SYNTHESIS OF POLYAMINOALKYL SUBSTITUTED CONJUGATES OF PYRROLO[2,1-*c*][1,4]BENZODIAZEPINE INVOLVING S_NAr REACTION OF 2-NITRO-5-FLUOROBENZOATE PRECURSORS

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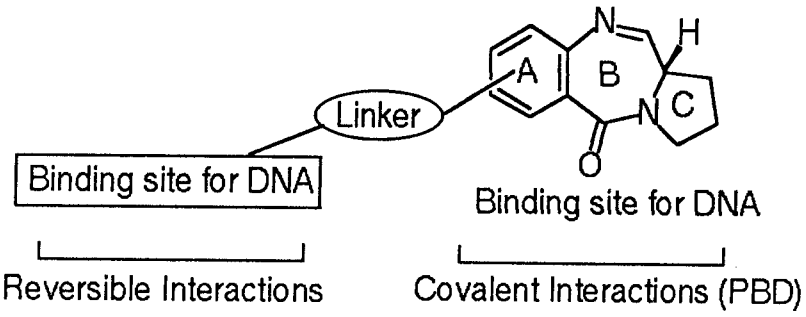
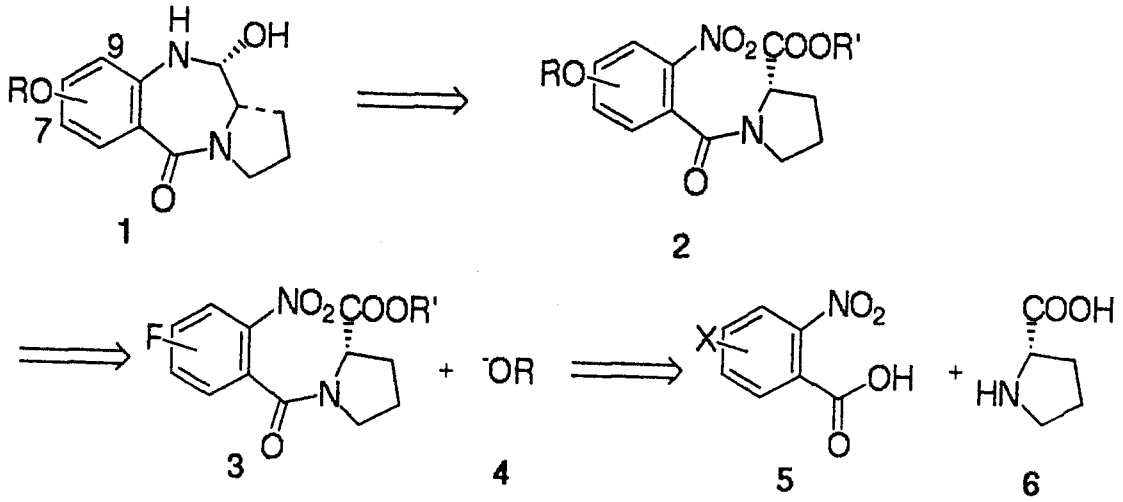
Abstract—A synthetic procedure is described for conjugating polyaminoalkyl groups to the pyrrolo[2,1-*c*][1,4]benzodiazepine pharmacophore in order to alter its characteristic DNA sequence binding preference. To this end S_NAr reactions of 2-nitro-5-fluorobenzoate esters with different polyaminoalkyl side chains were examined and incorporated in the synthetic scheme.

There is growing interest in pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) ring systems as synthetic targets and as potential anticancer agents. The PBDs are a class of antitumor antibiotics produced by various *actinomycetes* which include anthramycin, tomaymycin, neothramycin and DC-81.[1] These compounds can recognize and bind to preferred sequences in the minor groove of double helical DNA and have potential as therapeutic agents in the treatment of certain genetic disorders including some cancers.[2] The PBDs appear to exert their biological activity by reacting covalently in the minor groove of DNA to form an aminal linkage between the electrophilic carbinolamine present at the C-11 position and the N2 of guanine.[3] The preferred binding sequence involves a 5'-PuGPu motif.[1] In the last few years, various strategies have been proposed for the synthesis of these antibiotics and have met with varying degrees of success while exhibiting significant limitations.[4] In order to alter the DNA-recognition ability and selectivity of PBDs (Scheme 1), it was considered desirable to introduce, *inter aliai*, polyaminoalkyl groups as side-chain to the positions 7 and 9 of the A ring of PBD which is known to interact with DNA reversibly. Our strategy for this purpose is shown as Scheme 2. In this connection, we describe below S_NAr (nucleophilic aromatic substitution) reaction of the fluoro aromatics (**3**).

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.



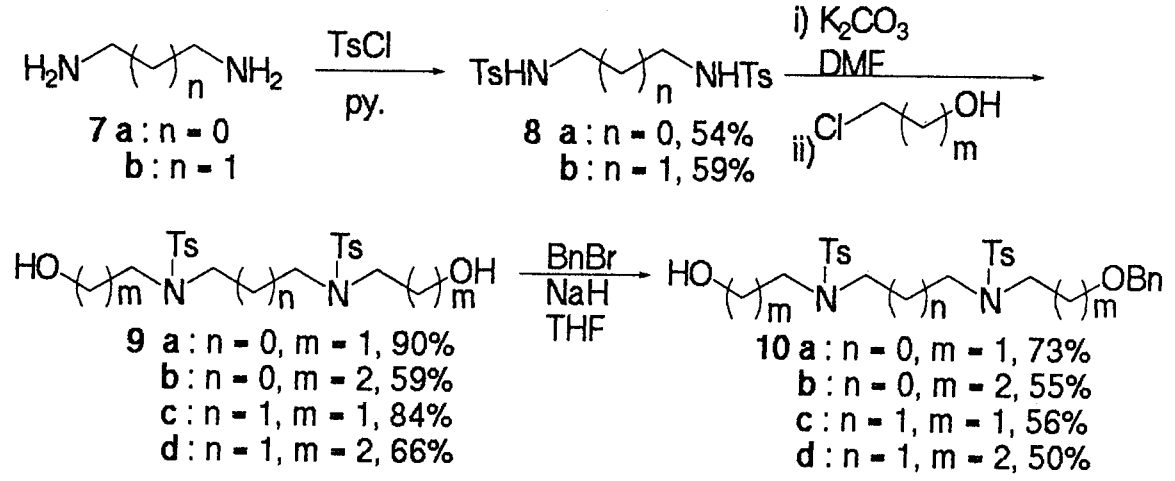
Scheme 1



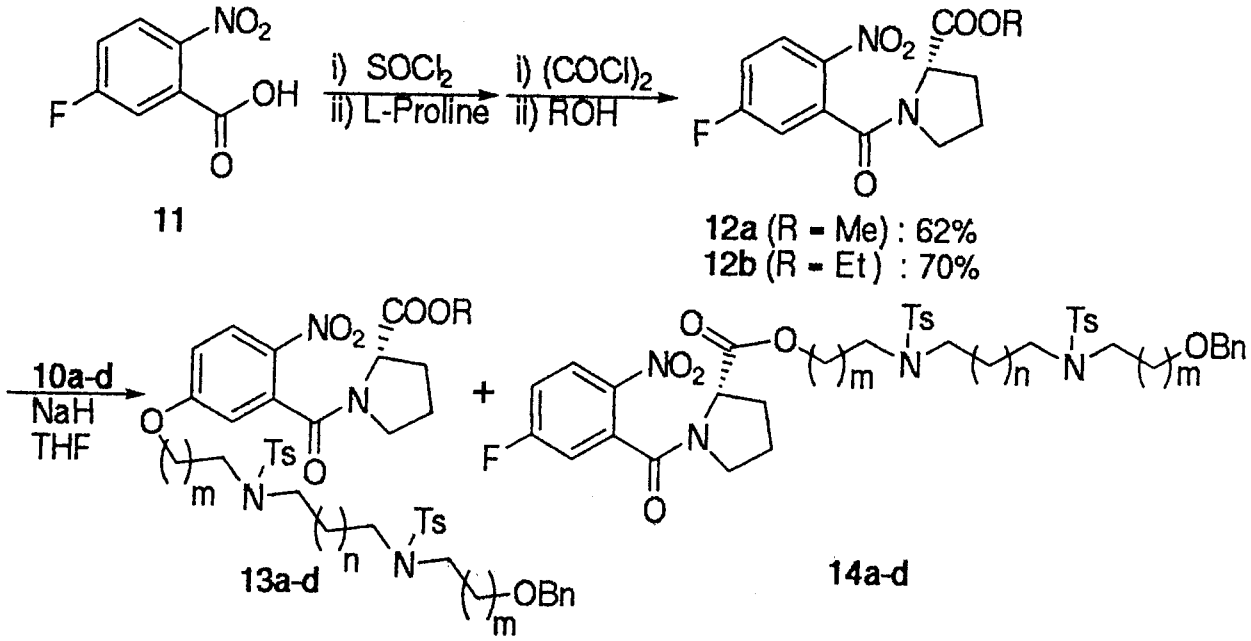
Scheme 2 Retrosynthetic analysis

The straight-chain polyaminoalkanes (**10a-e**) were chosen for the ready availability as side-chains interacting with DNA electrostatically. The amino part of 1,2-diaminoethane (**7a**) or 1,3-diaminopropane (**7b**) was *p*-toluenesulfonylated, metallized, and treated with 2-chloroethanol or 3-chloropropanol, and the diols (**9a-d**) were obtained in acceptable yields. Then the diols (**9a-d**) were selectively monobenzylated with dilute benzyl bromide in THF in the presence of sodium hydride, producing the corresponding monobenzyl alcohols (**10a-d**) (Scheme 3).

The intermediates (**12**), in which the proline moiety is already present, were prepared as outlined in Scheme 4. The nitrobenzoic acid (**11**) was converted to the corresponding acid chloride by treating with thionyl chloride and then, coupled with proline. The carboxylic acid moiety of proline was then converted into the acid chloride by treating with oxalyl chloride. Treatment of the acid chloride with methanol or ethanol produced the corresponding amide ester (**12a**) and (**12b**).



Scheme 3



Scheme 4

The results of the S_NAr reactions of **12a** and **12b** were summarized in Table 1. The reaction did not take place under the normal conditions and only the starting material was recovered. However, in the presence of a catalylic amount of 18-crown-6, the S_NAr reaction of **12** occured easily with the alcohol (**10a**) (n=0, m=1) and (**10c**) (n=1, m=1) giving the compounds (**13aa**, **13ab**, and **13bc**), respectively. In the cases of **10b** (n=0, m=2) and **10d** (n=1, m=2) in which m=2, however, the anticipated products (**13ba**) and (**13db**) were not obtained, instead reaction afforded the transesterification product (**14ba**). In order to prevent such transesterification reaction, the ester portion was,

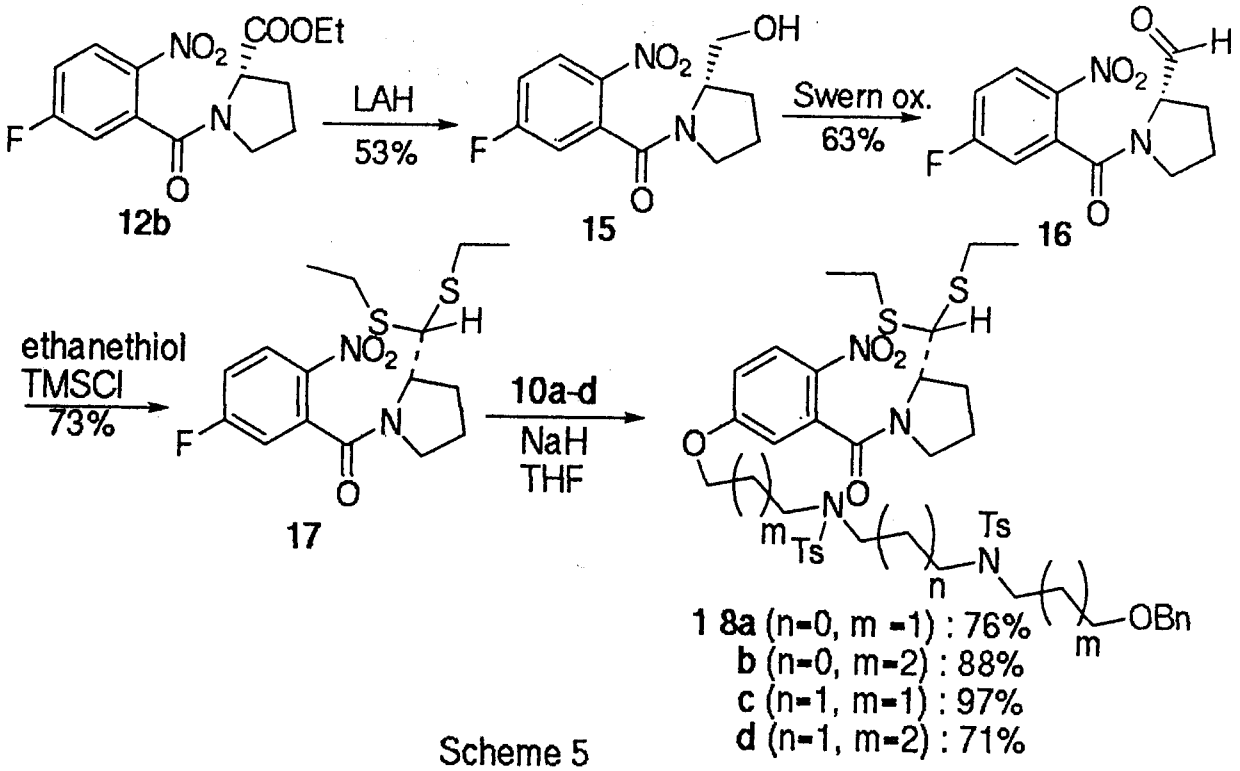
therefore, protected before S_NAr reaction e.g. the nitro ester (**12b**) was reduced to the alcohol (**15**) with LAH at low temperature, followed by Swern oxidation and subsequent protection producing the nitro compound (**17**). Thus, the yields of the S_NAr reaction

Table1 . S_NAr and transesterification reaction of 12

alcohol	benzoate	18-crown-6	13 (%)	14 (%)
10 a (n = 0, m = 1)	12a	—	no reaction	
a (n = 0, m = 1)	12b	—	no reaction	
a (n = 0, m = 1)	12a	cat.	67%	0%
a (n = 0, m = 1)	12b	cat.	46%	trace
b (n = 0, m = 2)	12a	cat.	trace	22%
b (n = 0, m = 2)	12b	cat.	20%	0%
c (n = 1, m = 1)	12b	cat.	44%	trace
d (n = 1, m = 2)	12b	cat.	complex mixture	

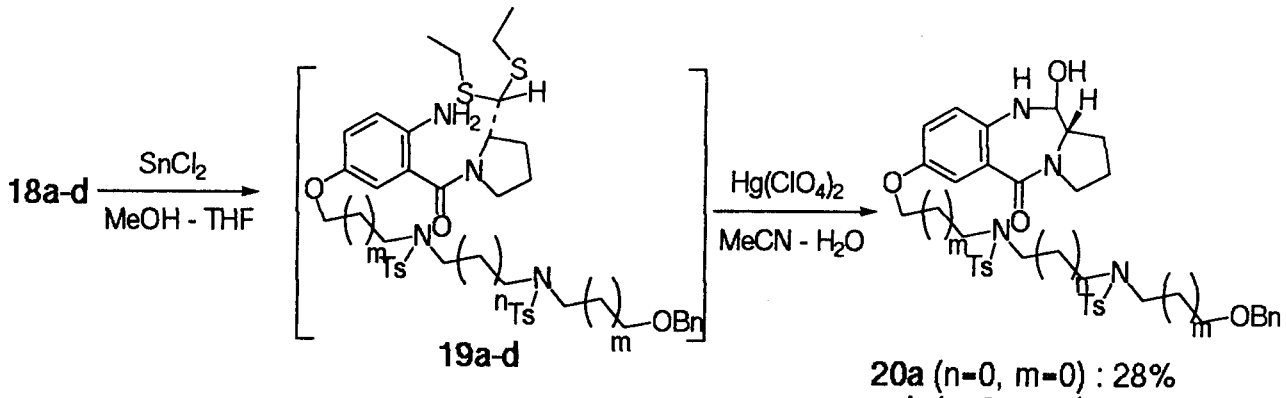
of **17** with **10** were good to moderate to afford the dithioacetals (**18a-d**) as shown in Scheme 5.

The completion of the PBD pharmacophore was accomplished on reduction of **18a-d** with stannous dichloride to the aniline intermediates (**19a-d**) which were converted the



Scheme 5

PBD conjugates (**20a-d**) on treatment with mercury perchlorate (Scheme 6). [5,6]
Recent progress in the development of sequence specific polyamides[7] and other minor groove binders augurs well for the future of such bioactive conjugates.



Scheme 6

ACKNOWLEDGMENTS

This work was in part supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan. H. I. expresses his gratitude for the Sasagawa Foundation for support of this research. The authors are also grateful to the Ministry of Education, Science, Sports, and Culture, Japan for purchasing the high-field NMR instruments (JEOL JNM-A500 and JNM-EX270) by the special fund (to K. M. as a representative in 1992). Thanks are also extended to the Memorial Foundation of Kyoto University for the travelling and staying expenses (to J. W. L.) in Japan.

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5. A general procedure for the preparation of **20** : To a solution of the thioacetal (**18a**) (77 mg, 0.086 mmol) in THF (5 mL) and methanol (5 mL) was added stannous dichloride dihydrate (174 mg, 0.75 mmol), and the mixture was refluxed overnight. Then the reaction mixture was adjusted to pH 8 with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate (15 mL, 3 times). The combined organic layer was washed with brine (10 mL), dried over sodium sulfate, and the solvent was removed *in vacuo* to afford the crude amine (**19a**) as a colorless oil.
To a solution of the crude amine (**19a**) in acetonitrile (5 mL) and water (2 mL) was added mercuric perchlorate trihydrate (156 mg, 0.34 mmol), and the mixture was stirred at rt for 5 min. The reaction mixture was diluted with ethyl acetate (15 mL) and water (3 mL) , and centrifuged at 3000 rpm for 5 min and the supernatant decanted and washed with saturated sodium hydrogen carbonate solution (10 mL, 3 times). The combined organic layer was washed with brine (10 mL), dried over sodium sulfate, and the solvent was removed *in vacuo*. This residue was further purified by column chromatography on silica gel (30 g) with ethyl acetate to afford **20a** (17 mg, 28.3 %) as a colorless oil.
20a : ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.88-2.10 (2H, m), 2.25-2.35 (2H, m), 2.40 (3H, s), 2.41 (3H, s), 3.32-3.90 (15H, m), 4.10 (1H, dd, J = 5.1, 3.5 Hz), 4.47 (2H, s), 6.95-7.72 (17H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 21.5, 24.1, 29.6, 46.7, 49.1, 49.3, 49.5, 49.9, 53.5, 67.2, 69.3, 73.1, 113.5, 119.4, 127.2, 127.3, 127.7, 127.8, 128.3, 128.8, 128.9, 129.7, 135.9, 136.0, 137.8, 139.9, 143.4, 143.5, 156.4, 162.7, 164.4; IR υmax (neat): 3380, 1630, 1598, 1498, 1452, 1344, 1158, 1090, 738, 720, 700 cm^{-1}. All new compounds had correct elemental and/or high resolution MS spectral analyses.
6. Attempts to perform reductive cyclization of the corresponding acetals led to formation of the complex mixture.
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Received, 6th July, 1999