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Synthesis of 9-Membered Masked Enediyne Analogues Possessing DNA Intercalator and Sugar Moieties

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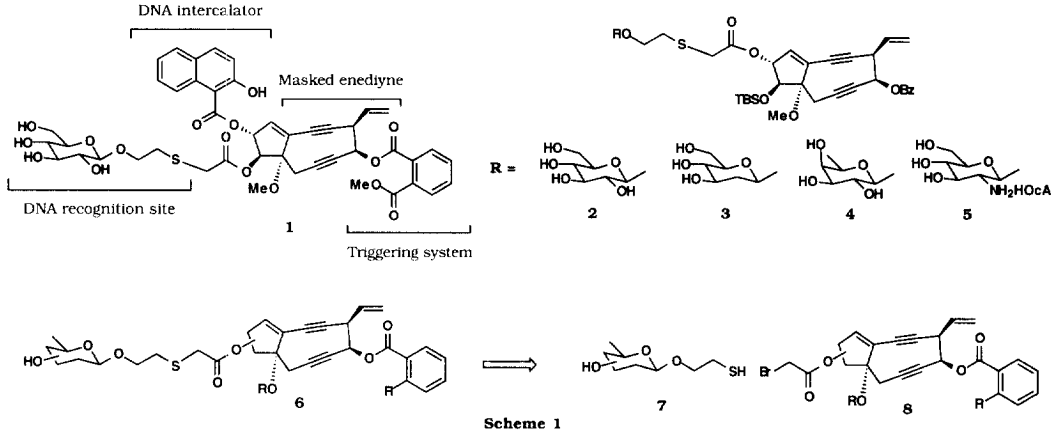
Abstract: Syntheses of hybrid DNA cleaving molecules which have the 9-membered enediyne structure of kedarcidin with the DNA intercalator of NCS and/or the sugar moieties were accomplished. Introduction of the sugar moieties to the masked enediyne was achieved via S-alkylation of a bromoacetate derivative with a sugar-containing thiol without the need for protection of the sugar moiety.

It has been proposed that the enediyne antitumor antibiotics including neocarzinostatin- (NCS-chr.), C-1027-, kedarcidin-chromophores, and calicheamicin, exert their biological activities through the cycloaromatization of the enediyne moieties.[1] This aromatization generates a highly reactive biradical species which abstracts hydrogen atoms from deoxyribose resulting in DNA strand scission. Despite the extensive structural diversity of these compounds, they all contain three important functional domains; a) the highly strained enediyne structure responsible for biradical generation, b) a triggering system to activate cycloaromatization, c) and minor groove binding functionalities, intercalation moieties, and/or combination of these motifs which can assist in association with DNA and in positioning the enediyne cores for maximum effectiveness. Therefore, hybridization of the 9-membered masked enediyne structure with a DNA intercalator and/or sugar moiety would be expected to produce new artificial DNA cleaving molecules that have both high DNA cleaving activity and base-sequence specificities. A number of hybrid molecules possessing a DNA cleaving moiety,[2] triggering system[3] and/or DNA binder[4] have been reported to improve DNA cleaving activity.[5] In this communication, we describe the synthesis of the masked enediynes **1**, **2**, **3**, **4** and **5** conjugated with a sugar moiety and/or naphthoate moiety.



Scheme 1

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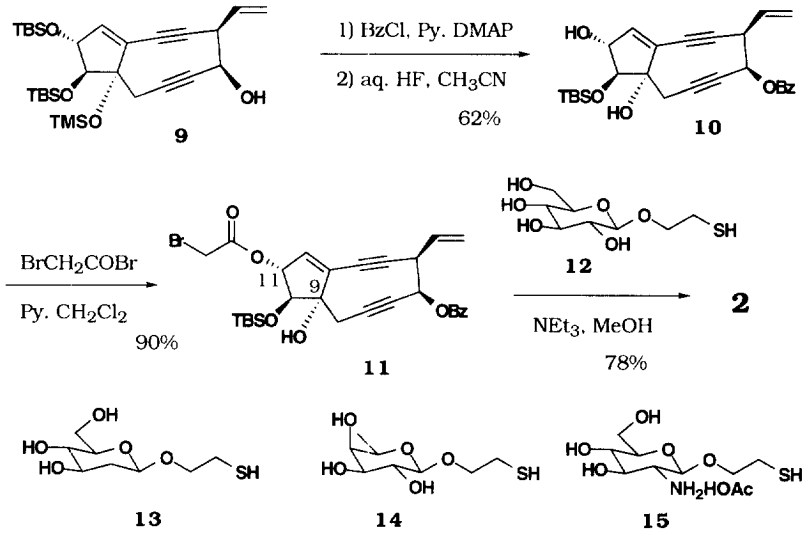
We have previously reported a facile approach to the 9-membered enediynes as analogues of esperamicin-calicheamicin[6] and NCS-chr.[7] This concept was applied to the synthesis of analogues **1**, **2**, **3**, **4** and **5**. Our synthetic plan for the introduction of the sugar moiety to the masked enediyne involves S-alkylation of α bromoacetate derivative **8** with the sugar-containing thiol **7**. (Scheme 1) This method would allow us to couple the labile diyne chemoselectively with the thiol derivative of various sugars possessing hydroxyl and/or amino groups without the need for protections on the sugar moiety.

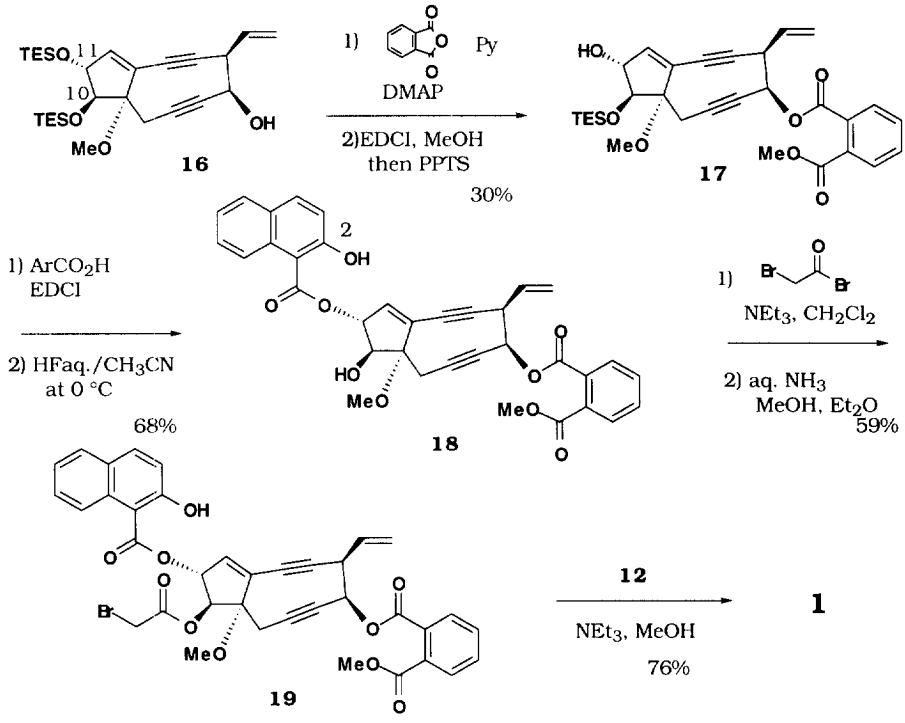
In order to investigate the feasibility of this method, synthesis of diyne **2** conjugated with glucose **12** via a thiol tether at C(11) was examined. (Scheme 2) Benzoylation of **9**, which was prepared according to our previous report,[11] followed by selective removal of the TBS group at C(11) and the TMS group at C(9) with aq. HF in CH_3CN gave allylic alcohol **10** in 62% yield. Bromoacetylation of **10** was performed with bromoacetyl bromide in CH_2Cl_2 to afford the desired product **11** in 90% yield. Coupling of **11** with **12** was accomplished by treatment with Et_3N in MeOH at 0 °C for 5 min to provide **2**[8] in 78% yield. Similarly, S-alkylation of bromoacetate **11** with 2-deoxyglucose **13**, fucose **14** and glucosamine **15** afforded the masked analogues **3**, **4** and **5** in 63%, 61% and 59% yields, respectively. The S-alkylation provides a versatile method for introducing the various sugars to the labile enediyne without protecting groups in the sugar moiety.



Scheme 2

Our attention next turned to the diyne **1** possessing naphthoate and glucose moieties. Synthesis of **1** was carried out from the 9-membered diyne **16** which was prepared according to the modified procedure developed in our laboratory.[7] (Scheme 3) Treatment of the alcohol **16** with phthalic anhydride at room temperature, followed by esterification with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDCI) in MeOH gave the phthalate, which was converted to the allylic alcohol **17** by selective removal of the TES group (PPTS, MeOH) at C(11) in 30% overall yield. Naphthoate derivative **18** was prepared by treatment of 2-hydroxy-1-naphthoic acid with EDCI in CH_2Cl_2 and deprotection of the TES group at C(10) with aq. HF

in CH_3CN at 0 °C (68% yield). Treatment of **18** with bromoacetyl bromide in the presence of Et_3N at 0 °C gave the dibromoacetate derivative. Selective removal of the bromoacetyl group at the naphthoate 2-position with aq. ammonia in MeOH afforded bromoacetate **19** in 59% overall yield from **18**. The resulting **19** was coupled with thiol **12** at 0 °C to form the desired analogue **1**[9] in 76% yield after gel permeation chromatography (JAIGEL-1H).



Scheme 3

In summary, we have succeeded in the synthesis of 9-membered masked enediyne analogues possessing a naphthoic acid intercalator and/or various monosaccharides appended via a thiol tether.

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8) NMR data of **2** (270 MHz, $CDCl_3$: CD_3OD = 5 : 1): δ = 7.96-8.02 (m, 2H; Ph), 7.56-7.64 (m, 1H; Ph), 7.43-7.50 (m, 2H; Ph), 5.94-5.80 (m,3H; vinyl, C5 and C12), 5.49-5.42 (m, 1H; vinyl), 5.37-5.35 (m, 1H; C11), 5.26-5.22 (m, 1H; vinyl), 4.36-4.31 (m, 2H; C10 and anomer), 4.13-4.00 (m, 2H; C4 and OCH_2RS-1H), 3.91-3.76 (m, 3H; OCH_2RS-1H and sugar-2H), 3.48-3.33 (m, 6H; SCH_2COOR and sugar-4H), 2.91-2.87 (m, 2H; SCH_2RO), 2.70-2.63 (m, 1H; C8-1H), 2.56-2.49 (m, 1H; C8-1H), 0.90 (m, 9H; $(CH_3)_3CSi$), 0.14-0.10 (m, 6H; CH_3Si); IR (KBr): ν = 3362, 2922, 1717, 1262, 1069, 838, 779, 709 cm^{-1}; FAB-MS:*m/z*: 745 [M^++H], 743 [M^+-H].

9) NMR data of **1** (270 MHz, CD_3OD): δ = 8.47 (d, 1H, *J* = 8.6 Hz; Ph), 7.95 (d, 1H, *J* = 8.9 Hz; Ph), 7.50-7.82 (m, 6H; Ph), 7.37 (brdd, 1H, *J* = 6.9, 6.9 Hz; Ph), 7.15 (d, 1H, *J* = 8.9 Hz; Ph), 6.30-6.25 (m, 1H; C12), 6.03-6.10 (m, 1H; C11), 5.78-5.95 (m, 3H; vinyl), 5.40 (brd, 1H, *J* = 17.1 Hz; vinyl), 5.21 (brd, 1H, *J* = 9.9 Hz; vinyl), 4.27 (brd, 1H, *J* = 7.6 Hz; anomer), 3.97-4.13 (m, 2H; C4 and OCH_2RS), 3.75-3.95 (m, 5H; $RCOOCH_3$, sugar-1H and OCH_2RS-1H), 3.60-3.70 (m, 1H; sugar-1H), 3.47-3.57 (m, 2H; SCH_2COOR), 3.42(s, 3H; $ROCH_3$), 3.23-3.37 (m, 3H; sugar-3H), 3.13-3.25 (m, 1H; sugar-1H), 2.80-2.95 (m, 4H; SCH_2RO and C8); IR ($CDCl_3$): ν = 2922, 2848, 1727, 1644, 1579, 1461, 1265, 1202, 1132, 1069, 830, 753 cm^{-1}; FAB-MS:*m/z*: 911 [M^++K], 895 [M^++Na], 871 [M^+-H].