Chemistry and Antimicrobial Activity of Caryoynencins Analogs

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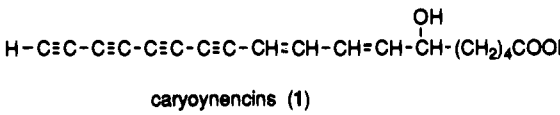
Caryoynencins (**1**) are antibiotics isolated from liquid cultures of a plant pathogen, *Pseudomonas caryophylli*, and are unstable C_{18} carboxylic acids with a conjugated dienetetrayne structure. Enyne analogs of caryoynencins were synthesized from monosilylated 1,3-butadiyne **2** ($n = 2$), 1,3,5-hexatriyne **2** ($n = 3$), and 1,3,5,7-octatetrayne **2** ($n = 4$) by alkynyl metal addition to 2,4-hexadienal (**3**) followed by allylic rearrangement and deprotection. Tetraynol **5** ($n = 4$) thus obtained was resolved by enzyme reactions. The conjugated dienetetrayne compounds are mixtures of 3*E*,5*E*- and 3*E*,5*Z*-isomers, which equilibrate by room light. ^{13}C-NMR chemical shifts of polyynes obey simple rules, which can be used for signal assignments. Antimicrobial activities of conjugated enynes and related compounds were examined. The tetrayne analog **6** ($n = 4$) possesses potent antibacterial and antifungal activities, while triyne and diyne analogs **6** ($n = 3$ and 2) are less active. Chirality does not affect the activities. An isomeric enyne compound, 2,4-tetradecadiene-7,9,11,13-tetrayn-6-ol (**8**), showed potent activity against *Tricophyton*.

A number of conjugated polyyne compounds have been obtained as natural products, and potent biological activities have been reported.[1] Although the polyyne moiety appears to be the origin of the activities, their structure–activity relationships have not been studied systematically.[2,3] Caryoynencins (**1**) are antibiotics isolated from liquid cultures of a plant pathogen, *Pseudomonas caryophylli*, by a Tsukuba group and show potent antimicrobial activities against Gram-positive and Gram-negative bacteria.[4] They are unstable C_{18} carboxylic acids with conjugated dienetetrayne structures and polymerize when concentrated. We previously reported the synthesis of racemic caryoynencins (**1**).[5] Here we describe the chemistry and antibiotic activities of their analogs.



caryoynencins (**1**)

Racemic tetradeca-9,11-diene-1,3,5,7-tetrayn-13-ol (**6**, $n = 4$), a partial structure of **1**, was first synthesized employing the strategy of caryoynencin synthesis: (i) addition of lithiated polyyne to dienal, (ii) allylic rearrangement of the hydroxyl group, and (iii) deprotection (Scheme 1). 2,4-Hexadienal (**3**) was treated with lithiated **2** ($n = 4$) in THF at −78 °C, and the resulting acetylenic alcohol **4** ($n = 4$) was rearranged with aqueous HF giving **5** ($n = 4$). Removal of the silyl protecting group with 3 M NaOH at 0 °C in the presence of a phase transfer catalyst[6] gave unstable **6** ($n = 4$), which was handled in solution throughout the workup procedures. Compound **6** ($n = 4$) was converted to pyrazole **7** (X = OH) by diazomethane treatment to further confirm the structure.

Compounds **5** ($n = 4$) and **6** ($n = 4$) were obtained as mixtures of 3*E*,5*E*- and 3*E*,5*Z*-isomers as were the natural products. These isomers are separable by silica gel chromatography and equilibrate under room light in solution. For example, 0.02 M (3*E*,5*E*)-**5** ($n = 4$) in

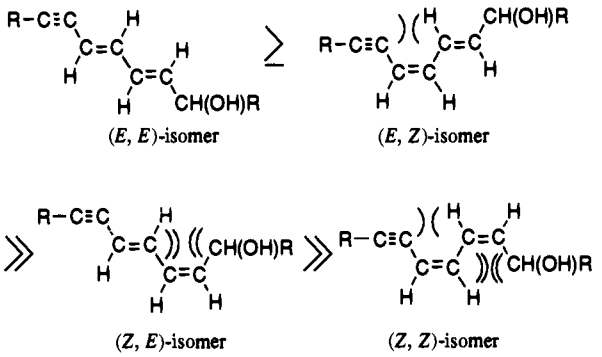


Figure 1. Thermodynamic stability of isomeric dienynes.

$CDCl_3$ reached equilibration after 20 h at room temperature, while no isomerization in the same solvent took place in the dark. Related photoisomerization of (*Z*)-dehydromatricaria ester, methyl (*Z*)-2-decene-4,6,8-triynoate, to its *E*-isomer has previously been reported.[7] Notably, all the conjugated dienepolyyne compounds **5** ($n = 2$–4), **6** ($n = 2$–4), **7** (X = OH, OAc), and **9**–**11** were obtained as similar mixtures of stereosiomers (*vide infra*).

We reasoned that the selective 5-olefin isomerization is due to the thermodynamic stability of the stereoisomers: 3*E*,5*E* ≥ 3*E*,5*Z* ≫ 3*Z*,5*E* ≫ 3*Z*,5*Z*. The fact that the 3*E*,5*Z*-isomer is more stable than the 3*Z*,5*E*-isomer can be rationalized by the lesser degree of steric repulsion between sp-C and sp^2-CH compared with that between sp^2-CH and sp^3-CHOH (Figure 1). The A-value of C≡CH (0.18 or 0.41) is much smaller than those of CH=CH_2 (1.35) and CH_3 (1.70).[8]

The racemic tetrayne **5** ($n = 4$) was resolved by enzyme reactions (Scheme 2). Acetylation with vinyl acetate in the presence of a lipase, Novo SP-435 (Novo Nordisk),[9] gave optically active acetate (*R*)-**10** (67% ee) and recovered (*S*)-**5** ($n = 4$) in 99% ee. (*R*)-**10** of relatively low optical purity was subjected to enzymatic hydrolysis with another lipase, lipase AK (Amano), giving (*R*)-**5** ($n = 4$) in 98% ee. Of several enzymes tested, this combination gave the best results. The ester hydrolysis of (*R*)-**10** under basic conditions failed to give either (*R*)-**5** ($n = 4$) or (*R*)-**6** ($n = 4$). Desilylation

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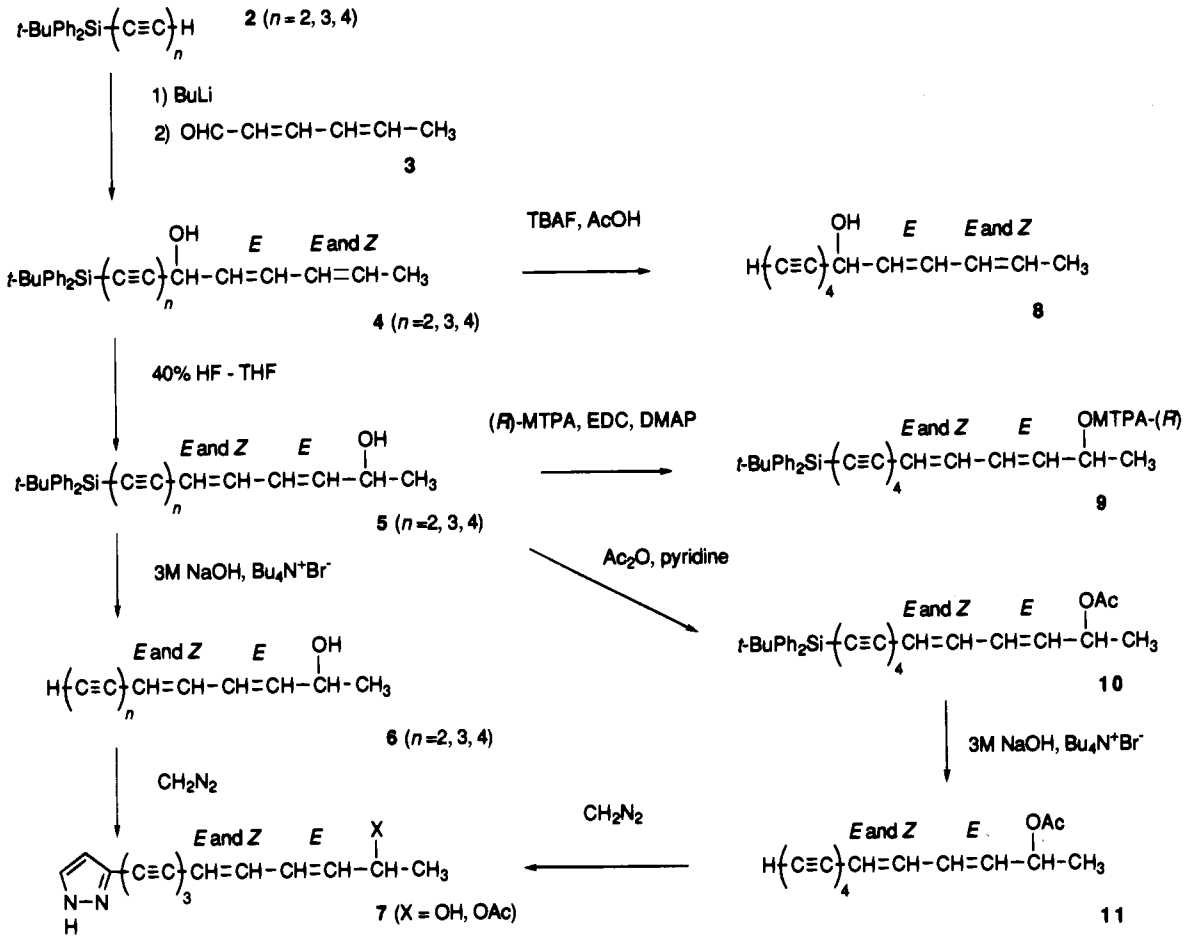
Scheme 1



prevailed over deacetylation, which was followed by decomposition. Thus, the enzyme reaction turned out to be effective for deacetylation without affecting the silyl protecting group. Optically active (*S*)- and (*R*)-**5** (n = 4) were converted to (*S*)- and (*R*)-**6** (n = 4), respectively.

Absolute configurations were determined by the MTPA (α-methoxy-α-(trifluoromethyl)phenylacetic acid) method.[10] Authentic samples of (*R*)-MTPA esters **9** were synthesized by using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (Scheme 1), and four stereoisomers, (2*R*,3*E*,5*E*)-, (2*R*,3*E*,5*Z*)-, (2*S*,3*E*,5*E*)-, and (2*S*,3*E*,5*Z*)-**9**, were separated by HPLC. The absolute configurations were determined by comparing ^{1}H-NMR chemical shifts. These isomers were handled in the dark in order to avoid equilibration. The enzyme-resolved (*S*)-**5** (n = 4) was converted to (*R*)-MTPA ester and compared spectroscopically with the authentic samples. Attempts to remove MTPA moiety from **9** failed as with the acetate (*R*)-**10**.

Racemic acetate **11** was synthesized by removing the silyl group from racemic **10**. Tetraynol **4** (n = 4) was desilylated with Bu_4NF–AcOH giving **8** (Scheme 1). Alkaline treatment used for the deprotection of **5** (n = 4) was not effective here due to serious decompositions.

Triyne and diyne analogs **6** (n = 2 and 3) were also synthesized from **2** (n = 2 and 3) (Scheme 1). We noticed a regularity on ^{13}C-NMR chemical shifts of **4** (n = 2–4) and (3*E*,5*E*)- and (3*E*,5*Z*)-**5** (n = 2–4) at the polyyne moiety. When acetylenic signals of **4** (n = 2) and **4** (n = 3) are compared, four peaks of the two compounds appear at very close chemical shifts (Table 1). Similarly, six peaks of **4** (n = 3) and **4** (n = 4) are very close. The regularity also holds for (3*E*,5*E*)- and (3*E*,5*Z*)-**5** (n = 2–4) within a range of 0.6 ppm in most cases (Tables 2 and 3).

The following rules rationalize the observations. The ^{13}C-NMR chemical shifts of conjugated polyynes are governed by (i) the nature of substituents on both terminal sp-carbons and (ii) the number of sp-carbons from the terminal (Figure 2). The number of acetylene conjugations does not affect the chemical shifts. If this empirical rule is accepted, it can also be used to assign ^{13}C-NMR absorptions of polyyne carbons with the aid of NMR techniques. For example, the four carbons A, B, G, and H of **4** (n = 2) are assigned by COLOC and gated decoupling methods as δ 83.6, 90.8, 71.0, and 76.9, respectively (Figure 2a). It is known that sp-carbons of silylacetylenes, especially β-carbons, are strongly deshielded.[11] Then, applying the rule, NMR absorptions of **4** (n = 3) and **4** (n = 4) can be assigned as shown in Figure 2a. Here, carbon C and F of **4** (n = 4) are discriminated by NMR techniques, and the results are applied to **4** (n = 3) according to the rule. The assignments of **4** (n = 3) and **4** (n = 4) are consistent with the results of COLOC and gated decoupling measurements. Analogously, (3*E*,5*E*)- and (3*E*,5*Z*)-**5** (n = 2–4) are assigned as shown in Tables 2 and 3 and Figure 2b,c. Several ^{13}C-NMR assignments of polyyne compounds have been reported[12] which also accord with the rules.

Summarized in Table 4 are the antimicrobial activities of synthetic caryoynencins (**1**) and analogs (±)-**6** (n

Scheme 2

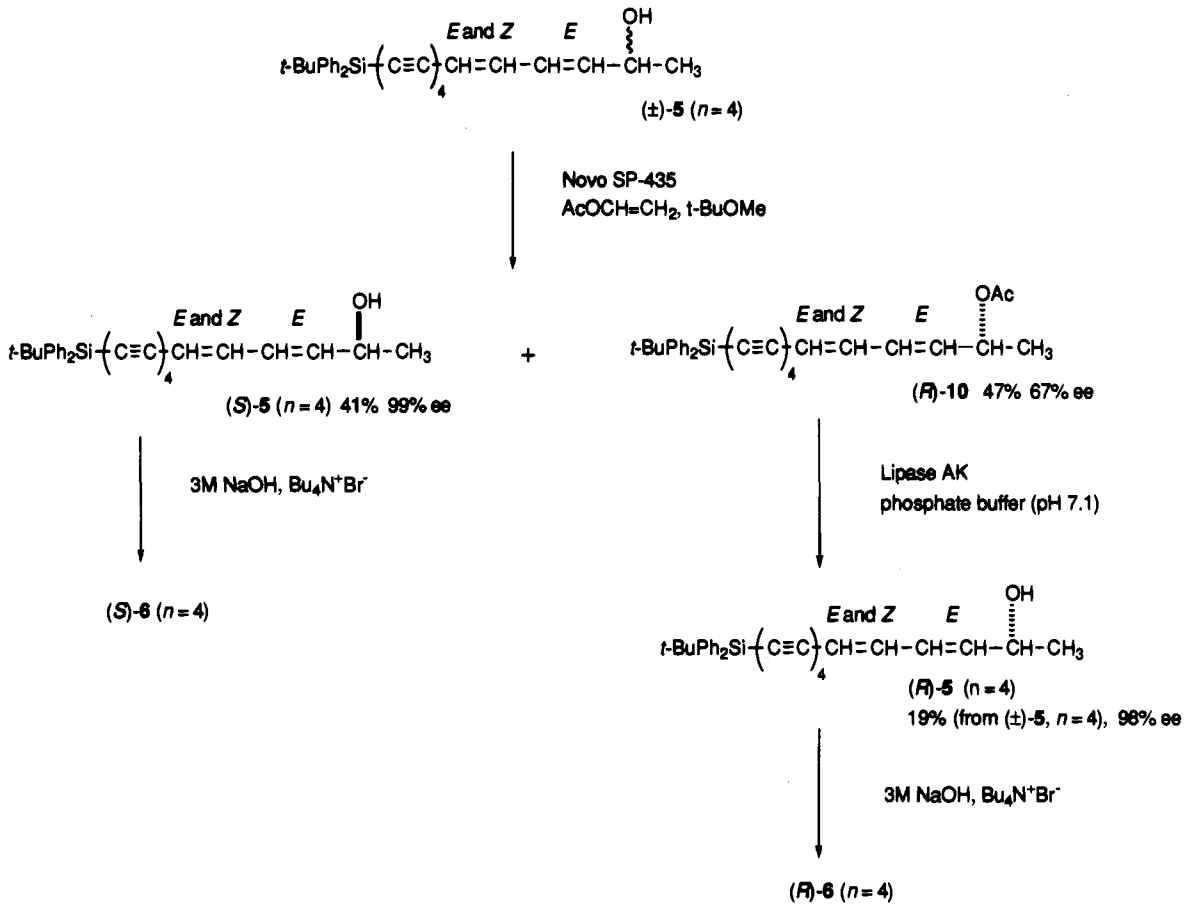


Table 1. ^{13}C-NMR (150 MHz, $CDCl_3$) Data of **4** (n = 2–4) at Polyyne Moiety[a]

	4		
carbon	$n = 2$	$n = 3$	$n = 4$
Si-C(A)	83.6 (s)	83.7 (s)	84.1 (s)
C(B)	90.8 (d)	91.3 (s)	91.2 (s)
C(C)		61.4 (d)	61.7 (s)
C(D)			62.9 (s)[b]
C(E)			62.5 (s)[b]
C(F)		64.4 (d)	64.4 (d)
C(G)	71.0 (d)	70.7 (d)	70.7 (d)
=CH-C(H)	76.9 (dd)	77.4 (dd)	77.4 (brdd)

[a] Shown in parentheses are couplings obtained by gated decoupling technique. [b] Assignments can be reversed.

Table 2. ^{13}C-NMR (150 MHz, $CDCl_3$) Data of (3*E*,5*E*)-**5** (n = 2–4) at Polyyne Moiety[a]

	(3*E*,5*E*)-**5**		
carbon	$n = 2$	$n = 3$	$n = 4$
Si-C(A)	86.8 (s)	85.1 (s)	84.7 (s)
C(B)	91.7 (d)	91.7 (s)	91.4 (s)
C(C)		62.2 (d)	62.8 (s)
C(D)			64.7 (s)
C(E)			62.4 (d)
C(F)		68.0 (d)	68.0 (d)
C(G)	77.0 (d)	76.7 (d)	76.8 (d)
=CH-C(H)	76.7 (d)	76.9 (d)	76.8 (d)

[a] Shown in parentheses are couplings obtained by gated decoupling technique.

= 3 and 4), (*R*)- and (*S*)-**6**, **8**, and **12**. The synthesis of **1** and **12** was previously reported.[5] Analogs **1** and (±)-**6** (n = 4) exhibit a broad spectra of activity not only against bacteria but also against fungi. Their strong inhibition of the growth of methicillin-resistant *Staphylococcus aureus* (MRSA) is notable. Rather surprisingly, the activities of **1** and (±)-**6** (n = 4) are comparable showing that the $(CH_2)_4COOH$ moiety is not necessary. The activity is reduced with triyne analog **6** (n = 3) and disappears with diyne analog **6** (n = 2) (MIC > 25 μg/mL) for all the organisms tested). Furthermore, **5** (n = 4) is not active at all (MIC > 25 μg/mL) indicating that the terminal tetrayne moiety is critical for antimicrobial activities. Chirality is unimportant as shown by the examinations of (±)-, (*R*)-, and (*S*)-**6** (n = 4). Enantiomers of safynol, (3*E*,11*E*)-3,11-tridecadiene-5,7,9-triyne-1,2-diol, showed a small difference in antifungal activity,[13] which might be related to our observations. Since the MICs of **11** were >25 μg/mL , the 2-hydroxyl group itself is required. Analog **8**, an isomer of **6** (n = 4), strongly inhibits the growth of *Tricophyton*, although it is not active against Gram-negative bacteria. The behavior of cyclohexyl analog **12** is similar to that of **8**, but **12** is less active.

Table 3. ^{13}C-NMR (150 MHz, $CDCl_3$) Data of (3*E*,5*Z*)-**5** (n = 2–4) at Polyyne Moiety[a]

	(3*E*,5*Z*)-**5**		
carbon	$n = 2$	$n = 3$	$n = 4$
Si-C(A)	87.5 (s)	85.5 (s)	84.9 (s)
C(B)	91.5 (d)	91.6 (s)	91.4 (s)
C(C)		62.0 (d)	62.7 (s)
C(D)			65.0 (s)
C(E)			62.1 (d)
C(F)		68.6 (d)	68.7 (d)
C(G)	80.4 (d)	80.2 (d)	80.3 (d)
=CH-C(H)	74.5 (d)	74.7 (d)	74.6 (d)

[a] Shown in parentheses are couplings obtained by gated decoupling technique.

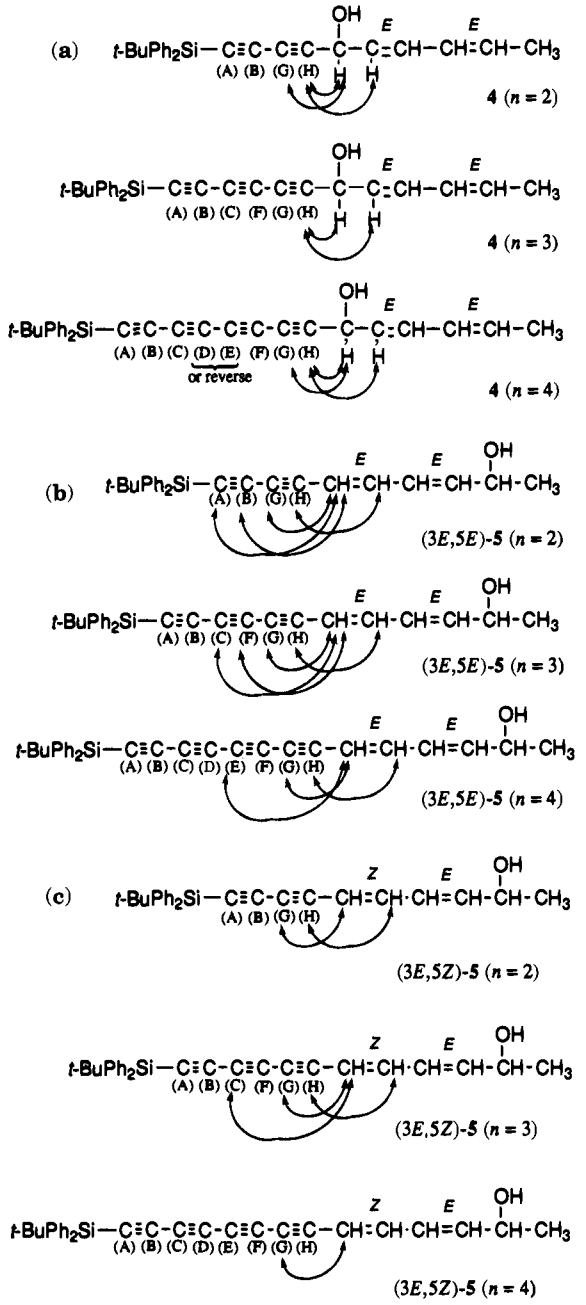
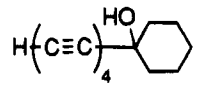


Figure 2. ^{13}C-NMR assignments and long range couplings observed by COLOC for (a) **4** (n = 2–4), (b) (3*E*,5*E*)-**5** (n = 2–4), and (c) (3*E*,5*Z*)-**5** (n = 2–4).

In conclusion, analogs of the polyyne antibiotics caryoynencins (**1**) were synthesized, and their antibacterial activities were examined. The terminal tetrayne moiety and the hydroxyl group were found to be essential for the activity (Figure 3). There have been few studies on the structure–activity relationships of polyyne antibiotics, and this study sheds new light on the properties of these interesting compounds. Further studies are now underway in our laboratory, which include the search for stable analogs with potent antibacterial activities.

Experimental Section

^{1}H- and ^{13}C-NMR spectra were obtained with a Varian Gemini 200 (200 MHz) or a Brucker AM-600 (600 MHz) spectrometer. Chemical shift values are given in ppm relative to internal Me_4Si or $CHCl_3$ (δ 7.24). IR spectra were recorded with a JASCO FT/IR-7000 spectrometer. MS spectra were



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obtained with a HITACHI M-52 or a JEOL HX-110 spectrometer, and UV spectra were obtained with a JASCO Ubest-30 spectrometer. Optical rotations were obtained with a JASCO DIP-370 polarimeter. THF was distilled from benzophenone ketyl just prior to use. HMPA was distilled from CaH_2 and stored over 4 Å molecular sieves. All the polyynes are unstable and were stored in solutions. Since monosubstituted polyynes polymerize instantaneously when concentrated, all manipulations with them were conducted in solution.

14-(*tert*-Butyldiphenylsilyl)-2,4-tetradecadiene-7,9,11,13-tetrayn-6-ol (4, *n* = 4). Under an argon atmosphere at −78 °C, butyllithium (0.3 mmol) in hexane (0.19 mL) was added to a hexane–THF (5 + 6 mL) solution of **2** (n = 4) prepared from 1,8-bis(*tert*-butyldiphenylsilyl)-1,3,5,7-octatetrayne (350 mg, 0.61 mmol).[5] After stirring for 0.5 h at this temperature, 2,4-hexadienal (**3**) (31 mg, 0.32 mmol) in THF (3 mL) was added. The mixture was stirred for 0.5 h at the same temperature, and the reaction was quenched by adding water. The organic materials were extracted twice with ether, washed with brine, and dried over Na_2SO_4. Solvents were removed *in vacuo*, and flash silica gel chromatography gave **4** (n = 4) (89 mg, 67%) as a 5:1 mixture of 2*E*,4*E*- and 2*Z*,4*E*-isomers: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.18 (9H, s), 1.82 (3H, d, J = 6.4 Hz), 2.7 (1H, br), 5.00 (1H, d, J = 6.2 Hz), 5.05, (d, J = 6 Hz, *EZ*), 5.65 (1H, dd, J = 15.8, 6.4 Hz), 5.75 (dd, J = 15.2, 6.4 Hz, *EZ*), 5.88 (1H, dq, J = 15.0, 6.4 Hz), 6.11 (1H, ddq, J = 15.2, 10.2, 1.2 Hz), 6.40 (1H, dd, J = 15.0, 10.2 Hz), 6.77 (ddt, J = 15.2, 11.2, 1.0 Hz, *EZ*), 7.40–7.48 (6*H*, m), 7.80–7.82 (4H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 18.2, 19.0, 27.0, 61.7, 62.5, 62.9, 63.0, 64.4, 70.7, 77.4, 84.1, 91.2, 126.5, 127.9, 129.8, 129.9, 131.6, 132.8, 133.7, 135.4; IR (neat) 3400, 2210, 2140, 2060, 1650 cm^{-1}; MS (DEI) *m/z* 375 (M − C_4H_9, 51), 327 (M − C_6H_8O, 32), 279 (M − $C_{10}H_{17}O$, 71), 199 (28), 167 (51), 149 (100).

14-(*tert*-Butyldiphenylsilyl)-3,5-tetradecadiene-7,9,11,13-tetrayn-2-ol (5, *n* = 4). To a THF solution (3 mL) of **4** (n = 4) (117 mg, 0.2 mmol) was added a mixture of 40% aqueous HF (7 mL) and THF (7 mL) at 0 °C. Then the mixture was warmed to room temperature and stirred for 1.5 h. After cooling to 0 °C, water was added, and the organic materials were extracted three times with ether. Combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel giving **5** (n = 4) (83 mg, 71%) as a 1:1 mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers: ^{1}H-NMR (600 MHz, $CDCl_3$) δ **1.14** (9H, s), 1.32 (1.5H, d, J = 6.4 Hz), 1.35 (1.5H, d, J = 6 Hz, *EZ*), 1.9 (1H, br), 4.41 (0.5H, quintet, J = 6.1 Hz), 4.47 (0.5H,quintet, J = 6.1 Hz, *EZ*), 5.49 (0.5H, d, J = 10.0 Hz, *EZ*), 5.65 (0.5H, d, J = 15.4 Hz), 5.96 (0.5H, dd, J = 15.2, 5.7 Hz), 6.05 (0.5H, dd, J = 15.3, 6.0 Hz, *EZ*), 6.32 (0.5H, dd, J = 15.3, 10.8 Hz), 6.66 (0.5H, t, J = 11.2 Hz, *EZ*), 6.77 (0.5H, dd, J = 15.2, 11.2 Hz, *EZ*), 6.85 (0.5H, dd, J = 15.6, 11.0 Hz), 7.39–7.46 (6H, m), 7.76–7.79 (4H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 19.0, 23.1 (*EZ*), 23.1, 27.0, 62.1 (*EZ*), 62.4, 62.7 (*EZ*), 62.8, 64.7, 65.0 (*EZ*), 67.9, 68.0, 68.0 (*EZ*), 68.7 (*EZ*), 74.6, 76.8 (two peaks overlapped, *EZ*), 80.3 (*EZ*), 84.7, 84.9 (*EZ*), 91.4 (*EZ*), 91.4 106.5 (*EZ*), 108.5, 126.1 (*EZ*), 127.8, 127.9, 129.9, 131.8, 135.4, 143.1, 143.9 (*EZ*), 146.3 (*EZ*), 147.2; IR (neat) 3400, 2200, 2130, 2060, 1630 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 396 (3.6), 367 (3.8), 343 (3.7), 320 (3.6), 303 (4.3), 287 (4.2), 274 (3.9) nm; MS (DEI) *m/z* 432 (M, 44), 375 (M − C_4H_9, 100); HRMS calcd for $C_{30}H_{28}OSi$ 432.1920, found 432.1891.

3,5-Tetradecadiene-7,9,11,13-tetrayn-2-ol (6, *n* = 4). A mixture of **5** (n = 4) (53 mg, 0.12 mmol), Bu_4NBr (40 mg, 0.12 mmol), 3 M NaOH (aqueous, 12 mL), and THF (20 mL) was stirred at 0 °C. Desilylation was completed within 1 h as monitored by UV spectra of aliquot samples. Then, the reaction was quenched by adding 2 M HCl, and organic materials were extracted twice with ether. The combined organic layers were washed with water and brine, dried over

Table 4. Antimicrobial Activities of Polyyne Compounds

microorganism	MIC (μg/mL)						
	1	(±)-**6** ($n = 4$)	**12**	**8**	**6** ($n = 3$)	(*R*)-**6** ($n = 4$)	(*S*)-**6** ($n = 4$)
Staphylococcus aureus 209P	0.1	0.2	1.5	0.2	0.8	0.2	0.2
S. aureus 56R	0.1	0.2	1.5	0.2	0.8	0.2	0.2
S. aureus 535 (MRSA)	0.1	0.2	0.8	0.2	0.8	0.1	0.2
Bacillus subtillis ATCC 6633	0.1	0.8	6.2	0.4	12.5	0.8	0.8
Enterococcus faecalis 681	0.2	3.1	12.5	3.1	12.5	3.1	6.2
Escherichia coli NIHJ	0.8	0.8	25	>25	25	0.8	1.5
E. coli 609	0.8	0.8	>25	>25	25	1.5	3.1
Salmonella enteritidis	0.8	0.8	25	>25	25	0.8	3.1
Klebsiella pneumoniae 806	0.8	1.5	>25	>25	>50	3.1	>25
K. pneumoniae 846 (R)	1.5	0.8	12.5	>25	12.5	0.8	3.1
Serratia marcescens 1184	0.8	0.8	>25	>25	>50	0.8	1.5
Proteus vulgalis 1420	0.2	0.8	3.1	0.8	12.5	0.8	1.5
Shigella flexneri IID 642	0.4	0.8	6.2	0.8	6.2	0.4	0.8
Enterobacter cloacae 963	6.2	>25	>25	>25	>50	>12.5	>25
Pseudomonas aeruginosa 1001	25	>25	>25	>25	>50	>12.5	>25
P. auruginosa N07	25	>25	>25	>25	>50	>12.5	>25
Candida albicans	0.05	1.5	6.2	3.1	1.5	0.8	1.5
C. albicans SC	ND	ND	ND	3.1	1.5	ND	ND
Cryptococcus neoformans 58063	ND	ND	ND	0.8	1.5	ND	ND
Mucor mucedo 14358	ND	ND	ND	0.2	6.2	ND	ND
Aspergillus fumigatus 10569	ND	ND	ND	1.5	6.2	ND	ND
Microsporum gypseum 11268	ND	ND	ND	0.4	0.8	ND	ND
Tricophyton mentagrophytes	0.05	ND	ND	≤0.1	0.8	0.2	0.4
T. interdigitale	0.02	0.8	1.5	≤0.1	0.8	0.2	0.4
T. rubrum	0.02	0.2	0.8	≤0.1	0.4	0.2	0.2
T. mentagrophytes SC	ND	ND	ND	≤0.02	0.4	ND	ND
T. rubrum SC	ND	ND	ND	≤0.02	0.4	ND	ND

[a] ND, not determined.

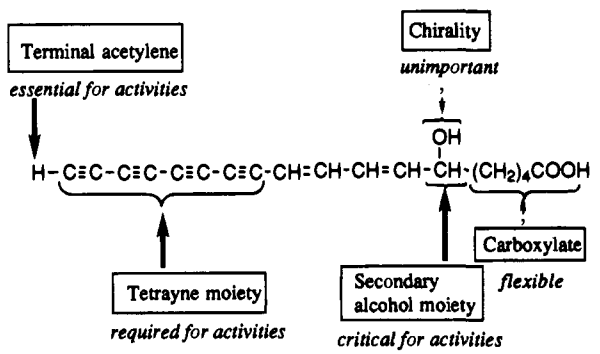

Figure 3. Antimicrobial activities of caryoynencins (**1**).

Na_2SO_4, and concentrated to a small volume. Flash silica gel chromatography gave **6** ($n = 4$) as a 1:1 mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers. Fractions containing **6** ($n = 4$) were combined and concentrated to a small volume. The solvents were exchanged to CCl_4 by repeated addition of CCl_4 and evaporation to a small volume. A sample for NMR measurement was prepared by adding $CDCl_3$ to the solution. The compound **6** ($n = 4$) should not be concentrated to dryness, otherwise **6** ($n = 4$) polymerized giving insoluble material: ^{1}H-NMR (600 MHz, $CDCl_3$–CCl_4) δ 1.31 (1.5 H, d, $J = 6.5$ Hz), 1.33 (1.5H, d, $J = 6.4$ Hz), 2.19 (0.5H, s), 2.22 (0.5H, s), 4.40 (1H, quintet, $J = 6.4$ Hz), 4.46 (0.5H, quintet, $J = 6.2$ Hz), 5.46 (0.5H d, $J = 10.5$ Hz), 5.61 (0.5H, d, $J = 15.6$ Hz), 5.96 (0.5H, ddt, $J = 15.2$, 5.7, 0.7 Hz), 6.03 (0.5H, ddt, $J = 15.7$, 6.1, 0.7 Hz), 6.30 (0.5H, dddd, $J = 15.2$ 11.0, 1.4, 0.7 Hz), 6.63 (0.5H, t, $J = 10.8$ Hz), 6.72 (0.5H, ddt, $J = 15.2$, 11.2, 1.0 Hz), 6.82 (0.5H, dd, $J = 15.5$, 10.9 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$–CCl_4) δ 23.2, 23.3, 61.1, 61.1, 61.2, 61.3, 64.3, 64.7, 68.0, 68.0, 68.0, 68.2, 68.5, 68.6, 68.7, 68.7, 74.0, 76.2, 76.9, 80.4, 106.7, 108.7, 126.3, 127.9, 143.1, 143.9, 146.3, 147.1; UV (MeOH) λ_{max} (rel intensity) 384 (0.25), 357 (0.34), 334 (0.28), 313 (0.22), 294 (1.0), 280 (0.69), 255 (0.27) nm; MS (APCI, MeOH) *m/z* 209 (M + CH_4, 65), 193 (M − H, 40), 177 (M − OH, 100).

The crude product in ethyl acetate was treated with excess diazomethane in ether at 0 °C for 2 h. Evaporation of the solvents and flash chromatography gave diazomethane adduct **7** (X = OH) in 56% yield from **5** ($n = 4$) as a 2:1 mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers: ^{1}H-NMR (600 MHz, acetone-d_6) δ 1.37 (2H, d, $J = 6.5$ Hz), 1.39 (1H, d, $J = 6.5$ Hz), 4.23 (0.6H, d, $J = 3.6$ Hz), 4.30 (0.3H, d, $J = 4.3$ Hz), 4.48–4.54 (0.6H, m), 4.54–4.60 (0.3H, m), 5.74 (0.3H, d, $J = 9.7$ Hz), 5.96 (0.6H, dd, $J = 15.6$, 0.5 Hz), 6.25 (0.6H, dd, $J = 15.2$, 5.3 Hz), 6.33 (0.6H, dd, $J = 13.8$, 5.1 Hz), 6.56 (0.6H, dd, $J = 14.6$, 10.9 Hz), 6.79 (1H, brs), 6.91–6.97 (0.6H, m), 7.10 (0.6H, dd, $J = 15.5$, 11.0 Hz), 7.95 (1H, brs), 12.84 (1H, br); ^{13}C-NMR (150 MHz, acetone-d_6) δ 24.0, 67.8, 68.0, 76.5, 80.1, 106.4, 108.5, 112.1, 126.0, 128.1, 130.5 (br), 146.5, 147.4, 147.9, 149.0 (all acetylenic carbons were not detected); IR (neat) 3148, 2200, 2164, 1634 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 370 (4.3), 354 (sh, 4.2), 344 (4.4), 332 (4.3), 322 (4.3), 311 (4.3), 292 (4.8), 276 (4.8) nm; MS (DEI) *m/z* 236 (M, 90), 221 (M − CH_3, 47), 193 (M − CH_3N_2, 100); HRMS calcd for $C_{15}H_{12}ON_2$ 236.0950, found 236.0942.

A part of the solution of **6** was taken, and the concentration of **6** was estimated by ^{1}H-NMR with benzene as the internal standard. A solution for a biological test was prepared by adding DMSO and removing the volatile materials *in vacuo*.

12-(*tert*-Butyldiphenylsilyl)-2,4-dodecadiene-7,9,11-triyn-6-ol (4, $n = 3$): obtained as a 5:1 mixture of 2*E*,4*E*- and 2*Z*,4*E*-isomers: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.14 (9H, s), 1.81 (3H, d, $J = 6.4$ Hz), 2.3 (1H, br), 4.98 (1H, d, $J = 6.0$ Hz), 5.04 (d, $J = 6.2$ Hz, *EZ*), 5.64 (1H, dd, $J = 6.2$, 16.0 Hz), 5.74 (dd, $J = 15.1$, 6.2 Hz, *EZ*), 5.86 (1H, dq, $J = 16.0$, 6.5 Hz), 6.09 (1H, dd, $J = 16.0$, 10.0 Hz), 6.39 (1H, dd, $J = 16.0$, 10.0 Hz), 6.75 (dd, $J = 15.1$, 11.7 Hz, *EZ*), 7.3–7.5 (6H, m), 7.7–7.9 (4H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 18.2, 18.9, 27.0, 61.4, 63.1, 64.4, 70.7, 77.4, 83.7, 91.3, 126.8, 127.9, 129.8, 129.9, 131.9, 132.8, 133.6, 135.5; IR (neat) 3410, 2166, 2082, 1657 cm^{-1}; MS (DEI) *m/z* 408 (M, 1), 351 (M − C_4H_9, 100); HRMS calcd for $C_{28}H_{28}OSi$ 408.1910, found 408.1906.

12-(*tert*-Butyldiphenylsilyl)-3,5-dodecadiene-7,9,11-triyn-2-ol (5, $n = 3$): obtained as a 2:1 mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.12 (6H, s), 1.13 (3H, s), 1.31 (2H, d, $J = 6.4$ Hz), 1.34 (1H, d, $J = 6.4$ Hz, *EZ*), 1.7 (1H, br), 4.40 (0.6H, quintet, $J = 6.0$ Hz), 4.46 (0.4H, quintet, $J = 6.2$ Hz), 5.49 (0.4H, d, $J = 10.4$ Hz, *EZ*), 5.64 (0.6H, d, $J = 15.6$ Hz), 5.96 (0.6H, dd, $J = 15.2$, 5.6 Hz), 6.03 (0.4H, dd, $J = 15.2$, 6.2 Hz *EZ*), 6.31 (0.6H, dd, $J = 15.2$, 11.2 Hz), 6.61 (0.4H, t, $J = 11.0$ Hz, *EZ*), 6.77 (0.6H, dd, $J = 15.0$, 9.5 Hz, *EZ*), 6.81 (0.6H, dd, $J = 15.6$, 10.8 Hz), 7.38–7.42 (6H, m), 7.77–7.79 (4H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 18.9, 23.1 (*EZ*), 23.1, 27.0, 62.0 (*EZ*), 62.2, 67.9, 67.9, 68.0 (*EZ*), 68.6 (*EZ*),

74.7, 76.7 (*EZ*), 76.9 (*EZ*), 80.2, 85.1, 85.5 (*EZ*), 91.6 (*EZ*), 91.7, 106.9 (*EZ*), 108.9, 126.1 (*EZ*), 127.8, 127.8, 129.7, 132.0, 135.5, 142.6, 143.4 (*EZ*), 145.6 (*EZ*), 146.5; IR (neat) 3422, 2164, 2072, 1636 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 360 (3.8), 336 (3.9), 315 (3.7), 297 (3.6), 279 (4.3), 267 (4.1) nm; MS (DEI) *m/z* 408 (M, 24), 351 (M − C_4H_9, 100); HRMS calcd for $C_{28}H_{28}OSi$ 408.1910, found 408.1905.

3,5-Dodecadiene-7,9,11-triyn-2-ol (6, *n* = 3): obtained as a 1:1 mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers: ^{1}H-NMR (600 MHz, $CDCl_3$–CCl_4) δ 1.30 (1.5H, d, J = 6.0 Hz), 1.33 (1.5H, d, J = 6.0 Hz, *EZ*), 2.29 (0.5H, s), 2.32 (0.5H, s, *EZ*), 4.40 (0.5H, quintet, J = 6.0 Hz), 4.47 (0.5H, quintet, J = 6.0 Hz, *EZ*), 5.46 (0.5H, d, J = 9.6 Hz, *EZ*), 5.61 (0.5H, d, J = 15.6 Hz), 5.95 (0.5H, dd, J = 15.0, 5.8 Hz), 6.03 (0.5H, dd, J = 15.0, 6.0 Hz, *EZ*), 6.30 (0.5H, dd, J = 15.2, 11.2 Hz), 6.61 (0.5H, t, J = 11.0 Hz, *EZ*), 6.73 (0.5H, dd, J = 15.2, 10.8 Hz, *EZ*), 6.80 (0.5H, dd, J = 15.2, 10.8 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$–CCl_4) δ 23.2 (*EZ*), 23.3, 60.4, 60.6, 67.4, 68.0, 68.2, 68.2 (*EZ*), 68.7, 68.8, 69.4, 69.8 (*EZ*), 73.4, 75.6, 76.9, 80.3, 107.0 (*EZ*), 109.0, 126.3 (*EZ*), 127.7, 142.6, 143.5 (*EZ*), 145.5 (*EZ*), 146.4; UV (MeOH) λ_{max} (rel intensity) 346 (0.37), 324 (0.42), 305 (0.32), 289 (0.21), 283 (0.21), 268 (1.00), 257 (0.65) nm; MS (APCI, MeOH) *m/z* 185 (M + CH_4, 67), 169 (M − H, 22), 153 (M − OH, 100).

10-(*tert*-Butyldiphenylsilyl)-2,4-dodecadiene-7,9-diyn-6-ol (4, *n* = 2): obtained as a 5:1 mixture of 2*E*,4*E*- and 2*Z*,4*E*-isomers: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.14 (9H, s), 1.80 (3H, d, J = 5.8 Hz), 2.4 (1H, br), 5.02 (1H, d, J = 6.8 Hz), 5.08 (d, J = 6.4 Hz, *EZ*), 5.79 (dd, J = 15.1, 6.4 Hz, *EZ*), 5.68 (1H, dd, J = 14.6, 6.4 Hz), 5.86 (1H, dq, J = 14.8, 6.4 Hz), 6.10 (1H, dd, J = 15.0, 10.8 Hz), 6.41 (1H, dd, J = 15.2, 10.2 Hz), 6.77 (ddt, J = 15.1, 11.1, 1.0 Hz, *EZ*), 7.4–7.5 (6H, m), 7.7–7.8 (4H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 18.2, 18.8, 27.0, 63.0, 71.0, 76.9, 83.6, 90.8, 127.1, 128.0, 130.0, 130.0, 132.2, 132.5, 133.3, 135.5; IR (neat) 3344, 2222, 2108, 1661 cm^{-1}; MS (EI) *m/z* 384 (M, 1), 328 (M − C_4H_8, 33), 327 (M − C_4H_9, 100); HRMS calcd for $C_{26}H_{28}OSi$ 384.1910, found 384.1909.

10-(*tert*-Butyldiphenylsilyl)-3,5-dodecadiene-7,9-diyn-2-ol (5, *n* = 2): obtained as a 4:1 mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.21 (7.4H, s), 1.22 (1.6H, s, *EZ*), 1.33 (2.4H, d, J = 6.6 Hz), 1.31 (0.6H, d, J = 5.8 Hz, *EZ*), 2.16 (1H, br), 4.40 (0.8H, quintet, J = 6.0 Hz), 4.44 (0.2H, quintet, J = 6.6 Hz, *EZ*), 5.54 (0.2H, d, J = 10.6 Hz, *EZ*), 5.73 (0.8H, d, J = 15.4 Hz), 5.96 (0.8H, dd, J = 15.2, 5.8 Hz), 6.04 (0.2H, dd, J = 16.0, 6.0 Hz, *EZ*), 6.33 (0.8H, dd, J = 15.2, 11.4 Hz), 6.62 (0.8H, t, J = 11.0 Hz, *EZ*), 6.84 (0.8H, dd, J = 15.6, 10.8 Hz), 6.86 (0.2H, dd, J = 15.2, 11.2 Hz, *EZ*), 7.38–7.46 (6H, m), 7.80–7.82 (4H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 18.7, 23.0, 26.9, 67.7, 67.9 (*EZ*), 74.5 (*EZ*), 76.7, 77.0, 80.4 (*EZ*), 86.8, 87.5 (*EZ*), 91.5 (*EZ*), 91.7, 107.1 (*EZ*), 109.1, 126.0 (*EZ*), 127.6, 127.7, 129.6, 132.3, 135.4, 142.0, 142.9 (*EZ*), 144.1 (*EZ*), 145.3; IR (neat) 3364, 2192, 2106, 1638 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 321 (3.7), 303 (3.7), 247 (3.9), 235 (3.8) nm; MS (EI) *m/z* 384 (M, 7), 327 (M − C_4H_9, 100); HRMS calcd for $C_{26}H_{28}OSi$ 384.1910, found 384.1911.

3,5-Dodecadiene-7,9-diyn-2-ol (6, *n* = 2): obtained as a 5:1 mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers: ^{1}H-NMR (600 MHz, $CDCl_3$–CCl_4) δ 1.29 (2.5H, d, J = 6.4 Hz), 1.31 (0.5H, d, J = 6.4 Hz, *EZ*), 1.7 (1H, br), 2.48 (0.8H, d, J = 1.0 Hz), 2.55 (0.2H, d, J = 1.0 Hz, *EZ*), 4.37 (0.8H, quintet, J = 6.6 Hz), 4.43 (0.2H, quintet, J = 6.0 Hz, *EZ*), 5.43 (0.2H, d, J = 10.4 Hz, *EZ*), 5.58 (0.8H, d, J = 15.6 Hz), 5.90 (0.8H, dd, J = 15.2, 6.0 Hz), 5.97 (0.2H, dd, J = 15.0, 6.0 Hz, *EZ*), 6.26 (0.8H, dd, J = 15.2, 11.0 Hz), 6.53 (0.2H, t, J = 10.6 Hz, *EZ*), 6.72 (0.2H, dd, J = ~15, 11 Hz), 6.73 (0.8H, dd, J = 15.4, 10.8 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$–CCl_4) δ 23.1 (*EZ*), 23.2, 68.0, 68.2, 68.2 (*EZ*), 68.4 (*EZ*), 72.1, 72.6 (*EZ*), 72.9 (*EZ*), 74.8, 76.1, 79.7 (*EZ*), 107.3 (*EZ*), 109.3, 126.2 (*EZ*), 127.9, 141.8, 142.7 (*EZ*), 144.1 (*EZ*), 145.2; UV (MeOH) λ_{max} (rel intensity) 286 (0.95), 233 (1.0), 223 (0.80 nm; MS (EI) *m/z* 146 (M, 100), 117 (M − CHO, 18), 103 (M − C_2H_3O, 67); HRMS calcd for $C_{10}H_{10}O$ 146.0732, found 146.0740.

2,4-Tetradecadiene-7,9,11,13-tetrayn-6-ol (8). Under an argon atmosphere, to a mixture of **4** (*n* = 4) (86 mg, 0.20 mmol), THF (30 mL), and acetic acid (0.41 mL) was added a 1.0 M THF solution (6.0 mL) of Bu_4NF at −78 °C. After the mixture was stirred for 0.5 h at that temperature, the reaction was quenched by adding water. Organic materials were extracted twice with ether, washed with brine, dried over Na_2SO_4, and concentrated to a small volume. Solutions of **8**, which was more unstable than **6** (*n* = 4), was obtained by flash chromatography on silica gel: ^{1}H-NMR (600 MHz, C_6D_6) δ 1.50 (1H, s), 1.65 (3H, d, J = 6.8 Hz), 4.52 (1H, d, J = 4.8 Hz), 5.33 (1H, dd, J = 15.2, 6.0 Hz), 5.60 (1H, dq, J = 14.7, 6.8 Hz), 5.89 (1H, dddq, J = 15.1, 10.5, 1.0, 0.6 Hz), 6.14 (1H, dd, J = 15.2, 10.6 Hz).

Diazomethane adduct was obtained in 32% yield from **4** (*n* = 4): ^{1}H-NMR (600 MHz, $CDCl_2$) δ 1.79 (3H, d, J = 6.7 Hz), 4.70 (1H, br), 5.00 (1H, d, J = 6.2 Hz), 5.63 (1H, ddq, J = 15.2, 6.3, 0.7 Hz), 5.84 (1H, dq, J = 14.8, 6.7 Hz), 6.06 (1H, dddq, J = 15.1, 10.5, 1.6, 0.5 Hz), 6.37 (1H, dd, J = 15.2, 10.4 Hz), 6.59 (1H, d, J = 2.3 Hz), 7.58 (1H, d, J = 2.3 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 18.2, 63.2, 63.4, 66.6, 68.5, 70.8, 76.5, 79.1, 111.7, 126.9, 129.9, 132.3, 132.8, 133.6 (one peak of pyrazole was obscured because of broadening); IR (neat) 3196, 2366, 2202, 1659 cm^{-1}; MS (APCI, MeOH) *m/z* 238 (M + 2H, 55), 237 (M + H, 61), 219 (M − OH, 100).

14-(*tert*-Butyldiphenylsilyl)-3,5-tetradecadiene-7,9,11,13-tetrayn-2-ol (*R*)-MTPA Esters (9). Under an argon atmosphere, to a CH_2Cl_2 solution (3.8 mL) of **5** (*n* = 4) (50 mg, 0.20 mmol) was added a mixture of (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ((*R*)-MTPA; 0.11 mL, 0.28 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC; 55.4 mg, 0.29 mmol), and 4-(*N*,*N*-dimethylamino)-pyridine (17 mg, 0.14 mmol) in CH_2Cl_2 (1.0 mL). After stirring for 2 h, water was added, and organic mateials were extracted twice with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography on silica gel gave an isomeric mixture of **9** (41 mg, 55%): IR (neat) 2120, 1750, 698, 505 cm^{-1}. (2*R*,3*E*,5*E*)-, (2*S*,3*E*,5*E*)-, (2*R*,3*E*,5*E*)-, and (2*S*,3*E*,5*Z*)-**9** were separated by silica gel HPLC and stored in the dark.

(2*R*)-9: $[\alpha]^{24}_D$ +63.2 (*c* 0.51, MeOH, an equilibrium mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers).

(2*S*)-9: $[\alpha]^{23}_D$ +41.7 (*c* 0.59, MeOH, an equilibrium mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers); MS (DEI) *m/z* 648 (M, 2), 591 (M − C_4H_9, 4), 517 (17), 279 (64), 189 (100).

(2*R*,3*E*,5*E*)-9: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.10 (9H, s), 1.37 (3H, d, J = 6.6 Hz), 3.52 (3H, q, J = 1.2 Hz), 5.65 (1H, d, J = 15.8 Hz), 5.66 (1H, quintet, J = 6.6 Hz), 5.89 (1H, dd, J = 15.0, 6.8 Hz), 6.32 (1H, dd, J = 15.0, 10.8 Hz), 6.79 (1H, dd, J = 15.6, 11.0 Hz), 7.4–7.6 (11H, m), 7.7–7.8 (4H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 19.0, 19.7, 27.0, 55.4, 62.1, 62.6, 64.9, 68.4, 72.6, 76.2, 77.6, 84.5 (q, J = 28 Hz), 84.9, 91.4, 110.6, 123.2 (q, J = 287 Hz), 127.3, 127.9, 128.5, 129.6, 129.9, 131.1, 131.8, 132.2, 135.5, 136.0, 146.0, 165.7.

(2*S*,3*E*,5*E*)-9: ^{1}H-NMR (200 MHz, $CDCl_3$ δ 1.10 (9H, s), 1.43 (3H, d, J = 6.7 Hz), 3.57 (3H, s), 5.56 (1H, d, J = 15.6 Hz), 5.65 (1H, quintet, J = 6.6 Hz), 5.80 (1H, dd, J = 15.0, 6.2 Hz), 6.15 (1H, dd, J = 15.0, 10.8 Hz), 6.73 (1H, dd, J = 15.2, 10.8 Hz), 7.3–7.6 (11H, m), 7.7–7.8 (4H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 19.0, 20.0, 27.0, 55.5, 62.1, 62.7, 64.9, 68.3, 72.3, 76.2, 77.5, 84.4 (q, J = 28 Hz), 84.9, 91.4, 110.3, 123.2 (q, J = 187 Hz), 127.2, 127.9, 128.4, 129.6, 129.9, 130.6, 131.8, 132.3, 135.5, 136.0, 146.1, 165.6.

(2*R*,3*E*,5*Z*)-9: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.11 (9H, s), 1.40 (3H, d, J = 6.5 Hz), 3.57 (3H, s), 5.54 (1H, d, J = 10.7 Hz), 5.71 (1H, quintet, J = 6.4 Hz), 5.99 (1*H*, dd, J = 15.3, 6.4 Hz), 6.61 (1H, t, J = 10.8 Hz), 6.81 (ddt, J = 15.3, 11.2, 1.0 Hz), 7.38–7.43 (9H, m), 7.50–7.52 (2H, m), 7.73 (4H, dd, J = 8.0, 1.4 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 19.0, 19.8, 27.0, 55.5, 61.8, 62.6, 65.2, 69.1, 72.7, 73.9, 80.9, 84.6 (q, J = 27 Hz), 85.1, 91.3, 108.4, 123.2 (q, J = 287 Hz), 127.3, 127.9, 128.4, 128.8, 129.6, 129.9, 131.8, 132.2, 135.5, 137.0, 145.2, 165.7.

(2*S*,3*E*,5*Z*)-9: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.11 (9H, s), 1.48 (3H, d, J = 6.6 Hz), 3.58 (3H, s), 5.52 (1H, d, J = 10.7 Hz), 5.71 (1H, quintet, J = 6.4 Hz), 5.92 (1H, dd, J = 15.3, 6.2 Hz), 6.58 (1H, t, J = 10.7 Hz), 6.73 (1H, dd, J = 15.2, 11.2 Hz), 7.37–7.45 (9H, m), 7.50–7.53 (2H, m), 7.73–7.76 (4H, m); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 19.0, 20.1, 27.0, 55.5, 61.9, 62.6, 65.1, 69.0, 72.6, 73.9, 80.8, 84.5 (q, J = 28 Hz), 85.0, 91.4,

108.2, 123.2 (q, J = 187 Hz), 127.2, 127.9, 128.4, 128.6, 129.7, 130.6, 131.8, 132.1, 135.5, 137.0, 145.2, 165.7.

2-Acetoxy-3,5-tetradecadiene-7,9,11,13-tetrayne (11). Under an argon atmosphere, a mixture of **5** (n = 4) (187 mg, 0.43 mmol), acetic anhydride (2 mL), and pyridine (4 mL) was stirred at room temperature for 1.5 h. The reaction was quenched by added water, and organic materials were extracted twice with ether. Combined extracts were washed with saturated aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine. After drying over Na_2SO_4, the solution was concentrated, and racemic **10** (174 mg, 85%) was obtained by flash chromatography as a 1:1 mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.10 (9H, s), 1.32 (1.5H, d, J = 6.8 Hz), 1.36 (1.5H, d, J = 6.8 Hz), 2.05 (0.5H, s), 2.08 (0.5H, s), 5.40 (0.5H, quintet, J = 6.6 Hz), 5.46 (0.5H, quintet, J = 6.5 Hz), 5.48 (0.5H, d, J = 10.0 Hz), 5.64 (0.5H, d, J = 15.4 Hz), 5.86 (0.5H, dd, J = 15.4, 6.4 Hz), 5.96 (0.5H, dd, J = 14.8, 6.0 Hz), 6.28 (0.5H, dd, J = 15.4, 10.8 Hz), 6.60 (0.5H, t, J = 11.2 Hz), 6.74 (0.5H, dd, J = 14.6, 10.4 Hz), 6.79 (0.5H, dd, J = 15.6, 11.0 Hz), 7.3–7.5 (6H, m), 7.6–7.8 (4H, m); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 18.9, 19.8, 21.1, 26.9, 62.0, 62.3, 62.6, 62.7, 64.7, 65.0, 68.1, 68.8, 69.8, 69.8, 74.3, 76.6, 77.1, 80.5, 84.8, 85.0, 91.3, 107.2, 109.2, 127.5, 127.8, 129.5, 129.8, 131.6, 135.4, 138.1, 139.0, 145.8, 146.7, 169.9; IR (neat) 2186, 2118, 2058, 1742 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 399 (4.5), 370 (4.7), 345 (4.6), 323 (4.5), 307 (5.2), 290 (5.0), 277 (4.8); MS (DEI) m/z 474 (M, 11), 432 (M − C_2H_2O, 31), 417 (M − C_4H_9, 100); HRMS calcd for $C_{32}H_{30}O_2Si$ 474.2016, found 474.2028.

Desilylation was carried out as described in the synthesis of **6** (n = 4). **11** was obtained as a 1:1 mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers: ^{1}H-NMR (600 MHz, $CDCl_3$–CCl_4) δ 1.33 (2H, d, J = 6.5 Hz), 1.37 (1H, d, J = 6.5 Hz), 2.05 (2H, s), 2.08 (1H, s), 2.20 (0.6H, s), 2.21 (0.4H, s), 5.38 (0.6H, quintet, J = 6.4 Hz), 5.44 (0.4H, quintet, J = 6.5 Hz), 5.49 (0.4H, d, J = 10.7 Hz), 5.63 (0.6H, d, J = 15.5 Hz), 5.85 (0.6H, dd, J = 15.3, 6.4 Hz), 5.95 (0.4H, dd, J = 15.2, 6.2 Hz), 6.27 (0.6H, dd, J = 15.3, 11.0 Hz), 6.60 (0.4H, t, J = 10.9 Hz), 6.70 (0.4H, dd, J = 15.3, 11.2 Hz), 6.77 (0.6H, dd, J = 15.5, 11.0 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$–CCl_4) δ 20.1, 20.1, 21.2, 21.2, 61.0, 61.1, 61.2, 61.3, 64.4, 64.8, 68.2, 68.6, 68.7, 68.7, 68.7, 68.9, 69.9, 69.9, 73.7, 76.0, 77.3, 80.7, 107.5, 109.7, 127.8, 129.9, 138.1, 139.0, 145.8, 146.6, 169.8, 169.9; UV (CH_2Cl_2) λ_{max} (rel intensity) 387 (0.22), 359 (0.30), 336 (0.23), 315 (0.17), 297 (1.0), 282 (0.63) nm; MS (APCI, MeOH) m/z 237 (M + H, 8), 209 (M − CH_3-COO + MeO, 58), 177 (M − CH_3COO, 100).

Diazomethane adduct **7** (X = OAc) was obtained as a 1:1 mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers in 69% yield from **10**: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.33 (1.5H, d, J = 6.6 Hz), 1.37 (1.5H, J = 6.5 Hz), 2.06 (1.5H, s), 2.09 (1.5H, s), 5.40 (0.5H, quintet, J = 6.4 Hz), 5.46 (0.5H, quintet, J = 6.4 Hz), 5.52 (0.5H, d, J = 10.7 Hz), 5.67 (0.5H, d, J = 15.6 Hz), 5.85 (0.5H, dd, J = 15.3, 6.3 Hz), 5.95 (0.5H, dd, J = 15.3, 6.2 Hz), 6.28 (0.5H, dd, J = 15.3, 11.0 Hz), 6.57 (0.5H, t, J = 10.8 Hz), 6.58 (0.5H, d, J = 2.3 Hz), 6.59 (0.5H, d, J = 2.3 Hz), 6.73 (0.5H, dd, J = 15.5, 11.1 Hz), 6.76 (0.5H, dd, J = 15.7, 11.1 Hz), 7.61 (0.5H, d, J = 2.3 Hz), 7.61 (0.5H, d, J = 2.3 Hz), 12.08 (1H, br); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 20.0, 21.2, 21.3, 67.0, 67.2, 67.7, 70.0, 70.1, 76.2, 76.4, 76.4, 77.1, 78.4, 80.5, 107.9, 110.0, 111.4, 111.4, 127.8, 129.9, 130.5, 131.9, 137.5, 138.4, 144.7, 145.7, 170.3, 170.3 (all acetylenic carbons were not detected); IR (neat) 3172, 2202, 2168, 1734 cm^{-1}; UV (CH_2Cl_2) λ_{max} (log ϵ) 372 (4.3), 346 (4.4), 334 (4.3), 324 (4.3), 313 (4.3), 294 (4.7), 277 (4.7) nm; MS (DEI) m/z 278 (M, 38), 236 (M − C_2H_2O, 52), 221 (M − C_3H_5O, 39), 218 (M − $C_2H_4O_2$, 100); HRMS calcd for $C_{17}H_{14}O_2N_2$ 278.1055, found 278.1058.

(*S*)- and (*R*)-14-(*tert*-Butyldiphenylsilyl)-3,5-tetradecadiene-7,9,11,13-tetrayn-2-ol ((*S*)- and (*R*)-5). Under an argon atmosphere, a mixture of lipase, Novo SP-435 (84 mg; Novo Nordisk), racemic **5** (n = 4) (134 mg, 0.31 mmol), and vinyl acetate (3 mL) in methyl *tert*-butyl ether (15 mL) was stirred for 3 days at 37 °C. The enzyme was filtered, and solvents were removed *in vacuo*. The residue was chromatographed over silica gel giving (*S*)-**5** (n = 4) (54 mg, 41%, 99% ee), $[\alpha]^{24}_D$ +33.2 (*c* 0.32, MeOH, an equilibrium mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers), and (*R*)-2-acetoxy-14-(*tert*-butyldiphenylsilyl)-3,5-tetradecadiene-7,9,11,13-tetrayne, (*R*)-**10** (70 mg, 47%, 67% ee).

A mixture of (*R*)-**10** (70 mg, 0.15 mmol, 67% ee), lipase AK (67 mg; Amano), NaN_3 (10 mg) in phosphate buffer (7 mL, 0.58 M, pH 7.1), and ethanol (2 mL) was stirred for 4 days at 37 °C. The mixture was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated *in vacuo*. Flash silica gel chromatography gave (*R*)-**5** (n = 4) (26 mg, 19% from racemic **5** (n = 4), 98% ee), $[\alpha]^{24}_D$ −33.4° (*c* 0.46, MeOH, an equilibrium mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers), and recovered (*R*)-**10** (22 mg, 16%, 45% ee). The optical purities were determined by HPLC analysis using CHIRALCEL OD (hexane:2-propanol = 125:1). (*S*)-**5** (n = 4) was converted to (*R*)-MTPA ester by treating with (*S*)-MTPA chloride (Aldrich).[14] The absolute configuration was determined spectroscopically by comparing with the authentic samples.

(*S*)- and (*R*)-3,5-Tetradecadiene-7,9,11,13-tetrayn-2-ol ((*S*)- and (*R*)-6 (*n* = 4)). Desilylation was carried out as described in the synthesis of racemic **6** (n = 4). (*S*)-**6** (n = 4): $[\alpha]^{24}_D$ +65 (*c* 0.25, MeOH, an equilibrium mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers). (*R*)-**6** (n = 4): $[\alpha]^{24}_D$ −68 (*c* 0.29, MeOH, an equilibrium mixture of 3*E*,5*E*- and 3*E*,5*Z*-isomers). Concentrations were determined by evaporating solvents and weighing the resulting polymers.

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Supporting Information Available: Copies of ^{1}H- and/or ^{13}C-NMR spectra of **4** (n = 2–4), **5** (n = 2–4), **6** (n = 2–4), **7** (X = OH, OAc), **8**, diazomethane adduct of **8**, and **9**–**11** (37 pages). Ordering information can be found on any current masthead page.

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