Chemistry and Antimicrobial Activities of 3,5,7,9-Decatetrayn-2-ol and Related Compounds

Masahiko Yamaguchi,*# Hyeon-Joo Park, and Masahiro Hirama
Department of Chemistry, Graduate School of Science, Tohoku University, Aoba, Sendai 980-77

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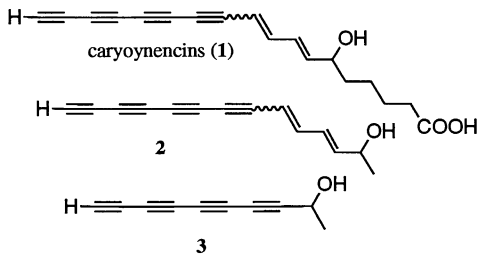
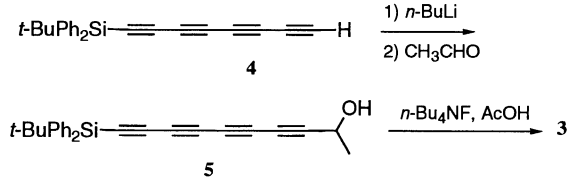
Unstable 3,5,7,9-octatetrayn-2-ol showed potent antimicrobial activity against bacteria and fungi. Its trimethylsilyl derivative, which possessed much improved stability, showed comparable activity. It is due to desilylation under neutral aqueous conditions.

Caryoynencins (**1**) are antibiotics isolated from liquid cultures of a plant pathogen, *Pseudomonas caryophylli*.[1] We have synthesized **1** and related polyynes, and examined their antimicrobial activities.[2,3] Analog **2** for example exhibited comparable activity to **1**. These studies revealed that both the tetrayne unit and the secondary alcohol unit were essential for the activity of **1**.[3] However, the effect of the diene moiety remained unclear. Described here is the chemistry and antimicrobial activities of 3,5,7,9-octatetrayn-2-ol (**3**) and its derivatives.

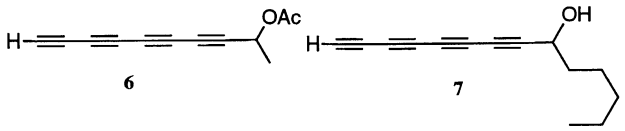


Tetrayne **4** was lithiated with butyllithium in THF at -78 °C, and was added to acetaldehyde giving silylated 3,5,7,9-decatetrayn-2-ol (**5**) in 67% yield (Scheme 1). Attempts to remove the silyl group under alkaline conditions failed presumably because of the C(*sp*)-C(sp^3) bond scission. After several trials, it was found that **5** could effectively be desilylated by the treatment with *n*-Bu_4NF-AcOH in THF at -70 °C for 1.5 h giving **3** in 42% yield.[3] ^{1}H-NMR (600 MHz, $CDCl_3$-CCl_4) δ 1.49 (3H, d, *J* = 6.7 Hz), 1.87 (1H, d, *J* = 5.5 Hz), 2.14 (1H, s), 4.59 (dq, *J* = 5.6, 6.7 Hz). ^{13}C-NMR (150 MHz, $CDCl_3$-CCl_4) δ 30.5, 65.5, 67.3, 67.6, 69.1, 70.7, 74.5, 75.2, 75.8, 86.3. Since the solution of **3** could not be concentrated to dryness without polymerization, the yield was estimated as a diazomethane adduct.[2,3]

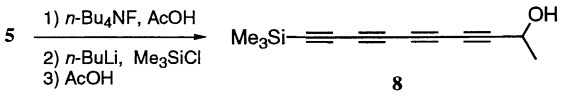


Scheme 1.

Several related compounds were also prepared. Acetate **6** was synthesized from **5**: i) Ac_2O, pyridine; r.t., 0.5 h, 84%, ii) *n*-Bu_4NF-AcOH, THF, -78 to –50 °C, 1 h, 59%. 7,9,11,13-Tetradecatetrayn-6-ol (**7**) was synthesized from **4**: i) *n*-BuLi then hexanal, THF, -78 °C, 1 h, 65%, ii) 3 M NaOH, THF, *n*-Bu_4NBr; r.t., 0.6 h, 41%. In the latter synthesis, the desilylation could be conducted under alkaline conditions probably because of the lower solubility of **7** in water compared to **3**.



The instability of the terminal polyynes is one of the drawbacks of these compounds to be used as antimicrobial agents. They polymerize instantaneously when concentrated. As an idea for the stabilization, introduction of small groups at the terminal polyyne moiety was examined. Since *t*-butyldiphenylsilyl derivative of **2** did not show any activity,[3] a trimethylsilyl derivative **8** was synthesized (Scheme 2). Thus, **3** prepared from **5** was treated with excess butyllithium and trimethylsilyl chloride in THF at -78 °C to give *C*,*O*-bissilylated product. *O*-Silyl group was removed selectively by treating with acetic acid in aqueous THF at r.t. giving **8** in 56% yield from **5**. The stability of the trimethylsilyl derivative **8** was much improved compared to **3**, and its solution could be concentrated without polymerization. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.30 (9H, s), 1.57 (3H, d, *J* = 6.6 Hz), 2.22 (1H, br), 4.68 (1H, q, *J* = 6.6 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$) δ -0.64, 23.7, 58.7, 61.2, 61.9, 62.6, 64.2, 69.1, 79.8, 87.7, 88.3. IR (neat) 3350, 2154, 2064 cm^{-1}. MS (EI) *m/e* 214 (**M**, 46), 199 (**M**–CH_3, 100). HRMS. Calcd for $C_{13}H_{14}OSi$: 214.0814. Found: 214.0819.



Scheme 2.

Notably, the antimicrobial activity of tetraynol **3** was comparable to dientetraynol **2** (Table 1). Thus, not only the butanoic acid moiety but also the diene moiety is unnecessary for the activity of **1**. The potent activity exhibited by such a simple molecule is remarkable. The MICs of acetate **6** and alcohol **7** with a longer side chain were much lower than the hydroxy derivative **3**. It appears that the hydrophilicity of the molecule is playing an important role. We would like to present here a hypothesis that molecules possessing terminal tetrayne unit and appropriate hydrophilic unit can exhibit potent antimicrobial activities. In this respect, conjugates of polyyne and sugars, amino acids, nucleic acids, *etc.*, are attractive molecules.

We were also pleased to find that the trimethylsilyl derivative **8** showed comparable activity to **3** (Table 1). Two

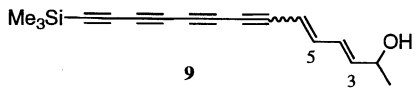
Table 1. Antimicrobial activities of polyyne compounds

Microorganism	MIC (μg/mL)					
	2	**3**	**6**	**7**	**8**	**9**
Staphylococcus aureus 209P	0.2	0.4	6.0	0.8	1.5	0.1
S. aureus 56R	0.2	0.8	6.0	1.6	1.5	0.2
S. aureus 535 (MRSA)	0.2	0.4	6.0	1.6	0.8	0.2
Bacillus subtillis ATCC 6633	0.8	3.2	12.2	N.D.	6.2	N.D.
Enterococcus faecalis 681	3.1	1.6	>50	>25	6.2	3.1
Escherichia coli NIHJ	0.8	0.4	>50	>25	3.1	1.5
E. coli 609	0.8	1.6	>50	>25	6.2	1.5
Salmonella enteritidis	0.8	1.6	>50	>25	6.2	1.5
Klebsiella pneumoniae 806	1.5	6.2	>50	>25	25	6.2
K. pneumoniae 846(R)	0.8	3.2	>50	>25	6.2	1.5
Serratia marcescens 1184	0.8	3.2	>50	>25	12.5	3.1
Proteus vulgalis 1420	0.8	0.4	25	>25	0.8	1.5
Shigella flexneri IID 642	0.8	0.4	>50	N.D.	0.8	N.D.
Enterobactor cloacae 963	>25	25	>50	N.D.	50	>50
Pseudomonas aeruginosa 1001	>25	12.1	>50	>25	25	>50
Candida albicans	1.5	1.6	>50	N.D.	1.5	N.D.
Tricophyton interdigitale	0.8	0.2	0.8	N.D.	0.8	N.D.
T. rubrum	0.2	0.4	0.8	N.D.	0.8	N.D.

N.D. Not determined.

reasons are conceivable for the origin of the activity; i) trimethylsilyl group is removed under the physiological conditions to give the active parent compound; ii) trimethylsilyl derivative itself is active. Since the antimicrobial spectra of **3** and **8** were very similar, the former appeared likely. Furthermore, it was found that the trimethylsilyl group was removed under neutral conditions in water or methanol. The desilylation was monitored by UV, and the half-life was estimated to be 4 h in 1.6×10^{-5} M water-methanol (1:1) solution at 18 °C. Facile removal of silyl protecting group for polyynes had a precedent, and higher conjugation showed higher tendency to basic hydrolysis.[4] For example, relative rates of hydrolysis for $Ph(C{\equiv}C)_nSiEt_3$ (n = 1,2,3) were 1 : 240 : 4100. An important point of our finding is that the trimethylsilyl group is removed under *neutral* aqueous conditions at ambient temperature.

Stable trimethylsilyl derivative **9** was prepared from **2** by the same methodology as a 1:1 mixture of (3*E*,5*E*)-isomer and (3*E*,5*Z*)-isomer. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 0.20 (4.5H, s), 0.21 (4.5H, s), 1.30 (1.5H, d, J = 6.5 Hz), 1.32 (1.5H, d, J = 6.5 Hz), 1.57 (1H, br), 4.40 (0.5H, quintet, J = 6.3 Hz), 4.56 (0.5H, quintet, J = 6.3 Hz), 5.46 (0.5H, d, J = 10.8 Hz), 5.61 (0.5H, d, J = 15.6 Hz), 5.95 (0.5H, dd, J = 5.8, 15.2 Hz), 6.02 (0.5H, dd, J = 6.1, 15.2 Hz), 6.30 (0.5H, dd, J = 11.0, 15.2 Hz), 6.62 (0.5H, t, J = 11.0 Hz), 6.73 (0.5H, dd, J = 11.0, 15.2 Hz), 6.81 (0.5H, dd, J = 11.0, 15.5 Hz). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 23.1, 23.2, 61.7, 62.0, 62.1, 62.2, 64.5, 64.9, 67.9, 68.1, 68.2, 68.8, 74.3, 76.6, 76.9, 80.3, 87.8, 87.9, 89.1, 89.2, 106.7, 108.7, 126.2, 127.8, 142.9, 143.7, 146.1, 147.0. IR (neat) 3356, 2186, 2120, 2058 cm^{-1}. MS (EI) *m/e* 266 (**M**, 100), 251 (**M**−CH_3, 76), 223 (**M**−C_2H_7O, 62). HRMS. Calcd for $C_{17}H_{18}OSi$: 266.1127. Found: 266.1132. The activity of **9** was again comparable to **2** (Table 1), and the rate of the desilylation was approximately the same with **8** in methanol-water (1:1). These observations are consistent with the discussions on the mechanism of antimicrobial activities noted above, and confirmed the efficiency of this method for the stabilization of polyyne antibiotics. Thus, trimethylsilyl derivatives can be stable pro-drugs for polyyne antimicrobial agents.



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References and Notes

Present address: Pharmaceutical Institute, Tohoku University, Aoba, Sendai 980-77.

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