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Dedicated to Professor Ion Grosu
on the occasion of his 65th anniversary

NEW TOCOPHEROL DERIVATIVES FOR FUNCTIONALIZATION OF AMINO OR CARBOXYL GROUPS WITH LIPID ANCHORS

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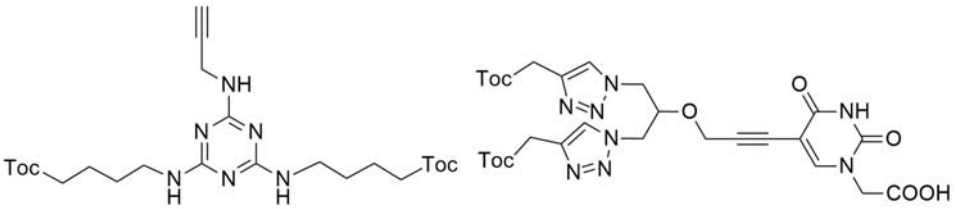
Lipid anchors play an important biological role in natural proteins in particular in lipid membrane anchoring. This principle was extended to non-natural nucleic acids, peptide nucleic acids (PNA) and peptides. In order to provide new lipophilic anchors for the introduction into peptide nucleic acids (PNA) or peptides, a number of new α-tocopherol derivatives were synthesized containing carboxylic acids, amino groups or alkyne groups as linking sites. Amongst them are compounds with one or with two tocopherol units. Sonogashira reaction turned out to be a useful tool in these approaches. The products were characterized by NMR-spectroscopy and MS. An unusual phenomenon was found in 2-propargylamino-4,6-difluorotriazine that exhibits two different chemical shifts in the ^{19}F-NMR spectrum for the two fluoro atoms.



INTRODUCTION

Lipid anchors play an important role in biochemistry, *e.g.* in fixing proteins to lipid membranes. In nature, isoprenoides or fatty acids often serve as lipid anchors. Unnatural anchoring of nucleic acid (DNA or RNA) sequences was achieved by the introduction of lipid anchors like fatty acids, long chain alkyl groups or isoprenoides, α-tocopherol or cholesterol.[1–3] Such chimers have found many interesting applications not only in the lipid membrane field. The strategy of introduction of lipid anchors was also applied to peptide nucleic acids (PNA) **1**.[4–8]

By proper choice of the type of anchor as well as the position of its fixation, domain-specific anchoring in lipid-ordered and lipid-disordered domains of vesicles was achieved.[1, 4, 5] In cases of PNA, lipid anchors were only covalently fixed at the N-terminus of PNAs. We report here the synthesis of new α-tocopherol derivatives that can be linked as termini to either ends of peptides or PNAs or in the middle of a PNA as lipophilic nucleobase. These derivatives contain either carboxyl or amino groups.

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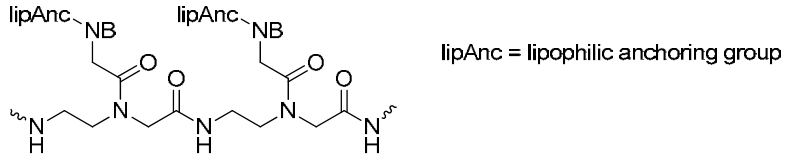

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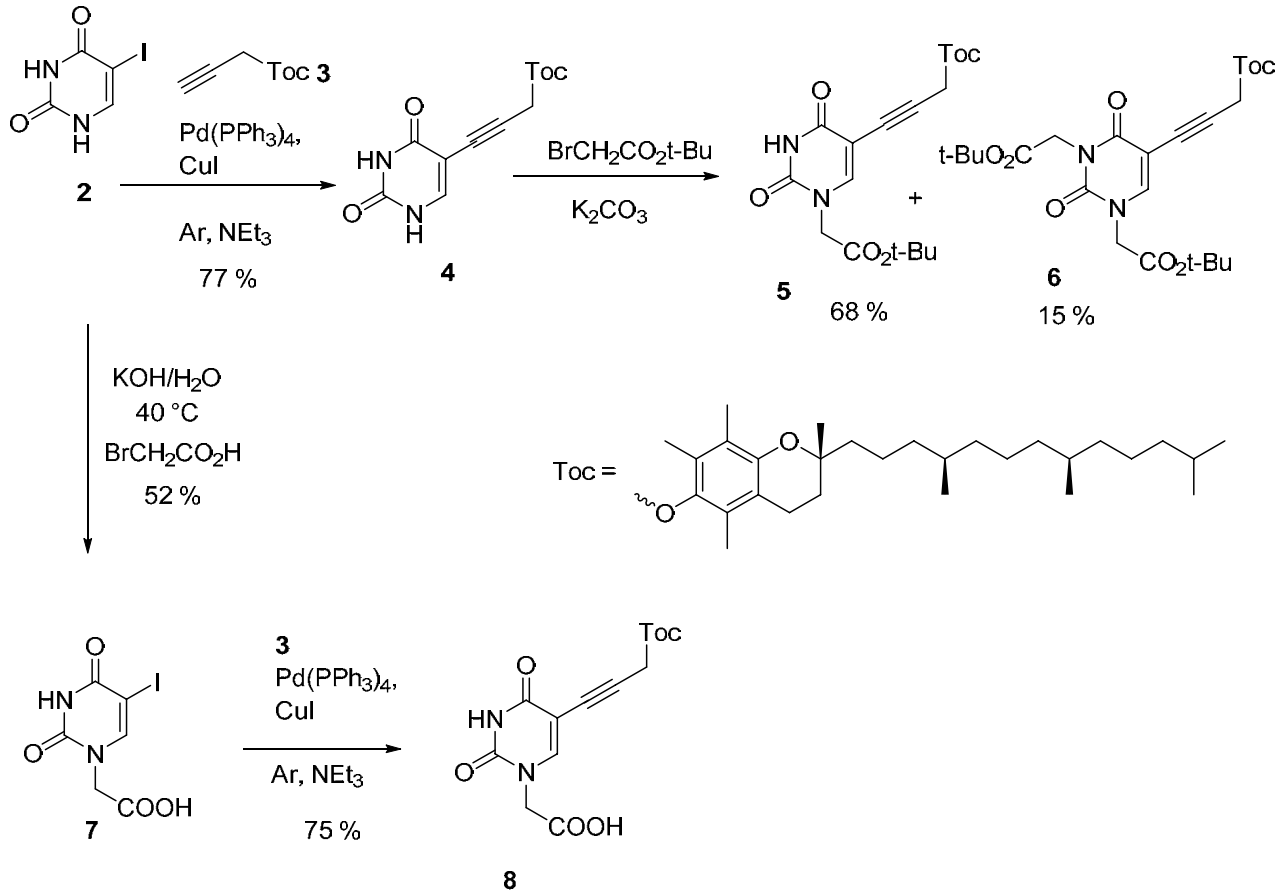
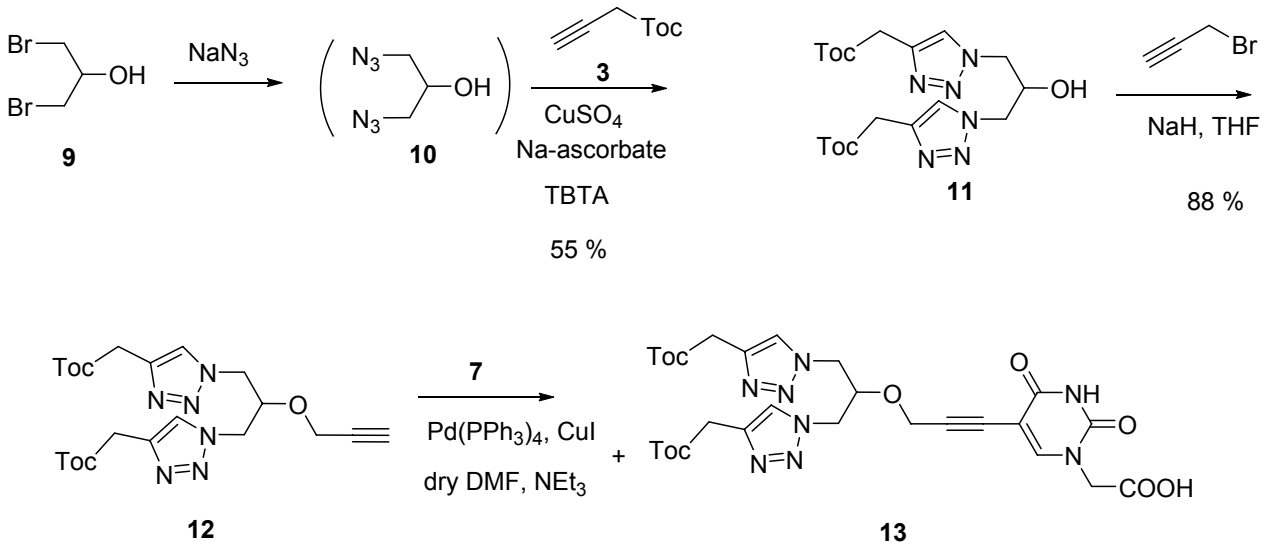
RESULTS AND DISCUSSION

In order to obtain derivatives of α-tocopherol with carboxyl groups, we aimed to compounds containing uracil as a recognition function in nucleic acid chemistry. 5-Iodouracil **2** underwent Sonogashira reaction with *O*-propargyltocopherol **3**[9] resulting in the coupling product **4** in 77 % yield (Scheme 1). Subsequent N-alkylation with *t*-butyl bromoacetate took predominately place in position 1 affording **5**. However, some dialkylation product **6** was observed in addition. Surprisingly, we encountered some decomposition problems in cleaving the *tert*-butyl ester moiety of **5**. Therefore we chose another way towards the synthesis of the corresponding acid **8** by reversing the sequence of Sonogashira reaction and N-alkylation. Reaction of 5-iodouracil with bromoacetic acid in the presence of potassium carbonate gave 52% of the (5-iodouracilyl) acetic acid **7**. Prolongation of the reaction time did not increase the yield. The following Sonogashira reaction of **7** with the propargylated α-tocopherol **3** performed satisfactorily (75 % yield) leading to the carboxylic acid **8** directly, *i.e.* without a deprotection step. This carboxylic acid **8** represents a candidate for the introduction of the tocopherol-uracil conjugate as a side chain in PNAs or at the N-terminus of peptides and PNAs by N-acylation.

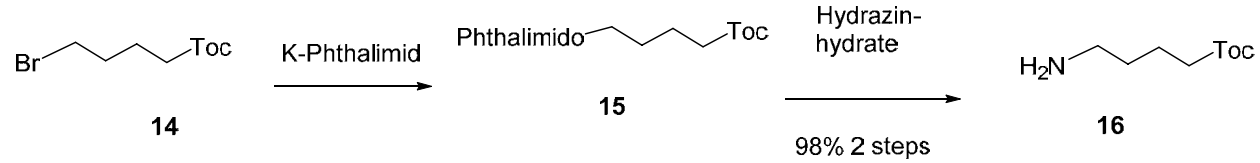


2 **4** **5** **6** **7** **8**

Scheme 1 – Synthesis of propargylated uracil-1-yl acetic acid **8**.



Scheme 2 – Synthesis of uracil-1-yl acetic acid **13** containing two α-tocopherol units.



Scheme 3 – Synthesis of *O*-(4-aminobutyl)-tocopherol **16**.

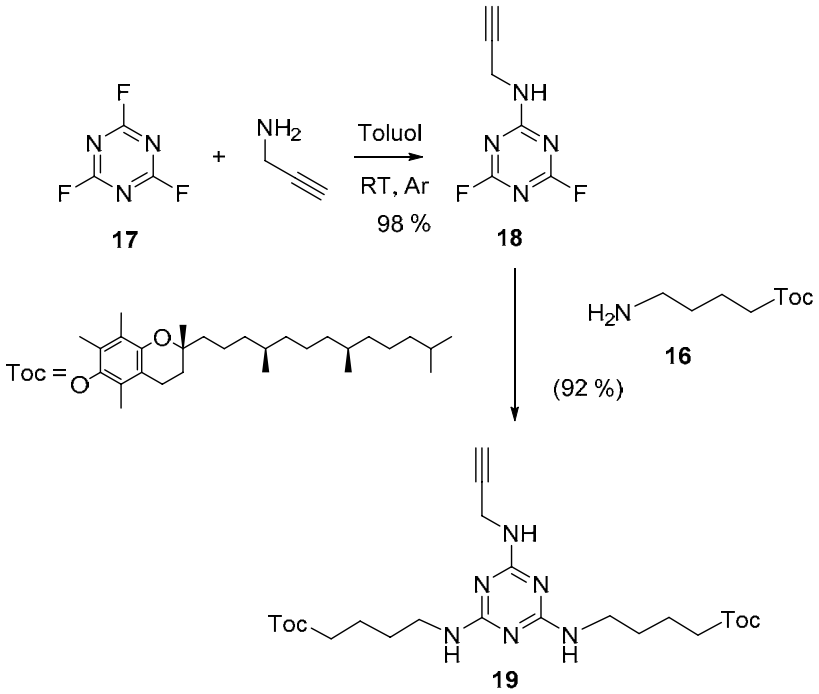
It can be surmised that a system containing two α-tocopherol units could eventually provide stronger anchoring properties in lipid membranes. Consequently, we tried to synthesize such an assembly. Again we chose a conjugate with uracil as target making use of the experiences with the synthesis of tocopherol-uracil-carboxylic acid **8**. Now, the two tocopherol units were linked to an isopropyl alcohol unit (Scheme 2). 2-Hydroxy-1,3-dibromopropane **9** was transformed into the diazide **10** by reaction with sodium azide following a modified reported procedure omitting the isolation of potentially explosive diazide.[10] **10** underwent *in situ* CuAAC click reaction with *O*-propargyltocopherol **3** resulting in ditriazole **11**. *O*-Propargylation was performed with propargyl bromide in the presence of sodium hydride giving access to the ether **12** in 88% yield. The Sonogashira reaction of the propargyl ether **12** with the iodouracilylacetic acid **7** to the target product **13** occurred as found by HPLC-MS. However, the isolation of the product in preparative yields turned out to be difficult.

We further envisaged synthesizing tocopherol anchors containing other tethers than carboxyl. A primary amino group was introduced into α-tocopherol in a straight forward 3-step synthesis. Alkylation of tocopherol with 1,4-dibromobutane resulted in the bromobutyl ether **14** that further underwent Gabriel synthesis by first reaction with phthalimide (formation of **15**) and subsequent hydrazinolysis. 98 % Yield of the *O*-(4-aminobutyl)-tocopherol **16** was obtained over the last two steps (Scheme 3). This product **16** is suitable for the introduction of tocopherol anchors at the C-terminus of peptides or PNAs.

On the other hand, **16** can also be used to construct a di-tocopheryl anchor useful as alkyne component in Sonogashira reactions. 2,4,6-Trifluoro-1,3,5-triazine (cyanuric fluoride) **17** is known to react selectively with amines by stepwise substitution of the fluoro atoms. In the first step, one fluoride was replaced by propargyl amine affording **18** (Scheme 4). The remaining two fluoro atoms were substituted by the *O*-(4-aminobutyl)-tocopherol **16** leading to the target molecule **19** in 92 % yield. The product is an interesting candidate that could be used for the introduction of a double lipid anchor into 5-iodouracil by Sonogashira reaction.

As an unexpected phenomenon, two different sets of signals were observed for the two fluoro atoms in the ^{19}F-NMR spectrum of the monosubstituted product **18**, although the molecule is symmetric. X-Ray crystal analysis of **18** confirmed the structure but also showed

intermolecular H-F bridging with a H-F distance of 2.8 Å of one of the fluoro atoms, rendering the two fluoro atoms non-equivalent. It is likely that the situation is similar in solution and thus can explain the non-equivalence of the two fluoro atoms in the ^{19}F-NMR-spectum.



Scheme 4 – Synthesis of 2-propargylamino-1,3,5-triazine **19** containing two tocopherol units in positions 4 and 6.

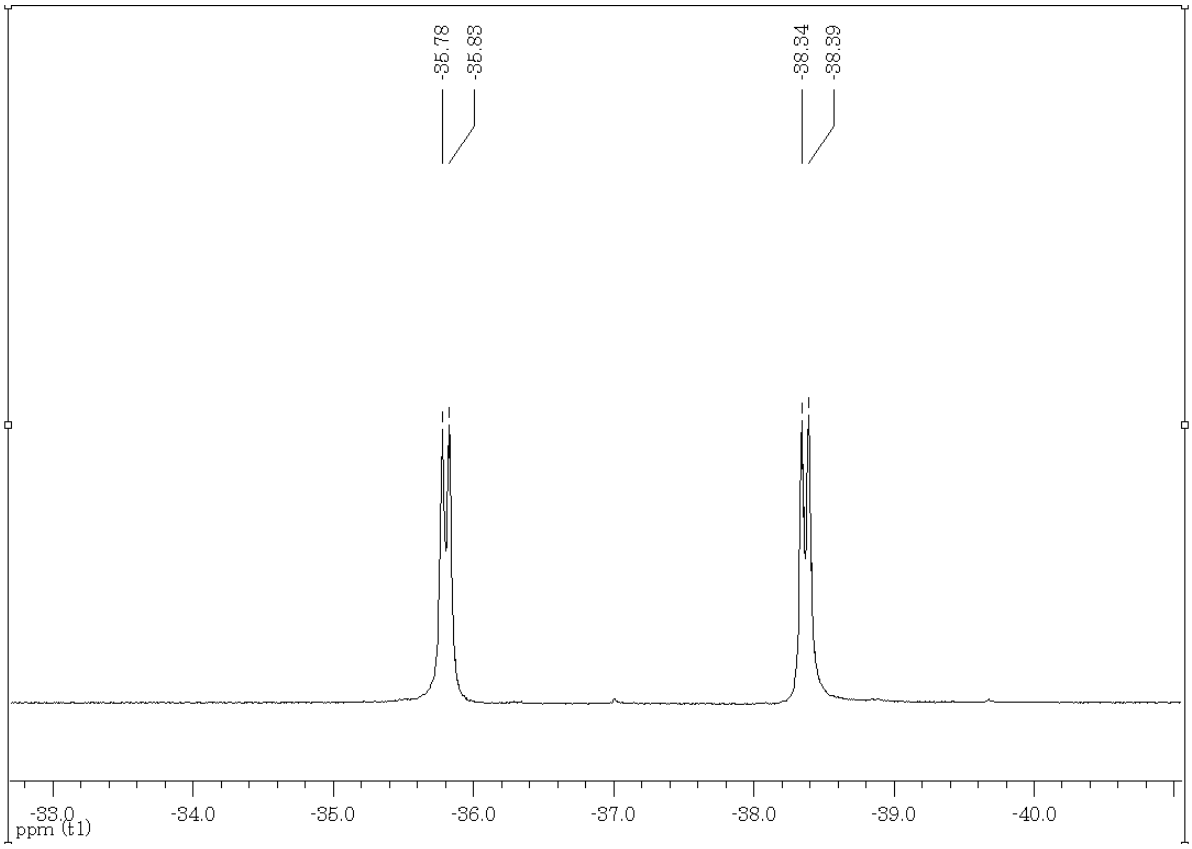


Fig. 1 – ^{19}F-NMR spectrum of 2-propargylamino-4,6-difluorotriazine **18**.

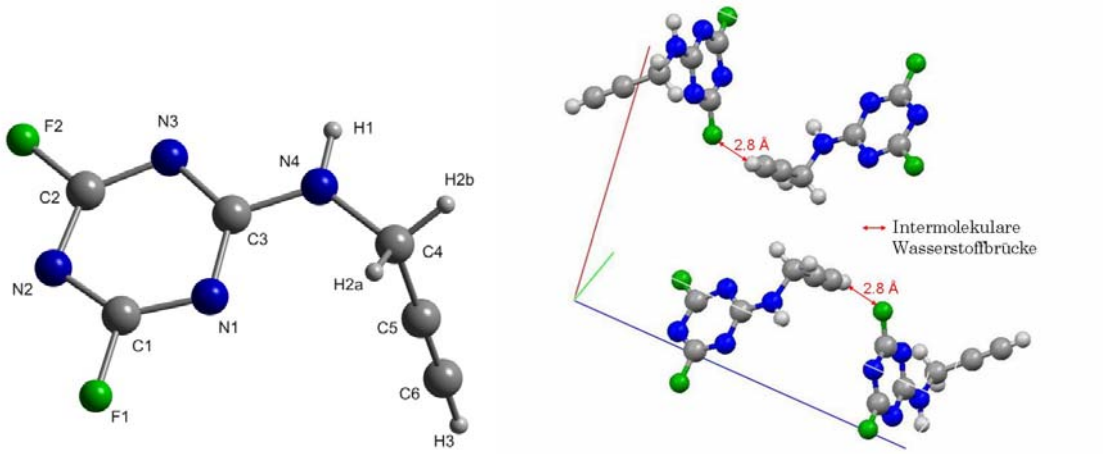


Fig. 2 – X-ray crystal analysis of 2-propargylamine-4,6-difluorotriazine **18**.

EXPERIMENTAL

Instruments

NMR-Spectra were recorded at a AV 300 or AV 400 spectrometer from Bruker. Internal standard: tetramethylsilane. EI-HRMS spectra were obtained by a spectrometer MAT 711 from Varian and ESI-HRMS spectra by a Finnigan LTQ FT-masspectrometer, Thermo Electron. Elemental analysis were determined with an EuroEA 3000 instrument from HEKAtech. X-Ray crystal analysis was performed with IPDS- or STADI-4 diffractometer from STOE & Cie.

Materials

Chemicals were purchased from Acros, Sigma Aldrich, IrisBiotech, NovoBiotech and Merck. The were used without further purification if not otherwise mentioned. *O*-Propargyltocopherol was obtained by a literature procedure.[9]

O-[1-(uracil-5-yl)-prop-1-yne-3-yl]-tocopherol) **(4)** (adapted from ref. [9])

$Pd(PPh_3)_4$ (0.20 g, 0.18 mmol) and CuI (0.11 g, 0.58 mmol) were added to a solution of iodouracil **2** (1.19 g, 5.00 mmol) in dry DMF (10 mL) under argon. A solution of (*O*-propargyl)-tocopherol **3** (9.38 g, 20.00 mmol) and triethyl amine (0.73 mL, 8.70 mmol) were added dropwise. After stirring overnight the solvent was removed under vacuum and the remainder purified by column chromatography (1000 g silica, cyclohexane/ethyl acetate 1 : 1) yielding product **4** (2.23 g, 77 %) as colorless yellowish solid. m. p. 174-176 °C. Anal. calcd for $C_{36}H_{55}N_2O_4$: C 74.70, H 9.40, N 4.84. Found: C 74.09, H 9.58, N 4.65. HRMS (ESI) *m/z* ($M+H^+$) $C_{36}H_{55}N_2O_4$ calcd. 579.4162, found: 579.4185. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.35 (d, *J* = 5.1 Hz, 1H (NH1)), 10.02 (s, 1H (NH3)), 7.61 (d, *J* = 6.0 Hz, 1H (CH6)), 4.54 (s, 2H (C≡C-CH_2-O)), 2.56 (t, *J* = 6.6 Hz, 2H (O-C_q-C$\underline{H_2}$-CH_2-C_q)), 2.20 (s, 3H ($C_{ar.}$-CH_3)), 2.16 (s, 3H ($C_{ar.}$-CH_3)), 2.07 (s, 3H ($C_{ar.}$-CH_3)), 1.71-1.82 (m, 2H (O-C_q-CH_2-C$\underline{H_2}$-C_q)), 1.07-1.59 (m, 24H (3×CH, 9×CH_2, 1×CH_3)), 0.80-0.89 (m, 12H (4×CH-C$\underline{H_3}$)). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 163.2 (O=C4), 151.7 (O=C2), 148.2 (O-$C_{ar.}$), 147.8 (O-$C_{ar.}$), 144.9 (CH6), 127.9 ($C_{ar.}$), 126.0 ($C_{ar.}$), 123.0 ($C_{ar.}$), 117.6 ($C_{ar.}$), 99.3 (C_{ar}5), 90.1 (-C≡C-CH_2), 76.8 (-C≡C-CH_2), 74.9 (O-C_q-$(CH_2)_2CH_3$), 61.2 (≡C-CH_2-O), 40.1 (CH_2), 39.3 (CH_2), 37.4 (CH_2), 37.4 (CH_2), 37.2 (CH_2), 32.7 (CH/CH_3), 32.7 (CH/CH_3), 31.2 ($C_{ar.}$-CH_2-CH_2), 31.1 (CH_2), 27.9 (CH/CH_3), 24.8 (CH_2), 24.4 (CH_2), 23.7 (CH/CH_3), 22.7 (CH/CH_3), 22.6 (CH/CH_3), 21.0 (CH_2), 20.6 (CH_2-CH_2-C_q), 19.7 (CH/CH_3), 19.6 (CH/CH_3), 13.1 ($C_{ar.}$-CH_3), 12.2 ($C_{ar.}$-CH_3), 11.8 ($C_{ar.}$-CH_3).

(Tocopher-6-yloxy)-prop-1-inyl)uracilyl)-substituted tert-butyl acetate **(5) and *dialkylation* product (6)**

The reaction was performed under argon with exclusion of light. *tert*-Butyl bromo acetate (0.30 mL, 2.00 mmol) in dry DMF (1 ml) was added dropwise at 0 °C to a suspension of lipidated 5-(tocopher-6-yloxy)-prop-1-inyl)uracil **4** (1.16 g, 2.00 mmol) and K_2CO_3 (0.30 g, 2.20 mmol) in dry DMF (8 ml). The mixture was allowed to warm up to room temperature (rt) and was stirred overnight. Solids were filtered off and washed with DMF several times. Combined filtrates were concentrated under vacuum and remainders of the solvents were removed by aceotropic distillation with toluene. The crude product was dissolved in ethyl acetate (EtOAc) (10 mL) and washed with water (8 mL) three times and once with brine. The aqueous washing phases were re-extracted with EtOAc (10 mL) three times and the combined organic phases were dried over Na_2SO_4. After removing the solvent under vacuum the remainder was purified by column chromatography (250 g silica, cyclohexane/ethyl acetate 7 : 3) yielding 0.94 g (68 %) of **5** as yellowish solid and 0.31 g (15 %) of the dialkylation product **6** as brownish oil.

5: R_f = 0.29 (cyclohexane/EtOAc 7 : 3). m. p. 102-104 °C. HRMS (ESI) *m/z* ($M+H^+$) $C_{42}H_{65}N_2O_6$ calcd. 693.4843, found 693.4858. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.58 (s, 1H (NH3)), 7.41 (s, 1H (CH6)), 4.55 (s, 2H (C≡C-CH_2-O)), 4.37 (s, 2H (N1-CH_2-CO_2)), 2.57 (t, *J* = 6.7 Hz, 2H (O-C_q-C$\underline{H_2}$-CH_2-C_q)), 2.21 (s, 3H ($C_{ar.}$-CH_3)), 2.17 (s, 3H ($C_{ar.}$-CH_3)), 2.07 (s, 3H ($C_{ar.}$-CH_3)), 1.71-1.85 (m, 2H, (O-C_q-CH_2-C$\underline{H_2}$-C_q)), 1.49 (s, 9H (3×O-C_q-CH_3)), 0.99-1.60 (m, 24H (3×CH, 9×CH_2, 1×CH_3)), 0.80-0.89 (m, 12H (4×CH-C$\underline{H_3}$)). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 165.9 (-C$\underline{O_2}$), 161.5 (O=C4), 149.7 (O=C2), 148.2 (O-$C_{ar.}$), 147.7 (O-$C_{ar.}$), 147.7 (C$\underline{H}$6), 128.0 ($C_{ar.}$), 126.1 ($C_{ar.}$), 122.9 ($C_{ar.}$), 117.6 ($C_{ar.}$), 99.8 ($C_{ar.}$5), 90.1 (-C≡C-CH_2), 83.8 (O-C_q-$(CH_3)_3$), 76.7 (-C≡C-CH_2), 74.9 (O-C_q-$(CH_2)_2CH_3$), 61.1(C≡C-CH_2), 49.6 (N1-CH_2-CO_2), 40.1 (CH_2), 39.3 (CH_2), 37.5 (CH_2), 37.4 (CH_2), 37.2 (CH_2), 32.7 (CH/CH_3), 32.7 (CH/CH_3), 31.2 ($C_{ar.}$-CH_2-CH_2), 31.1 (CH_2), 28.0 (O-C_q-CH_3), 24.8 (CH_2), 24.4 (CH_2), 23.8 (CH/CH_3), 22.7 (CH/CH_3), 22.6 (CH/CH_3), 21.0 (CH_2), 20.6 (CH_2-CH_2-C_q), 19.7 (CH/CH_3), 19.6 (CH/CH_3), 19.6 (CH/CH_3), 13.1 ($C_{ar.}$-CH_3), 12.2 ($C_{ar.}$-CH_3), 11.8 ($C_{ar.}$-CH_3).

Dialkylation product 6

R_f = 0.59 (cyclohexane/EtOAc 7 : 3). Anal. calcd. for $C_{48}H_{74}N_2$: C 71.43, H 9.24, N 3.47, found C 71.59, H 9.38, N 3.25. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.43 (s, 1H (CH6)), 4.60 (s, 2H (N1-CH_2-CO_2))*, 4.54 (s, 2H (C≡C-CH_2-O)), 4.37 (s, 2H (N3-CH_2-CO_2))*, 2.57 (t, *J* = 6.7, 2H (O-C_q-CH_2-CH_2-C_q)), 2.21 (s, 3H ($C_{ar.}$-CH_3)), 2.17 (s, 3H ($C_{ar.}$-CH_3)), 2.07 (s, 3H ($C_{ar.}$-CH_3)), 1.68-1.85 (m, 2H, (O-C_q-CH_2-CH_2-C_q)), 1.01-1.59 (m, 24H (3×CH, 9×CH_2, 1×CH_3)), 1.48 (s, 9H (3×O-C_q-CH_3)), 1.46 (s, 9H (3×O-C_q-CH_3)), 0.81-0.91 (m, 12H (4×CH-CH_3)). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.2 (N3-CH_2-CO_2), 166.0 (N1-CH_2-CO_2), 160.9 (O=C4), 150.2 (O=C2), 148.2 (O-$C_{ar.}$), 147.8 (O-$C_{ar.}$), 146.5 (CH6), 128.0 ($C_{ar.}$), 126.1 ($C_{ar.}$), 122.9 ($C_{ar.}$), 117.5 ($C_{ar.}$), 98.7 ($C_{ar.}$5), 89.5 (-C≡C-CH_2), 83.4 (O-C_q-$(CH_3)_3$), 82.3 (O-C_q-$(CH_3)_3$), 77.4 (-C≡C-CH_2), 74.8 (O-C_q-$(CH_2)_2CH_3$), 61.2 (C≡C-CH_2), 50.8 (N3-CH_2-CO_2), 43.1 (N1-CH_2-CO_2), 40.1 (CH_2), 39.4 (CH_2), 37.5 (CH_2), 37.4 (CH_2), 37.3 (CH_2), 32.8 (CH/CH_3), 32.7 (CH/CH_3), 31.2 ($C_{ar.}$-CH_2-CH_2), 28.0 (O-C_q-CH_3), 27.9 (O-C_q-CH_3), 26.9 (CH_2), 24.8 (CH_2), 24.4 (CH_2), 23.8 (CH/CH_3), 22.8 (CH/CH_3), 22.7 (CH/CH_3), 21.0 (CH_2), 20.6 (CH_2-CH_2-C_q), 19.8 (CH/CH_3), 19.7 (CH/CH_3), 19.6 (CH/CH_3), 13.1 ($C_{ar.}$-CH_3), 12.3 ($C_{ar.}$-CH_3), 11.8 ($C_{ar.}$-CH_3).

***(5-Iodouracil-1-yl) acetic acid* (7)**[11]

KOH (3.62 g, 64.40 mmol) and 5-iodouracil **2** (4.00 g,16.80 mmol) were dissolved in water (40 mL) and heated to 40 °C. A solution of bromo acetic acid ((3.48 g, 25.20 mmol) in water (10 mL) was slowly added under stirring over a period of 30 min. Stirring at 40 °C was continued for 30 min. After cooling to room temperature the pH was adjusted to 5 by addition of conc. hydrochloric acid. After standing in a refrigerator for 2 h the precipitate of unreacted starting material **2** was filtered off. The filtrated was further acidified with conc. HCl to pH 2. After 2 h the colorless product **7** was filtered off, washed with water and dried under vaccum. Yield 2.59 g (52 %), colorless solid. ^{1}H-NMR (300 MHz, DMSO-D_6): δ (ppm) = 11.74 (s, 1H (NH3)), 8.20 (s, 1H (CH6)), 4.40 (s, 2H (N1-CH_2-CO_2)). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 169.8 (N1-CH_2-CO_2), 161.5 (O=C4), 151.1 (O=C2), 150.7 (CH6), 68.5 (C_q-I), 49.0 (N1-CH_2-CO_2).

***2-(5-((Tocopher-6-yloxy)-prop-1-inyl)uracilyl) acetic acid* (8)**[12]

$Pd(PPh_3)_4$ (0.07 g, 0.06 mmol) und CuI (0.04 g, 0.20 mmol) were added to a solution of 5-iodouracil acetic acid **7** (0.50 g, 1.69 mmol) in dry DMF (5 mL) under argon. A solution of (*O*-propargyl)-tocopherol **3** (3.17 g, 6.76 mmol) in dry DMF (6 mL) and triethyl amine (0.63 mL, 4.56 mmol) were added dropwise. After stirring at rt under argon for 2 d the solvent was stripped off under vacuum and the remainder purified by column chromatography (300 g silica, cyclohexane/EtOAc/formic acid 1:1:0.5%) affording 0.80 g (75 %) product **8** as a sand-colored solid. R_f = 0.13 (cyclohexane/EtOAc/formic acid 1:1:0.5%). m. p. 145-148 °C. Anal. calcd. for $C_{36}H_{56}N_2O_4$: C 71.67, H 8.86, N 4.40. Found C 72.25, H 8.95, N 4.20. HRMS (ESI) *m/z* ($M+H^+$) $C_{36}H_{57}N_2O_4$ calcd. 635.4060, found635.4050. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 11.76 (s, 1H (NH3)), 8.12 (s, 1H (CH6)), 4.54 (s, 2H (C≡C-CH_2-O)), 4.44 (s, 2H (N1-CH_2-CO_2)), 2.49-2.52 (m, 2H (O-C_q-CH_2-CH_2-C_q)), 2.11 (s, 3H ($C_{ar.}$-CH_3)), 2.09 (s, 3H ($C_{ar.}$-CH_3)), 1.97 (s, 3H ($C_{ar.}$-CH_3)), 1.63-1.77 (m, 2H (O-C_q-CH_2-CH_2-C_q)), 0.93-1.56 (m, 24H (3×CH, 9×CH_2, 1×CH_3)), 0.80-0.89 (m, 12H (4×CH-CH_3)). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 169.6 (-CO_2), 162.4 (O=C4), 150.4 (O=C2), 150.3 (CH6), 147.9 (O-$C_{ar.}$), 127.7 ($C_{ar.}$), 126.1 ($C_{ar.}$), 122.2 ($C_{ar.}$), 117.7 ($C_{ar.}$), 97.3 ($C_{ar.}$5), 88.9 (-C≡C-CH_2), 78.8 (-C≡C-CH_2), 74.8 (O-C_q-$(CH_2)_2CH_3$), 61.2 (C≡C-CH_2), 49.2 (N1-CH_2-CO_2), 37.3 (CH_2), 37.2 (CH_2), 37.2 (CH_2), 37.1 (CH_2), 32.5 (CH/CH_3), 32.4 (CH/CH_3), 31.2 (CH_2), 31.2 ($C_{ar.}$-CH_2-CH_2), 31.1 (CH_2), 27.8 (CH/CH_3), 24.6 (CH_2), 24.2 (CH_2), 23.8 (CH/CH_3), 22.9 (CH/CH_3), 22.8 (CH/CH_3), 20.8 (CH_2), 20.4 (CH_2-CH_2-C_q), 19.9 (CH/CH_3), 19.9 (CH/CH_3), 13.3 ($C_{ar.}$-CH_3), 12.4 ($C_{ar.}$-CH_3), 12.0 ($C_{ar.}$-CH_3).

***1,3-Bis(4-Tocopherylmethyl-1,2,3-triazol-1-yl)-propan-2-ol* (11)**

NaN_3 (7.48 g, 115.00 mmol) was suspended in a 4 :1 mixture of DMF/water (40 ml) and combined with 1,3-dibromopropan-2-ol (2.50 g, 11.50 mmol). The mixture was heated to 60 °C and stirred for 2 days. The resulting 1,3-diazidopropan-2-ol **10** was not isolated but combined with a suspension of *O*-propargyltocopherol **3** (10.76 g, 23.00 mmol) in a 4: 1 mixture of DMF/water (30 mL) under argon. After the addition of $CuSO_4$-monohydrate (0.18 g, 1.15 mmol), Na-ascorbate (0.91 g, 4.60 mmol) und tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (0.61 g, 1.15 mmol) under argon the mixture was stirred at 60 °C for 6 d. The crude product **11** was dissolved in EtOAc and solid remainders were filtered off. The filtrate was concentrated under vacuum and the remainder was purified by column chromatography (2000 g silica, cyclohexane/EtOAc 7:3) yielding 6.82 g (55 %) of the product **11** as sticky yellow oil. R_f = 0.09 (cyclohexane/EtOAc 7 : 3). HRMS (ESI) *m/z* ($M+H^+$) $C_{67}H_{110}N_6O_5$ calcd. 1079.8616, found 1079.8573. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.84-8.02 (m, 2H (2×N-CH)), 4.33-4.94 (m, 9H (2×HC=CN-CH_2-O, 2×N-CH_2-CH, 1×CH_2-CH- CH_2), 2.46-2.73 (m, 4H (2×O-C_q-CH_2-CH_2-C_q)), 2.00-2.32 (m, 18H (6×$C_{ar.}$-CH_3)), 1.71-1.91 (m, 4H (2×O-C_q-CH_2-CH_2-C_q)), 1.02-1.69 (m, 48H (6×CH, 18×CH_2, 2×CH_3)), 0.79-1.04 (m, 24H (8×CH-CH_3)). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 148.1 (O-$C_{ar.}$), 147.7 (CH_2-CN-CH), 144.3 (O-$C_{ar.}$), 127.7 ($C_{ar.}$), 125.8($C_{ar.}$), 125.0 (CH_2-CN-CH-N), (122.9 ($C_{ar.}$), 117.5 ($C_{ar.}$), 74.7 (O-C_q-$(CH_2)_2CH_3$), 65.9 (CH-OH), 60.3 (NC=CH-CH_2-O), 53.2 (N-CH_2-CH), 40.2 (CH_2), 39.4 (CH_2), 37.6 (CH_2), 37.5 (CH_2), 37.4 (CH_2), 37.4 (CH_2), 37.3 (CH_2), 32.7 (CH/CH_3), 32.7 (CH/CH_3), 31.3 ($C_{ar.}$-CH_2-CH_2), 31.2 (CH_2), 27.9 (CH/CH_3), 24.8 (CH_2), 24.4 (CH_2), 23.7 (CH/CH_3), 22.7 (CH/CH_3), 22.6(CH/CH_3), 21.1 (CH_2), 21.0 (CH/CH_3), 20.9 (CH_2-CH_2-C_q), 20.6 (CH_2), 19.8 (CH/CH_3), 19.7 (CH/CH_3), 19.6 (CH/CH_3), 12.8 ($C_{ar.}$-CH_3), 12.0 ($C_{ar.}$-CH_3), 11.8 ($C_{ar.}$-CH_3).

***2-Propargyl-1,3-bis(4-tocopherylmethyl-1,2,3-triazol-1-yl)-propane* (12)**

NaH (0.11 g, 4.65 mmol) was added to a solution of **11** (4.56 g, 4.23 mmol) in dry THF (150 mL). After stirring at room temperature for 2 h propargyl bromide (0.55 g, 4.65 mmol) was added dropwise and stirring continued overnight. The solvent was removed under vacuum and the remainder dissolved in diethyl ether, washed with water (50 mL) three times and with brine (40 mL) twice. After drying with $MgSO_4$ the solvent was stripped off and the remainder purified by column chromatography (500 g silica, cyclohexane/EtOAc 7 : 3) yielding 4.17 g (88 %) of the product **12** as yellow sticky oil. R_f = 0.25 (cyclohexane / EtOAc 7 : 3). HRMS (ESI) *m/z* ($M+H^+$) $C_{70}H_{112}N_6O_5$ calcd. 1116.8694, found 1116.8663. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.92 (s, 2H (2×N-CH)), 4.87 (s, 4H (2×HC=CN-CH_2-O)), 4.40-4.74 (m, 5H, 2×N-CH_2-CH, 1×CH_2-CH- CH_2)),

4.03-4.20 (m, 2H (HC≡C-CH_2-O)), 2.54-2.68 (m, 4H (2×O-C_q-C$\underline{H_2}$-CH_2-C_q)), 2.51 (s, 1H (H$\underline{C}$≡C-CH_2-O)), 2.24 (s, 6H (2×$C_{ar.}$-CH_3)), 2.20 (s, 6H (2×$C_{ar.}$-CH_3)), 2.13 (s, 6H (2×$C_{ar.}$-CH_3)), 1.71-1.93 (m, 4H (2×O-C_q-CH_2-C$\underline{H_2}$-C_q)), 1.05-1.69 (m, 48H (6×CH, 18×CH_2, 2×CH_3)), 0.81-1.03 (m, 24H (8×CH-C$\underline{H_3}$)). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 148.1 (O-$C_{ar.}$), 147.8 (CH_2-$\underline{C}$N-CH), 144.8 (O-$C_{ar.}$), 127.8 ($C_{ar.}$), 125.8 ($C_{ar.}$), 124.7 (CH_2-CN-$\underline{C}$H-N), 122.9 ($C_{ar.}$), 117.5 ($C_{ar.}$), 78.6 (CH-O-CH_2), 76.1 (HC≡$\underline{C}$-CH_2-O), 76.0 (H$\underline{C}$≡C-CH_2-O), 74.8 (O-$\underline{C_q}$-$(CH_2)_2CH_3$), 66.2 (NC=CH-$\underline{C}H_2$-O), 58.1 (HC≡C-$\underline{C}H_2$-O), 50.6 (N-$\underline{C}H_2$-CH), 40.1 (CH_2), 39.4 (CH_2), 37.6 (CH_2), 37.5 (CH_2), 37.4 (CH_2), 37.3 (CH_2), 37.3 (CH_2), 32.8 (CH/CH_3), 32.7 (CH/CH_3), 31.2 ($C_{ar.}$-$\underline{C}H_2$-CH_2), 31.2 (CH_2) 28.0 (CH/CH_3), 26.9 (CH_2), 24.8 (CH_2), 24.4 (CH_2), 23.8 (CH/CH_3), 22.7 (CH/CH_3), 22.6 (CH/CH_3), 21.0 (CH_2), 20.6 (CH_2-$\underline{C}H_2$-C_q), 19.8 (CH/CH_3), 19.7 (CH/CH_3), 19.6 (CH/CH_3), 12.9 ($C_{ar.}$-$\underline{C}H_3$), 12.1 ($C_{ar.}$-$\underline{C}H_3$), 11.8, ($C_{ar.}$-$\underline{C}H_3$).

Conjugate (13) of *2-propargyl-1,3-bis(4-tocopherylmethyl-1,2,3-triazol-1-yl)-propane* (12) with *5-iodouracil-1-yl) acetic acid* (7)

12 (0.21 g, 0.89 mmol), $Pd(PPh_3)_4$ (0.04 g, 0.03 mmol) and CuI (0.02 g, 0.10 mmol) were dissolved in dry DMF (4 ml) and put under argon. A solution of **7** (4.00 g, 3.58 mmol) in dry DMF (8 ml) was added under argon . After 24 h stirring at room temperature, a solution containing product **13** was formed. R_f = 0.23 (cyclohexane / EtOAc 1 : 1). HRMS (ESI) *m/z* ($M+H^+$) $C_{70}H_{112}N_6O_5$ calcd. 1313.9508, found 1313.9429.

***O-(4- Bromobutyl)-tocopherol* (14)**

The reaction was performed in a flask covered with aluminium foil in order to exclude light. 50 % Aqueous KOH (30 ml) and a small amount of tetrabutylammonium bromide were added to a solution of α-tocopherol (30.00 g, 69.65 mmol) in THF (180 ml) at 0 °C under argon. 1,4-Dibromobutane (24.79 mL, 208.96 mmol) was added dropwise at 0 °C and stirring . The solution was stirred at 0 °C for 30 min and at rt overnight. THF was distilled off under vacuum and the crude product was dissolved in EtOAc. The solution was washed with water (75 mL) and aqueous ammonium chloride. The aqueous phase was twice re-extracted with EtOAc (25 mL) and the combined organic phases were dried over $MgSO_4$.The solvent and unreacted, excess dibromo butane were removed at 65°C under reduced pressure providing product **14** as yellow oil in quantitative yield. R_f = 0.13 (cyclohexane / AcOEt 19 : 1). HRMS (ESI) *m/z* ($M+H^+$) $C_{36}H_{55}N_2O_4$ calcd. 565.3615, found 565. 3618. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.69 (t, *J* = 6.2 Hz, 2H (-CH_2-C$\underline{H_2}$-O)), 3.54 (t, *J* = 6.7 Hz, 2H (Br-C$\underline{H_2}$-CH_2-), 2.59 (t, *J* = 6.7 Hz, 2H (O-C_q-C$\underline{H_2}$-CH_2-C_q)), 2.04-2.23 (m, 11H 1×(Br-CH_2-C$\underline{H_2}$-CH_2), (3×$C_{ar.}$-CH_3)), 1.90-2.04 (m, 2H , (-C$\underline{H_2}$-CH_2-O), 1.71-1.89 (m, 2H (O-C_q-CH_2-C$\underline{H_2}$-C_q)), 1.06-1.65 (m, 24H (3×CH, 9×CH_2, 1×C-CH_3)), 0.83-0.93 (m, 12H (4×CH-C$\underline{H_3}$)). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 148.2 (O-$C_{ar.}$), 147.8 (O-$C_{ar.}$), 128.0 ($C_{ar.}$), 126.1($C_{ar.}$), 123.0 ($C_{ar.}$), 117.6 ($C_{ar.}$), 127.7 ($C_{ar.}$), 125.7 ($C_{ar.}$), 122.9 ($C_{ar.}$), 117.5 ($C_{ar.}$), 74.8 (O-$\underline{C_q}$-$(CH_2)_2CH_3$), 71.8 (CH_2-$\underline{C}H_2$-O-$C_{ar.}$), 40.1 (CH_2), 39.4 (CH_2), 37.6 (CH_2), 37.5 (CH_2), 37.4 (CH_2), 37.3 (CH_2), 33.7 (Br-$\underline{C}H_2$-CH_2), 32.8 (CH/CH_3), 32.7 (CH/CH_3), 31.3 (Br-CH_2-$\underline{C}H_2$), 31.2 (CH_2), 29.8 ($C_{ar.}$-$\underline{C}H_2$-CH_2), 29.0 ($\underline{C}H_2$-CH_2-O-$C_{ar.}$), 28.0 (CH/CH_3), 24.8 (CH_2), 24.4 (CH_2), 23.9 (CH/CH_3), 22.7 (CH/CH_3), 22.6 (CH/CH_3), 21.0 (CH_2), 20.6 (CH_2-$\underline{C}H_2$-C_q), 19.7 (CH/CH_3), 19.6 (CH/CH_3), 12.7 ($C_{ar.}$-$\underline{C}H_3$), 11.9 ($C_{ar.}$-$\underline{C}H_3$), 11.8 ($C_{ar.}$-$\underline{C}H_3$).

O-(4-Phthalimidobutyl)-tocopherol (15)

K-Phthalimide in dry DMF (50 ml) was added to a solution of *O*-(4-brombutyl)-tocopherol **14** in dry DMF (100 mL) under argon. The mixture was heated to 60 C and stirred overnight, cooled to rt and concentrated to 30 mL under vacuum. Water (120 mL) was added and the product extracted twice with dichloromethane (50 mL). The organic layer was washed with 0.1 N NaOH (80 ml) three times and brine. After drying with $MgSO_4$ the solvent was removed under vacuum. Product **15** was obtained in quantitative yield as yellowish oil. HRMS (ESI) *m/z* ($M+H^+$) $C_{41}H_{62}NO_4$ calcd.32.4673, found 632.4665. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.85 (dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H ($CH_{ar.}$)), 7.70 (dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 2H ($CH_{ar.}$)), 3.80 (t, *J* = 6.9 Hz, 2H (N-C$\underline{H_2}$-CH_2-)), 3.66 (t, *J* = 6.1 Hz, 2H(-CH_2-C$\underline{H_2}$-O)), 2.57 (t, *J* = 6.6 Hz, 2H (O-C_q-C$\underline{H_2}$-CH_2-C_q)), 2.16 (s, 3H ($C_{ar.}$-CH_3)), 2.11 (s, 3H ($C_{ar.}$-CH_3)), 2.08 (s, 3H ($C_{ar.}$-CH_3)), 1.89-2.00 (m, 2H (N-CH_2-C$\underline{H_2}$-CH_2)), 1.82-1.89 (m, 2H , (-C$\underline{H_2}$-CH_2-O), 1.70-1.82 (m, 2H (O-C_q-CH_2-C$\underline{H_2}$-C_q), 0.98-1.62 (m, 24H (3×CH, 9×CH_2, 1×C-CH_3)), 0.80-0.90 (m, 12H (4×CH-C$\underline{H_3}$)). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 168.4 (N-$\underline{C}$O-C_q), 148.1 (O-$\underline{C}_{ar.}$), 147.7 (O-$\underline{C}_{ar.}$), 133.9 ($\underline{C}H_{ar.}$), 132.2 ($\underline{C}_{ar.}$), 127.8 ($C_{ar.}$), 125.8 ($C_{ar.}$), 123.2 ($CH_{ar.}$), 122.8 ($C_{ar.}$), 117.5 ($C_{ar.}$), 74.7 (O-$\underline{C_q}$-$(CH_2)_2CH_3$), 72.1 (CH_2-$\underline{C}H_2$-O-$C_{ar.}$), 40.1 (CH_2), 39.4 (CH_2), 38.0 (N-CH_2), 37.5 (CH_2), 37.4 (CH_2), 37.3 (CH_2), 32.8 (CH/CH_3), 32.7 (CH/CH_3), 31.3 ($\underline{C}H_2$-CH_2-O-$C_{ar.}$), 28.0 (CH/CH_3), 27.8 ($C_{ar.}$-$\underline{C}H_2$-CH_2), 25.7 (N-CH_2-$\underline{C}H_2$), 24.8 (CH_2), 24.7 (CH_2), 24.5 (CH_2), 23.9 (CH/CH_3), 22.8 (CH/CH_3), 22.7 (CH/CH_3), 21.1 (CH_2), 20.7 (CH_2-$\underline{C}H_2$-C_q), 19.8 (CH/CH_3), 19.7 (CH/CH_3), 12.8 ($C_{ar.}$-$\underline{C}H_3$), 11.9 ($C_{ar.}$-$\underline{C}H_3$), 11.8 ($C_{ar.}$-$\underline{C}H_3$).

O-(4-Aminobutyl)-tocopherol (16)

A mixture of the phthalimid **15**, 55 % hydrazine monohydrate (4.38 ml, 88.40 mmol) and ethanol (50 mL) was refluxed for 3 h. After cooling to rt the solvent was removed under vacuum and the remainder dissolved in diethyl ether (40 mL). The solution was washed three times with 0.1 N NaOH (15 mL) and with brine. After drying over Na_2SO_4 and removing the solvent 8.74 g (98 %) of the product **16** were obtained. HRMS (ESI) *m/z* ($M+H^+$) $C_{33}H_{60}NO_2$ calcd. 502.4624, found 502.4660. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.35 (s-br, 2H (N$\underline{H_2}$), 3.64 (t, *J* = 5.6 Hz, 2H (-CH_2-C$\underline{H_2}$-O)), 3.13 (s-br, 2H (H_2N-C$\underline{H_2}$-CH_2)), 2.53 (t, *J* = 6.6 Hz, 2H (O-C_q-C$\underline{H_2}$-CH_2-C_q)), 1.96-2.20 (m, 11H (1×H_2N-CH_2-C$\underline{H_2}$-CH_2), (3×$C_{ar.}$-CH_3)), 1.82-1.96 (m, 2H, (-C$\underline{H_2}$-CH_2-O), 1.64-1.83 (m, 2H (O-C_q-CH_2-C$\underline{H_2}$-C_q)), 1.01-1.55 (m, 24H (3×CH, 9×CH_2, 1×C-CH_3)), 0.81-0.89 (m, 12H (4×CH-C$\underline{H_3}$)). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 148.1 (O-$\underline{C}_{ar.}$), 127.6 ($C_{ar.}$), 125.6 ($C_{ar.}$), 122.9 ($C_{ar.}$), 117.5 ($C_{ar.}$), 74.8 (O-$\underline{C_q}$-$(CH_2)_2CH_3$), 71.8 (CH_2-$\underline{C}H_2$-O-$C_{ar.}$), 40.2 (N-CH_2), 40.1 (CH_2), 39.4 (CH_2), 37.5 (CH_2), 37.4 (CH_2), 37.3 (CH_2), 32.8 (CH/CH_3), 32.7 (CH/CH_3), 31.3 ($\underline{C}H_2$-CH_2-O-$C_{ar.}$), 31.2 (CH_2), 28.0 (CH/CH_3), 27.4 ($C_{ar.}$-$\underline{C}H_2$-CH_2), 24.8 (CH_2), 24.8 (CH_2), 24.5 (CH_2), 23.7 (CH/CH_3), 22.7 (CH/CH_3), 22.6 (CH/CH_3), 21.1 (CH_2), 20.6 (CH_2-$\underline{C}H_2$-C_q), 19.8 (CH/CH_3), 19.7 (CH/CH_3), 12.9 ($C_{ar.}$-$\underline{C}H_3$), 12.0 ($C_{ar.}$-$\underline{C}H_3$), 11.8 ($C_{ar.}$-$\underline{C}H_3$).

***4,6-Difluoro-2-(prop-2-yn-1-yl-amino)-1,3,5-triazine* (18)**

Propargylamine (0.64 mL, 10.00 mmol) was added dropwise under argon to a solution of cyanuric fluoride **17** (8.88 mL, 10.00 mmol) in dry DMF. The mixture was stirred overnight and the product isolated by column chromatography

(250 g silica, cyclohexane / EtOAc 7 : 3) yielding 1.66 g (98 %) of **18** as crystalline solid. R_f = 0.43 (cyclohexane / EtOAc 7 : 3). HRMS (ESI) *m/z* ($M+H^+$) $C_6H_4F_2N_4$ calcd. 171.0482, found 171.0519. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.82 (s, 1H (NH)), 4.30 (dd, J_1 = 5.7 Hz, J_2 = 2.6 Hz, 2H (CH_2)), 2.32 (t, J = 2.6, 1H (CH)). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 172.8 (dd, J_1 = 43.1 Hz, J_2 = 20.0 Hz, 1C (C-F)), 169.8 (dd, J_1 = 42.6 Hz, J_2 = 20.0 Hz, 1C (C-F)), 169.4 ($C_{ar.}$), 72.9 (-CH_2-), 31.4 (-CH). ^{19}F-NMR (282 MHz, $CDCl_3$): δ (ppm) = -35.80 (d, J = 13.9 Hz, 1F), -38.37 (d, J = 13.9 Hz, 1F).

***2-Propargylamino-4,6-bis(tocopherylbutylamino)-1,3,5-triazine* (19)**

A solution of **16** (3.00 g, 10.00 mmol) in toluene (10 mL) was added dropwise to a solution of **18** (0.34 g, 5.98 mmol) in toluene (5 mL). After refluxing for 4 h the mixture was stirred for 3 d. After chromatographic separation (300 silica, dichloromethane / methanol 95 : 5) 2.08 g (92 %) of the product **19** were obtained as yellow sticky oil. R_f = 0.69 (DCM / MeOH / formic acid 89.50 : 10 : 0.5%). HRMS (ESI) *m/z* ($M+H^+$) $C_{72}H_{121}N_6O_4$ calcd. 1133.9449, found 1133.9429. ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.23 (s-br, 2H (HC≡C-C$\underline{H_2}$-NH)), 3.70 (s-br, 4H (2×-CH_2-C$\underline{H_2}$-O)), 3.52 (s-br, 4H (2×HN-C$\underline{H_2}$-CH_2)), 2.54-2.67 (m, 4H (2×O-C_q-C$\underline{H_2}$-CH_2-C_q)), 2.08-2.26 (m, 19H (1×$\underline{H}$C≡C-CH_2-NH, 6×$C_{ar.}$-CH_3)), 1.72-2.00 (m, 12H (2×HN-CH_2-C$\underline{H_2}$-CH_2), (2×C$\underline{H_2}$-CH_2-O), (2×O-C_q-CH_2-C$\underline{H_2}$-C_q)), 1.06-1.67 (m, 48H (6×CH, 18×CH_2, 2×CH_3)), 0.86-0.97 (m, 24H (8×CH-C$\underline{H_3}$)). ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.0 (HN-$C_{ar.}$), 165.6 (HN-$C_{ar.}$), 148.3 (O-$C_{ar.}$), 147.7 (O-$C_{ar.}$), 127.8 ($C_{ar.}$), 125.7 ($C_{ar.}$), 122.8 ($C_{ar.}$), 117.4 ($C_{ar.}$), 74.7 (O-$\underline{C_q}$-$(CH_2)_2CH_3$), 72.5($\underline{C}$≡CH), 70.8 (CH_2-$\underline{C}H_2$-O-$C_{ar.}$), 40.6 (CH_2), 40.1 (CH_2), 39.4 (CH_2), 37.6 (CH_2), 37.5 (CH_2), 37.4 (CH_2), 37.3 (CH_2), 32.8 (CH/CH_3), 32.7 (CH/CH_3), 31.3 (CH_2), 31.3 ($C_{ar.}$-$\underline{C}H_2$-CH_2), 30.3 (CH_2), 28.0 (CH/CH_3), 27.8 (CH_2), 26.9 (CH_2), 24.9 (CH_2), 24.5 (CH_2), 23.9 (CH_2), 22.8 (CH/CH_3), 22.7 (CH/CH_3), 21.1 (CH_2), 20.7 (CH_2-$\underline{C}H_2$-C_q), 19.8 (CH/CH_3), 19.7 (CH/CH_3), 19.6 (CH/CH_3), 12.8 ($C_{ar.}$-$\underline{C}H_3$), 12.0 ($C_{ar.}$-$\underline{C}H_3$), 11.9 ($C_{ar.}$-$\underline{C}H_3$).

X-Ray crystal analysis of *2-propargylamino-4,6-difluorotriazine* (18)

Table 1

Crystal data and structure refinement

Empirical formula	$C_6H_4F_2N_4$
Formula weight	170.13
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P 21/c
Unit cell dimensions	a = 10.6922(15) Å alpha = 90 deg.
	b = 4.9262(5) Å beta = 93.263(11) deg.
	c = 13.3325(18) Å gamma = 90 deg.
Volume	701.11(15) $Å^3$
Z, Calculated density	4, 1.612 Mg/m^3
Absorption coefficient	0.144 mm^{-1}
F(000)	344
Crystal size	0.50 x 0.50 x 0.20 mm
Theta range for data collection	3.06 to 27.49 deg.
Limiting indices	-13<=h<=13, -6<=k<=6, 0<=l<=17
Reflections collected / unique	2904 / 1608 [R(int) = 0.0205]
Completeness to theta = 27.49	99.8 %
Absorption correction	None
Max. and min. transmission	0.9717 and 0.9314
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1608 / 0 / 126
Goodness-of-fit on F^2	1.288
Final R indices [I>2sigma(I)]	R1 = 0.0456, wR2 = 0.1236
R indices (all data)	R1 = 0.0531, wR2 = 0.1257
Extinction coefficient	0.022(3)
Largest diff. peak and hole	0.239 and -0.271 $e.A^{-3}$

Table 2

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3).
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor

	x	y	z	U(eq)
C(1)	8018(2)	10461(5)	6714(2)	19(1)
C(2)	9944(2)	9679(5)	6406(2)	18(1)
C(3)	8443(2)	7144(5)	5668(2)	17(1)
C(4)	6787(2)	4526(6)	4769(2)	22(1)
C(5)	6216(2)	6472(6)	4044(2)	21(1)
C(6)	5747(3)	8027(6)	3461(2)	29(1)
F(1)	7182(1)	11934(3)	7173(1)	27(1)
F(2)	11151(1)	10349(3)	6517(1)	22(1)
N(2)	9192(2)	11207(5)	6909(2)	20(1)
N(3)	9695(2)	7667(4)	5794(1)	17(1)
N(1)	7549(2)	8551(5)	6123(2)	19(1)
N(4)	8101(2)	5141(5)	5046(2)	19(1)

Table 3

Bond lengths [Å]

Bond	Length [Å]
C(1)-N(1)	1.309(3)
C(1)-N(2)	1.319(3)
C(1)-F(1)	1.328(3)
C(2)-N(3)	1.301(3)
C(2)-N(2)	1.313(3)
C(2)-F(2)	1.332(3)
C(3)-N(4)	1.327(3)
C(3)-N(1)	1.352(3)
C(3)-N(3)	1.364(3)
C(4)-N(4)	1.464(3)
C(4)-C(5)	1.469(4)
C(4)-H(2a)	0.96(3)
C(4)-H(2b)	0.96(3)
C(5)-C(6)	1.182(4)
C(6)-H(3)	0.88(4)
N(4)-H(1)	0.93(4)

Table 4

Bond angles [deg]

Bond	Angle
N(1)-C(1)-N(2)	130.3(2)
N(1)-C(1)-F(1)	115.2(2)
N(2)-C(1)-F(1)	114.5(2)
N(3)-C(2)-N(2)	130.3(2)
N(3)-C(2)-F(2)	114.9(2)
N(2)-C(2)-F(2)	114.7(2)
N(4)-C(3)-N(1)	119.0(2)
N(4)-C(3)-N(3)	116.8(2)
N(1)-C(3)-N(3)	124.2(2)
N(4)-C(4)-C(5)	112.8(2)
N(4)-C(4)-H(2a)	108.0(18)
C(5)-C(4)-H(2a)	108.5(19)
N(4)-C(4)-H(2b)	107.4(18)
C(5)-C(4)-H(2b)	112.4(18)
H(4A)-C(4)-H(1b)	107(3)
C(6)-C(5)-C(4)	179.5(3)
C(5)-C(6)-H(3)	178(2)
C(2)-N(2)-C(1)	110.0(2)
C(2)-N(3)-C(3)	112.7(2)
C(1)-N(1)-C(3)	112.4(2)
C(3)-N(4)-C(4)	122.5(2)
C(3)-N(4)-H(1)	117(2)
C(4)-N(4)-H(1)	120(2)

Symmetry transformations used to generate equivalent atoms:

Table 5

Anisotropic displacement parameters (A^2 x 10^3). The anisotropic displacement factor exponent takes the form: -2 π^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C(1)	19(1)	21(1)	19(1)	3(1)	3(1)	3(1)
C(2)	16(1)	21(1)	17(1)	6(1)	-2(1)	-2(1)
C(3)	15(1)	19(1)	16(1)	5(1)	0(1)	-1(1)
C(4)	17(1)	23(1)	24(1)	0(1)	-1(1)	-4(1)
C(5)	15(1)	23(1)	26(1)	-4(1)	-1(1)	-4(1)
C(6)	24(1)	28(2)	34(2)	3(1)	-8(1)	-3(1)
F(1)	21(1)	30(1)	30(1)	-8(1)	4(1)	4(1)
F(2)	16(1)	26(1)	25(1)	2(1)	-1(1)	-5(1)
N(2)	20(1)	19(1)	21(1)	0(1)	-2(1)	-1(1)
N(3)	15(1)	20(1)	17(1)	3(1)	0(1)	0(1)
N(1)	16(1)	21(1)	20(1)	1(1)	1(1)	0(1)
N(4)	15(1)	21(1)	20(1)	-2(1)	0(1)	0(1)

Table 6

Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3)

	x	y	z	U(eq)
H(2a)	6330(30)	4580(70)	5370(20)	26(8)
H(2b)	6750(30)	2700(70)	4520(20)	24(8)
H(3)	5370(30)	9210(80)	3040(30)	44(10)
H(1)	8740(30)	4260(80)	4720(30)	41(10)

Table 7

Torsion angles [deg]

Atoms	Dieder Angle
N(3)-C(2)-N(2)-C(1)	-0.6(4)
F(2)-C(2)-N(2)-C(1)	177.1(2)
N(1)-C(1)-N(2)-C(2)	-0.5(4)
F(1)-C(1)-N(2)-C(2)	-178.6(2)
N(2)-C(2)-N(3)-C(3)	0.7(4)
F(2)-C(2)-N(3)-C(3)	-177.01(19)
N(4)-C(3)-N(3)-C(2)	179.2(2)
N(1)-C(3)-N(3)-C(2)	0.2(3)
N(2)-C(1)-N(1)-C(3)	1.2(4)
F(1)-C(1)-N(1)-C(3)	179.3(2)
N(4)-C(3)-N(1)-C(1)	180.0(2)
N(3)-C(3)-N(1)-C(1)	-1.0(3)
N(1)-C(3)-N(4)-C(4)	4.9(3)
N(3)-C(3)-N(4)-C(4)	-174.2(2)
C(5)-C(4)-N(4)-C(3)	75.6(3)

Table 8

Hydrogen bonds [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)

CONCLUSIONS

α-Tocopherol turned out to be a versatile moiety for the development of new uracil derivatives as promising candidates for the introduction of lipophilic anchors into peptide nucleic acids (PNA) or peptides. Systems can be obtained containing one or two tocopherol units

and carboxylic, amino or alkyne groups as tethering units. Sonogashira reaction turned out to be a useful tool in these approaches. An unusual phenomenon was found in 2-propargylamine-4,6-difluorotriazine that exhibits two different chemical shifts for the two fluoro atoms.

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