

3-Tocopherylisoxazolines by [2+3] Cycloaddition^[‡]

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New isoxazoline derivatives of α -tocopherol (**1**), the main component of vitamin E, were synthesized in a facile, two-step sequence consisting of nitration followed by 1,3-dipolar cycloaddition. 5-Nitromethyl- γ -tocopheryl acetate (**3**), obtained from the cheap α -tocopheryl acetate (**2**) by direct nitration in one step, acted as the nitrile oxide precursor in the reaction with various alkenes. The facile conversion proceeded in the presence of equimolar amounts of PhNCO and

catalytic amounts of triethylamine. The NMR spectra of the product isoxazolines **5–13**, showing strongly temperature-dependent resonances of the 4'-CH, 4-CH₂ and the acetyl group, are discussed, and the crystal structures of model compounds containing a methyl group instead of the isoprenoid side chain are presented.

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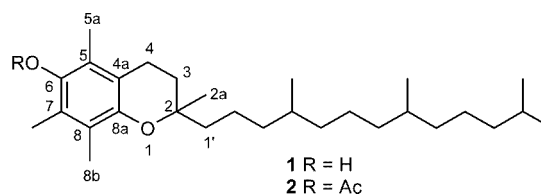
Introduction

α -Tocopherol (**1**), the component of vitamin E with the highest biological activity, acts mainly in lipidic mammalian tissues. It is known to be one of the most effective chain-breaking phenolic antioxidants, and is used in countless formulations, cosmetics, food additives and medications, but also as a stabilizer for polymers.^[1–3] Both substituent effects,^[4–6] and stereoelectronic influences^[7] have been invoked as possible reasons for the exceptionally high effectiveness of vitamin E as a phenolic antioxidant. Due to its lability and sensitivity towards air, tocopherol is mainly used in the form of simple, readily hydrolyzable esters, such as tocopheryl benzoate, succinate, or, most frequently, the acetate (**2**), from which the active free phenol is regenerated in vivo or in vitro.

A current topic in the field of vitamin E chemistry is the synthesis of novel tocopherol derivatives with changed properties, as, for instance, the presence of anchor groups or altered lipophilicity. However, α -tocopheryl acetate completely lacks functionalities that can readily be used for modification as the phenolic OH group needs to remain protected as a readily cleavable ester function in order to assure higher long-term efficiency as an antioxidant. Our current synthetic efforts are directed towards the generation

of tocopheryl derivatives with stable, non-hydrolyzable linkages to other moieties, which should, moreover, offer further positions for chemical modification or anchoring. These studies are aimed at developing novel multifunctional antioxidants and at providing model compounds for studies of the physiologically important tocopherol system.

In the present work, the synthesis of 4,5-substituted 3-tocopherylisoxazolines, starting from readily available tocopheryl acetate (**2**), is described. The approach is the first example of a chemical modification starting from OH-protected tocopherol with retention of the protection, i.e., without involvement of deprotection-reprotection steps. The new vitamin E derivatives have a stable, non-hydrolyzable carbon–carbon bond extending from C-5a of the tocopheryl part to the attached isoxazoline moiety, and they offer ample opportunities for further modification, for example by the choice of isoxazoline substituents or by reductive cleavage of the N–O bond.



Results and Discussion

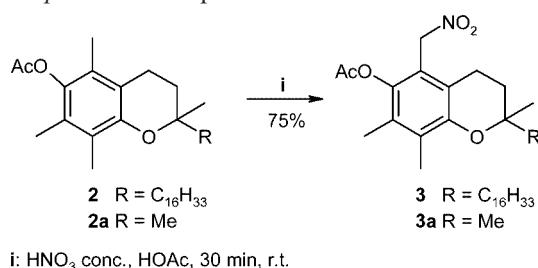
Reaction of α -tocopheryl acetate (**2**) with concentrated nitric acid produced 5-nitro- α -tocopheryl acetate (**3**)^[8,9] in

[‡] Novel Tocopheryl Compounds, XVII. Part XVI: Ref.^[11]

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good yields (Scheme 1 and Table 1). With the α -tocopherol model compound 6-acetoxy-2,2,5,7,8-pentamethylchroman (**2a**),^[10] which possesses a methyl group instead of the isoprenoid side chain, the nitration proceeded analogously to give the nitro derivative **3a** in similar yields (Table 1, Entry 4). In previous work, the unusual one-step formation of the nitration products has been shown to proceed according to a heterolytic, two-step mechanism involving a resonance-stabilized cationic intermediate.^[11] This reaction converts the 5a-methyl group into a reactive nitromethyl function. It is remarkable insofar as it represents the only reaction known so far to effect a high-yield modification directly at the *OH*-protected tocopherol skeleton.



Scheme 1

Table 1. Synthesis of 5a-nitrochromanol derivatives **3** and **3a**

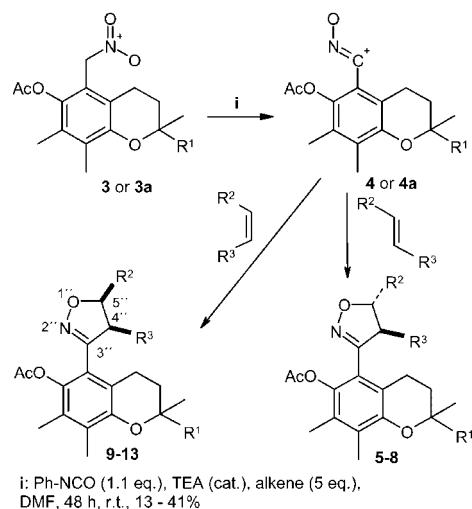
Entry	Product	R	Conditions	Yield (%) ^[a]
1	3	$\text{C}_{16}\text{H}_{33}$	AcOH/room temp.	75
2	3	$\text{C}_{16}\text{H}_{33}$	CH_2Cl_2 /room temp.	0
3	3	$\text{C}_{16}\text{H}_{33}$	CH_2Cl_2 /–70 °C	37
4	3a	CH_3	AcOH/room temp.	71

^[a] Isolated yields in %.

Nitromethyl compounds can be employed as nitrile oxide precursors in [2+3] cycloadditions with alkenes. The established one-pot procedure for this reaction,^[12] which uses phenyl isocyanate and triethylamine to effect nitrile oxide formation and subsequent cyclization, was modified, as **3** and **3a** are unstable in basic media and at temperatures above 40 °C.^[13] The best results were obtained with PhNCO

being applied in equimolar amounts, but not in excess, and with TEA in only catalytic amounts. The use of DMF as solvent had the expected, positive effect on the yield, which increased to 41%, as compared to 30% and 21% in the case of the less-polar solvents CH_2Cl_2 and *n*-hexane, respectively (see Table 2, Entry 3).^[14]

Formation of the isoxazoline derivatives **5–13** proceeded according to the mechanism in Scheme 2, giving moderate yields. TEA catalyzed the formation of the *aci*-nitro form of **3** (or **3a**), from which water was eliminated, which in turn was bound by the PhNCO present. The resulting nitrile oxide intermediate **4** reacted with excess alkene^[15] in a stereospecific 1,3-dipolar cycloaddition to give the desired isoxazolines.



Scheme 2

The products obtained from the truncated model **3a** were crystallized from *n*-hexane or ethanol, and their crystal structures were determined by X-ray diffraction.^[16] Figures 1 and 2 show the crystal structures of **6** and **9** as examples, the *trans* and *cis* arrangement of the two phenyl substituents reflecting the geometry of the starting alkenes, *trans*- and *cis*-stilbene, respectively. In all crystal structures obtained, the pyrano ring adopts the expected twisted-chair conformation. The isoxazoline rings in **6**, with a *trans* con-

Table 2. Synthesis of 3-tocopherylisoxazolines **5–13**

Entry	Product	Co-reactants	R ¹ [a]	R ² [a]	R ³ [a]	Yield (%) ^[b]
1	5	3 , <i>trans</i> -stilbene	$\text{C}_{16}\text{H}_{33}$	Ph	Ph	32
2	6	3a , <i>trans</i> -stilbene	CH_3	Ph	Ph	39
3	7	3 , maleic acid	$\text{C}_{16}\text{H}_{33}$	COOEt	COOEt	41
4	8	3a , maleic acid	CH_3	COOEt	COOEt	40
5	9	3a , <i>cis</i> -stilbene	CH_3	Ph	Ph	35
6	10	3 , <i>cis</i> -1,4-dibenzoyloxybut-2-ene	$\text{C}_{16}\text{H}_{33}$	CH_2OBz	CH_2OBz	16
7	11	3a , <i>cis</i> -1,4-dibenzoyloxybut-2-ene	CH_3	CH_2OBz	CH_2OBz	18
8	12	3 , ethyl vinyl ether	$\text{C}_{16}\text{H}_{33}$	OEt	H	31
9	13	3 , 3,4-dihydro-2 <i>H</i> -pyran	$\text{C}_{16}\text{H}_{33}$		$\text{OCH}_2[\text{CH}_2]_2$	41

^[a] See Scheme 2. ^[b] Isolated yields in %.

figuration of the diphenyl substituents, are planar, whereas in **9**, with a *cis* configuration of the diphenyl substituents, they show envelope conformations with C14 lying out of the plane of the other four ring atoms by 0.21 and 0.50 Å, respectively, for the two independent molecules, one of which is shown in Figure 2. The torsion angles between the mean planes of the isoxazoline and the aromatic rings vary between 42 and 88°, depending on the substituent.

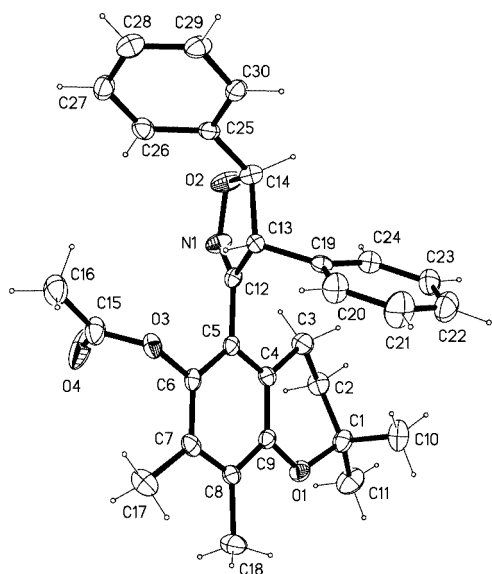


Figure 1. Thermal ellipsoid plot (20% ellipsoids) and crystallographic atom labeling of tocopherylisoxazoline **6** (4,5-diphenyl substituents in *trans* configuration)

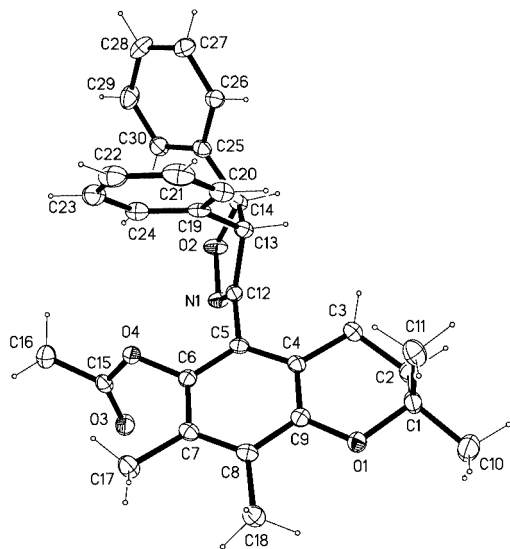
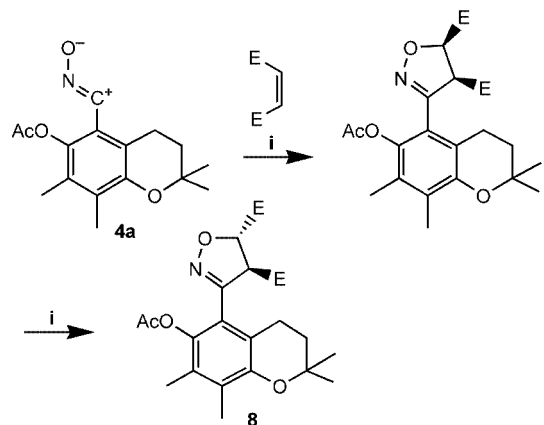


Figure 2. Thermal ellipsoid plot (40% ellipsoids) and crystallographic atom labeling of tocopherylisoxazoline **9** (4,5-diphenyl substituents in *cis* configuration) showing only one of the two conformationally different independent molecules

Interestingly, under the cycloaddition conditions used, maleic acid afforded exclusively the thermodynamically

more stable *trans* product,^[17] due to isomerization of the primarily formed *cis* product. The basicity of the TEA present is evidently sufficient to induce isomerization according to a deprotonation–reprotonation mechanism at C-4''. Reaction of the isolated nitrile oxide **4a**^[18] with maleic acid under neutral conditions gave exclusively the *cis* product, which, upon treatment with TEA, was isomerized into the *trans*-configured **8** (Scheme 3).



i: Ph-NCO (1.1 equiv.), alkene (5 equiv.), DMF, 24 h, 60°C, 62%
ii: TEA (0.05 equiv.), DMF, r.t., quant.

Scheme 3

The crystal structure of the isomerized product **8** is shown in Figure 3. One of the ethyl ester groups is placed in close to the aromatic ring, so that the resulting magnetic anisotropy is able to explain the comparatively large differences between the ¹H NMR shifts of the two ethoxy groups, being $\delta = 4.07$ vs. 4.30 (OCH₂) and 1.04 vs. 1.36 ppm (CH₃), respectively.

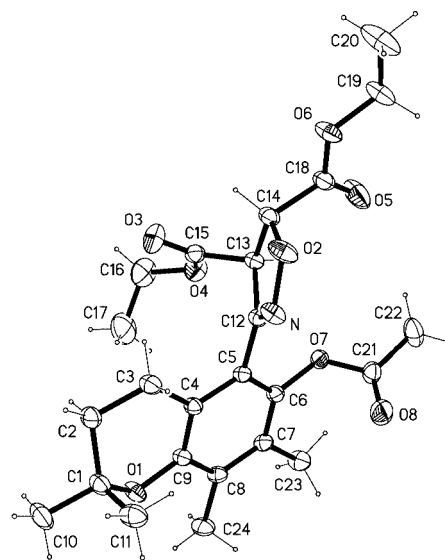


Figure 3. Thermal ellipsoid plot (25% ellipsoids) and crystallographic atom labeling of tocopherylisoxazoline **8**

In all the ¹H NMR spectra of the isoxazolines, the methylene groups of the substituents R² and R³ adjacent to the

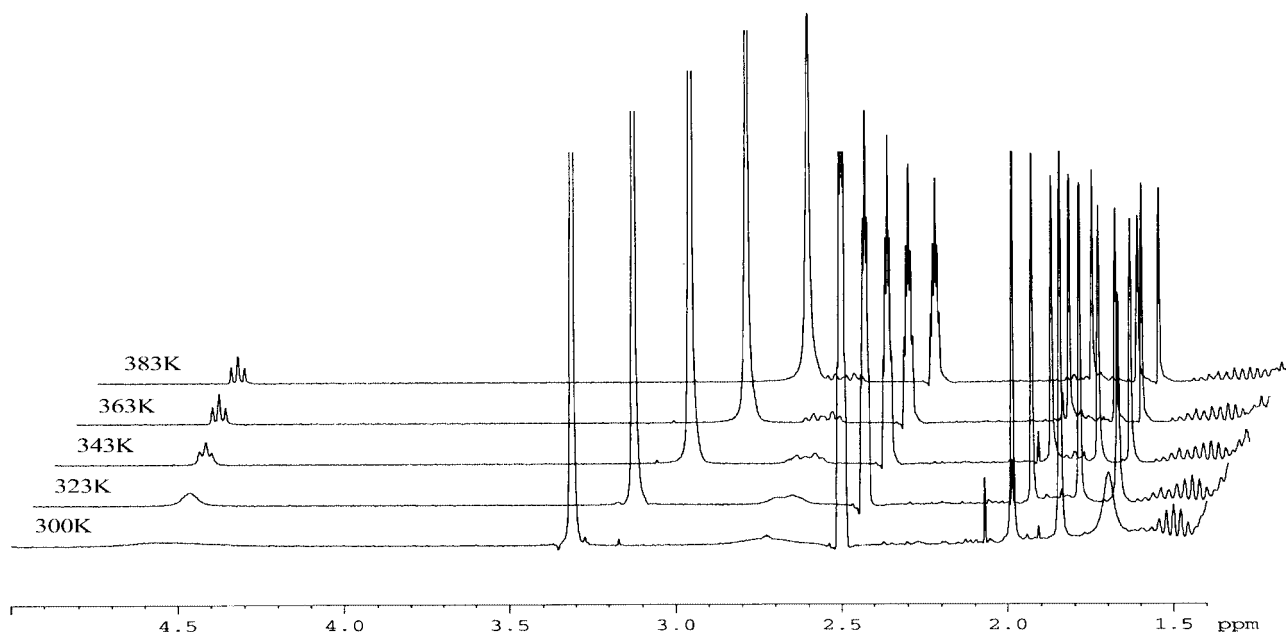


Figure 4. Stacked plots of ^1H NMR spectra (region between $\delta = 1.5$ and 5.0 ppm) of isoxazoline **6**, recorded at different temperatures in $[\text{D}_6]\text{DMSO}$; note the temperature-dependent line shape and chemical-shift changes of the resonances of $4''\text{-CH}$ ($\delta \approx 4.5$ ppm), 4-CH_2 ($\delta \approx 2.6\text{--}2.8$ ppm) and the acetyl group ($\delta \approx 1.6\text{--}1.8$ ppm)

stereogenic centers show a pronounced diastereotopic splitting. In addition, an altered signal of the C-4 methylene group is observed. This peak, which in almost all tocopherol derivatives known so far appears as a sharp triplet at $\delta \approx 2.60$ ppm, now shows two broad, largely temperature-independent multiplets at $\delta \approx 2.50$ and 2.80 ppm. The acetyl group is found as a sharp singlet at $\delta = 2.25\text{--}2.30$ ppm, with the exception of **5** and **6** (see below).

The room-temperature spectrum of isoxazoline derivatives **5** and **6**, with their relatively bulky, *trans*-configured phenyl substituents, shows an interesting feature: three broad peaks originating from $4''\text{-H}$ in the isoxazoline moiety, from the 4-CH_2 methylene group and, surprisingly, from the acetyl group, indicating restricted mobility of these protons (see Figure 4). The crystal structure of **6**, as shown in Figure 1, suggests that this behavior is due to the proximity of the bulky phenyl substituents. With increasing temperature, the broad resonances sharpen into a triplet, multiplet and singlet, respectively. In addition, the acetyl CH_3 group in **5** and **6** experiences a pronounced high-field shift to $\delta = 1.6$ ppm (at 298 K; $\delta = 1.8$ ppm at 383 K), as compared to the “usual” appearance in the other isoxazolines at $\delta \approx 2.2\text{--}2.3$ ppm.

Further experiments will focus on the reaction of 5-nitro- α -tocopheryl acetate (**3**) with alkenes to link the tocopheryl moiety to a polymer support, and on further modifications starting from the isoxazoline moiety.

Experimental Section

General Remarks: All chemicals were commercially available. All-racemic α -tocopherol and α -tocopheryl acetate were used as the

starting materials. 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 ($40\text{--}63$ μm). Melting points, determined with a Kofler-type micro hot stage apparatus with a Reichert–Biovar microscope, are uncorrected. ^1H NMR spectra were recorded at 300 MHz for ^1H and at 75.47 MHz for ^{13}C NMR in CDCl_3 , unless stated otherwise. Chemical shifts, relative to TMS as internal standard, are given in δ values. ^{13}C peaks were assigned by means of APT, HMQC and HMBC spectra. The resonances of the isoprenoid side chain of tocopherols are not influenced by modifications of the chroman ring, and are therefore not listed; “d.i.” denotes peaks with double intensity. Computations, as implemented through Spartan Pro 02 by Wavefunction, Inc., Irvine, CA, USA, were carried out on geometries pre-optimized by the semi-empirical PM3 method. For full geometry optimization the widely employed B3LYP hybrid method, which includes a mixture of HF and DFT exchange terms and the gradient-corrected correlation functional of Lee, Yang and Parr^[19,20] parametrized by Becke,^[21,22] was used, along with the double-zeta split valence basis set $6\text{-}31+\text{G}^*$,^[23,24] which includes diffuse functions.

Acetoxychroman 2a: Compound **2a** was obtained by acetylation of the vitamin E model compound 2,2,5,7,8-pentamethylchroman-6-ol (PMC, 0.10 g, 0.45 mmol) by acetyl chloride (0.32 mL, 0.50 mmol) in CH_2Cl_2 in the presence of TEA (55 mg, 0.50 mmol). After addition of water (100 mL) and extraction with EtOAc, **2a** was isolated quantitatively. Analytical data are consistent with those given in the literature.^[25]

Nitrotocopherol 3 and Nitrochromanol 3a: Concentrated nitric acid (16 mL) was added dropwise at ambient temperature to a solution of **2** or **2a** (6.70 mmol) in glacial acetic acid (50 mL). After stirring for 30 min, the solution was diluted with water (100 mL) and extracted repeatedly with *n*-hexane. The combined organic layers were neutralized with saturated NaHCO_3 solution, washed with water and brine, dried with MgSO_4 , and filtered. The solvent was re-

moved in vacuo and the crude product was purified by column chromatography (EtOAc/*n*-hexane, 1:20, v/v). 3,4-Dihydro-5-nitro-methyl-2,2,7,8-tetramethyl-2*H*-chroman-6-yl acetate (**3a**). White solid, m.p. 122–124 °C. ¹H NMR: δ = 5.38 (s, 2 H, 5a-H), 2.76 (t, ³*J* = 6.8 Hz, 2 H, 4-H), 2.34 (s, 3 H, acetyl CH₃), 2.13 (s, 3 H, 8b-H), 2.03 (s, 3 H, 7a-H), 1.82 (t, ³*J* = 6.8 Hz, 2 H, 3-H), 1.31 (s, 6 H, 2a-H) ppm. ¹³C NMR: δ = 169.3 (CO), 150.1 (C-8b), 141.7 (C-6), 129.0 (C-8), 128.2 (C-7), 118.6 (C-4a), 117.9 (C-5), 73.7 (C-2), 71.5 (C-5a), 32.3 (C-3), 26.8 (C-2a), 20.4 (acetyl CH₃), 20.3 (C-4), 13.2 (C-8b), 12.4 (C-7a) ppm. IR (KBr): ν̄ = 2978, 2939, 1749, 1560, 1427, 1373, 1218, 1170, 1014 cm⁻¹. C₁₆H₂₁NO₅ (307.34): calcd. C 62.53, H 6.89, N 4.56; found C 62.44, H 6.79, N 4.46.

Tocopherylisoxazolines 5–13: Phenyl isocyanate (0.050 g, 0.43 mmol), a catalytic amount of triethylamine (5 drops) and alkene component (5 equiv., 2 mmol) were added to **3** or **3a** (0.40 mmol) in dry DMF (50 mL). The mixture was stirred for 48 h under argon (nitrogen) at room temp., quenched with water, extracted repeatedly with *n*-hexane, dried with MgSO₄, and filtered. The solvent was removed in vacuo, and the crude product was purified by column chromatography (EtOAc/*n*-hexane, 1:10, v/v) at least twice.

trans-Diphenyl-tocopherylisoxazoline 5: 5-(*trans*-4,5-Diphenyl-4,5-dihydroisoxazol-3-yl)-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-6-yl acetate, colorless oil. ¹H NMR: δ = 7.59–7.49 (m, 10 H, Ar-H), 5.90 (d, ³*J* = 4.4 Hz, 1 H, 5'-H), 4.50 (br. s, 1 H, 4'-H), 2.75 (br. s, 2 H, 4-H), 2.04 (s, 3 H, 8b-H), 1.91 (s, 3 H, 7a-H), 1.62 (br. s, 3 H, acetyl), 1.60–1.45 (m, 2 H, 3-H) ppm. ¹³C NMR: δ = 168.9 (CO), 155.6 (C=N), 149.6 (C-8a), 141.7 (C-6), 128.9, 127.9, 127.8, 127.6, 124.9 (C^{Ar}), 127.7 (C-8), 127.5 (C-7), 118.9 (C-5), 118.0 (C-4a), 88.1 (C-5'), 75.8 (C-2), 66.2 (C-4'), 30.7 (C-3), 21.0 (C-4), 22.6 (acetyl CH₃), 12.9 (C-8b), 12.3 (C-7a) ppm. IR (film): ν̄ = 2971, 1768, 1755, 1452, 1367, 1195, 1101, 1076, 752, 700 cm⁻¹. HRMS for [C₄₅H₆₁NO₄ + Na]⁺: calcd. 702.48, found 702.46.

trans-Diphenyl-chromanylisoxazoline 6: 5-(*trans*-4,5-Diphenyl-4,5-dihydroisoxazol-3-yl)-2,2,7,8-tetramethylchroman-6-yl acetate, white crystals, m.p. 171–171 °C. ¹H NMR (room temp.): δ = 7.45–7.20 (m, 10 H, Ar-H), 5.90 (d, ³*J* = 3.9 Hz, 1 H, 5'-H), 4.48 (br. s, 1 H, 4'-H), 2.83 (br. s, 2 H, 4-H), 2.04 (s, 3 H, 8b-H), 1.91 (s, 3 H, 7a-H), 1.60 (br. s, 3 H, acetyl), 1.60–1.45 (m, 2 H, 3-H) ppm. ¹³C NMR: δ = 168.9 (CO), 155.6 (C=N), 149.6 (C-8a), 141.7 (C-6), 128.9, 127.9, 127.8, 127.6, 124.9 (C^{Ar}), 127.7 (C-8), 127.5 (C-7), 118.9 (C-5), 118.0 (C-4a), 88.1 (C-5'), 75.8 (C-2), 66.2 (C-4'), 30.7 (C-3), 22.6 (acetyl CH₃), 21.0 (C-4), 12.9 (C-8b), 12.3 (C-7a) ppm. IR: ν̄ = 3030, 2972, 2920, 1770, 1452, 1369, 1193, 1068, 1074, 700 cm⁻¹. C₃₀H₃₁NO₄ (469.6): calcd. C 76.73, H 6.65, N 2.98; found C 76.66, H 6.76, N 2.90.

Tocopherylisoxazoline trans-Diester 7: Diethyl 3-[6-acetoxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-5-yl]-4,5-dihydroisoxazole-*trans*-4,5-dicarboxylate, colorless oil. ¹H NMR: δ = 5.48 (d, ³*J* = 6.3 Hz, 1 H, 5'-H), 4.81 (m, 1 H, 4'-H), 4.30 (q, ³*J* = 7.2 Hz, 2 H, OCH₂), 4.07 (m, 2 H, OCH₂), 2.95–2.75 (m, 1 H, 4-H), 2.57–2.44 (m, 1 H, 4-H), 2.25 (s, 3 H, acetyl CH₃), 2.14 (s, 3 H, 7a-H), 2.01 (s, 3 H, 8b-H), 1.50 (m, 2 H, 3-H), 1.36 (t, ³*J* = 7.2 Hz, 3 H, ethyl CH₃), 1.04 (m, 3 H, ethyl CH₃) ppm. ¹³C NMR: δ = 169.0 (acetyl CO and COOEt), 167.2 (COOEt), 150.7 (C=N), 149.7 (C-8a), 140.4 (C-6), 128.1 (C-8), 128.0 (C-7), 118.3 (C-5), 117.1 (C-4a), 81.0 (C-5'), 75.4 (C-2), 62.3 and 62.2 (2 × OCH₂), 59.1 (C-4'), 27.9 (C-3), 21.0 (C-4), 14.1 and 13.7 (ethyl CH₃), 13.0 (C-8b), 12.3 (C-7a) ppm. IR (film): ν̄ = 2947, 2862, 1768, 1737, 1452, 1367, 1188, 1080, 1076, 1026, 862 cm⁻¹. HRMS for [C₃₉H₆₁NO₈ + H]⁺: calcd. 672.45, found 672.46.

Chromanylisoxazoline trans-Diester 8: Diethyl 3-[6-acetoxy-2,2,7,8-tetramethyl-2-chroman-5-yl]-4,5-dihydroisoxazole-*trans*-4,5-dicarboxylate, white solid, m.p. 191–193 °C. ¹H NMR: δ = 5.48 (d, ³*J* = 6.3 Hz, 1 H, 5'-H), 4.81 (m, 1 H, 4'-H), 4.30 (q, ³*J* = 7.2 Hz, 2 H, OCH₂), 4.07 (m, 2 H, OCH₂O), 2.95–2.75 (m, 1 H, 4-H), 2.57–2.44 (m, 1 H, 4-H), 2.25 (s, 3 H, acetyl CH₃), 2.14 (s, 3 H, 7a-H), 2.01 (s, 3 H, 8b-H), 1.82–1.62 (m, 2 H, 3-H), 1.36 (m, 12 H, ethyl CH₃, 2a-H, 2b-H), 1.04 (t, ³*J* = 7.2 Hz, 3 H, ethyl CH₃) ppm. ¹³C NMR: δ = 169.0 (acetyl CO and COOEt), 167.2 (COOEt), 150.7 (C=N), 149.8 (C-8a), 140.5 (C-6), 128.2 (C-8), 128.1 (C-7), 118.1 (C-5), 117.2 (C-4a), 81.0 (C-5'), 73.8 (C-2), 62.4 and 62.2 (2 × OCH₂), 59.1 (C-4'), 32.4 (C-3), 27.8 and 26.0 (C-2a, C-2b), 20.9 (C-4), 14.1 and 13.7 (ethoxy CH₃), 13.0 (C-8b), 12.3 (C-7a) ppm. IR (film): ν̄ = 2950, 2865, 1769, 1740, 1450, 1364, 1189, 1079, 1076 cm⁻¹. C₂₄H₃₁NO₈ (461.51): calcd. C 62.46, H 6.77, N 3.03; found C 62.18, H 6.48, N 2.95.

cis-Diphenyl-chromanylisoxazoline 9: 5-(*cis*-4,5-Diphenyl-4,5-dihydroisoxazol-3-yl)-2,2,7,8-tetramethylchroman-6-yl acetate, white crystals, m.p. 181–183 °C. ¹H NMR (room temp.): δ = 7.13 (m, 5 H, Ar-H), 6.99 (m, 3 H, Ar-H), 6.88 (m, 2 H, Ar-H), 5.95 (d, ³*J* = 9.8 Hz, 1 H, 5'-H), 4.93 (br. d, ³*J* = 9.8 Hz, 1 H, 4'-H), 2.92 (br. s, 1 H, 4-H), 2.38 (s, 3 H, acetyl), 2.35 (br. m, 1 H, 4-H), 2.05 (s, 3 H, 8b-H), 1.98 (s, 3 H, 7a-H), 1.76–1.48 (m, 2 H, 3-H), 1.17 (s, 6 H, 2a-H) ppm. ¹³C NMR: δ = 168.4 (CO), 158.0 (C=N), 149.8 (C-8a), 140.4 (C-6), 135.6, 133.4, 129.3, 128.0 (C^{Ar}), 128.0 (C-8), 127.9 (C-7), 127.8, 127.3, 127.2, 126.6 (C^{Ar}), 118.9 (C-5), 117.7 (C-4a), 86.2 (C-5'), 73.6 (C-2), 61.4 (C-4'), 32.3 (C-3), 27.5 (C-2a), 26.1 (C-2a'), 21.2 (C-4), 20.8 (acetyl CH₃), 12.9 (C-8b), 12.3 (C-7a) ppm. IR: ν̄ = 3057, 2972, 2925, 1759, 1452, 1359, 1205, 1080, 698 cm⁻¹. C₃₀H₃₁NO₄ (469.6): calcd. C 76.74, H 6.65, N 2.98; found C 76.66, H 6.76, N 2.90.

[Bis(benzoyloxymethyl)tocopheryl]isoxazoline 10: 3-[6-Acetoxy-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)chroman-5-yl]-4,5-*cis*-bis(phenylcarbonyloxymethyl)-4,5-dihydroisoxazole, colorless oil. ¹H NMR: δ = 8.06 (d, ³*J* = 7.3 Hz, 2 H, Ar-H), 7.77 (d, ³*J* = 7.3 Hz, 2 H, Ar-H), 7.59–7.49 (m, 2 H, Ar-H), 7.43 (t, ³*J* = 7.8 Hz, 2 H, Ar-H), 7.34 (t, ³*J* = 7.8 Hz, 2 H, Ar-H), 5.15–5.07 (m, 1 H, 5'-H), 4.80 (dd, ²*J* = 11.9, ³*J* = 4.7 Hz, 1 H, 5'-CHCH₂O), 4.69 (dd, ²*J* = 11.9, ³*J* = 7.2 Hz, 1 H, 5'-CHCH₂O), 4.32–4.41 (m, 2 H, 4'-CHCH₂O), 4.25–4.13 (m, 1 H, 4'-H), 2.95–2.80 (m, 1 H, 4-H), 2.60–2.41 (m, 1 H, 4-H), 2.25 (s, 3 H, acetyl CH₃), 2.10 (s, 3 H, 7a-H), 1.96 (s, 3 H, 8b-H), 1.76–1.66 (m, 2 H, 3-H) ppm. ¹³C NMR: δ = 168.9 (acetyl CO), 166.2 (benzoyl CO), 165.8 (benzoyl CO), 155.2 (C=N), 150.1 (C-8a), 140.2 (C-6), 133.3, 129.8, 129.4 (C^{Ar}), 129.1 (C-8), 128.4, 128.3, 129.5 (C^{Ar}), 128.2 (C-7), 118.2 (C-5), 117.9 (C-4a), 79.6 (C-5'), 75.4 (C-2), 62.3 (CH₂O), 60.3 (CH₂O), 52.2 (C-4'), 30.4 (C-3), 21.1 (C-4), 20.6 (acetyl CH₃), 13.0 (C-7a), 12.3 (C-8b) ppm. IR (film): ν̄ = 2935, 2866, 1760, 1724, 1450, 1373, 1269, 1195, 1140, 1109, 709 cm⁻¹. HRMS for [C₄₉H₆₅NO₈ + H]⁺: calcd. 796.48, found 796.50.

[Bis(benzoyloxymethyl)chromanyl]isoxazoline 11: 3-[6-Acetoxy-2,2,7,8-tetramethylchroman-5-yl]-4,5-*cis*-bis(phenylcarbonyloxymethyl)-4,5-dihydroisoxazole, white crystals, m.p. 131–133 °C. ¹H NMR: δ = 8.06 (d, ³*J* = 7.3 Hz, 2 H, Ar-H), 7.77 (d, ³*J* = 7.3 Hz, 2 H, Ar-H), 7.59–7.49 (m, 2 H, Ar-H), 7.42 (t, ³*J* = 7.8 Hz, 2 H, Ar-H), 7.33 (t, ³*J* = 7.8 Hz, 2 H, Ar-H), 5.16–5.08 (m, 1 H, 5'-H), 4.80 (dd, ²*J* = 11.9, ³*J* = 4.7 Hz, 1 H, 5'-CHCH₂O), 4.69 (dd, ²*J* = 11.9, ³*J* = 7.2 Hz, 1 H, 5'-CHCH₂O), 4.53–4.42 (m, 2 H, 4'-CHCH₂O), 4.21 (m, 1 H, 4'-H), 2.91 (m, 1 H, 4-H), 2.50 (m, 1 H, 4-H), 2.25 (s, 3 H, acetyl CH₃), 2.09 (s, 3 H, 7a-H), 1.96 (s, 3 H, 8b-H), 1.74–1.44 (m, 2 H, 3-H), 1.24 (s, 6 H, 2a-H) ppm. ¹³C NMR: δ = 168.9 (acetyl CO), 166.1 (benzoyl CO), 165.7 (benzoyl

CO), 155.2 (C=N), 150.0 (C-8a), 140.2 (C-6), 133.21, 133.24, 129.7, 129.5, 129.4 (^{13}C), 129.0 (C-7), 128.4, 128.2 (^{13}C), 128.1 (C-8), 118.2 (C-4a), 117.5 (C-5), 79.5 (C-5'), 73.7 (C-2), 62.1 (CH_2O), 60.3 (CH_2O), 51.1 (C-4'), 32.1 (C-3), 27.9, 25.9 (C-2a), 21.2 (C-4), 20.9 (acetyl CH_3), 12.9 (C-7a), 12.2 (C-8b) ppm. IR (KBr): $\tilde{\nu}$ = 3060, 2993, 2972, 1757, 1720, 1600, 1450, 1367, 1271, 1197, 1070, 707 cm^{-1} . $\text{C}_{34}\text{H}_{35}\text{NO}_8$ (585.7): calcd. C 69.73, H 6.02, N 2.39; found C 69.97, H 6.06, N 2.60.

Ethoxy-tocopherylisoaxazoline 12: 2,7,8-Trimethyl-5-(5-ethoxy-4,5-dihydroisoxazol-3-yl)-2-(4,8,12-trimethyltridecyl)chroman-6-yl acetate, colorless oil. ^1H NMR: δ = 5.58 (d, 3J = 6.3 Hz, 1 H, 5'-H), 3.98–3.88 (m, 1 H, OCH_2), 3.65–3.55 (m, 1 H, OCH_2), 3.22 (m, 1 H, 4'-H), 3.00 (m, 1 H, 4'-H), 2.83–2.73 (m, 1 H, 4-H), 2.59–2.48 (m, 1 H, 4-H), 2.26 (s, 3 H, acetyl CH_3), 2.13 (s, 3 H, 8b-H), 2.03 (s, 3 H, 7a-H), 1.83–1.69 (m, 2 H, 3-H) ppm. ^{13}C NMR: δ = 169.6 (CO), 154.7 (C=N), 149.7 (C-8a), 140.0 (C-6), 128.0 (C-8), 127.6 (C-7), 119.3 (C-5), 117.6 (C-4a), 102.3 (C-5'), 75.7 (C-2), 63.6 (OCH_2), 47.8 (C-4'), 30.2 (C-3), 20.6 (C-4), 15.1 (ethyl CH_3), 12.8 (C-7a), 12.2 (C-8b) ppm. IR (film): $\tilde{\nu}$ = 2937, 1776, 1457, 1400, 1377, 1195, 1110, 752, 700 cm^{-1} . HRMS for $[\text{C}_{35}\text{H}_{57}\text{NO}_5 + \text{H}]^+$: calcd. 572.43, found 572.44.

Pyrano-tocopherylisoaxazoline 13: 6-Acetoxy-2,7,8-trimethyl-5-(3a,5,6,7a-tetrahydro-4H-pyrano[3,2-d]isoxazol-3-yl)-2-(4,8,12-trimethyltridecyl)chroman, colorless oil. ^1H NMR: δ = 5.74 (d, 3J = 6.2 Hz, 1 H, 5'-H), 3.90–3.83 (m, 1 H, OCH_2), 3.58–3.50 (m, 2 H, OCH_2 , 4'-H), 2.88 (br. s, 1 H, 4-H), 2.66–2.51 (m, 1 H, 4-H), 2.25 (s, 3 H, acetyl CH_3), 2.15 (s, 3 H, 8b-H), 2.03 (s, 3 H, 7a-H), 1.89–1.58 (m, 3×2 H, 3-H, H in pyran) ppm. ^{13}C NMR: δ = 168.7 (CO), 158.1 (C=N), 150.1 (C-8a), 140.4 (C-6), 128.2 (C-8), 128.1 (C-7), 118.0 (C-5), 118.0 (C-4a), 99.9 (C-5'), 76.0 (C-2), 61.3 (O-CH_2), 47.8 (pyran CH_2), 30.7 (C-3), 24.4 (pyran CH_2), 20.6 (C-4), 19.6 (pyran CH_2), 13.0 (C-8b), 12.3 (C-7a) ppm. IR (film): $\tilde{\nu}$ = 2973, 2937, 1776, 1460, 1409, 1365, 1195, 1107, 1076, 752, 700 cm^{-1} . HRMS for $[\text{C}_{36}\text{H}_{57}\text{NO}_5 + \text{Na}]^+$: calcd. 606.41, found 606.40.

X-ray Crystallographic Study: X-ray data collection was performed with a Bruker AXS Smart APEX CCD diffractometer and graphite-monochromated Mo- K_α radiation, λ = 0.71073 Å; corrections for absorption with the program SADABS, structure solution with direct methods, 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). CCDC-220789 to -220791 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-0333; E-mail: deposit@ccdc.cam.ac.uk].

trans-Diphenyl-chromanylisoxazoline 6: $\text{C}_{30}\text{H}_{31}\text{NO}_4$, M = 469.56, monoclinic, space group $P2_1/c$, a = 10.465(2) Å, b = 22.554(4) Å, c = 10.925(2) Å, β = 94.470(4)°, V = 2570.6(8) Å³, Z = 4, $D_{\text{calcd.}}$ = 1.213 g/cm^3 , T = 299 K, μ = 0.080 mm^{-1} , $F(000)$ = 1000, colorless plate ($0.66 \times 0.45 \times 0.08$ mm); total reflections = 11812, unique reflections = 3690, R_{int} = 0.054, final refinement: data/restraints/parameters = 3690/0/321, goodness-of-fit on F^2 = 1.112, R_1 = 0.078 [$I > 2\sigma(I)$], wR_2 = 0.65 (all data).

cis-Diphenyl-chromanylisoxazoline 9: The compound contains two conformationally different molecules, which are distinguished by the orientation of isoxazole and phenyl rings. $\text{C}_{30}\text{H}_{31}\text{NO}_4$, M = 469.56, monoclinic, space group $P2_1/n$, a = 15.020(2) Å, b = 18.676(3) Å, c = 18.438(3) Å, β = 105.229(3)°, V = 4990.4(12) Å³,

Z = 8, $D_{\text{calcd.}}$ = 1.250 g/cm^3 , T = 100 K, μ = 0.082 mm^{-1} , $F(000)$ = 2000, colorless block, ($0.64 \times 0.32 \times 0.24$ mm); total reflections = 26853, unique reflections = 8762, R_{int} = 0.042, final refinement: data/restraints/parameters = 8762/0/641, goodness-of-fit on F^2 = 1.028, R_1 = 0.050 [$I > 2\sigma(I)$], wR_2 = 0.124 (all data).

Chromanylisoxazoline trans-Diester 8: $\text{C}_{24}\text{H}_{31}\text{NO}_8$, M = 461.50, monoclinic, space group Cc (No. 9), a = 17.1462(9) Å, b = 9.8498(5) Å, c = 15.4341(8) Å, β = 112.754(2)°, V = 2403.8(2) Å³, Z = 4, $D_{\text{calcd.}}$ = 1.275 g/cm^3 , T = 297 K, μ = 0.096 mm^{-1} , $F(000)$ = 984, colorless block ($0.75 \times 0.45 \times 0.35$ mm); total reflections 17535, unique reflections 6926, R_{int} = 0.017, final refinement: data/restraints/parameters = 6926/2/301, goodness-of-fit on F^2 = 1.044, R_1 = 0.052 [$I > 2\sigma(I)$], wR_2 = 0.138 (all data).

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