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Synthesis of a Hybrid Molecule Containing Neocarzinostatin Chromophore Analogue and Minor Groove Binder

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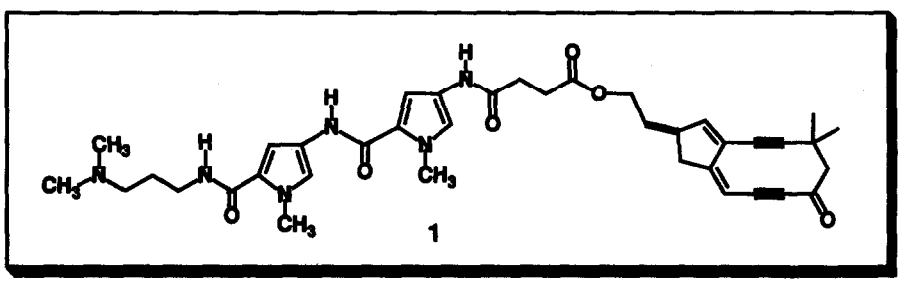
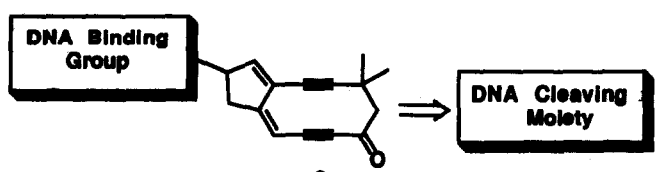
Abstract: *A designed hybrid (1) of neocarzinostatin chromophore model and netropsin-type minor groove binder was synthesized and its improved ability of DNA cleavage has been demonstrated.*

Design and synthesis of new DNA cleaving molecules are currently a topic of intense research investigations.[1] We have synthesized neocarzinostatin chromophore analogues such as **3**-**5** and have disclosed their mode of aromatization leading to generation of carbon radicals.[2] Their DNA cleaving abilities,[2b] however, are proven to be not so high as those of neocarzinostatin[3] and the related enediyne antibiotics.[4] To improve the DNA cutting ability and render the higher base- and site-selectivities we have designed hybrid molecules containing the DNA cleaving moiety[2b] and the DNA binder, represented by **2**. In this communication we disclose a synthesis of the hybrid **1** possessing a netropsin type minor groove binder.[1,5,6]



1



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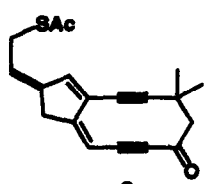

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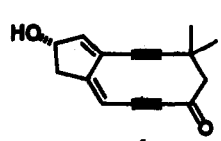

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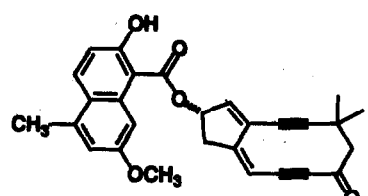
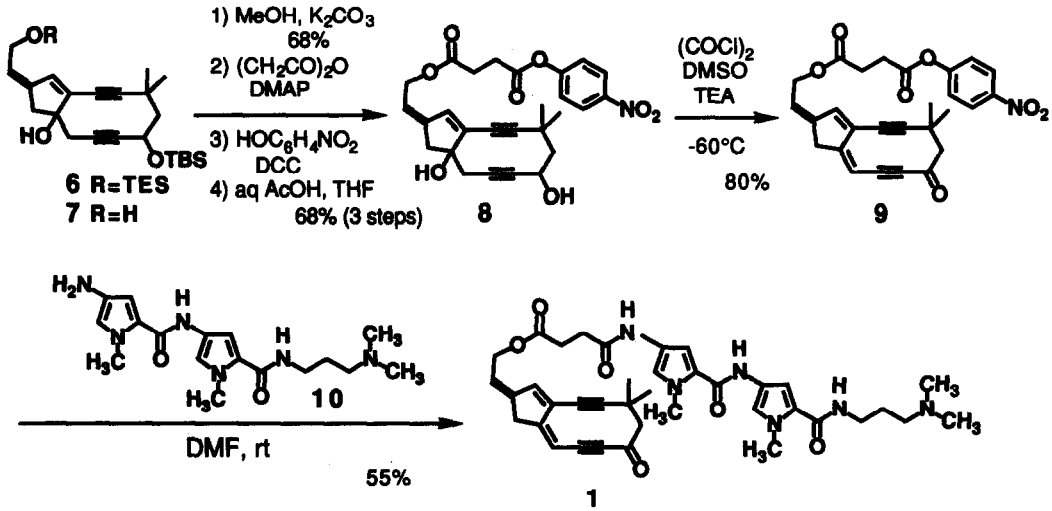


5

After considerable preliminary experiments we found that the 10 membered ring dienediynone **9** possessing an active ester is a versatile intermediate for preparing the hybrids such as **1**. Synthesis of **9** was accomplished from the known racemic intermediate **6**[2a] in 5 steps (Scheme I): Triethylsilyl group of **6** was removed selectively with alkaline MeOH (68%). To the resulting alcohol **7** succinic acid linker was attached, condensed with p-nitrophenol, and t-butyldimethylsilyl ether was hydrolized to afford **8** in 68% overall yield. Swern oxidation of **8** with excess reagents[2] gave unstable **9**[7] (80% yield). This key intermediate was coupled with netropsin analogue **10**, prepared from *N*-methyl pyrrole according to Shibuya's method,[8] leading to the racemic hybrid **1** as a pale yellow oil in 55% yield after silica gel chromatography (eluent: EtOH to 3% Et_3N/EtOH).[7,9]



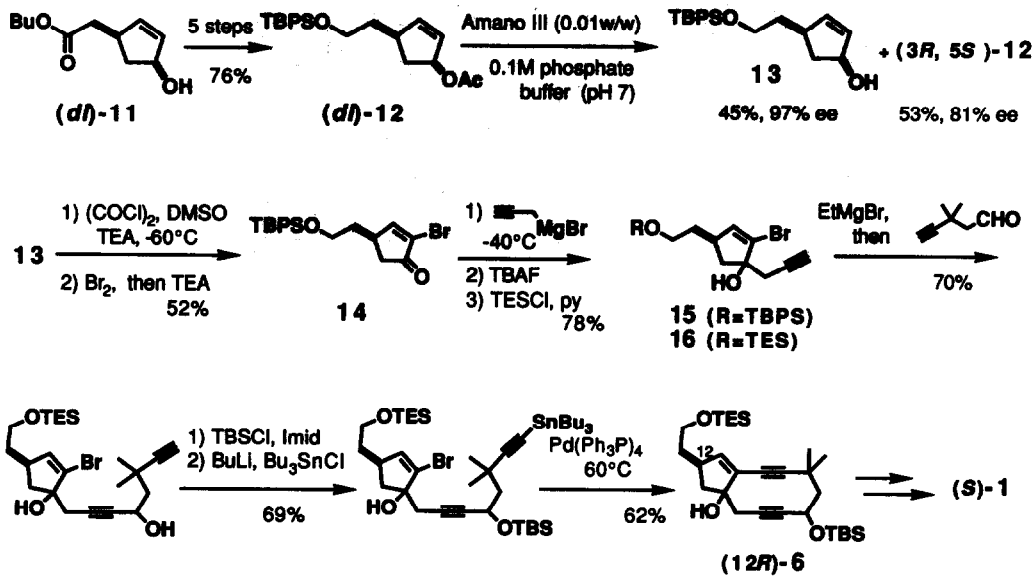
Scheme I

Synthesis of the optically active (*S*)-**1** was also achieved as shown in Scheme II. Readily available (*dl*)-**11**[10] was converted to acetate (*dl*)-**12** by conventional manner (5 steps, 76% yield). This t-butyldiphenylsilyl (TBPS) ether monoacetate (*dl*)-**12** turned out to be a good substrate for enzymatic asymmetric hydrolysis by the lipoprotein lipase Amano III® to afford the optically active alcohol **13** {$[\alpha]_D^{24}$, +0.72° (c 1.2, $CHCl_3$), 3*S*, 5*R* : 97% ee} and (3*R*, 5*S*)-**12** {$[\alpha]_D^{24}$ +20.4° (c 0.89, $CHCl_3$), 81% ee} in 45% and 53% yield, respectively.[11] Oxidation and bromination of **13** gave **14** {$[\alpha]_D^{26}$ +30.2° (c 1.0, $CHCl_3$), 52% yield for 2 steps} and 1,2-addition of propargyl magnesium bromide proceeded smoothly to afford **15** {$[\alpha]_D^{28}$ +24.1° (c 1.1, $CHCl_3$)} in 94% yield as a 12:1 diastereomeric mixture. To remove the protecting group of the primary alcohol selectively at the later stage, the TBPS group of **15** was replaced by the triethylsilyl (TES) and the resulting TES ether **16** {83% yield for 2 steps, $[\alpha]_D^{26}$ +24.0° (c 1.0, $CHCl_3$)} was transformed to (*S*)-**1** {$[\alpha]_D^{26}$ +4.2° (c 1.0, $CHCl_3$)} *via* (12*R*)-**6** {$[\alpha]_D^{27}$ +62.1° (c 1.0, $CHCl_3$)} as described for the racemic series[2a] (*vide supra*).

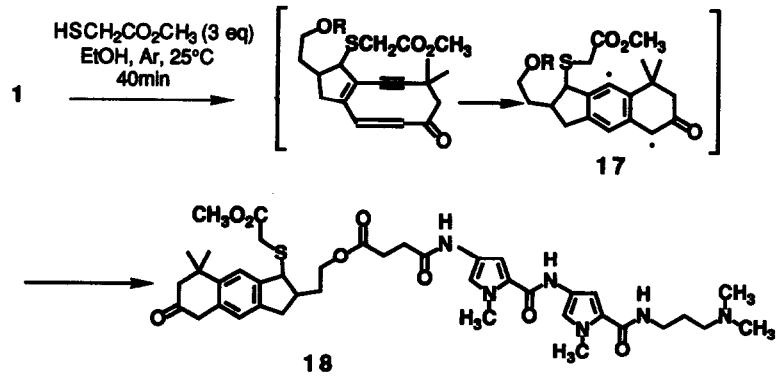
Thiol triggering aromatization of **1** was caused smoothly by addition of 3 equivalent of methyl thioglycolate in a degassed ethanol solution at 25°C without addition of an external base[2] and completed within 40 min, yielding the indane derivative **18** in 64% yield probably through mercapto hydrogen abstraction from the excess thiol by diradical intermediate **17** (Scheme III).[2a]

The racemic hybrid **1** cleaved the covalently closed supercoiled pBR322 DNA (form I) to the open circular DNA (form II) and the linear DNA (form III) more effectively than **3** and **4** as shown in Figure 1.

Thus, the several times augmentation in DNA cutting ability by combining the netropsin-type DNA binding unit to the chromophore analog has been demonstrated. The precise mechanism, the effect of stereochemical difference, and the site selectivity of the DNA cleavage will be reported in due course.



Scheme II



Scheme III

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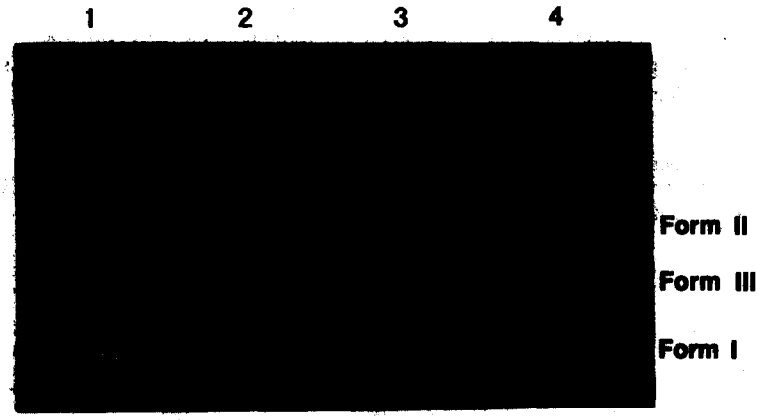

Figure 1. Agarose gel electrophoretic patterns of ethidium bromide stained pBR322 DNA, after treatment with NCS chromophore models (0.32 mM) in the presence of methyl thioglycolate (10 mM) at 37°C for 18 h (pH 7.5). Lane 1: DNA alone, lane 2: **4**, lane 3: **1**, lane 4: **3**.

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9. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (6H, s), 1.69 (1H, dddd, J=14.0, 8.0, 6.8, 6.2 Hz), 1.74 (2H, quint., J=6.3 Hz), 1.80 (1H, dtd, J=14.0, 6.2, 6.0 Hz), 2.30 (6H, s), 2.37 (1H, dt, J=17.8, 2.1 Hz), 2.46 (2H, t, J=6.3 Hz), 2.60 (1H, d, J=13.0 Hz), 2.63 (1H, d, J=13.0 Hz), 2.64 (2H, m), 2.75 (2H, m), 2.91 (1H, ddd, J=17.8, 7.0, 2.0 Hz), 2.96 (1H, m), 3.45 (2H, br q, J=6.3 Hz), 3.86 (3H, s), 3.89 (3H, s), 4.12 (1H, ddd, J=11.0, 6.8, 6.0 Hz), 4.17 (1H, dt, J=11.0, 6.2 Hz), 5.49 (1H, m), 6.46 (1H, d, J=1.9 Hz), 6.47 (1H, m), 6.50 (1H, d, J=1.9 Hz), 7.01 (1H, d, J=1.9 Hz), 7.19 (1H, d, J =1.9 Hz), 7.73 (1H, br t, J=5 Hz), 7.76 (1H, br s), 7.97 (1H, br s); IR (film): 3296, 2942, 2168, 1736, 1651, 1582, 1537, 1466, 1437, 1406, 1261, 913, 731 cm^{-1} ; HRMS (FAB): Calcd. for $C_{38}H_{47}O_6N_6$ 683.3457, Found 683.3569 (M+H).
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11. The enantiomeric excess was determined by HPLC analysis using Chiralcel OD column (Daicel Co., hexane/i-PrOH=250:1) for the corresponding benzoate, and the absolute configuration was assigned by conversion to known 4-(butoxycarbonylmethyl)cyclopent-2-en-1-one[10] and comparison of $[\alpha]_D$.

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