_{4',5'} = J_{5',6'}$ = 7.5, C-4'-H and C-6'-H), 6.50 (s, 1H, C-2-H), 6.15 (d, 1H, $J_{7,8}$ = 15, C-8-H), 4.75 (m, 1H, C-5-H), 3.97 (s, 3H, C-3'-$OCH_3$), 3.90 (m, 2H, C-6-$H_2$), 3.05 (s + m, 7H, $N(CH_3)_2$ and C-4-Ha), 2.65 (dd, 1H, $J_{4a,4b}$ = 16, $J_{4b,5}$ = 4, C-4-Hb) ; MS : 375 ($M^{+\cdot}$), 357, 331, 310, 180 (100%), 120, 76, 72 ; HRMS : ($M^{+\cdot}$) 375.1424, calcd. for $C_{18}H_{21}N_3O_6$ : 375.1431.

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17 a)**13a** : $[\alpha]_D$ = -126 (c = 0.96, $CHCl_3$) ; IR : 3300, 2920, 1720 weak (± hydrated depending on the isolation conditions), 1630, 1595 ; $^1H$ NMR (250 MHz) : 9.90 (s, 1H, CHO), 8.26 (dd, 1H, $J_{3',4'}$ = 7.5, C-3'-H), 7.82 and 7.70 (2dd, 2H, $J_{3',4'} = J_{4',5'} = J_{5',6'}$ = 7.5, C-4'-H and C-5'-H), 7.57 (d, 1H, $J_{5',6'}$ = 7.5, C-6'-H), 7.23 (d, 1H, $J_{7,8}$ = 15, C-7-H) ; 6.33 (s, 1H, C-2-H), 6.14 (d, 1H, $J_{7,8}$ = 15, C-8-H), 5.20 (dd, 1H, J = 11.5 and 5, C-5-H), 3.08 and 3,00 (2s + m, 8H, $N(CH_3)_2$ and C-4-$H_2$) ; MS : 343 ($M^{+\cdot}$), 269, 220, 208, 150 (100%) : HRMS : ($M^{+\cdot}$) 343.1147, calcd. for $C_{17}H_{17}N_3O_5$ : 343.1161. b) **13b** : $[\alpha]_D$ = -110 (c = 0.40, $CHCl_3$) ; IR : 3300, 2980, 1730, 1640 ; $^1H$ NMR (200MHz) : 9.75 (s, 1H, CHO), 7.27 (d, 1H, $J_{7,8}$ = 15, C-7-H), 7.58, 7.25 (masked) and 7.10 (aromatic H), 6.65 (bs, 1H, C-2-H), 6.16 (d, 1H, $J_{7,8}$ = 15, C-8-H), 5.12 (m, 1H, C-5-H), 3.99 (s, 3H, C-3'-$OCH_3$), 3.17 and 3.10 (2s + m, 8H, $N(CH_3)_2$ and C-4-$H_2$) ; MS : 373 ($M^{+\cdot}$), 344, 310, 299, 180 (100%) ; HRMS : ($M^{+\cdot}$) 373.1277, calcd. for $C_{18}H_{19}N_3O_6$ : 373.1273.

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19. a) **3a** : mp inst. (dec.) : 228 °C (MeOH) ; $[\alpha]_D$ = +775 (c = 0.2, $CH_2Cl_2$) ; IR : 3320, 2924, 2850, 1620 ; $^1H$ NMR(400MHz) : 8.03 and 6.65 (2d, 2H, $J_{6,7} = J_{8,9}$ = 7.5, C-6-H and C-9-H), 7.30 and 6.87 (2dd, 2H, $J_{6,7} = J_{7,8} = J_{8,9}$ = 7.5, C-7-H and C-8-H), 7.53 (s, 1H, C-3-H), 7.52 (d, 1H, $J_{12,13}$ = 15, C-12-H), 6.06 (d, 1H, $J_{12,13}$ = 15, C-13-H), 5.34 (d, 1H, $J_{10,11}$ = 5.6, N-10-H), 4.61 (d, 1H, $J_{10,11}$ = 5.6, C-11-H), 4.30 (dd, 1H, $J_{1a,11a}$ = 10.5, $J_{1b,11a}$ = 4.5, C-11a-H), 3.38 (s, 3H, $OCH_3$), 3.16 (masked m, 1H, C-1-Ha), 3.11 (s, 3H, NMe), 3.05 (s, 3H, NMe), 2.87 (dd, 1H, $J_{1a,1b}$ = 15.5 et $J_{1b,11a}$ = 4.5, C-1-Hb) ; MS : 327 ($M^{+\cdot}$ very weak), 295 (100%), 251, 249 (100%), 223, 120 ; HRMS : ($M^{+\cdot}$ - $CH_3OH$) 295.1321, calcd. for $C_{17}H_{17}N_3O_2$ : 295.1321. b) **3b** : mp inst. (dec.) : 164-7 °C (MeOH-AcOEt) ; $[\alpha]_D$ = +622 (c = 0.2, $CHCl_3$), comparison of $^1H$ NMR, MS and HRMS data.[7]

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