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Short Note

N-1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl (*N*-Dde) Lipoamino Acids

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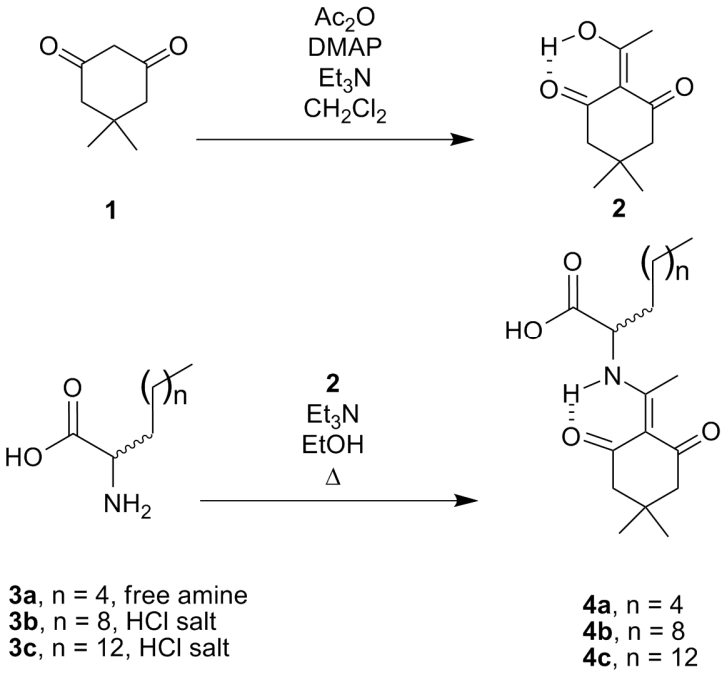
The conjugation of a drug with one or more lipoamino acids (LAAs; 2-aminoalkanoic acids; e.g. **3**) can impart upon the drug steric protection from enzymatic degradation, increased lipophilicity, increased passive membrane diffusion and therefore may improve drug bioavailability [1]. A variety of small molecules have been conjugated with LAAs [2], and many promising conjugates are peptides [3, 4]. *N*-*tert*-Butoxycarbonyl (*N*-Boc) LAAs are commonly used to introduce the LAA moiety into a peptide [3], however, *N*-Boc LAAs are incompatible with the popular 9-fluorenylmethoxycarbonyl (Fmoc) strategy of solid-phase peptide synthesis [5-7]. *N*-Fmoc LAAs have been prepared, but these compounds were poorly soluble in most organic solvents and therefore difficult to handle [8]. The stability of the *N*-1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl (*N*-Dde) group to both acidic and some basic conditions [9], and its facile removal by hydrazine or hydroxylamine [9-11], have led to its successful incorporation into many solid-phase methodologies [9, 10, 12-14]. Kellam et al. [15] used a *N*-Dde LAA (**4c**) in the synthesis of a glycolipopeptide by Fmoc-chemistry, however, **4c** was only partially characterized. Malkinson et al. [16, 17] used *N*-Dde LAAs in the synthesis of somatostatin

analogues, but the preparation of the *N*-Dde LAAs was not described. Herein we report the spectra of **4c** and the novel homologues **4a** and **4b**, which were prepared by a method similar to that of Kellam et al. [15].



2-Acetyldimedone (**2**) was synthesized by acylation of dimedone (**1**) with acetic anhydride. In a modification to the procedures that require one equivalent of 4-dimethylaminopyridine (DMAP) [18-20], it was found that purification was easier and by-product formation less significant when triethylamine was used as the base in the presence of a catalytic quantity of DMAP. The *N*-Dde LAAs (**4a-c**) were prepared by reaction of the LAAs (**3a-c**) with 2-acetyldimedone (**2**) in the presence of triethylamine in refluxing ethanol.

2-Acetyldimedone (2)

Dimedone (**1**, 15.0 g, 107 mmol) was dissolved in CH_2Cl_2 (100 mL). DMAP (2.61 g, 21.4 mmol) and triethylamine (29.8 mL, 214 mmol) were added and the mixture was stirred for 10 min. Acetic anhydride (12.2 mL, 129 mmol) was added and the mixture was stirred under an atmosphere of argon for 48 h. The solvent was removed by co-evaporation with toluene and the residue was dissolved in ethyl acetate (300 mL) and washed with 5% HCl (3 ´ 300 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to produce an oil. This oil was filtered through a column of silica (silica gel 60, 230-400 mesh, ethyl acetate:*n*-hexane, 2:3) and the solvent was evaporated to afford the title compound (**2**) as pale yellow crystals (11.3 g, 58%).

Melting point 35-36 °C (literature melting point 36-38 °C [21]).

ESI-MS, *m/z*: 183 $[M + H]^+$.

^{1}H NMR (500 MHz, $CDCl_3$) d 18.02 (1H, s, H-bonded OH), 2.54 (3H, s, CH_3), 2.48 (2H, s, CH_2), 2.30 (2H, s, CH_2), 1.02 [6H, s, $C(CH_3)_2$].
^{13}C NMR (125 MHz, $CDCl_3$) d 202.2, 197.7, 194.9, 112.2, 52.3, 46.8, 30.5, 28.3, 28.0.

2-[(4,4-Dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-D,L-octanoic Acid (4a)

2-Amino-D,L-octanoic acid [22, 23] (**3a**, 5.67 g, 35.6 mmol) and 2-acetyldimedone (**2**, 7.14 g, 39.2 mmol) were suspended in ethanol (200 mL). Triethylamine (5.40 g, 7.44 mL, 53.4 mmol) was added and the mixture was refluxed under an atmosphere of argon for 18 h. The solvent was removed in vacuo and the residue was taken up in ethyl acetate (250 mL) and washed with 5% HCl solution (3 ´ 200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo to give a pale yellow solid which was triturated with diethyl ether to afford the title compound (**4a**) as a white solid (6.16 g, 54%).

Melting point 156-158 °C.

ESI-MS, *m/z*: 324 $[M + H]^+$.

^{1}H NMR (500 MHz, $CDCl_3$) d 13.69 (1H, d, *J* 7.3 Hz, H-bonded NH), 11.18 (1H, br s, COOH), 4.37 (1H, m, a-CH), 2.52 (3H, s, $C(NH)CH_3$), 2.39 (4H, s, $2CH_2CO$), 2.02-1.87 (2H, m, b-CH_2), 1.45-1.21 (8H, m, $4CH_2$), 1.01 [6H, s, $C(CH_3)_2$], 0.84 (3H, t, *J* 6.8 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) d 198.9, 174.0, 172.1, 108.0, 56.5, 52.3, 32.5, 31.3, 30.1, 28.7, 28.1, 25.2, 22.4, 18.7, 13.9.

HRMS calcd for $[M + H]^+$ 324.2174, found 324.2165; calcd for $[M + Na]^+$ 346.1994, found 346.1999.

2-[(4,4-Dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-D,L-dodecanoic Acid (4b)

2-Amino-D,L-dodecanoic acid hydrochloride [24] (**3b**, 12.3 g, 48.7 mmol) and 2-acetyldimedone (**2**, 9.76 g, 53.5 mmol) were suspended in ethanol (200 mL). Triethylamine (12.3 g, 17.0 mL, 122 mmol) was added and the mixture was refluxed under an atmosphere of argon for ~32 h. The solvent was removed in vacuo and the residue was taken up in ethyl acetate (250 mL) and washed with 5% HCl solution (3 ´ 200 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated in vacuo to give a pale yellow solid which was triturated with diethyl ether to afford the title compound (**4b**) as a white solid (10.0 g, 54%).

Melting point 110-112 °C.

ESI-MS, *m/z*: 380 $[M + H]^+$.

^{1}H NMR (500 MHz, $CDCl_3$) d 13.70 (1H, d, *J* 7.2 Hz, H-bonded NH), 11.74 (1H, br s, COOH), 4.37 (1H, m, a-CH), 2.52 [3H, s, C(NH)CH_3], 2.39 (4H, s, 2CH_2CO), 2.02-1.87 (2H, m, b-CH_2), 1.43-1.23 (16H, m, 8CH_2), 1.01 [6H, s, C(CH_3)$_2$], 0.85 (3H, t, *J* 6.9 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) d 198.9, 174.0, 172.1, 108.0, 56.5, 52.3, 32.6, 31.8, 30.1, 29.4, 29.2, 29.1, 28.2, 25.3, 22.6, 18.7, 14.0.

HRMS calcd for $[M + H]^+$ 380.2801, found 380.2802.

2-[(4,4-Dimethyl-2,6-dioxocyclohex-1-ylidene)ethylamino]-D,L-hexadecanoic Acid (4c)

Compound **4c**, a white solid, was prepared from 2-amino-D,L-hexadecanoic acid hydrochloride [22] by following the procedure described for **4b**: scale 38.9 mmol; yield 6.61 g (39%).

Melting point 101-105 °C (literature melting point 115-117 °C [15]).

ESI-MS, *m/z*: 436 $[M + H]^+$.

^{1}H NMR (500 MHz, $CDCl_3$) d 13.70 (1H, d, *J* 7.3 Hz, H-bonded NH), 10.7 (1H, br s, COOH), 4.37 (1H, m, a-CH), 2.52 [3H, s, C(NH)CH_3], 2.39 (4H, s, 2CH_2CO), 2.01-1.88 (2H, m, b-CH_2), 1.43-1.23 (24H, m, 12CH_2), 1.02 [6H, s, C(CH_3)$_2$], 0.85 (3H, t, *J* 6.9 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) d 199.0, 174.1, 172.3, 108.2, 56.7, 52.5, 52.4, 32.7, 32.0, 30.2, 29.8, 29.7, 29.7, 29.6, 29.4, 29.4, 29.3, 28.3, 28.2, 25.5, 22.7, 18.8, 14.2.

HRMS calcd for $[M + H]^+$ 436.3427, found 436.3426.

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