# Synthesis of novel bioconjugates of α-tocopherol with lupane triterpenoids

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The first representatives of α-tocopherol bioconjugates with lupane triterpenoids were synthesized using amino acid residues and dipeptides as linkers between the antioxidant molecule and the terpenoid C(28) atom. The synthetic combination of natural compounds was carried out by the reaction of lupane acid chlorides (betulonic and betulinic acid chlorides) with amino acid and dipeptide derivatives of α-tocopherol.

**Key words:** bioconjugates, spacers, α-tocopherol, peptides, triterpenoids, lupane derivatives, betulinic acid, amides.

Currently, bioconjugates of natural compounds or hybrid molecules combined from pharmacophores of native and synthetic biologically active compounds are used most often in the development of new polyfunctional pharmaceutical agents in combinatorial and medical chemistry.[1] Interesting results along this line were obtained by involving the lipophilic antioxiodant α-tocopherol (Vitamin E) and related chromanols in combinations with other molecules. Thus by modification of known camptotecin- and taxol-based antitumor agents by α-tocopherol, the problems related to poor solubility of these agents in fats were solved, their lipophilicity and retention in membranes increased and, as a consequence, a higher therapeutic efficiency was attained.[2,3] The previously prepared[4] α-tocopherol conjugates with 5-aminolevulinic acid are of interest for the photodynamic therapy. Heterodimers based on available water-soluble chromanol, the Trolox acid, behaved as multifunctional agents exhibiting high antioxiodant,[5] antitumor,[6] antiinflammatory,[7] and antiarrhythmic activities.[8]

No data on bioconjugates of α-tocopherol with lupane triterpenoids can be found in the literature, although a combination of the potent lipophilic antioxiodant with lupane terpenoids having diverse biological activities[9,10] could lead to mutual synergistic influence of the combined molecules or new valuable biological activity of the hybrid compound. In the preliminary communication,[11] we reported the synthesis of α-tocopherol conjugate with betulonic acid with glycine residue as the spacer. Here we synthesized a number of structurally related hybrids of α-tocopherol and lupane acids conjugated by L-amino acids and dipeptides through amide and ester bonds.

## Results and Discussion

The target conjugates were synthesized by acylation of α-tocopherol (**1**) with *N*-benzyloxycarbonyl derivative of glycine (**2a**), L-valine (**2b**), L-phenylalanine (**2c**), or L-lysine (**2d**) in the presence of DCC and DMAP. The amino group in the synthesized *O*-acyl derivatives **3a—d** was deprotected by hydrogenolysis in the presence of a palladium catalyst. The obtained conjugates **4a—d** with free amino group were converted into oxalates **5a—d** stable on storage by adding a specified amount of oxalic acid to the reaction medium during the removal of the benzyloxycarbonyl (Cbz) protecting group (Scheme 1). In the $^1$H NMR spectra of salts **5a—d**, the signals of protons at the carbon atoms connected to nitrogen are shifted downfield ($\Delta\delta \approx 0.6$—$0.9$), whereas the $^{13}$C NMR spectra of oxalates show upfield ($\Delta\delta \approx 5$) shifts for the signals of carbonyl C atoms with respect to the corresponding signals in the spectra of amines **4a—d** (Table 1).

Amino acid derivatives **4a**,**b** were converted into dipeptide conjugates **6a**,**b**, under conditions used in the synthesis of **3a—d**. After amino group deprotection, compounds **6a**,**b** were transformed into dipeptide derivatives **7a,b** with free amino group.

Coupling of betulonic (**8a**), betulinic (**8b**), and *O*-acetylbetulinic (**8c**) acid chlorides, obtained immediately prior to the reaction by treatment of the acids with oxalyl chloride by a known procedure,[13] with conjugates **4a—c** resulted in hybrids of α-tocopherol with betulonic (**9a—c**), betulinic (**9d**), and *O*-acetylbetulinic (**9e**) acids with α-amino acid **2a—c** residues as spacers. The reactions proceeded on short-term refluxing (0.5—1 h) in benzene. The yields of hybrids isolated by column chromatography on

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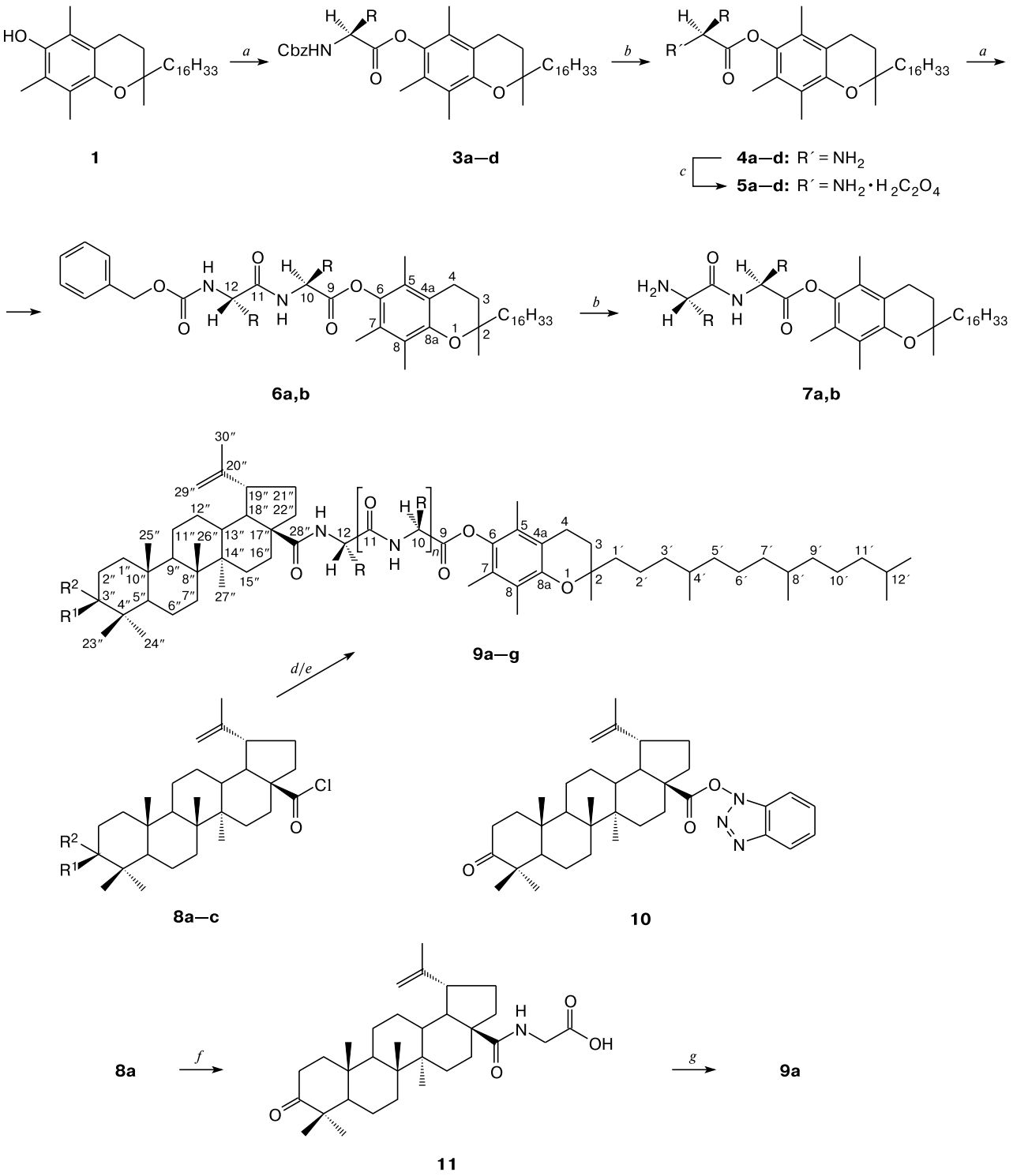
**Scheme 1**




**Reagents and conditions:** *a*. CbzNHCHRCO$_2$H (**2a**—**d**), DCC, DMAP (10 mol.%), $CH_2Cl_2$, ~20 °C; *b*. $H_2$, 10% Pd/C, EtOH; *c*. $H_2C_2O_4$, EtOH; *d*. **4a**—**c**, PhH, refluxing for 0.5—1 h; *e*. **7a**,**b**, EDC, $CH_2Cl_2$, 20 °C; *f*. 1) HCl·$NH_2CH_2CO_2Me$, $Et_3N$, $CHCl_3$, 20 °C; 2) 4 *M* NaOH, MeOH, THF, 20 °C (see Ref. 12); *g*. **1**, DCC, DMAP (10 mol.%), $CH_2Cl_2$, 20 °C.

R = H (**2a**—**7a**, **9a**,**d**—**f**), $Me_2CH$ (**2b**—**7b**, **9b**,**g**), $PhCH_2$ (**2c**—**5c**, **9c**), CbzHN(CH$_2$)$_4$ (**2d**, **3d**), $H_2N(CH_2)_4$ (**4d**), $H_2C_2O_4$·$H_2N(CH_2)_4$ (**5d**); $R^1R^2$ = O (**8a**, **9a**—**c**,**f**,**g**); $R^1$ = OH, $R^2$ = H (**8b**, **9d**); $R^1$ = OAc, $R^2$ = H (**8c**, **9e**); *n* = 0 (**9a**—**e**), 1 (**9f**,**g**)

**Table 1.** $^{13}C$ NMR spectra of compounds **3b—d** and **4b—d**

| Atom or group | δ | | | | | |
|---|---|---|---|---|---|---|
| | **3b** | **3c** | **3d** | **4b** | **4c** | **4d** |
| C(2) | 75.11 | 75.14 | 74.94 | 75.06 | 75.10 | 75.00 |
| $C(3)H_2$ | 30.91 | 31.08 | 31.65 | 31.07 | 31.05 | 31.04 |
| $C(4)H_2$ | 20.63, 21.04 | 20.63, 21.07 | 20.46, 20.91 | 20.62, 21.02 | 20.62, 21.05 | 20.59, 21.01 |
| C(4a) | 126.56 | 126.61 | 126.50 | 126.58 | 126.58 | 126.48 |
| C(5) | 117.48 | 117.50 | 117.33 | 117.42 | 117.46 | 117.43 |
| C(6) | 149.59 | 149.65 | 149.41 | 149.48 | 149.54 | 149.47 |
| C(7) | 123.18 | 123.18 | 122.97 | 123.10 | 123.15 | 123.11 |
| C(8) | 124.86 | 124.91 | 124.50 | 124.84 | 124.83 | 124.72 |
| C(8a) | 140.35 | 140.32 | 140.12 | 140.40 | 140.27 | 140.26 |
| O—C(9)=O | 170.89 | 170.69 | 171.20 | 173.40 | 173.51 | 174.55 |
| NC(10)H(R) | 58.00 | 55.02 | 53.89 | 59.82 | 56.11 | 54.49 |
| $C(1')H_2$ | 40.42 | 40.25 | 40.00 | 40.32 | 40.10 | 40.00 |
| $C(2')H_2$ | 24.46 | 24.85 | 24.32 | 24.44 | 24.47 | 24.42 |
| $C(3')H_2$ | 37.30 | 37.33 | 37.16 | 37.29 | 37.32 | 37.27 |
| C(4′)H | 32.71 | 32.73 | 32.55 | 32.69 | 32.71 | 32.67 |
| $C(5')H_2$ | 37.41 | 37.44 | 37.27 | 37.40 | 37.42 | 37.37 |
| $C(6')H_2$ | 24.71 | 24.48 | 24.70 | 24.81 | 24.83 | 24.79 |
| $C(7')H_2$ | 37.54 | 37.49 | 37.33 | 37.45 | 37.42 | 37.39 |
| C(8′)H | 32.79 | 32.82 | 32.65 | 32.78 | 32.80 | 32.75 |
| $C(9')H_2$ | 37.54 | 37.57 | 37.43 | 37.53 | 37.55 | 37.44 |
| $C(10')H_2$ | 24.71 | 24.85 | 24.70 | 24.81 | 24.83 | 24.80 |
| $C(11')H_2$ | 39.38 | 39.41 | 39.25 | 39.37 | 39.39 | 39.36 |
| C(12′)H | 27.99 | 28.02 | 27.85 | 27.97 | 28.00 | 27.96 |
| BnO—C=O | 156.45 | 155.89 | 156.20, 156.52 | — | — | — |
| $(CH_2)_4NH_2$ | — | — | 29.17, 29.59, 30.92, 40.27 | — | — | 34.44, 23.17, 32.28, 41.46 |
| $\underline{C}H(Pr^i)$ | 31.05 | — | — | 31.37 | — | — |
| Me(Ar) | 11.85, 12.25, 13.10 | 11.86, 12.16, 13.01 | 11.71, 11.97, 12.82 | 11.80, 12.13, 13.00 | 11.85, 12.10, 12.95 | 11.81, 12.12, 12.97 |
| $\underline{Me}(Pr^i)$ | 17.09 | — | — | 16.75 | — | — |
| C(4′)Me | 19.71 | 19.74 | 19.61 | 19.69 | 19.72 | 19.68 |
| C(8′)Me | 19.77 | 19.81 | 19.68 | 19.88 | 19.78 | 19.75 |
| C(12′)Me | 22.65, 22.74 | 22.68, 22.78 | 22.55, 22.64 | 22.63, 22.72 | 22.66, 22.75 | 22.62, 22.71 |
| C(2)Me | 23.91 | 23.94 | 24.00 | 23.91 | 23.94 | 24.00 |
| $Ph\underline{C}H_2O$ | 68.00 | 67.04 | 66.42, 66.83 | — | — | — |
| Ph | 128.11, 128.20, 128.56, 136.25 | 127.23, 128.07, 128.17, 128.53, 128.76, 129.42, 135.86 | 127.86, 127.92, 128.31, 128.34, 136.17, 136.52 | — | 128.68, 129.46, 137.47 | — |
| $\underline{C}H_2Ph$ | — | 38.13 | — | — | 41.24 | — |

*Note*. Here and Table 2, the signals of C(4) are doubled, because we used racemic α-tocopherol. The numbering of C(1′)—C(12′) atoms of the aliphatic chain at C(2) is given in Scheme 1 (compound **9**).

$SiO_2$ were 61—82%. Conjugates **9f,g** were prepared by coupling of acid chloride **8a** with α-tocopherol dipeptide derivatives **7a,b**. As the coupling agent, it is necessary to use *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC) (the presence of *N*-hydroxybenzotriazole (HOBT)[14] is not necessary).

The attempts to couple free betulonic acid with amino acid derivatives of tocopherol **4a** or **4b** upon activation of

**Table 2.** $^{13}C$ NMR spectra of compounds **5a—d**, **6a,b**, and **7a,b**

| Atom or group | δ | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **5a** | **5b** | **5c** | **5d** | **6a** | **6b** | **7a** | **7b** |
| C(2) | 75.37 | 75.03 | 75.03 | 75.33 | 75.17 | 75.11 | 75.14 | 75.06 |
| $C(3)H_2$ | 30.94 | 31.10 | 30.91 | 29.98 | 31.00 | 31.02 | 31.00 | 30.86 |
| $C(4)H_2$ | 20.33, 20.82 | 20.55, 21.04 | 20.46, 22.02 | 20.35, 20.84 | 20.58, 21.04 | 20.61, 21.03 | 20.57, 21.02 | 20.61, 21.01 |
| C(4a) | 126.70 | 127.27 | 127.44 | 126.60 | 126.51 | 126.49 | 126.55 | 126.59 |
| C(5) | 117.99 | 116.93 | 117.35 | 117.99 | 117.55 | 117.48 | 117.30 | 117.44 |
| C(6) | 149.44 | 149.61 | 149.67 | 149.49 | 149.68 | 149.63 | 149.62 | 149.50 |
| C(7) | 122.49 | 123.39 | 123.03 | 122.53 | 123.21 | 123.20 | 123.17 | 123.09 |
| C(8) | 125.39 | 125.33 | 124.85 | 125.30 | 124.83 | 124.77 | 124.86 | 124.80 |
| C(8a) | 140.06 | 140.33 | 140.16 | 140.09 | 140.12 | 140.32 | 140.16 | 140.40 |
| O—C(9)=O | 167.21 | 168.32 | 168.31 | 168.71 | 169.64 | 171.55 | 172.99 | 174.64 |
| NC(10)H(R) | 43.32 | 58.39 | 54.29 | 52.09 | 41.03 | 61.22 | 40.73 | 60.33 |
| C(11)ONH | — | — | — | — | 168.67 | 170.58 | 168.84 | 170.81 |
| NC(12)H(R) | — | — | — | — | 44.39 | 57.07 | 44.39 | 56.77 |
| $C(1')H_2$ | 40.00 | 40.00 | 40.00 | 40.00 | 40.00 | 40.00 | 40.00 | 40.00 |
| $C(2')H_2$ | 24.14 | 24.47 | 24.46 | 24.18 | 24.45 | 24.44 | 24.44 | 24.43 |
| $C(3')H_2$ | 37.14 | 37.29 | 37.18 | 37.05 | 37.30 | 37.29 | 37.28 | 37.28 |
| C(4′)H | 32.45 | 32.79 | 32.74 | 32.47 | 32.71 | 32.70 | 32.69 | 32.68 |
| $C(5')H_2$ | 37.15 | 37.40 | 37.29 | 37.16 | 37.40 | 37.39 | 37.38 | 37.30 |
| $C(6')H_2$ | 24.59 | 24.80 | 24.80 | 24.60 | 24.82 | 24.81 | 24.80 | 24.79 |
| $C(7')H_2$ | 37.16 | 37.43 | 37.44 | 37.21 | 37.46 | 37.40 | 37.44 | 37.35 |
| C(8′)H | 32.47 | 32.79 | 32.79 | 32.51 | 32.80 | 32.78 | 32.77 | 32.77 |
| $C(9')H_2$ | 37.16 | 37.64 | 37.44 | 37.23 | 37.56 | 37.45 | 37.54 | 37.39 |
| $C(10')H_2$ | 24.59 | 24.80 | 24.80 | 24.60 | 24.82 | 24.81 | 24.95 | 24.79 |
| $C(11')H_2$ | 39.37 | 39.37 | 39.37 | 39.37 | 39.38 | 39.38 | 39.37 | 39.37 |
| C(12′)H | 27.82 | 27.97 | 27.97 | 27.82 | 27.99 | 27.98 | 27.97 | 27.97 |
| BnO—C=O | — | — | — | — | 156.72 | 156.41 | — | — |
| $(CH_2)_4NH_2$ | — | — | — | 22.03 | — | — | — | — |
| $\underline{C}H(Pr^i)$ | — | 29.77 | — | — | — | 30.82, 31.20 | — | 30.74, 31.06 |
| Me(Ar) | 12.00, 12.37, 13.22 | 11.72, 12.21, 13.11 | 11.70, 12.00, 12.80 | 11.98, 12.34, 13.19 | 11.82, 12.11, 12.96 | 11.83, 12.23, 13.08 | 11.80, 12.10, 12.92 | 11.81, 12.24, 13.09 |
| $\underline{Me}(Pr^i)$ | — | 17.35, 17.93 | — | — | — | 17.25, 17.51, 17.93, 19.13 | — | 17.25, 17.51, 17.93, 19.13 |
| C(4′)Me | 19.98 | 19.68 | 19.59 | 19.87 | 19.71 | 19.72 | 19.68 | 19.68 |
| C(8′)Me | 19.99 | 19.74 | 19.68 | 19.97 | 19.77 | 19.69 | 19.74 | 19.94 |
| C(12′)Me | 22.89, 22.98 | 22.62, 22.72 | 22.62, 22.71 | 22.86, 22.95 | 22.65, 22.74 | 22.63, 22.72 | 22.62, 22.72 | 22.63, 22.72 |
| C(2)Me | 23.80 | 23.79 | 23.50 | 23.50 | 24.10 | 23.87 | 23.78 | 23.91 |
| $Ph\underline{C}H_2O$ | — | — | — | — | 67.24 | 67.03 | — | — |
| Ph | — | — | 128.73, 129.52, 133.99 | — | 128.10, 128.23, 128.54, 136.11 | 127.99, 128.12, 128.50, 136.27 | — | — |
| $\underline{C}H_2Ph$ | — | — | 39.38 | — | — | — | — | — |
| $C{=}O(H_2C_2O_4)$ | 163.04 | 163.93 | 162.71 | 163.36 | — | — | — | — |

**Table 3.** $^{13}C$ NMR spectra of compounds **9b—g**, **10**, and **11**

| Atom or group | δ | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **9b** | **9c** | **9d** | **9e** | **9f** | **9g** | **10** | **11** |
| C(2) | 75.12 | 75.12 | 75.12 | 75.09 | 75.12 | 75.12 | — | — |
| $C(3)H_2$ | 30.81 | 31.02 | 30.97 | 30.80 | 30.80 | 30.80 | — | — |
| $C(4)H_2$ | 20.61 | 20.59 | 20.58 | 20.60 | 20.57 | 20.61 | — | — |
| C(4a) | 126.46 | 126.46 | 126.43 | 126.55 | 126.48 | 126.50 | — | — |
| C(5) | 117.49 | 117.50 | 117.58 | 117.45 | 117.46 | 117.48 | — | — |
| C(6) | 149.59 | 149.54 | 149.77 | 150.75 | 149.63 | 149.63 | — | — |
| C(7) | 123.18 | 123.20 | 123.29 | 123.14 | 123.14 | 123.22 | — | — |
| C(8) | 124.74 | 124.70 | 124.75 | 123.84 | 124.78 | 124.72 | — | — |
| C(8a) | 140.34 | 140.27 | 140.05 | 149.61 | 140.13 | 140.28 | — | — |
| O—C(9)=O | 176.30 | 175.92 | 181.99 | 176.79 | 177.58 | 176.29 | — | — |
| NC(10)H(R) | — | — | — | — | 41.10 | 57.00 | — | — |
| C(11)ONH | — | — | — | — | 168.36 | 170.45 | — | — |
| NC(12)H(R) | 56.33 | 52.61 | 41.32 | 40.78 | 43.32 | 58.29 | — | 41.27 |
| $C(1')H_2$ | 40.00 | 40.00 | 40.68 | 40.72 | 40.00 | 39.66 | — | — |
| $C(2')H_2$ | 24.43 | 24.44 | 24.44 | 24.43 | 24.42 | 24.43 | — | — |
| $C(3')H_2$ | 37.28 | 37.29 | 37.39 | 37.39 | 37.27 | 37.29 | — | — |
| C(4′)H | 32.69 | 32.70 | 32.68 | 32.69 | 32.67 | 32.71 | — | — |
| $C(5')H_2$ | 37.32 | 37.39 | 37.39 | 37.39 | 37.32 | 37.43 | — | — |
| $C(6')H_2$ | 24.80 | 24.80 | 24.81 | 24.80 | 24.79 | 24.80 | — | — |
| $C(7')H_2$ | 37.38 | 37.54 | 37.39 | 37.39 | 37.37 | 37.39 | — | — |
| C(8′)H | 32.78 | 32.77 | 32.77 | 32.77 | 32.76 | 32.77 | — | — |
| $C(9')H_2$ | 37.40 | 37.66 | 37.41 | 37.45 | 37.54 | 37.43 | — | — |
| $C(10')H_2$ | 24.80 | 24.80 | 23.81 | 23.72 | 24.79 | 24.80 | — | — |
| $C(11')H_2$ | 39.37 | 39.37 | 39.37 | 39.37 | 39.37 | 39.37 | — | — |
| C(12′)H | 27.97 | 27.97 | 27.98 | 27.96 | 27.96 | 27.97 | — | — |
| $C(1'')H_2$ | 39.67 | 39.61 | 37.10 | 37.13 | 39.61 | 39.66 | 39.63 | 39.61 |
| $C(2'')H_2$ | 34.14 | 34.16 | 27.98 | 27.96 | 34.12 | 34.13 | 34.10 | 34.12 |
| C(3″) | 218.23 | 218.10 | 84.93 | 80.96 | 218.13 | 218.10 | 217.86 | 218.89 |
| C(4″) | 47.32 | 47.35 | 37.39 | 37.79 | 47.29 | 47.31 | 47.33 | 47.95 |
| C(5″)H | 55.01 | 55.05 | 55.37 | 55.49 | 54.93 | 54.98 | 54.99 | 54.97 |
| $C(6'')H_2$ | 19.30 | 19.40 | 18.12 | 18.17 | 19.46 | 19.38 | 19.40 | 19.64 |
| $C(7'')H_2$ | 33.76 | 33.51 | 34.20 | 34.24 | 33.58 | 33.73 | 33.66 | 33.64 |
| C(8″) | 40.74 | 40.54 | 40.69 | 40.72 | 40.67 | 40.73 | 40.73 | 40.67 |
| C(9″)H | 49.94 | 49.90 | 49.23 | 50.09 | 49.94 | 50.01 | 49.90 | 49.95 |
| C(10″) | 36.93 | 36.88 | 37.29 | 37.29 | 36.89 | 36.93 | 36.91 | 36.89 |
| $C(11'')H_2$ | 21.50 | 21.29 | 21.02 | 21.28 | 21.45 | 21.51 | 21.33 | 21.43 |
| $C(12'')H_2$ | 25.68 | 25.52 | 23.73 | 23.72 | 25.62 | 25.66 | 25.42 | 25.60 |
| C(13″)H | 37.90 | 37.81 | 38.32 | 38.43 | 37.73 | 37.94 | 36.74 | 37.78 |
| C(14″) | 42.58 | 42.39 | 42.43 | 42.49 | 42.50 | 42.54 | 42.52 | 42.54 |
| $C(15'')H_2$ | 29.54 | 29.08 | 29.67 | 29.70 | 29.46 | 29.49 | 29.68 | 29.34 |
| $C(16'')H_2$ | 33.82 | 33.51 | 32.14 | 33.62 | 33.41 | 33.73 | 30.08 | 33.52 |
| C(17″) | 56.16 | 55.78 | 55.37 | 55.81 | 55.74 | 55.98 | 56.98 | 55.74 |
| C(18″)H | 50.04 | 49.90 | 50.39 | 50.57 | 50.00 | 50.01 | 49.90 | 49.95 |
| C(19″)H | 46.66 | 46.59 | 46.92 | 46.68 | 46.61 | 46.76 | 46.55 | 46.60 |
| C(20″) | 150.83 | 150.83 | 150.36 | 150.75 | 150.65 | 150.75 | 149.12 | 150.62 |
| $C(21'')H_2$ | 30.96 | 29.70 | 30.56 | 30.80 | 31.02 | 31.05 | 31.34 | 30.71 |
| $C(22'')H_2$ | 37.99 | 37.92 | 38.11 | 38.24 | 38.29 | 38.08 | 38.56 | 38.26 |
| $C(23'')H_3$ | 26.64 | 26.57 | 25.42 | 25.60 | 26.64 | 26.65 | 26.60 | 26.61 |
| $C(24'')H_3$ | 21.00 | 21.03 | 16.52 | 16.50 | 21.01 | 21.00 | 21.03 | 21.01 |
| $C(25'')H_3$ | 15.98 | 15.82 | 16.14 | 16.19 | 15.94 | 15.98 | 15.94 | 15.94 |
| $C(26'')H_3$ | 15.98 | 15.85 | 16.00 | 15.98 | 15.81 | 15.98 | 15.89 | 15.80 |
| $C(27'')H_3$ | 14.61 | 14.49 | 14.65 | 14.60 | 14.53 | 14.61 | 14.75 | 14.30 |
| C(28″) | 171.45 | 171.32 | 167.71 | 169.46 | 170.33 | 171.68 | 171.83 | 171.40 |
| $C(29'')H_2$ | 109.43 | 109.39 | 109.76 | 109.48 | 109.50 | 109.48 | 107.89 | 109.53 |

(*to be continued*)

**Table 3** (*continued*)

| Atom or group | δ | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **9b** | **9c** | **9d** | **9e** | **9f** | **9g** | **10** | **11** |
| C(30″)$H_3$ | 19.46 | 19.64 | 19.35 | 19.46 | 19.64 | 19.38 | 19.60 | 19.43 |
| COOH | — | — | — | — | — | — | — | 173.93 |
| Me(Ar) | 11.83, 12.28, 13.13 | 11.84, 12.18, 13.02 | 11.83, 12.17, 13.01 | 11.83, 12.17, 13.01 | 11.82, 12.12, 12.96 | 11.83, 12.24, 13.08 | — | — |
| Me($Pr^i$) | 17.46 | — | — | — | — | 17.25, 18.39 | — | — |
| C(12′)Me | 22.62, 22.71 | 22.64, 22.73 | 22.64, 22.73 | 22.64, 22.74 | 22.64, 22.73 | 22.62, 22.71 | — | — |
| C(2)Me | 23.91 | 23.91 | 23.46 | 23.72 | 23.91 | 23.88 | — | — |
| C$H(Pr^i)$ | 29.69 | — | — | — | — | 29.69 | — | — |
| C(4′)Me | 19.67 | 19.69 | 19.69 | 19.70 | 19.68 | 19.69 | — | — |
| C(8′)Me | 19.74 | 19.76 | 19.76 | 19.77 | 19.76 | 19.72 | — | — |
| C$H_2$Ph | — | 37.39 | — | — | — | — | — | — |
| Ph | — | 126.58, 126.89, 128.68, 129.46, 137.47 | — | — | — | — | 110.45, 120.67, 124.70, 128.68 | — |
| MeCOO | — | — | — | 170.93 | — | — | — | — |
| MeCOO | — | — | — | 20.93 | — | — | — | — |

the carboxylic acid by *N*,*N*′-carbonyldiimidazole (CDI)[15], *N*-hydroxysuccinimide (HOSu), or DCC[16] failed and the use of EDC/HOBT[14] resulted in *N*-benzotriazole ester of betulonic acid **10** stable under column chromatography ($SiO_2$) and unable to form the amide bond.

The synthesis of hybrid **9a** using the carbodiimide coupling of α-tocopherol (**1**) with amide **11** (the latter was obtained in two steps[12] from acid chloride **8a**) was of low efficiency. This reaction gave a mixture of products from which target compound **9a** was isolated by repeated column chromatography ($SiO_2$) in a yield of less than 30%.

The $^1$H and $^{13}$C NMR spectra of the obtained amino acid and peptide derivatives of α-tocopherol **3b—d**, **4b—d**, **5a—d**, **6a**,**b**, and **7a,b** and bioconjugates **9b—g** fully correspond to their structures (Tables 1—3). The $^{13}$C NMR spectra of bioconjugates **9b—g** exhibit signals for all carbon atoms corresponding to triterpenoid and α-tocopherol residues and the amino acid linkers (see Table 3) (the assignment was done using data of HH COSY, $^{13}$C—$^1$H HSQC and HMBC, $^{15}$N—$^1$H HSQC and HMBC 2D experiments).

Thus, we obtained new amino acid and peptide derivatives of α-tocopherol and its bioconjugates with lupane triterpenoids, which are promising for the development of drugs.

## Experimental

IR spectra were measured on a Specord IR-75 spectrometer in thin film or in $CHCl_3$ solution, UV spectra were measured on a Specord M-40 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AVANCE-400 instrument (operating at 400.13 ($^1$H) and 100.62 MHz ($^{13}$C)) using $Me_4Si$ as the internal standard, $CDCl_3$ or $CD_3OD$ as solvents, and $(CD_3)_2SO$ as the solvent for compounds **5a,d**. Optical rotation was determined on a Perkin—Elmer-141 polarimeter. The specific rotation was expressed in deg mL $g^{-1}$ $dm^{-1}$ and the solution concentration is in g (100 mL)$^{-1}$. TLC was carried out on Sorbfil plates (Sorbpolymer, Krasnodar, Russia) in chloroform (A); chloroform—methanol, 20 : 1 (B); and chloroform—methanol, 10 : 1 (C) systems; the spots were visualized by phosphomolybdic acid and anisaldehyde. Column chromatography was carried out on KSKG silica gel L (50—160 μm). Commercial racemic α-tocopherol (a mixture of eight diastereomers), DCC, DMAP, EDC, HOBT, Cbz-L-Val, Cbz-L-Phe, Cbz-Gly, $N_\alpha$,$N_\varepsilon$-$(Cbz)_2$-L-Lys, 10% Pd on activated carbon, and oxalyl chloride (Fluka) were used. Betulin was isolated by a known procedure,[17] betulonic, betulinic, and 3-*O*-acetylbetulinic acids and their chlorides were prepared by reported procedures.[13,16,18,19] The IR, UV, and $^1$H and $^{13}$C NMR spectra of compounds **3a**, **4a**, and **9a** were reported in our earlier study.[11] The $^{13}$C NMR spectra of compounds **3b—d**, **4b—d**, **5a—d**, **6a,b**, and **7a**,**b** are summarized in Tables 1 and 2 and the $^{13}$C NMR spectra of **9b—g**, **10**, and **11** are in Table 3.

**(*RS*)-α-Tocopheryl α-(*N*-benzyloxycarbonylamino)carboxylates 3a—d (general procedure).** DMAP (0.13 mmol), *N*-Cbz-amino acid **2a—d** (1.1 mmol), and DCC (1.1 mmol) were added with stirring to a solution of α-tocopherol (**1**) (1 mmol) in dry $CH_2Cl_2$ (20 mL). The mixture was vigorously stirred for 2—3 h (20 °C, TLC monitoring in system A). The precipitated dicyclohexylurea was filtered off, and the filtrate was concentrated. The residue was chromatographed on a column with $SiO_2$ (elution with *n*-hexane—AcOEt, 3 : 1) to give compounds **3a—d**.

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2*S*-(benzyloxycarbonylamino)-3-methylbutanoate (3b).** Yield 91%, $[\alpha]_D^{20}$ −11.9 (*c* 1.6, $CHCl_3$). Found (%): C, 76.11; H, 9.56; N, 2.10. $C_{42}H_{65}NO_5$. Calculated (%): C, 75.97; H, 9.87; N, 2.11. IR, ν/cm$^{-1}$: 1650 (CONH); 1715 (C=O); 1755 (O—C=O); 3400 (NH). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 287 (4600). $^1$H NMR, δ: 0.87 (m, 12 H, 4 Me); 1.05, 1.15 (both d, 3 H each, 2 Me(Pr$^i$), *J* = 6.8 Hz); 1.10—1.90 (m, 26 H, C(2)Me, $CH_2$, CH); 1.99, 2.03, 2.11 (all s, 3 H each, Me(Ar)); 2.51 (m, 1 H, Pr$^i$); 2.61 (t, 2 H, $H_2C$(4), *J* = 6.5 Hz); 4.67 (dd, 1 H, C<u>H</u>NH, *J* = 9.2 Hz, *J* = 3.6 Hz); 5.17 (s, 2 H, PhC<u>H</u>$_2$O); 5.37 (d, 1 H, NH, *J* = 9.2 Hz); 7.38 (m, 5 H, Ph).

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2*S*-(benzyloxycarbonylamino)-3-phenylpropanoate (3c).** Yield 90%, $[\alpha]_D^{20}$ −10.1 (*c* 0.9, $CHCl_3$). Found (%): C, 77.49; H, 9.23; N, 2.01. $C_{46}H_{65}NO_5$. Calculated (%): C, 77.60; H, 9.20; N, 1.97. IR, ν/cm$^{-1}$: 1640 (CONH); 1705 (C=O); 1760 (O—C=O); 3450 (NH). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 288 (3000). $^1$H NMR, δ: 0.91 (m, 12 H, 4 Me); 1.00—1.90 (m, 26 H, C(2)Me, $CH_2$, CH); 1.94, 1.98, 2.13 (all s, 3 H each, Me(Ar)); 2.62 (t, 2 H, $H_2C$(4), *J* = 6.4 Hz); 3.19 (dd, 1 H, C<u>H</u>$_2$Ph, *J* = 14.0 Hz, *J* = 8.4 Hz); 3.46 (dd, 1 H, C<u>H</u>$_2$Ph, *J* = 14.0 Hz, *J* = 5.2 Hz); 5.01 (m, 1 H, C<u>H</u>NH); 5.10 (s, 2 H, PhC<u>H</u>$_2$O); 5.36 (m, 1 H, NH); 7.33 (m, 10 H, 2 Ph).

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2*S*,6-bis(benzyloxycarbonylamino)hexanoate (3d).** Yield 71%, $[\alpha]_D^{20}$ −9.5 (*c* 2.7, $CH_2Cl_2$). Found (%): C, 73.98; H, 9.06; N, 3.41. $C_{51}H_{74}N_2O_7$. Calculated (%): C, 74.06; H, 9.02; N, 3.39. IR, ν/cm$^{-1}$: 1650 (CONH); 1700 (C=O); 1740 (O—C=O); 3390 (NH). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 286 (2115). $^1$H NMR, δ: 0.87 (m, 12 H, 4 Me); 1.00—1.90 (m, 32 H, C(2)Me, $CH_2$, CH); 1.93, 1.99, 2.10 (all s, 3 H each, Me(Ar)); 2.58 (t, 2 H, $H_2C$(4), *J* = 6.5 Hz); 3.25 (m, 2 H, C<u>H</u>$_2$NH); 4.70 (m, 1 H, C<u>H</u>NH); 4.85 (m, 1 H, NH); 5.10, 5.15 (both s, 2 H each, PhC<u>H</u>$_2$O); 5.50 (m, 1 H, NH); 7.40 (m, 10 H, 2 Ph).

**(*RS*)-α-Tocopheryl α-aminocarboxylates 4a—d (general procedure).** The 10% Pd/C catalyst (20% w/w with respect to **3a—d**) was added to a solution of compound **3a—d** (1 mmol) in ethanol (15 mL), and the mixture was stirred for 2—4 h at room temperature under hydrogen. After completion of the reaction (TLC monitoring in system A), the catalyst was filtered off and washed with ethanol, and the filtrate was concentrated. The compounds **4a—d** thus obtained were unstable on storage; therefore, they were used in the subsequent reactions without chromatographic purification.

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2*S*-amino-3-methylbutanoate (4b).** Yield 85%, $[\alpha]_D^{20}$ −8.1 (*c* 2.9, $CHCl_3$). IR, ν/cm$^{-1}$: 1750 (C=O); 3400 ($NH_2$). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 287 (3024). $^1$H NMR, δ: 0.87 (m, 12 H, 4 Me); 1.06, 1.15 (both d, 3 H each, 2 Me(Pr$^i$), *J* = 6.8 Hz); 1.10—1.90 (m, 26 H, C(2)Me, $CH_2$, CH); 1.99, 2.03, 2.10 (all s, 3 H each, Me(Ar)); 2.41 (m, 1 H, Pr$^i$); 2.60 (t, 2 H, $H_2C$(4), *J* = 6.4 Hz); 2.74 (m, 2 H, $NH_2$); 3.69 (m, 1 H, C<u>H</u>$NH_2$).

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2*S*-amino-3-phenylpropanoate (4c).** Yield 92%, $[\alpha]_D^{20}$ +0.3 (*c* 1.7, $CHCl_3$). IR, ν/cm$^{-1}$: 1730 (C=O); 3400 ($NH_2$). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 287 (2716). $^1$H NMR, δ: 0.80 (m, 12 H, 4 Me); 0.98—1.80 (m, 26 H, C(2)Me, $CH_2$, CH); 1.88, 1.90, 2.10 (all s, 3 H each, Me(Ar)); 2.52 (t, 2 H, $H_2C$(4), *J* = 6.5 Hz); 2.70 (m, 2 H, $NH_2$); 2.88 (dd, 1 H, C<u>H</u>$_2$Ph, *J* = 13.4 Hz, *J* = 9.0 Hz); 3.35 (dd, 1 H, C<u>H</u>$_2$Ph, *J* = 13.4 Hz, *J* = 5.0 Hz); 4.00 (dd, 1 H, C<u>H</u>$NH_2$, *J* = 9.0 Hz, *J* = 5.0 Hz); 7.30 (m, 5 H, Ph).

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2*S*,6-diaminohexanoate (4d).** Yield 87%, $[\alpha]_D^{20}$ +9.2 (*c* 5.8, $CH_2Cl_2$). IR, ν/cm$^{-1}$: 1740 (C=O); 3300 ($NH_2$). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 287 (2674). $^1$H NMR, δ: 0.83 (m, 12 H, 4 Me); 1.00—1.90 (m, 32 H, C(2)Me, $CH_2$, CH); 1.95, 1.99, 2.15 (all s, 3 H each, Me(Ar)); 2.58 (t, 2 H, $H_2C$(4), *J* = 6.4 Hz); 2.63 (m, 4 H, $NH_2$); 2.79 (m, 2 H, C<u>H</u>$_2NH_2$); 3.74 (m, 1 H, C<u>H</u>$NH_2$).

**(*RS*)-α-Tocopheryl α-aminocarboxylate oxalates 5a—d (general procedure).** The 10% Pd/C catalyst (20% w/w with respect to **3a—d**) and oxalic acid (1 mmol for **3a—c** and 2 mmol for **3d**) were added to a solution of the corresponding compound **3a—d** (1 mmol) in ethanol (15—20 mL). The mixture was vigorously stirred for 2—4 h at room temperature in a hydrogen atmosphere. After completion of the reaction (TLC monitoring in system A), the catalyst was filtered off and washed with ethanol, and the filtrate was concentrated *in vacuo*. The amorphous powders of oxalates thus formed were dried in a vacuum dessicator over $P_2O_5$ for several days.

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2-ammonioethanoate oxalate (5a).** Yield 67%. Found (%): C, 68.71; H, 9.52; N, 2.39. $C_{31}H_{53}NO_3 \cdot H_2C_2O_4$. Calculated (%): C, 68.60; H, 9.59; N, 2.42. IR, ν/cm$^{-1}$: 1770 (C=O). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 287 (1755). $^1$H NMR, δ: 0.82 (m, 12 H, 4 Me); 1.00—1.85 (m, 26 H, C(2)Me, $CH_2$, CH); 1.92, 1.94, 2.00 (all s, 3 H each, Me(Ar)); 4.22 (m, 2 H, C<u>H</u>$_2NH_2$).

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2*S*-ammonio-3-methylbutanoate oxalate (5b).** Yield 83%, $[\alpha]_D^{20}$ +1.7 (*c* 1.34, $CHCl_3$). Found (%): C, 69.67; H, 9.89; N, 2.21. $C_{34}H_{59}NO_3 \cdot H_2C_2O_4$. Calculated (%): C, 69.75; H, 9.92; N, 2.26. IR, ν/cm$^{-1}$: 1750 (C=O). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 287 (1792). $^1$H NMR, δ: 0.87 (m, 12 H, 4 Me); 1.00—1.90 (m, 32 H, C(2)Me, 2 Me(Pr$^i$), $CH_2$, CH); 1.90, 1.95, 2.10 (all s, 3 H each, Me(Ar)); 2.50 (m, 3 H, 2 H, $H_2C$(4), 1 H, Pr$^i$); 4.49 (m, 1 H, C<u>H</u>$NH_2$).

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2*S*-ammonio-3-phenylpropanoate oxalate (5c).** Yield 92%, $[\alpha]_D^{20}$ −80.0 (*c* 0.01, $CHCl_3$). Found (%): C, 72.02; H, 9.14; N, 2.08. $C_{38}H_{59}NO_3 \cdot H_2C_2O_4$. Calculated (%): C, 71.93; H, 9.21; N, 2.10. IR, ν/cm$^{-1}$: 1750 (C=O). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 287 (1737). $^1$H NMR, δ: 0.87 (m, 12 H, 4 Me); 1.00—1.80 (m, 26 H, C(2)Me, $CH_2$, CH); 1.80—2.00 (m, 9 H, Me(Ar)); 2.40 (m, 2 H, $H_2C$(4)); 3.33—3.39 (m, 2 H, C<u>H</u>$_2$Ph); 4.90 (m, 1 H, C<u>H</u>$NH_2$); 7.11 (m, 5 H, Ph).

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2*S*,6-diammoniohexanoate dioxalate (5d).** Yield 68%. Found (%): C, 63.45; H, 8.97; N, 3.75. $C_{35}H_{62}N_2O_3 \cdot 2H_2C_2O_4$. Calculated (%): C, 63.39; H, 9.00; N, 3.79. IR, ν/cm$^{-1}$: 1760 (C=O). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 287 (1768). $^1$H NMR, δ: 0.85 (m, 12 H, 4 Me); 1.00—1.85 (m, 32 H, C(2)Me, $CH_2$, CH); 1.91, 1.93, 2.00 (all s, 3 H each, Me(Ar)); 2.54 (m, 2 H, $H_2C$(4)); 2.80 (m, 2 H, C<u>H</u>$_2NH_2$); 4.40 (m, 1 H, C<u>H</u>$NH_2$); 8.03 (m, 4 H, $NH_2$).

**(*RS*)-α-Tocopheryl α-(*N*-benzyloxycarbonylamino)carboxylates 6a,b (general procedure).** DMAP (0.13 mmol), the corresponding *N*-Cbz-amino acid **2a** or **2b** (1.1 mmol), and DCC (1.1 mmol) were added to a solution of compound **4a** or **4b** (1 mmol) in dry $CH_2Cl_2$ (20 mL), and the mixture was worked-

up as described above for the synthesis of compounds **3a**—**d**. Column chromatography ($SiO_2$, elution with hexane—AcOEt, 3 : 1) gave compound **6a** or **6b**, respectively.

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2-[*N*-(*N*-benzyloxycarbonylaminoacetyl)-amino]ethanoate (6a).** Yield 79%. Found (%): C, 72.51; H, 9.23; N, 4.10. $C_{41}H_{62}N_2O_6$. Calculated (%): C, 72.53; H, 9.20; N, 4.13. IR, ν/cm$^{-1}$: 1650 (CONH); 1700 (C=O), 1750 (O—C=O); 3400 (NH). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 287 (2300). $^1$H NMR, δ: 0.88 (m, 12 H, 4 Me); 1.00—1.90 (m, 26 H, C(2)Me, $CH_2$, CH); 1.97, 2.00, 2.10 (all s, 3 H each, Me(Ar)); 2.59 (t, 2 H, $H_2$C(4)); 3.93 (br.s, 2 H, C$\underline{H}_2$NH); 4.31 (br.s, 2 H, C$\underline{H}_2$NH); 5.12 (s, 2 H, PhC$\underline{H}_2$O); 5.72 (br.s, 1 H, NH); 6.93 (br.s, 1 H, NH); 7.33 (m, 5 H, Ph).

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2*S*-{*N*-[2*S*-(*N*-benzyloxycarbonylamino)-3-methylbutanoyl]amino}-3-methylbutanoate (6b).** Yield 79%, $[\alpha]_D^{20}$ −15.5 (*c* 1.9, $CHCl_3$). Found (%): C, 73.89; H, 9.74; N, 3.71. $C_{47}H_{74}N_2O_6$. Calculated (%): C, 73.97; H, 9.77; N, 3.67. IR, ν/cm$^{-1}$: 1640 (CONH); 1700 (C=O); 1730 (O—C=O); 3450 (NH). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 286 (1900). $^1$H NMR, δ: 0.87 (m, 12 H, 4 Me); 0.90—1.88 (m, 26 H, C(2)Me, $CH_2$, CH); 1.03, 1.09 (both d, 12 H, 4 Me(Pr$^i$), $J$ = 6.4 Hz); 1.97, 2.01, 2.09 (all s, 3 H each, Me(Ar)); 2.15, 2.50 (both m, 1 H each, Pr$^i$); 2.59 (t, 2 H, $H_2$C(4), $J$ = 6.5 Hz); 4.20 (t, 1 H, C$\underline{H}$NH, $J$ = 7.6 Hz); 4.91 (dd, 1 H, C$\underline{H}$NH, $J$ = 8.0 Hz, $J$ = 3.6 Hz); 5.12 (s, 2 H, PhC$\underline{H}_2$O); 5.45 (d, 1 H, NH, $J$ = 8.0 Hz); 6.43 (d, 1 H, NH, $J$ = 7.6 Hz); 7.35 (m, 5 H, Ph).

**(*RS*)-α-Tocopheryl α-aminocarboxylates 7a,b (general procedure).** The 10% Pd/C catalyst (20% w/w with respect to **6a** or **6b**) was added to a solution of compound **6a** or **6b** (1 mmol) in ethanol (15 mL), and the mixture was stirred for 4 h at room temperature under hydrogen. After completion of the reaction (TLC monitoring in system C), the catalyst was filtered off and washed with ethanol, and the filtrate was concentrated. Compounds **7a**,**b** were unstable on storage; therefore, they were used in the subsequent reactions without chromatographic purification.

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl (aminoacetylamino)ethanoate (7a).** Yield 82%. IR, ν/cm$^{-1}$: 1700 (CONH); 1760 (C=O); 3350 ($NH_2$). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 289 (2384). $^1$H NMR, δ: 0.87 (m, 12 H, 4 Me); 1.00—1.90 (m, 26 H, C(2)Me, $CH_2$, CH); 1.98, 2.02, 2.09 (all s, 3 H each, Me(Ar)); 2.59 (t, 2 H, $H_2$C(4), $J$ = 6.4 Hz); 3.46 (s, 2 H, C$\underline{H}_2$NH); 4.37 (s, 2 H, C$\underline{H}_2$NH); 7.89 (1 H, NH).

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2*S*-[*N*-(2*S*-amino-3-methylbutanoyl)-amino]-3-methylbutanoate (7b).** Yield 93%, $[\alpha]_D^{20}$ −38.4 (*c* 3.2, $CHCl_3$). IR, ν/cm$^{-1}$: 1700 (CONH); 1740 (C=O); 3400 ($NH_2$). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 287 (2090). $^1$H NMR, δ: 0.87 (m, 12 H, 4 Me); 1.03, 1.06 (both d, 6 H each, 4 Me(Pr$^i$), $J$ = 6.8 Hz); 1.10—1.90 (m, 26 H, C(2)Me, $CH_2$, CH); 1.98, 2.02, 2.12 (all s, 3 H each, Me(Ar)); 2.36, 2.53 (both m, 1 H each, Pr$^i$); 2.56 (t, 2 H, $\underline{H}_2$C(4), $J$ = 6.3 Hz); 3.33 (d, 1 H, C$\underline{H}$NH, $J$ = 4.0 Hz); 4.89 (dd, 1 H, C$\underline{H}$NH, $J$ = 4.0 Hz, $J$ = 9.2 Hz); 7.94 (d, 1 H, NH, $J$ = 9.2 Hz).

***N*-[3-Oxolup-20(29)-en-28-oyl]-1-benzotriazole (10).** EDC (0.12 g, 0.75 mmol), HOBT (0.1 g, 0.75 mmol), and betulonic acid (0.18 g, 0.4 mmol) were added with stirring to a solution of amine **4b** (0.26 g, 0.5 mmol) in dry $CH_2Cl_2$ (3 mL). The reaction mixture was vigorously stirred for 6 h at room temperature, left for ~14 h, diluted with $CH_2Cl_2$ (20 mL), washed with water (3×50 mL), dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on a column with $SiO_2$ (elution with chloroform). Yield 78%. Found (%): C, 75.68; H, 8.59; N, 7.31. $C_{36}H_{49}N_3O_3$. Calculated (%): C, 75.62; H, 8.64; N, 7.35. IR, ν/cm$^{-1}$: 1700 (C=O); 1740 (O—C=O). $^1$H NMR, δ: 0.89, 0.94, 1.04, 1.07, 1.09 (all s, 3 H each, C(4)Me, C(8)Me, C(10)Me, C(14)Me); 1.20—2.20 (m, 21 H, $CH_2$, CH); 1.69 (s, 3 H, C(20)Me); 2.30—2.70 (m, 3 H, C(13)H, C(16)$H_2$); 3.02 (m, 1 H, C(19)H); 4.65, 4.74 (both s, 1 H each, C(29)$H_2$); 7.39 (d, 1 H, H arom., $J$ = 8.0 Hz); 7.44, 7.57 (both t, 1 H each, H arom., $J$ = 8.0 Hz); 8.10 (d, 1 H, H arom., $J$ = 8.0 Hz).

***N*-[3-Oxolup-20(29)-en-28-oyl]aminoacetic acid (11)** was prepared by a known procedure.[12] Yield 85%. Found (%): C, 75.15; H, 9.62; N, 2.70. $C_{32}H_{49}NO_4$. Calculated (%): C, 75.11; H, 9.65; N, 2.74. IR, ν/cm$^{-1}$: 1640 (CONH); 1700 (C=O); 3450 (NH). $^1$H NMR, δ: 0.91, 0.95, 0.97, 1.01, 1.06 (all s, 3 H each, C(4)Me, C(8)Me, C(10)Me, C(14)Me); 1.18—2.10 (m, 21 H, $CH_2$, CH); 1.67 (s, 3 H, C(20)Me); 2.30—2.55 (m, 3 H, C(13)H, C(16)$H_2$); 3.07 (m, 1 H, C(19)H); 4.03 (m, 2 H, C$\underline{H}_2$NH); 4.59, 4.72 (both s, 1 H each, C(29)$H_2$); 6.32 (1 H, NH).

**(*RS*)-α-Tocopheryl α-{*N*-[3-oxolup-20(29)-en-28-oyl]amino}carboxylates 9a—e (general procedure).** ***A.*** A solution of the corresponding acid chloride **8a**—**c** (1 mmol) and amine **4a**—**c** (1.1 mmol) in dry benzene (10—12 mL) was refluxed for 0.5—1 h (TLC monitoring in system C). The mixture was cooled to room temperature, washed with a 10% solution of $NaHCO_3$ and water, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on a column with $SiO_2$ (elution with $CHCl_3$) to give the corresponding conjugate **9a**—**e**.

***B.*** DMAP (0.004 g, 0.03 mmol), betulonic acid amide **11** (0.16 g, 0.31 mmol) (prepared by a described procedure[12]), and DCC (0.06 g, 0.28 mmol) were added with stirring to a solution of α-tocopherol (**1**) (0.11 g, 0.25 mmol) in dry $CH_2Cl_2$ (5 mL). The reaction mixture was vigorously stirred for 4 h at room temperature. The precipitated dicyclohexylurea was filtered off, and the filtrate was concentrated. The residue was chromatographed on a column with $SiO_2$ (elution with $CHCl_3$) to give 0.19 g of a product mixture. Repeated column chromatography ($SiO_2$, elution with $CHCl_3$) gave 0.07 g (29%) of compound **9a** the $^1$H and $^{13}$C NMR spectra of which were identical to the spectra of the product obtained by procedure ***A***.

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2*S*-{*N*-[3-oxolup-20(29)-en-28-oyl]amino}-3-methylbutanoate (9b).** Yield 72%, $[\alpha]_D^{20}$ −4.1 (*c* 1.6, $CHCl_3$). Found (%): C, 79.49; H, 10.78; N, 1.43. $C_{64}H_{103}NO_5$. Calculated (%): C, 79.53; H, 10.74; N, 1.45. IR, ν/cm$^{-1}$: 1640 (CONH); 1700 (C=O); 1730 (O—C=O); 3390 (NH). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 287 (1785). $^1$H NMR, δ: 0.87 (m, 12 H, C(4′)Me, C(8′)Me, C(12′)Me); 0.90, 0.92, 0.93, 1.00, 1.08 (all s, 3 H each, C(4″)Me, C(8″)Me, C(10″)Me, C(14″)Me); 1.14 (d, 6 H, 2 Me(Pr$^i$), $J$ = 5.6 Hz); 1.20—1.92 (m, 21 H, $CH_2$, CH in the betulonic acid residue, 1 H, Pr$^i$ and 26 H, C(2)Me, $CH_2$, CH in α-tocopherol residue); 1.69 (s, 3 H, C(20″)Me); 1.97, 2.01, 2.09 (all s, 3 H each, Me(Ar)); 2.35—2.55 (m, 3 H, C(13″)H, C(16″)$H_2$); 2.70 (t, 2 H, C(4)$H_2$, $J$ = 6.2 Hz); 3.14 (m, 1 H, C(19″)H); 4.60, 4.75 (both s, 1 H each, C(29″)$H_2$); 4.59 (dd, 1 H, C$\underline{H}$NH), $J$ = 9.2 Hz, $J$ = 3.6 Hz); 6.10 (d, 1 H, NH, $J$ = 9.2 Hz).

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 2*S*-{*N*-[3-oxolup-20(29)-en-28-oyl]amino}-3-phenylpropanoate (9c).** Yield 70%, $[\alpha]_D^{20}$ −1.3 (*c* 6.1,

$CHCl_3$). Found (%): C, 80.43; H, 10.16; N, 1.34. $C_{68}H_{103}NO_5$. Calculated (%): C, 80.50; H, 10.23; N, 1.38. IR, ν/cm$^{-1}$: 1660 (CONH); 1700 (C=O); 1740 (O—C=O); 3400 (NH). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 286 (2688). $^1$H NMR, δ: 0.87 (m, 12 H, C(4´)Me, C(8´)Me, C(12´)Me); 0.89, 0.91, 0.95, 1.04, 1.08 (all s, 3 H each, C(4″)Me, C(8″)Me, C(10″)Me, C(14″)Me); 1.20—1.90 (m, 21 H, $CH_2$, CH in the betulonic acid residue and 26 H, C(2)Me, $CH_2$, CH in α-tocopherol residue); 1.65 (s, 3 H, C(20″)Me); 1.96, 2.00, 2.10 (all s, 3 H each, Me(Ar)); 2.30—2.55 (m, 3 H, C(13″)H, C(16″)$H_2$); 2.60 (t, 2 H, C(4)$H_2$, $J$ = 6.2 Hz); 3.10 (m, 2 H, C(19″)H, H (C$\underline{H}_2$Ph)); 3.52 (dd, 1 H, C$\underline{H}_2$Ph, $J$ = 14.0 Hz, $J$ = 4.5 Hz); 4.58, 4.71 (both s, 1 H each, C(29″)$H_2$); 5.20 (m, 1 H, C$\underline{H}$NH); 5.96 (d, 1 H, NH, $J$ = 8.0 Hz); 7.33 (m, 5 H, Ph).

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl {*N*-[3β-hydroxylup-20(29)-en-28-oyl]amino}ethanoate (9d).** Yield 61%, $[\alpha]_D^{20}$ +12.5 (*c* 0.52, $CHCl_3$). Found (%): C, 79.03; H, 10.81; N, 1.50. $C_{61}H_{99}NO_5$. Calculated (%): C, 79.08; H, 10.77; N, 1.51. IR, ν/cm$^{-1}$: 1700 (CONH); 1770 (O—C=O); 3450 (NH, OH). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 286 (1776). $^1$H NMR, δ: 0.84—0.89 (m, 21 H, Me); 0.95, 0.99 (both s, 3 H each, Me); 1.00—1.90 (m, 23 H, $CH_2$, CH in the betulinic acid residue and 26 H, C(2)Me, $CH_2$, CH in α-tocopherol residue); 1.70 (s, 3 H, C(20″)Me); 1.98, 2.02, 2.10 (all s, 3 H each, Me(Ar)); 2.21—2.30 (m, 1 H, C(13″)H); 2.60 (t, 2 H, C(4)$H_2$, $J$ = 6.4 Hz); 3.02 (m, 1 H, C(19″)H); 4.43 (br.s, 2 H, C$\underline{H}_2$NH); 4.67 (m, 2 H, C(3″)H, C(29″)H); 4.75 (s, 1 H, C(29″)H); 7.64 (br.s, 1 H, NH).

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl {*N*-[3β-acetoxylup-20(29)-en-28-oyl]amino}etanoate (9e).** Yield 82%, $[\alpha]_D^{20}$ +6.5 (*c* 0.7, $CHCl_3$). Found (%): C, 78.08; H, 10.54; N, 1.42. $C_{63}H_{101}NO_6$. Calculated (%): C, 78.13; H, 10.51; N, 1.45. IR, ν/cm$^{-1}$: 1650 (CONH); 1700 (C=O); 1750 (O—C=O); 3400 (NH). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 287 (1608). $^1$H NMR, δ: 0.84—0.88 (m, 21 H, Me); 0.92, 0.97 (both s, 3 H each, Me); 1.00—1.93 (m, 23 H, $CH_2$, CH in the betulinic acid residue and 26 H, C(2)Me, $CH_2$, CH in α-tocopherol residue); 1.69 (s, 3 H, C(20″)Me); 1.99, 2.03, 2.10 (all s, 3 H each, Me(Ar)); 2.04 (s, 3 H, OAc); 2.50 (m, 1 H, C(13″)H); 2.59 (t, 2 H, C(4)$H_2$, $J$ = 6.4 Hz); 3.11 (m, 1 H, C(19″)H); 4.27 (dd, 1 H, C$\underline{H}$NH, $J$ = 18.0 Hz, $J$ = 4.4 Hz); 4.36 (dd, 1 H, C$\underline{H}$NH, $J$ = 18.0 Hz, $J$ = 5.2 Hz); 4.47 (dd, 1 H, C(3″)H, $J$ = 8.8 Hz, $J$ = 4.4 Hz); 4.60, 4.75 (both s, 1 H each, C(29″)H); 6.23 (dd, 1 H, NH, $J$ = 5.2 Hz, $J$ = 4.4 Hz).

**(*RS*)-α-Tocopheryl-α-{*N*-[3-oxolup-20(29)-en-28-oyl]amino}carboxylates 9f,g (general procedure).** EDC (0.7 mmol) and freshly prepared chloride **8a** (0.4 mmol) were added dropwise to a stirred solution of compound **7a** or **7b** (0.5 mmol) in dry $CH_2Cl_2$ (10 mL). The reaction mixture was kept for 18 h at room temperature, washed with water, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on a column with $SiO_2$ (elution with $CHCl_3$) to give conjugates **9f,g**, respectively.

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl [(3-oxolup-20(29)-en-28-oyl)aminoacetylamino]etanoate (9f).** Yield 79%, $[\alpha]_D^{20}$ +9.7 (*c* 0.3, $CHCl_3$). Found (%): C, 77.14; H, 10.23; N, 2.87. $C_{63}H_{100}N_2O_6$. Calculated (%): C, 77.10; H, 10.27; N, 2.85. IR, ν/cm$^{-1}$: 1660 (CONH); 1700 (C=O); 1760 (O—C=O); 3350 (NH). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 287 (2361). $^1$H NMR, δ: 0.87 (m, 12 H, C(4´)Me, C(8´)Me, C(12´)Me); 0.90, 0.93, 0.96, 1.01, 1.06 (all s, 3 H each, C(4″)Me, C(8″)Me, C(10″)Me, C(14″)Me); 1.10—1.90 (m, 21 H, $CH_2$, CH in the betulonic acid and 26 H, C(2)Me, $CH_2$, CH in α-tocopherol residue); 1.67 (s, 3 H, C(20″)Me); 1.95, 1.99, 2.07 (all s, 3 H each, Me(Ar)); 2.35—2.55 (m, 3 H, C(13″)H, C(16″)$H_2$); 2.60 (t, 2 H, C(4)$H_2$, $J$ = 6.4 Hz); 3.07 (m, 1 H, C(19″)H); 3.98 (br.s, 2 H, C$\underline{H}_2$NH); 4.28 (br.s, 2 H, C$\underline{H}_2$NH); 4.59, 4.71 (both s, 1 H each, C(29″)H); 6.87 (m, 2 H, NH).

**2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-3,4-dihydro-2*H*-chromen-6-yl 3-methyl-2*S*-[2*S*-(3-oxolup-20(29)-en-28-oyl)amino-3-methylbutanoylamino]butanoate (9g).** Yield 44%, $[\alpha]_D^{20}$ −16.4 (*c* 2.25, $CHCl_3$). Found (%): C, 77.81; H, 10.53; N, 2.65. $C_{69}H_{112}N_2O_6$. Calculated (%): C, 77.77; H, 10.59; N, 2.63. IR, ν/cm$^{-1}$: 1650 (CONH); 1700 (C=O); 1740 (O—C=O); 3380 (NH). UV ($CHCl_3$), $\lambda_{max}$/nm (ε): 286 (2800). $^1$H NMR, δ: 0.88 (m, 12 H, C(4´)Me, C(8´)Me, C(12´)Me); 0.92, 0.97, 0.99, 1.01, 1.04, 1.07, 1.09, 1.11 (all s, 3 H each, C(4″)Me, C(8″)Me, C(10″)Me, C(14″)Me, 12 H, 4 Me(Pr$^i$)); 1.20—1.95 (m, 21 H, $CH_2$, CH in the betulonic acid residue, 2 H, Pr$^i$ and 26 H, C(2)Me, $CH_2$, CH in α-tocopherol residue); 1.68 (s, 3 H, C(20″)Me); 1.97, 2.04, 2.10 (all s, 3 H each, Me(Ar)); 2.40—2.55 (m, 3 H, C(13″)H, C(16″)$H_2$); 2.62 (t, 2 H, C(4)$H_2$, $J$ = 6.0 Hz); 3.13 (m, 1 H, C(19″)H); 4.31 (t, 1 H, C$\underline{H}$NH, $J$ = 8.0 Hz); 4.60, 4.75 (both s, 1 H each, C(29″)$H_2$); 4.93 (dd, 1 H, C$\underline{H}$NH, $J$ = 8.4, $J$ = 4.4 Hz); 6.30 (t, 1 H, NH, $J$ = 8.4 Hz); 6.90 (m, 1 H, NH).

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