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단 신

Enediyne Lactone 합성의 중요 중간물질인 Enyne Alcohol 유도체의 합성

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Synthesis of Enyne Alcohol Derivative-Key Intermediate for Synthesis of Enediyne Lactones

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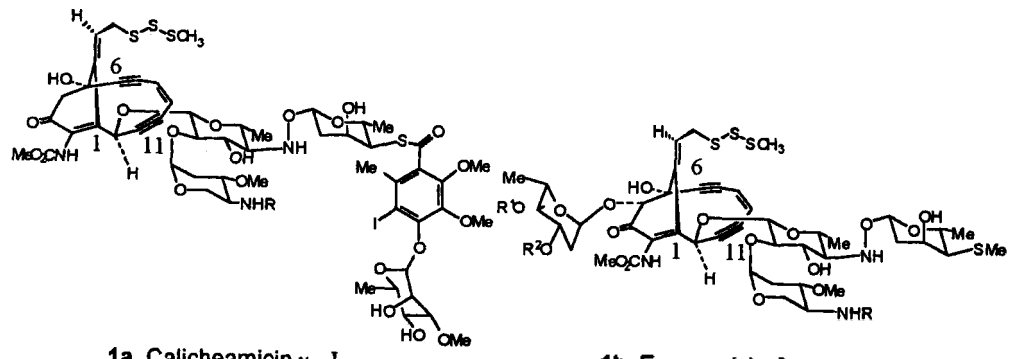
INTRODUCTION

In 1987 the Lederle[1] and Bristol-Myers[2] groups reported the unprecedented structures of calicheamicinγ1I (**1a**), esperamicin A (**1b**) (*Fig.* 1). These natural products were isolated from fermentation products of *Micromonospora echinospora* ssp. *calichensis* and cultures of *Actinomadura verrucosospora* BBM 1675 respectively. At present, these compounds are the most potent antitumor antibiotics known, being approximatly 1000 times more active than adriamycin, a clinically useful antitumor antibiotics, when tested in murin tumor models, and represent a new class of natural products based upon the (Z)-enediyne functionality.

The proposed mechanism of these antitumor antibiotics against tumor DNA is as follows. The trisulfide is cleaved by nucleophilic attack at the central sulfide atom to give thiol (or thiolate), which can add in a Michael fashion to C-1 to give the dihydrothiophene derivative.[1,2] The resulting hybridization change at C-1 from sp^2 to sp^3 brings about a reduction of the C-6/C-11 distance from 3.35 to 3.16 Å, thereby causing spontaneous cycloaromatization at ambient temperature to produce 1,4-diyl, a reaction known as the Bergman cycl-



1a Calicheamicin γ_1 I

1b Esperamicin A

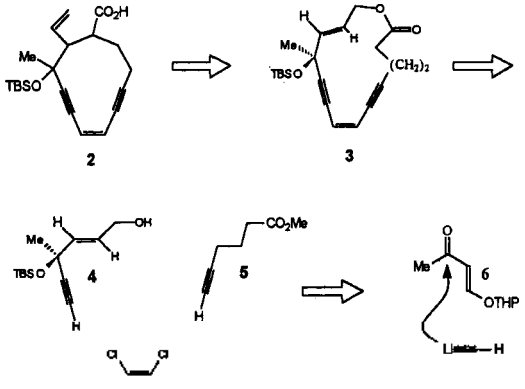
Fig. 1.

ization.[3] Studies on the interaction of **1** with DNA suggested that it binds into the minor groove and the corresponding diyl can abstract a 5'-hydrogen from the sugar phosphate backbone of DNA which ultimatly results in strand scission.

Intrigued by the fascinating mode of action of the enediyne antitumor antibiotics, we designed a general methodology for the synthesis of cyclic enediyne systems which can be served as the substrates of Bergman aromatization studies.

RESULTS AND DISCUSSION

From a retosynthetic point of view, cyclic enediyne system **2** can be prepared from a enediyne lactone **3** via an Ireland-Claisen rearrangement of the corresponding ketene acetal intermediate (*Scheme* 1). Consequently, developing an efficient way of construction of the enediyne lactone **3** should be a primary goal of this research. Although K. C. Nicolaou and coworkers[4] reported a general strategy for the synthesis of cyclic enediyne systems by using Ramberg-Backlund reaction, this methodology carries a difficulty of introducing functionalities to the molecules.

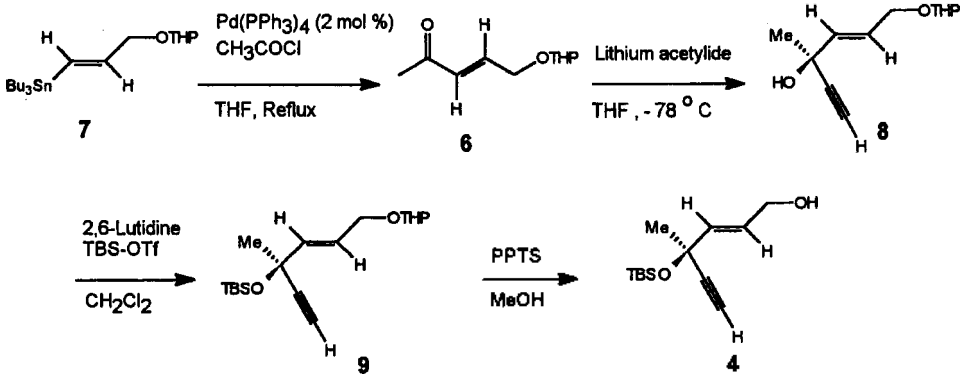


Scheme 1.

It is clear that disconnection of lactone 3 to three components as shown in *Scheme* 1 provides for a convergent synthesis,[5] since the required cis-1,2-dichloroethylene and methy hexynoate (**5**) are commercially and readily available respectively. Therefore, the challenging part in the synthesis of lactone **3** remains the construction of enyne alcohol derivative **4** which can in principle be derived by addition of lithium acetylide to conjugated ketone **6**.

As shown in *Scheme* 2, enyne alcohol **4** – the key intermediate for the synthesis of 15-membered lactone, can be prepared from vinyltin compound **7**.[6]

Guibe and coworker had reported that (*E*)-tributylstannyl alkene **7** could be made from terminal bromoalkyne which in turn can be prepared from THP propargyl ether.[6] Pd(0)-catalyzed coupling reaction of this vinyltin **7** with acetyl chloride in refluxing THF according to Stille and Kosugi *et al.*[7] gave the conjugated ketone **6** in 65% yield with retention of double bond geometry. Generation of lithium acetylide[8] by introducing *n*-butyllithium to an acetylene solution in THF at −78 ℃ followed by addition of conjugated ketone **6** gave rise to the desired enyne alcohol **8** in 92% yield. Use of commercially available ethylenediamine complexed monolithium acetylide proved to be much less ef-



Scheme 2.

fective in that **8** was produced in only 36% yield.

Protection of the tertiary hydroxy group of **8** with 1.1 equiv of TBS-OTf and 2.0 equiv of 2,6-lutidine in methylene chloride and selective deprotection of the primary THP ether of the resulting TBS ether **9** with pyridinium para-toluenesulfonate in methanol provided the required enyne alcohol **4** in 83% overall yield from **8**.[5] Synthesis of enediyne lactone utilizing enyne alcohol **4** is currently pursuing in our lab.

EXPERIMENTAL

^{1}H (270 MHz) and ^{13}C (67.9 MHz) NMR spectra were recorded on JEOL GX-270 NMR spectrometer with $CDCl_3$ as solvent and $CHCl_3$(^{1}H δ 7.26) or $CDCl_3$(^{13}C δ 77.02) as a internal standard. IR spectra were taken on Perkin-Elmer 1600 FTIR spectrometer using sodium chloride plates. Data are reported in wavenumbers (cm $^{-1}$). High-resolution mass spectral analyses were performed by the Mass Spectral Facility at the State University of New York at Stony Brook.

THF and methylene chloride were distilled from sodium benzophenone ketyl and calcium hydride under argon prior to use respectively. Other reagents were purified by procedure described in the literature.[9] All reagents were purchased from Aldrich chemical co. and used directly.

(2*E*)-1-[(Tetrahydro-2H-pyran-2-yl)oxy]penten-4-one (6). To a flame dried 50 mL round bottomed flask were added **7** (4.3 g, 10 mmol),[6] freshly distilled THF (15 mL), palladium tetrakistriphenylphsphine (Pd(0), 115 mg, 1 mol%) and acetyl chloride (950 mg, 12 mmol, 1.2 equiv). The reaction flask was then equipped with a reflux condenser fitted with a drying tube on top. The reaction mixture was heated at reflux temperature for 1 h. The resulting brownish solution was poured into water (50 mL) and extracted with ether (2×40 mL). The combined organic layer was washed with sat. $NaHCO_3$ (70 mL), brine (70 mL), dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by gradient chromatography on silica gel with 20% ether/80% hexane to give **6** as a light yellow oil (1.2 g, 65%): Rf (50% ether/50% hexane) 0.35.

^{1}H NMR ($CDCl_3$): 6.83 (dt, *J*=16.2, 4.2 Hz, 1H), 6.33 (dt, *J*=16.1, 2.0 Hz, 1H), 4.67 (t, *J*=5.4 Hz, 1H), 4.45 (ddd, *J*=18.9, 5.4, 3.2 Hz, 1H), 4.17 (ddd, *J*=18.9, 5.6, 3.1 Hz, 1H), 3.84 (m, 1H), 3.53 (m, 1H), 2.29 (s, 3H), 1.91~1.21 (m, 6H).

(2*E*)-4-Methyl-1-[(tetrahydro-2H-pyran-2-yl)oxy]hexen-5-yn-4-ol (8). A flame dried 50 mL round bottomed flask equipped with a magnetic stirrer and nitrogen inlet (through septum cap) was connected to a mercury bubbler and flushed with nitrogen. THF (18 mL) was added and the flask was cooled to −78 ℃. Acetylene (14.9 mmol, 3 equiv) was introduced by means of a large gas syringe. *n*-Butyllithium (1.5 M in pentane, 4.95 mL, 1.5 equiv) was then added dropwise into the reaction flask over a 20 min period. After stirring for 10 min, enone **6** (912 mg, 4.96 mmol) dissolved in THF (6 mL) was added during 20 min to the generated monolithium acetylide at −78 ℃. The resulting solution was stirred for 20 min at that temperature and then warmed to room temperature. Water (4 mL) was added followed by anhydrous K_2CO_3 until the aqueous phase became pasty. The organic phase was decanted and the aqueous layer was extracted with ether (2×10 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residual light yellow oil was purified by flash chromatography using 20% ether/80% hexane as the eluent to afford **8** (961 mg, 92%): Rf (50% ether/ 50% hexane) 0.35.

^{1}H NMR ($CDCl_3$): 6.07 (dt, *J*=15.5, 5.5 Hz, 1H), 5.83 (ddd, *J*=15.4, 2.8, 1.5 Hz, 1H), 4.63 (s, 1H), 5.24 (ddt, *J*=13.2, 5.1, 1.1 Hz, 1H), 3.98 (ddt, *J*=13.2, 5.9, 1.5 Hz, 1H), 3.83 (m, 1H), 3.50 (m, 1H), 2.55 (s, 1H), 1.82~1.22 (m, 6H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$): One diastereomer: 135.6, 125.5, 97.9, 86.1, 72.7, 67.4, 66.5, 62.0, 30.5, 30.1, 25.4, 19.2. The other diastereomer: 135.5, 126.5, 97.9, 86.1, 72.7, 67.4, 66.4, 62.0, 30.5, 30.1, 25.4, 19.2; IR (neat): 3404, 3293, 2110 cm^{-1}.

(2*E*)-4-[(tert-Butyldimethylsilyl)oxy]-4-methyl-1-[(tetrahydro-2H-pyran-2-yl)oxy]hexen-5-yne (9). A 50 mL round bottomed flask fitted with a mag-

netic stirrer was charged with enyne alcohol **8** (2.92 g, 13.9 mmol), freshly distilled methylene chloride (15 mL), and 2,6-lutidine (3.87 mL, 41.7 mmol, 3 equiv). To the solution was added TBS-OTf (3.4 mL, 14.6 mmol, 1.05 equiv) and the resulting solution was stirred at room temperature for 1 h. The resulting mixture was poured into dilute ice-cold HCl (80 mL, 0.5 N) and extracted with ether (2× 70 mL). The combined organic layer was washed successively with sat. $NaHCO_3$ (70 mL), water (70 mL), and brine (150 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography with 5% ether/95% hexane to furnish **9** in quantitative yield (4.5 g): Rf (15% ether/85% hexane) 0.45.

^{1}H NMR ($CDCl_3$): 6.00 (dtd, J=15.2, 5.5, 1.1 Hz, 1H), 5.77 (dd, J=15.4, 1.5 Hz, 1H), 4.65 (m, 1H), 4.25 (dd, J=12.8, 4.6 Hz, 1H), 4.01 (dd, J= 12.8, 5.9 Hz, 1H), 3.87 (m, 1H), 3.49 (m, 1H), 2.54 (s, 1H), 1.87~1.18 (m, 6H), 1.52 (s, 3H), 0.87 (s, 9H), 0.17 (s, 3H, for both diastereomer), 0.13 (s, 3H, for one diastereomer), 0.12 (s, 3H, for the other diastereomer).

(2*E*)-4-[(tert-butyldimethylsilyl)oxy]-4-methylhexen-5-yn-1-ol (4). In a 50 mL round bottomed flask equipped with a magnetic stirrer were placed protected diol **9** (1.2 g, 3.7 mmol), methanol (20 mL), and pyridinium para-toluenesulfonate (465 mg, 0.5 equiv). After stirring for 2 h, most of methanol was evaporated and the residual liquid was transferred to a separatory funnel with water (50 mL) and extracted with ether (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by gradient chromatography with ether/hexane to yield enyne alcohol **4** (734 mg, 83%): Rf (25% ether/75% hexane) 0.30.

^{1}H NMR ($CDCl_3$): 6.04 (dt, J=15.4, 5.3 Hz, 1H), 5.75 (dt, J=15.4, 1.1 Hz, 1H), 4.18 (dd, J=5.3, 1.3 Hz, 2H), 2.54 (s, 1H), 1.51 (s, 3H), 0.87 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H); ^{13}C NMR ($CDCl_3$): 136.3, 127.4, 86.6, 73.4, 68.5, 63.7, 32.4, 25.8, 18.1, −2.9; IR (neat): 3309, 2114 cm^{-1}; HRMS calcd for $C_{13}H_{24}O_2Si$ 240.1545, found 240.1549.

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