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Synthesis of 5a-α-Tocopheryl Azide and Its Reaction to 1-(5a-α-Tocopheryl)-1,2,3-triazols by [2+3]-Cycloaddition

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1,2,3-Triazoles with 1-position substituents, derived from α-tocopherol (vitamin E), were synthesized by 1,3-dipolar cycloaddition reactions of 5a-azido-α-tocopheryl acetate with alkynes, and were fully analytically characterized. NMR spectra of the compounds and crystal structures of derivatives with a truncated isoprenoid side chain are presented. The tocopheryl moiety is readily cleaved in basic media, as a prerequisite for the use in delivery systems showing pH-dependent drug release.

Introduction

1,2,3-Triazoles having a wide range of biological activities are found in bioactive compounds such as anti-HIV agents,[1] antimicrobial compounds,[2] and β_3-selective adrenergic receptor agonists.[3] Indeed, the 1,2,3-triazole moiety is present in a number of drugs, for example, the β-lactam antibiotic tazobactam and the cephalosporine cefatrizine. In addition, 1,2,3-triazoles have found ample usage as agrochemicals, dyes, photographic materials, and corrosion inhibitors.[4]

Within our current project on directed drug delivery systems, we were interested in 1,2,3-triazoles with lipophilic, cleavable carriers. For that purpose, we chose the 5a-tocopheryl residue, which was supposed to serve three functions. First, it renders the moderately hydrophilic triazoles much more lipophilic; second, it acts as a drug carrier anchoring the compound in lipid membranes in a way similar to tocopherols themselves; and third, it undergoes pH-dependent cleavage. In this study, we communicate the synthesis and analytical properties of 1-(5a-tocopheryl)-1,2,3-triazoles, along with example crystal structures of short-chain analogues.

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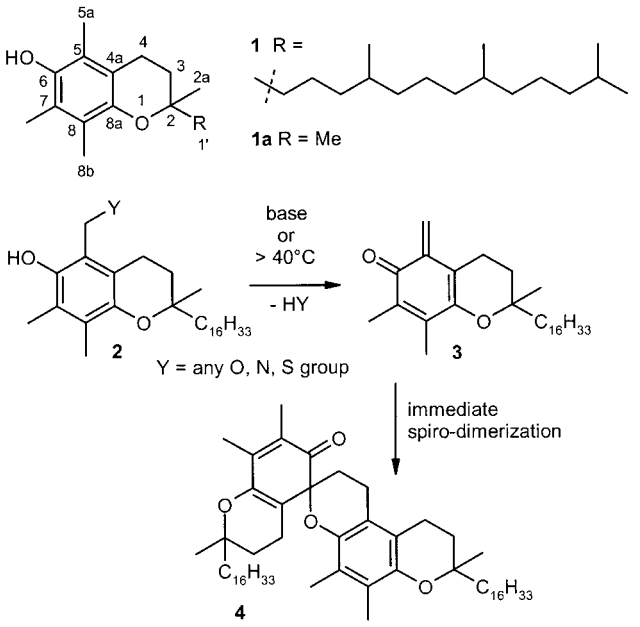
Results and Discussion

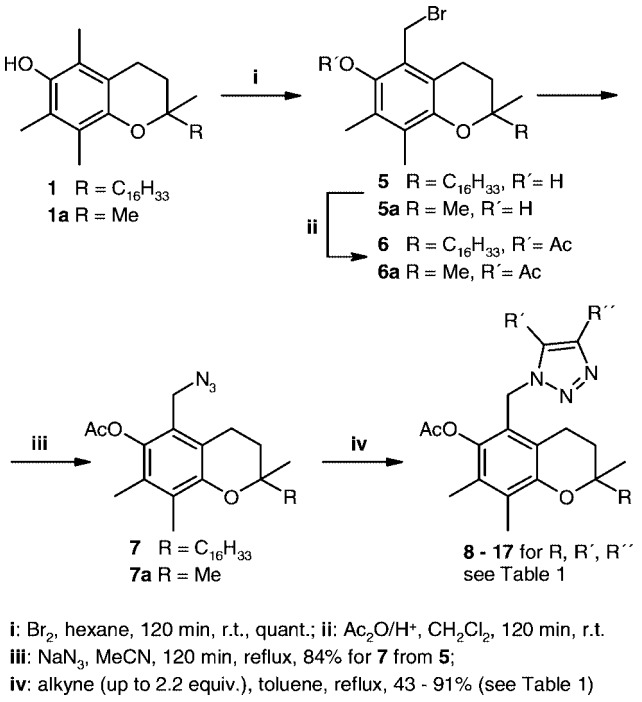
Several methods have been described for the synthesis of 1,2,3-triazoles; the most prominent approach is the cycloaddition reaction of organic azides with alkynes.[5] This conversion usually needs elevated temperatures and forms mixtures of 1,4- and 1,5-regioisomers in the case of non-symmetric alkynes. Studies on the regioselective course were reported by Sharpless,[6] who used Cu^I salts as catalysts[7] to obtain 1,4-substituted products with high regioselectivity from terminal alkynes, and by Meldal,[8] who regioselectively synthesized 1,4-substituted 1,2,3-triazoles by employing polymer-supported terminal alkynes. Usually, the 1-position of the 1,2,3-triazoles is substituted, since preparation started from an organic (alkyl or aryl) azide.

α-Tocopherol (**1**), the main component of vitamin E which mainly acts in lipidic mammalian tissues, is known to be one of the most effective chain-breaking phenolic antioxidants.[9] It finds the most widespread uses in medications, healthcare products, cosmetic formulations, and as a stabilizer for food, synthetic polymers, and plastics (Scheme 1).[10]

Room-temperature bromination of α-tocopherol, which proceeds according to a two-step oxidation-addition mechanism, provides 5a-bromo-α-tocopherol, which can be neatly converted into a variety of 5a-substituted tocopherols. In the case of electronegative 5a-substituents, such as OR, NR_2, or SR, the derivatives readily eliminate the 5a-substituent in basic media (pH > 8), whereas they are completely stable in neutral and acidic media.[11] Upon elimination, the tocopherol part forms an *ortho*-quinone methide intermediate **3**,[12] which immediately undergoes spiro-dimerization to **4**, a natural vitamin E metabolite (Scheme 1). We intended to employ this chemistry in the synthesis of



Scheme 1. Chemical behavior of 5a-substituted α-tocopherols.



Scheme 2. Preparation of 1-(5a-tocopheryl)-1,2,3-triazoles from α-tocopherol.

5a-tocopheryl-substituted 1,2,3-triazoles, which would release the tocopherol carrier upon contact with basic media, so that a pH-dependent drug release in response to changes in tissue pH would be feasible. As this elimination principle fails with carbon substituents at C-5a, the tocopheryl substituent must be bound to either of the nitrogen atoms of the triazole moiety. As the most obvious choice, 5a-tocopheryl azide had to be reacted with alkynes in a [3+2]-cycloaddition reaction (Scheme 2).

Reaction of α-tocopherol (**1**) with bromine in dry hexane produced 5a-bromo-α-tocopherol (**5**) quantitatively.[13] The reaction of the truncated α-tocopherol model compound 2,2,5,7,8-pentamethylchroman-6-ol (**1a**) proceeded analogously. After acetylation of the bromo derivatives, which had to be performed in the absence of basic auxiliaries to avoid elimination of HBr, reaction with sodium azide provided the novel 5a-azidotocopheryl acetate **7** and the 5a-azidochromanyl acetate **7a** in good yields (Scheme 2). Conversion of the free phenols into the acetates considerably increased the temperature stability, which allowed us to conduct subsequent reactions of **7** at temperatures above 100 °C without losses due to decomposition. The [3+2]-cycloaddition of the tocopheryl azide with alkynes in refluxing toluene provided the 1-(5a-tocopheryl)-1,2,3-triazoles **8**–**17** in excellent to fair yields. The time until complete conversion was dependent on the alkyne used; electron-withdrawing substituents favored fast reactions. A regiospecific reaction was not attempted in our case, as synthesis and characterization of both isomers were of interest, *cf.* the pairs **13/14** and **15/16** in Table 1. For these pairs, the overall yields of the cycloaddition reactions are the sums of the individual yields of the two regioisomers.

All tocopheryl-1,2,3-triazoles were purified by flash chromatography (EtOAc/*n*-hexane, v/v = 1:5) to provide colorless, waxy products. The products obtained from **7a**, which has the isoprenoid side chain replaced by a methyl group, are white solids with a pronounced tendency to crystallize in fine, long needles. For two examples, crystal structures are reported here. The preliminary room-temperature X-ray structure of diphenyltriazole **9a** was later complemented by a low-temperature structure (173 K) of crystals obtained from DMF, which provided better parameters (Figure 1). Diester derivative **11** was crystallized from ethylene glycol after several unsuccessful attempts with more common solvents due to acicular growth (Figure 2). Both triazole derivatives crystallized in the monoclinic system, although in different unit cells. Both showed the same rod-like stacking with a translation period of 5.6 Å along the needle axis, which is the b-axis of a *C*2/*c* cell for **9**, and the a-axis of a $P2_1/c$ cell in the case of **11**. The arrangement of the chroman moieties and the triazole units along the rod axis was similar for both structures.

In all crystal structures obtained, the pyran ring of the tocopheryl substituent adopted a twisted chair conformation. The 1,2,3-triazole rings exhibited a nearly perfect planarity. The torsion angles between the mean planes of the triazole and the aromatic rings of the tocopherol moiety varied between 35° and 84°, depending on the substituent.

An interesting feature common to all the tocopheryltriazoles we studied is the broad shape of the ^{13}C resonances of C-3, C-4, C-2a, and C-1′, which indicates reduced flexibility of the pyran ring in the tocopheryl moiety. At temperatures above 60 °C, these resonances change into the common sharp singlets, reflecting largely unrestricted high-temperature mobility. The 1,4- and 1,5-regioisomers (the pairs **13/14**, **15/16**, **17/18**) can be readily distinguished by their ^{13}C NMR spectroscopic data. While the C-4 and C-

Table 1. 1-(5a-Tocopheryl)-1,2,3-triazoles.

	Co-reactants	R[a]	R′[a]	R′′[a]	Yield[b]
8	**7**, diphenylacetylene	$C_{16}H_{33}$	Ph	Ph	61
9	**7a**, diphenylacetylene	CH_3	Ph	Ph	58
10	**7**, diethyl acetylenedicarboxylate	$C_{16}H_{33}$	COOEt	COOEt	91
11	**7a**, diethyl acetylenedicarboxylate	CH_3	COOEt	COOEt	90
12	**7**, di-*tert*-butyl butynedicarboxylate	$C_{16}H_{33}$	COO*t*Bu	COO*t*Bu	81
13	**7**, ethyl propiolate	$C_{16}H_{33}$	H	COOEt	55
14	**7**, ethyl propiolate	$C_{16}H_{33}$	COOEt	H	28
15	**7**, phenylacetylene	$C_{16}H_{33}$	H	Ph	52
16	**7**, phenylacetylene	$C_{16}H_{33}$	Ph	H	18
17	**7**, 2-amino-5-ethynyl-1,3,4-oxadiazole	$C_{16}H_{33}$	H	Oxa[c]	84
18	**7**, 2-amino-5-ethynyl-1,3,4-oxadiazole	$C_{16}H_{33}$	Oxa[c]	H	11

[a] See Scheme 2. [b] Isolated yields in %. [c] Oxa = 2-amino-1,3,4-oxadiazol-5-yl.

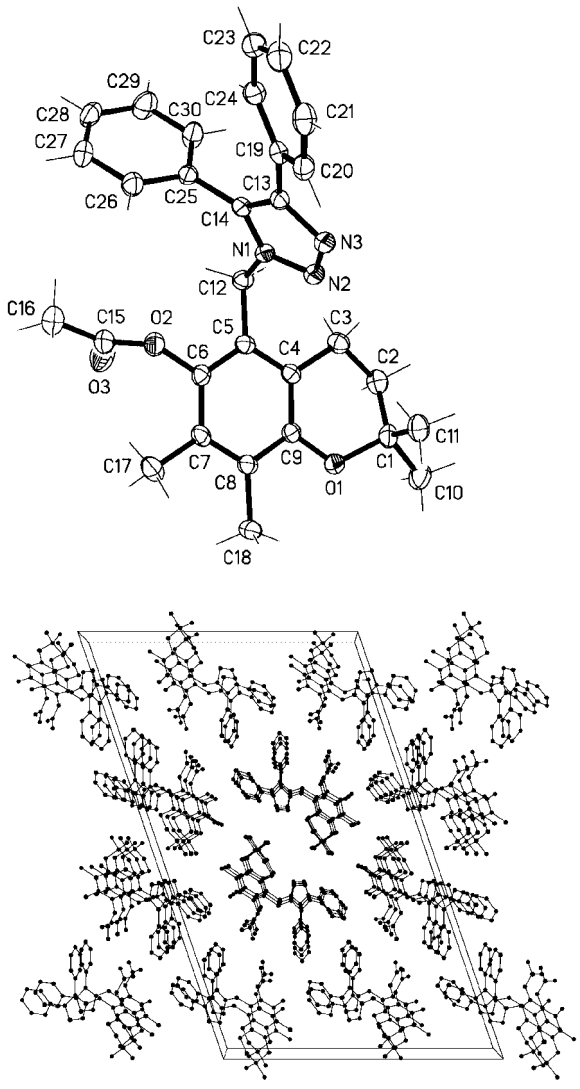


Figure 1. Thermal ellipsoid plot (40% ellipsoids), crystallographic atom labeling (top) and stacking plot along the b-axis (bottom) of tocopheryl-triazole **9** (4,5-diphenyl substituents).

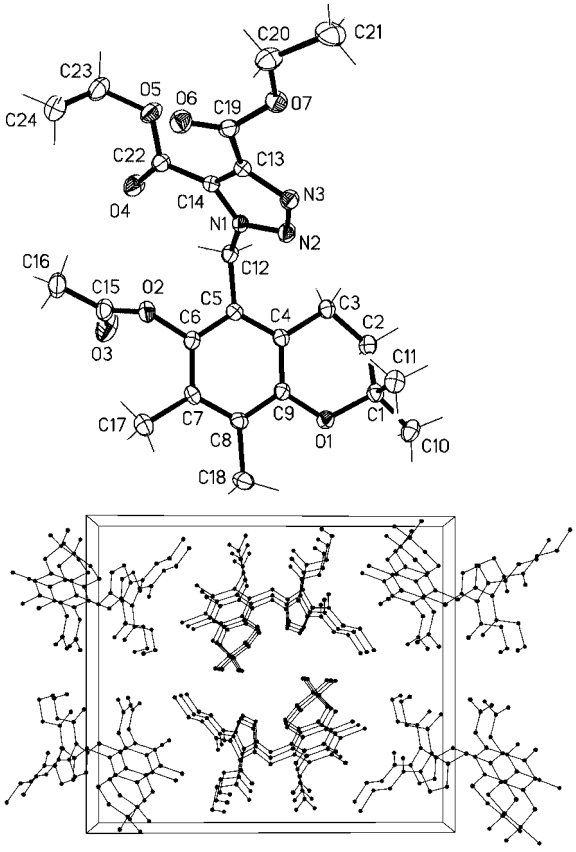


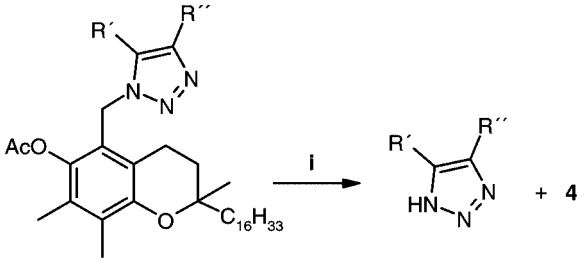
Figure 2. Thermal ellipsoid plot (20% ellipsoids), crystallographic atom labeling (top) and stacking plot along the a-axis (bottom) of tocopheryl-triazole **11** (4,5-diester substituents).

5 resonances of the triazole appeared quite close at about 130 ppm in the 1,5-isomers, there was a significant chemical shift difference in the 1,4-counterpart: 119 ppm for C-5 and 150 ppm for C-4. In addition, C-5a in the 1,5-isomer experienced a 4 ppm downfield shift relative to the 1,4-isomers and the 4,5-disubstituted tocopheryl triazoles (approx. 46 ppm).

The room-temperature ^{1}H NMR spectrum of the 1-(5a-tocopheryl)-1,2,3-triazole derivatives **8** and **9**, with their relatively bulky phenyl substituents, showed an interesting feature: a broad peak originating from the 4-CH_2 group indicated restricted mobility of these protons. A similar behavior was observed for the recently described tocopherylisoxazolines.[14] The crystal structure of **9**, as shown in Figure 1, makes plausible that this behavior is due to the proximity and reduced rotational ability of the bulky diphenyltriazole substituents. With increasing temperature, the broad reso-

nance sharpened into a triplet, as usually observed for tocopherols. In addition, the C-4 methylenes in **8** and **9** experienced a pronounced high-field shift (to 2.3 ppm at 298 K and to 2.55 ppm at 333 K) compared to their "usual" appearance in the other tocopheryltriazoles (and α-tocopherol derivatives in general) around 2.6–2.7 ppm. In compound **11** one of the ethyl ester groups is placed into closer proximity to the aromatic ring, as also indicated by the crystal structure of **11** in Figure 2, so that the resulting magnetic anisotropy is able to explain the comparatively large differences between the ^{1}H NMR shifts of the two ethoxy groups: 4.38 vs. 4.08 (OCH_2) and 0.92 vs. 1.24 ppm (CH_3).

Finally, the base-induced cleavage of the tocopheryl moiety was verified for compounds **9** and **15**. Treatment with base both in organic media, i.e. with the equivalent amount of NaOH in MeOH, and in aqueous media, i.e. in phosphate buffer pH 9 containing sodium dodecyl sulfate as a micelle formation agent, caused cleavage of the tocopheryl carrier and quantitative release of the respective 1-dealkylated triazole moieties (Scheme 3). Thus the requirements mentioned in the introduction section are fully met. Preliminary experiments showed that removal of the lipophilic carrier can even be performed under near-neutral (slightly basic) conditions in the presence of deacetylating enzymes, which liberated the phenolic hydroxy of the tocopheryl moiety, thus rendering it much more prone to base-induced elimination of the 1,2,3-triazole substituent.



i: 1 equiv. 10% NaOH in MeOH or SDS in phosphate buffer, pH 9

Scheme 3. Base-induced cleavage of the lipophilic 5a-tocopheryl moiety.

Conclusion

The facile preparation of 5a-azido-α-tocopheryl acetate from commercially available α-tocopherol, and its further reaction with alkynes in a [3+2]-cycloaddition reaction opens the way to 1-(5a-tocopheryl)-substituted 1,2,3-triazoles, which were fully analytically characterized. The structure of the compounds was supported by crystal structure analysis of derivatives with truncated isoprenoid side chains. NMR spectra indicated a reduced mobility of the pyran ring in the tocopherol moiety due to the bulky triazole substituent, with especially strong influences on the C-4 methylene group. The target tocopheryltriazole exhibited the desired property of base-induced cleavage of the lipophilic tocopheryl moiety to be used in drug delivery systems.

Experimental Section

All-racemic α-tocopherol and α-tocopheryl acetate were used as the starting materials. Thin layer chromatography (TLC) was performed on silica gel 60 plates (5 × 10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. Column chromatography was performed on silica gel G60 (40-63 μm). Melting points, determined on a Kofler-type micro hot stage with Reichert-Biovar microscope, are uncorrected. NMR spectra were recorded at 300.13 MHz for ^{1}H and at 75.47 MHz for ^{13}C in $CDCl_3$ if not otherwise stated. Chemical shifts, relative to TMS as internal standard, are given in δ values; coupling constants are reported in Hz. ^{13}C peaks were assigned by means of APT, HMQC and HMBC spectra. The influence of modifications at the chroman ring on the resonances of the isoprenoid side chain of tocopherols is negligible (< 0.1 ppm for ^{13}C and < 0.01 ppm for ^{1}H). The ^{13}C resonances are therefore listed only for one example, the starting material 5a-tocopheryl azide (**7**). "d.i." denotes peaks with double intensity, E stands for the ethoxycarbonyl ("ester") group. High-resolution MS data were obtained with a Waters ESI Q-TOF spectrometer. All new compounds exhibited satisfactory purity data.

Preparation of Tocopheryl Azide 7 and Chromanyl Azide 7a: To a solution of α-tocopherol or pentamethylchromanol in dry *n*-hexane (1% solution), a solution of bromine (1.1 equiv.) in a tenfold volume of *n*-hexane was added at once at room temperature. The mixture was stirred for 2 h. The initial dark red color of the solution changed to dark yellow within seconds, and the evolution of HBr started. The solvent and the small excess of bromine, along with dissolved HBr, were removed in vacuo at room temperaure. 5a-Bromo-tocopherol (**5**) was obtained in quantitative yield, and no further purification was required. The product was dissolved in dichloromethane (1% solution), and acetic anhydride (1.1 equiv.) and concentrated sulfuric acid (2 drops) were added. The mixture was stirred overnight at room temperature, quenched with water under ice-cooling, and stirred for an additional 2 hours. After repeated extraction with *n*-hexane, the organic layer was neutralized with a saturated $NaHCO_3$ solution, washed with water, and dried with $MgSO_4$. After filtration, the solvent was removed in vacuo. The product, 5a-bromo-tocopheryl acetate (**6**), was dissolved in acetonitrile (1% solution). After addition of sodium azide (1.3 equiv.), the mixture was refluxed for two hours. After cooling to room temperature, the solids were filtered off and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (EtOAc/*n*-hexane, v/v = 1:20) to provide 5a-tocopheryl azide as a yellow wax in 84% overall yield. Preparation of the corresponding model azide, containing a methyl group instead of the isoprenoid side chain, proceeded analogously with 2,2,5,7,8-pentamethylchroman-6-ol (**1a**) as the starting material, providing **7a** (84%) as colorless solid.

5a-Azido-tocopheryl Acetate (7): ^{1}H NMR: δ = 4.19 (s, 2 H, 5a-H), 2.73 (t, ^3J = 6.7 Hz, 4-H), 2.36 (s, 3 H, CH_3CO), 2.12 (s, 3 H, 8b-H), 2.03 (s, 3 H, 7a-H), 1.90–1.72 (m, 2 H, 3-H) ppm. ^{13}C NMR: δ = 169.7 (COO), 149.8 (C-8a), 141.1 (C-6), 127.8 (C-7), 127.0 (C-8), 122.0 (C-5), 117.9 (C-4a), 75.5 (C-2), 46.3 (C-5a), 40.2 (C-1′), 39.4 (C-11′), 37.2, 37.3, 37.4, 37.5 (C-3′, C-5′, C-7′, C-9′), 32.6, 32.7 (C-4′, C-8′), 30.8 (C-3), 28.0 (C-12′), 24.8, 24.4 (C-6′, C-10′), 23.9 (C-2a), 22.6, 22.7 (C-12a′, C-13′), 21.0 (C-4), 20.6 (*C*H_3CO), 19.9 (C-2′), 19.6, 19.7 (C-4a′, C-8a′), 13.1 (C-7a), 12.2 (C-8b) ppm. $C_{31}H_{51}N_3O_3$ (513.77): calcd. C 72.47, H 10.01, N 8.18; found C 72.63, H 10.23, N 7.98.

6-Acetoxy-5-azidomethyl-2,2,7,8-tetramethylchroman (7a): M.p. 73 °C (dec.), ^{1}H NMR: δ = 4.19 (s, 2 H, 5a-H), 2.75 (t, ^3J = 6.8 Hz, 4-H), 2.36 (s, 3 H, CH_3CO), 2.12 (s, 3 H, 8b-H), 2.03 (s, 3 H, 7a-

H), 1.80 (t, J = 6.8 Hz, 2 H, 3-H), 1.31 (s, 6 H, 2a-H, 2b-H) ppm. ^{13}C NMR: δ = 169.7 (COO), 149.9 (C-8a), 141.1 (C-6), 127.8 (C-7), 127.0 (C-8), 122.0 (C-5), 117.7 (C-4a), 73.4 (C-2), 46.3 (C-5a), 32.4 (C-3), 26.9 (C-2a, C-2b), 20.6 (*C*H$_3$CO), 20.4 (C-4), 13.1 (C-7a), 12.2 (C-8b) ppm. $C_{16}H_{21}N_3O_3$ (303.36): calcd. C 63.35, H 6.98, N 13.85; found C 63.16, H 7.12, N 13.78.

General Procedure for the 1,3-Dipolar Cycloaddition Leading to 1-(5a-Tocopheryl)-1,2,3-triazols: To **7** or **7a** (1.0 mmol) in dry toluene (5 mL), the alkyne component (1–2.2 equiv.) was added. The mixture was refluxed for 1–3 d under argon or nitrogen (TLC control), and cooled to room temp. The solvent was removed in vacuo and the crude product was purified by column chromatography (EtOAc/*n*-hexane, v/v = 1:5).

6-Acetoxy-5-[(4,5-diphenyl-1,2,3-triazol-1-yl)methyl]-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman (8): ^{1}H NMR: δ = 7.54–7.08 (m, 10 H, Ar-H), 5.25 (s, 2 H, 5a-H), 2.27 (t, 2 H, ^3J = 6.4 Hz, 4-H), 2.20 (s, 3 H, CH$_3$CO), 2.08 (s, 3 H, 8b-H), 1.90 (s, 3 H, 7a-H), 1.52 (m, 2 H, 3-H) ppm. ^{13}C NMR: δ = 170.1 (COO), 150.0 (C-8a), 145.0 (C-6), 141.8 (C-5′′), 134.1 (C-4′′), 131.5 (Ph, C-1), 130.7 (d.i.), 129.8 (Ph, C-4), 129.2 (d.i.), 128.7 (d.i.), 128.6 (Ph, C-1), 128.4 (C-7), 128.0 (Ph, C-4), 127.4 (C-8), 127.1 (d.i.), 121.9 (C-5), 118.5 (C-4a), 75.7 (C-2), 45.9 (C-5a), 33.1 (C-3), 20.2 (*C*H$_3$CO), 20.0 (C-4), 13.3 (C-7a), 12.6 (C-8b) ppm. HRMS for $C_{45}H_{61}N_3O_3$ (692.01): calcd. 693.01 [M + H$^+$]; found 693.04.

6-Acetoxy-5-[(4,5-diphenyl-1,2,3-triazol-1-yl)methyl]-2,2,7,8-tetramethylchroman (9): M.p. 105–107 °C. ^{1}H NMR: δ = 7.49–7.10 (m, 10 H, Ar-H), 5.29 (br. s, 2 H, 5a-H), 2.31 (t, ^3J = 6.5 Hz, 2 H, 4-H), 2.14 (s, 3 H, CH$_3$CO), 2.08 (s, 3 H, 8b-H), 1.91 (s, 3 H, 7a-H), 1.56 (m, 2 H, 3-H), 1.21 (s, 6 H, 2a-H, 2b-H) ppm. ^{13}C NMR: δ = 169.6 (COO), 149.6 (C-8a), 144.5 (C-6), 141.4 (C-5′′), 133.6 (C-4′′), 131.0 (Ph, C-1), 130.3 (d.i.), 129.4 (Ph, C-4), 128.8 (d.i.), 128.3 (d.i.), 128.0 (Ph, C-1), 127.7 (C-7), 127.4 (Ph, C-4), 127.0 (C-8), 126.6 (d.i.), 121.5 (C-5), 117.8 (C-4a), 73.1 (C-2), 45.4 (C-5a), 32.4 (C-3), 20.6 (CH$_3$ in acetyl), 20.1 (C-4), 12.9 (C-7a), 12.2 (C-8b) ppm. HRMS for $C_{30}H_{31}N_3O_3$ (481.60): calcd. 482.60 [M + H$^+$]; found 482.55.

Diethyl 1-[6-Acetoxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-5-ylmethyl]-1*H*-1,2,3-triazole-4,5-dicarboxylate (10): ^{1}H NMR: δ = 5.57 (s, 2 H, 5a-H), 4.39 (q, 2 H, ^3J = 7.1 Hz, OCH$_2$), 4.16 (q, 2 H, ^3J = 7.1 Hz, OCH$_2$), 2.71 (m, 2 H, 4-H), 2.24 (s, 3 H, CH$_3$CO), 2.11 (s, 3 H, 8b-H), 1.97 (s, 3 H, 7a-H), 1.78 (m, 2 H, 3-H) ppm. ^{13}C NMR: δ = 169.6 (COO in Ac), 160.1 (COO in E), 159.3 (COO in E), 150.0 (C-8a), 141.3 (C-6), 139.1 (C-5′′), 131.4 (C-4′′), 128.0, 127.9 (C-7, C-8), 120.5 (C-5), 118.7 (C-4a), 75.8 (C-2), 63.0 (OCH$_2$), 61.7 (OCH$_2$), 46.8 (C-5a), 30.7 (C-3), 21.1 (C-4), 20.6 (*C*H$_3$CO), 14.3 (CH$_3$ in E), 13.7 (CH$_3$ in E), 13.0 (C-7a), 12.3 (C-8b) ppm. HRMS for $C_{39}H_{61}N_3O_7$ (683.45): calcd. 684.45 [M + H$^+$]; found 684.46.

Diethyl 1-[(6-Acetoxy-2,2,7,8-tetramethylchroman-5-yl)methyl]-1*H*-1,2,3-triazole-4,5-dicarboxylate (11): M.p. 83–87 °C. ^{1}H NMR: δ = 5.55 (s, 2 H, 5a-H), 4.38 (q, 2 H, ^3J = 7.1 Hz, OCH$_2$), 4.18 (q, 2 H, ^3J = 7.1 Hz, OCH$_2$), 2.70 (t, J = 6.8 Hz, 2 H, 4-H), 2.24 (s, 3 H, CH$_3$CO), 2.11 (s, 3 H, 8b-H), 1.98 (s, 3 H, 7a-H), 1.79 (t, J = 6.8 Hz, 2 H, 3-H), 1.26 (s, 6 H, 2a-H, 2b-H), 1.24 (s, 3 H, CH$_3$ in E), 0.92 (s, 3 H, CH$_3$ in E) ppm. ^{13}C NMR: δ = 170.4 (COO in Ac), 160.4 (COO in E), 159.8 (COO in E), 149.8 (C-8a), 141.3 (C-6), 139.1 (C-5′′), 131.4 (C-4′′), 128.2, 128.1 (C-7, C-8), 120.7 (C-5), 118.8 (C-4a), 73.3 (C-2), 62.5 (OCH$_2$), 61.4 (OCH$_2$), 46.1 (C-5a), 32.4 (C-3), 20.6 (*C*H$_3$CO), 20.4 (C-4), 14.2 (CH$_3$ in E), 13.9 (CH$_3$ in E), 13.0 (C-7a), 12.3 (C-8b) ppm. HRMS for $C_{24}H_{31}N_3O_7$ (473.22): calcd. 474.22 [M + H$^+$]; found 474.22.

Di-*tert*-butyl 1-{[6-Acetoxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-5-yl]methyl}-1*H*-1,2,3-triazole-4,5-dicarboxylate (12): ^{1}H NMR: δ = 5.54 (s, 2 H, 5a-H), 2.65 (m, 2 H, 4-H), 2.26 (s, 3 H, CH$_3$CO), 2.10 (s, 3 H, 8b-H), 1.97 (s, 3 H, 7a-H), 1.82 (m, 2 H, 3-H), 1.60 (s, 9 H, *t*Bu), 1.44 (s, 9 H, *t*Bu) ppm. ^{13}C NMR: δ = 170.1 (COOCH$_3$), 160.0 (COO*t*Bu), 158.4 (COO*t*Bu), 150.3 (C-8a), 141.7 (C-5′′), 141.3 (C-6), 131.8 (C-4′′), 128.2, 127.8 (C-7, C-8), 121.1 (C-5), 119.0 (C-4a), 85.0 (*t*Bu), 83.0 (*t*Bu), 75.9 (C-2), 46.8 (C-5a), 31.2 (C-3), 28.5 (*t*Bu), 28.1 (*t*Bu), 21.8 (C-4), 20.4 (*C*H$_3$CO), 13.4 (C-7a), 12.6 (C-8b) ppm. HRMS for $C_{43}H_{69}N_3O_7$ (740.05): calcd. 741.05 [M + H$^+$]; found 740.54.

6-Acetoxy-2,7,8-trimethyl-5-[(4-phenyl-1,2,3-triazol-1-yl)methyl]-2-(4,8,12-trimethyltridecyl)chroman (15): ^{1}H NMR: δ = 7.76 (d, ^3J = 8.7 Hz, 2 H, Ar-H), 7.56 (s, 1 H, CHN), 7.36 (t, ^3J = 7.1 Hz, 2 H, Ar-H), 7.27 (t, ^3J = 7.3 Hz, 1 H, Ar-H), 5.45 (s, 2 H, 5a-H), 2.54 (br. s, 2 H, 4-H), 2.33 (s, 3 H, CH$_3$CO), 2.15 (s, 3 H, 8b-H), 2.06 (s, 3 H, 7a-H), 1.72 (m, 2 H, 3-H) ppm. ^{13}C NMR: δ = 170.2 (COO), 150.6 (C-Ph), 148.3 (C-8a), 141.6 (C-6), 131.0 (Ph, C-1), 129.1 (d.i.), 129.6, 128.4 (C-7, C-8), 128.4 (Ph, C-4), 126.1 (d.i.), 121.5 (C-5), 119.6 (CHN), 118.8 (C-4a), 76.1 (C-2), 46.5 (C-5a), 30.9 (C-3), 21.4 (C-4), 20.2 (*C*H$_3$CO), 13.6 (C-7a), 12.7 (C-8b) ppm. HRMS for $C_{39}H_{57}N_3O_3$ (615.91): calcd. 616.92 [M + H$^+$]; found 619.90.

6-Acetoxy-2,7,8-trimethyl-5-[(5-phenyl-1,2,3-triazol-1-yl)methyl]-2-(4,8,12-trimethyltridecyl)chroman (16): ^{1}H NMR: δ = 7.75 (s, 1 H, CHN), 7.73 (m, 2 H, Ar-H), 7.36 (m, 3 H, Ar-H), 5.52 (br. s, 2 H, 5a-H), 2.74 (br. s, 2 H, 4-H), 2.35 (s, 3 H, CH$_3$CO), 2.11 (s, 3 H, 8b-H), 2.00 (s, 3 H, 7a-H), 1.82 (m, 2 H, 3-H) ppm. ^{13}C NMR: δ = 169.6 (COO), 149.8 (C-8a), 141.3 (C-6), 130.9 (CHN), 130.5 (Ph, C-1), 129.4 (C-Ph), 128.7 (d.i.), 128.1 (Ph, C-4), 127.9, 127.1 (C-7, C-8), 125.8 (d.i.), 122.0 (C-5), 118.6 (C-4a), 75.5 (C-2), 50.3 (C-5a), 30.6 (C-3), 21.0 (C-4), 20.8 (*C*H$_3$CO), 13.2 (C-7a), 12.2 (C-8b) ppm. HRMS for $C_{39}H_{57}N_3O_3$ (615.91): calcd. 616.92 [M + H$^+$]; found 619.88.

Ethyl 1-[6-Acetoxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-5-ylmethyl]-1*H*-1,2,3-triazole-4-carboxylate (13): ^{1}H NMR: δ = 5.52 (s, 2 H, 5a-H), 4.42 (q, ^3J = 7.3 Hz, 2 H, OCH$_2$), 2.58 (m, 2 H, 4-H), 2.22 (s, 3 H, CH$_3$CO), 2.13 (s, 3 H, 8b-H), 2.06 (s, 3 H, 7a-H), 1.73 (m, 2 H, 3-H) ppm. The signal of the methyl group of E is overlapped by the signals of the isoprenoid side chain. ^{13}C NMR: δ = 169.6 (COO in Ac), 160.5 (COO in E), 148.6 (C–E), 148.1 (C-8a), 141.6 (C-6), 129.1, 128.8 (C-7, C-8), 123.6 (CHN), 121.0 (C-5), 118.1 (C-4a), 76.0 (C-2), 61.5 (OCH$_2$), 46.3 (C-5a), 30.4 (C-3), 20.9 (C-4), 20.4 (*C*H$_3$CO), 14.2 (CH$_3$ in E), 13.6 (C-7a), 12.7 (C-8b) ppm. HRMS for $C_{36}H_{57}N_3O_5$ (611.87): calcd. 612.87 [M + H$^+$]; found 612.88.

Ethyl 1-{[6-Acetoxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-5-yl]methyl}-1*H*-1,2,3-triazole-5-carboxylate (14): ^{1}H NMR: δ = 5.41 (s, 2 H, 5a-H), 4.30 (q, ^3J = 7.3 Hz, 2 H, OCH$_2$), 2.74 (m, 2 H, H-4), 2.21 (s, 3 H, CH$_3$CO), 2.11 (s, 3 H, 8b-H), 2.03 (s, 3 H, 7a-H), 1.78 (m, 2 H, 3-H) ppm. The signal of the methyl group of E is overlapped by the signals of the isoprenoid side chain. ^{13}C NMR: δ = 169.6 (COO), 160.1 (COO in E), 149.4 (C-8a), 141.8 (C-6), 131.3 (C-E), 127.9 (CHN), 127.8, 127.7 (C-7, C-8), 122.2 (C-5), 118.0 (C-4a), 75.5 (C-2), 61.0 (O–CH$_2$), 48.9 (C-5a), 31.2 (C-3), 21.1 (C-4), 20.4 (*C*H$_3$CO), 14.3 (CH$_3$ in E), 13.2 (C-7a), 12.2 (C-8b). HRMS for $C_{36}H_{57}N_3O_5$ (611.87): calcd. 612.87 [M + H$^+$]; found 612.85.

6-Acetoxy-5-{[4-(2-amino-1,3,4-oxadiazol-5-yl)-1,2,3-triazol-1-yl]methyl}-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman (17): ^{1}H NMR: δ = 5.47 (s, 2 H, 5a-H), 5.08 (br. s, NH$_2$), 2.58 (br. s, 2 H, 4-H), 2.30 (s, 3 H, CH$_3$CO), 2.14 (s, 3 H, 8b-H), 2.04 (s, 3 H,

7a-H), 1.74 (m, 2 H, 3-H). ^{13}C NMR: δ = 164.2 (C-2 in oxadiazole), 160.4 (C-5 in oxadiazole), 148.1 (C-4 in triazole), 147.9 (C-8a), 140.9 (C-6), 129.2 (C-7), 128.0 (C-8), 121.3 (C-5), 120.5 (CH-5 in triazole), 118.4 (C-4a), 75.7 (C-2), 45.9 (C-5a), 30.9 (C-3), 22.2 (C-4), 20.4 (CH_3 in acetyl), 13.7 (C-7a), 12.4 (C-8b). HRMS for $C_{35}H_{54}N_6O_4$ (622.86): calcd. 622.87 [M + H$^+$], found: 622.76.

6-Acetoxy-5-{[5-(2-Amino-1,3,4-oxadiazol-5-yl)-1,2,3-triazol-1-yl]methyl}-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman (18): ^{1}H NMR: δ = 6.24 (br. s, NH_2), 5.53 (s, 2 H, 5a-H), 2.79 (br. s, 2 H, 4-H), 2.36 (s, 3 H, CH_3CO), 2.11 (s, 3 H, 8b-H), 2.02 (s, 3 H, 7a-H), 1.81 (m, 2 H, 3-H). ^{13}C NMR: δ = 163.9 (C-2 in oxadiazole), 163.0 (C-5 in oxadiazole), 149.1 (C-8a), 144.5 (C-6), 132.1 (CH-4 in triazole), 129.1 (C-5 in triazole), 127.4 (C-7), 127.0 (C-8), 122.1 (C-5), 118.3 (C-4a), 75.4 (C-2), 50.5 (C-5a), 30.2 (C-3), 21.4 (C-4), 20.4 (CH_3 in acetyl), 13.4 (C-7a), 12.1 (C-8b). HRMS for $C_{35}H_{54}N_6O_4$ (622.86): calcd. 622.87 [M + H$^+$], found: 622.89.

X-ray Crystallographic Study: X-ray data collection was performed with a Bruker AXS Smart APEX CCD diffractometer and graphite-monochromatized Mo-K_α radiation, λ = 0.71073 Å. Corrections for absorption and related effects were done with the program SADABS, structure solution was performed with direct methods, and structure refinement on F^2 (Bruker AXS, 2001: programs SMART, version 5.626; SAINT, version 6.36A; SADABS version 2.05; XPREP, version 6.12; SHELXTL, version 6.10. Bruker AXS Inc., Madison, WI, USA).

Chromanyl-diphenyltriazole 9: $C_{30}H_{31}N_3O_3$, M = 481.58, monoclinic, space group $C2/c$, a = 39.376(2) Å, b = 5.5254(2) Å, c = 24.340(1) Å, β = 108.569(1)°, V = 5019.9(3) Å^3, Z = 8, D_c = 1.274 g/cm^3, T = 173 K, μ = 0.083 mm^{-1}, F(000) = 2048, colorless block (0.45 × 0.21 × 0.12 mm); total reflections: 29022, unique reflections: 5445, R_{int} = 0.0303, final refinement: data/restraints/parameters: 5445/99/328, goodness-of-fit on F^2 = 1.027, R_1 = 0.0448 [$I > 2\sigma(I)$], wR_2 = 0.1239 (all data).

Diethyl Chromanyl-triazoledicarboxylate 11: $C_{24}H_{31}N_3O_7$, M = 473.52, monoclinic, space group $P2_1/c$, a = 5.628(2) Å, b = 19.315(8) Å, c = 22.561(9) Å, β = 91.17(2)°, V = 2452.1(17) Å^3, Z = 4, D_c = 1.283 g/cm^3, T = 298 K, μ = 0.095 mm^{-1}, F(000) = 1008, colorless rod, (0.69 × 0.05 × 0.03 mm); total reflections: 12063, unique reflections: 3398, R_{int} = 0.0668, final refinement: data/restraints/parameters: 3398/89/310, goodness-of-fit on F^2 = 1.018, R_1 = 0.0483 [$I > 2\sigma(I)$], wR_2 = 0.1535 (all data).

CCDC-289354 and -289355 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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