Synthesis and Self-Assembly of Bolaamphiphiles Based on β-Amino Acids or an Alcohol

by **Prathama S. Mainkar**, **Chirumarry Sridhar**, **Ambadi Sudhakar**, and **Srivari Chandrasekhar***

Division of Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad – 500007, India (phone: +91-40-27193210; fax: +91-40-27160512; e-mail: srivaric@iict.res.in)

The synthesis of bolaamphiphiles from unusual β-amino acids or an alcohol and C_{12} or C_{20} spacers is described. Unusual β-amino acids such as a sugar amino acid, an AZT-derived amino acid, a norbornene amino acid, and an AZT-derived amino alcohol were coupled with spacers under standard conditions to get the novel bolaamphiphiles **5**–**8** (*Scheme 1*), **12** and **13** (*Scheme 2*), and **17** and **20** (*Scheme 3*). Some of these compounds, on precipitation from MeOH/H_2O, self-assembled into organized molecular structures.

Introduction. – Bolaamphiphiles are potential monomers for self-assembly and comprise two hydrophilic groups connected by a hydrophobic chain. The synthetic bolaamphiphiles try to reproduce the unusual architecture of the monolayered membrane found in archaebacteria [1]. These molecules tend to self-organize in H_2O to form molecular aggregates, *viz.*, micelles, sheets, vesicles, rings, and fibres [2]. The parameters which hold the molecules together, other than hydration, include *i*) length of the hydrophobic chain, *ii*) nature of counter ions, *iii*) chirality, *iv*) temperature, *v*) secondary amide functions, *vi*) ionic strength, and *vii*) pH.

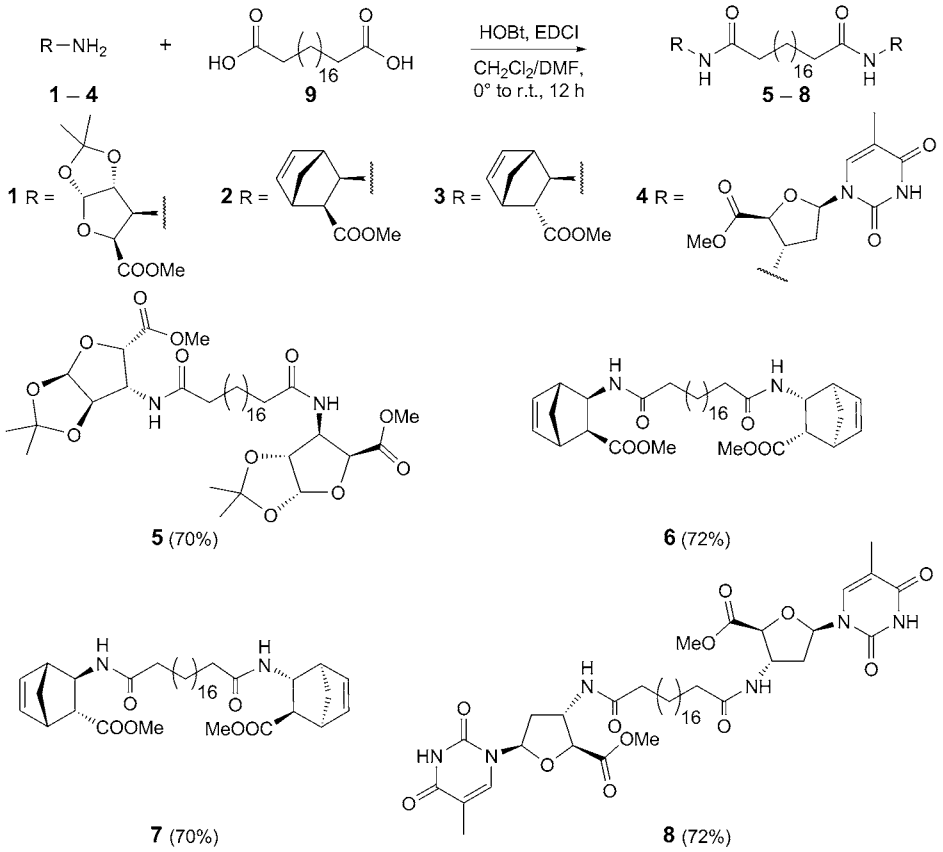
Several studies have been carried out towards the synthesis of diverse bolaamphiphiles. Some of the compounds include D-galactose or lactose as polar head groups [3], 1,ω-thymidylic acid appended bolaamphiphiles [4], cholesterol derivatives [5], 1-glucosamine supramolecular assemblies [6], and 3′-phosphorylated thymidine connected to both ends of an oligomethylene spacer [7]. Amino acids have also been used to prepare bolaamphiphiles [8]. A recent publication by *Bordes* and co-workers [9] signifies the role of an amide bond for self-assembly of surfactants. According to this report, the amide bond contributed significantly to the hydrophilicity of the surfactant. This also supported our view that amides would help in self-assembly, and hence we concentrated on the synthesis of bolaamphiphiles derived from unusual β-amino acids to check this hypothesis.

Our continued interest in design and synthesis of various β-amino acid monomers in foldamer research [10] prompted us to explore the possibility of utilizing these β-amino acids as potential hydrophilic head groups connecting through hydrophobic spacers of varying lengths. Several reports, over the years, have discussed effects of the length of the hydrophobic spacer and gelating properties of the molecules. *Bozell* and co-workers [11] have used a spacer of 12 C-atoms exhibiting self-assembly compared to spacers of smaller chain-lengths. *Shimizu* and co-workers [7] indicated that a C_{18} spacer formed

giant vesicles, and a C_{20} spacer resulted in robust hydrogels, whereas C_{15}, C_{14}, *etc.*, spacers did not show any interesting results. Keeping these results and observations in mind, we designed compounds containing both C_{12} and C_{20} hydrophobic spacers (hydrocarbon chains). We wish to report herein the synthesis and self-assembling properties of this new class of molecules having an unusual β-amino acid or an alcohol motif as head group.

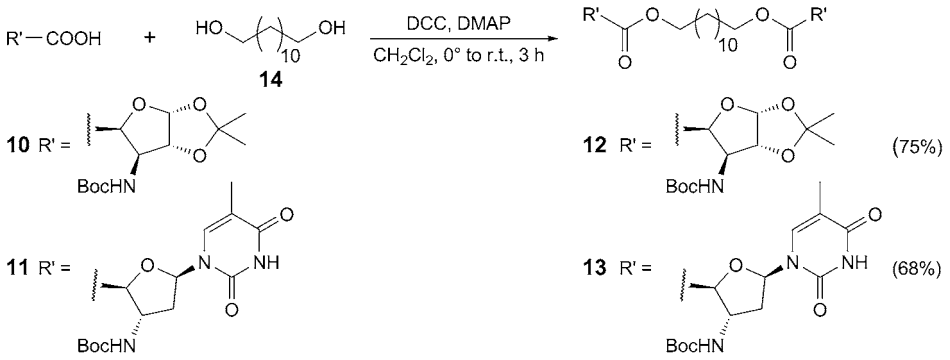
Results and Discussion. – Unusual β-amino acids that are used in the present work are derived from D-glucose [12], norbornene [13], and AZT (= 3′-azido-3′-deoxythymidine) [14]. Thus, the methyl esters **1**–**4** [15–17] of β-amino acids were prepared following the protocols published earlier by us. These building blocks were then converted to the potential bolaamphiphiles **5**–**8** by a standard peptide-coupling reaction with eicosanedioic acid (**9**), 2 equiv. of amino ester **1**–**4** and 1-hydroxy-1*H*-benzotriazole/1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (HOBt/EDCI) [18] in CH_2Cl_2/DMF in good yields (*Scheme 1*).

Scheme 1. *Synthesis of Amide Bolaamphiphiles*



The ester-linked bolaamphiphiles **12** and **13** (*Scheme 2*) were prepared from Boc-protected β-amino acids **10** and **11** (Boc = (*tert*-butoxy)carbonyl). In this instance, condensation of dodecane-1,12 diol (**14**) with acid **10** or **11** (2 equiv.) in CH_2Cl_2 in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and *N*,*N*-dimethylpyridin-4-amine (DMAP) [19] gave the bolaamphiphiles **12** and **13**.

Scheme 2. *Synthesis of Ester Bolaamphiphiles*

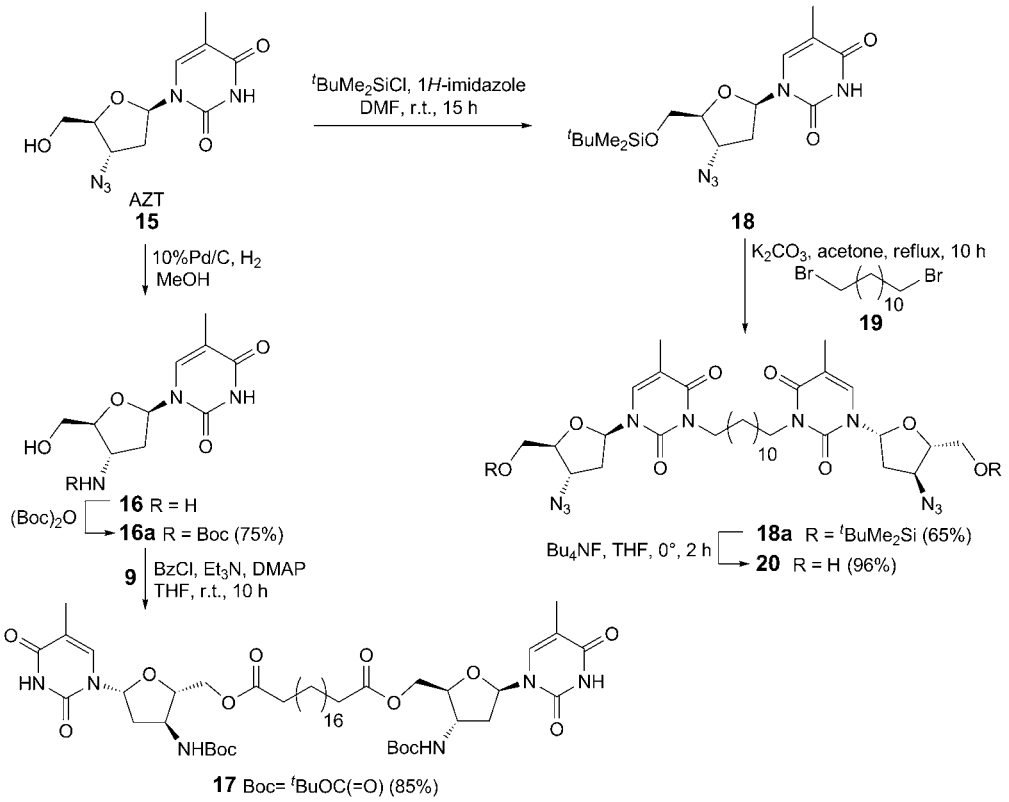


The alcohol-derived bolaamphiphiles **17** (diester-linked) and **20** (alkanediyl-linked) were prepared from the known antiretroviral drug 3′-azido-3′-deoxythymidine (= AZT; **15**; *Scheme 3*). Thus **15** was treated with 10% Pd/C under H_2 in MeOH to give amino derivative **16**, which was immediately Boc-protected (→ **16a**). The primary-alcohol derivative **16a** (2.07 equiv.) was treated with eicosanodioic acid (**9**) and benzoyl chloride/Et_3N/DMAP [20] to furnish bolaamphiphile **17** in 85% yield. AZT (**15**) was also treated with ^{t}BuMe$_2$SiCl and 1*H*-imidazole to yield **18**. The latter was treated with 1,12-dibromododecane (**19**), K_2CO_3, and acetone to give the protected derivative **18a**, followed by reaction with tetrabutylammonium fluoride (Bu_4NF) to obtain alkanediyl-linked bolaamphiphile **20**.

After successfully synthesizing the eight bolaamphiphiles **5**–**8**, **12**, **13**, **17**, and **20**, these compounds were screened for self-assembly. CD is an excellent method of determining secondary structures [21]. When the chromophores of the amide groups of polypeptides are arranged in arrays, their optical transitions are shifted or split into multiple transitions due to 'exciton' interactions. The result is that different structural elements have characteristic CD spectra. The CD spectrum of **8** (*Fig. 1*) showed a negative band at 195 nm and two positive bands at 215 and 270 nm. Similarly, compound **13** (*Fig. 2*) had positive peaks at 200 and 275 nm and a negative one at 230 nm, and compound **17** (*Fig. 3*) showed positive bands at 210 and 275 nm and two negative peaks at 220 and 240 nm respectively. The presence of both positive and negative peaks in these CD spectra confirmed the presence of secondary structures.

Carbohydrate-based bolaamphiphiles and related systems are known to form noncovalently bonded nanoscale polymers linked through an extensive H-bonding network established between the carbohydrate head groups during self-assembly [11]. The here synthesized bolaamphiphiles were dispersed in H_2O followed by slow addition of MeOH. The transmission electron microscopy (TEM) images of the

Scheme 3. *Synthesis of AZT-Derived Bolaamphiphiles*



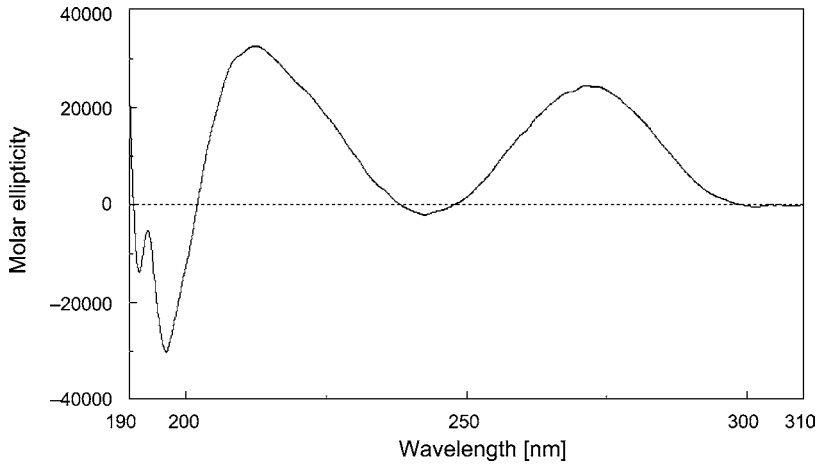


Fig. 1. *CD Spectrum of bolaamphiphile* **8**

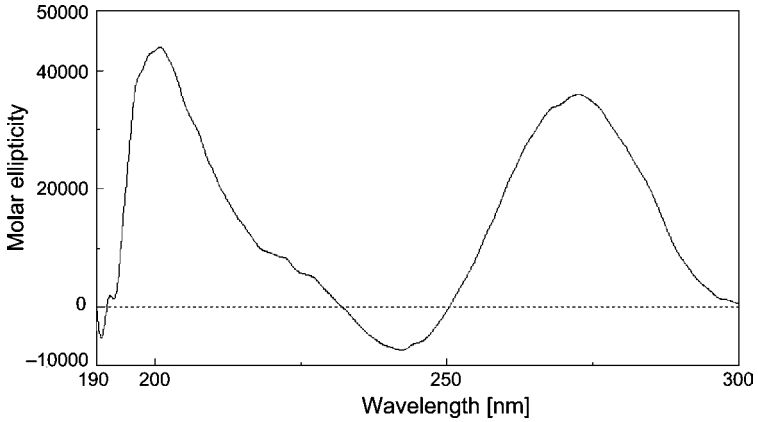


Fig. 2. *CD Spectrum of bolaamphiphile* **13**

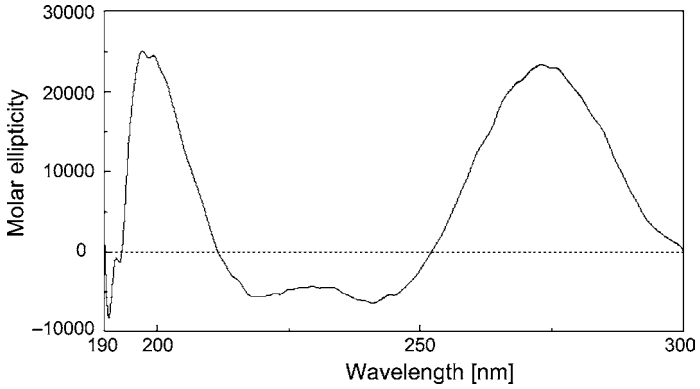


Fig. 3. *CD Spectrum of bolaamphiphile* **17**

dispersed compounds **5** (*Fig. 4*) and **8** (*Fig. 5*) revealed as fibers and vescicles, respectively, as secondary structures.

Based on the TEM, atomic-force microscopy (AFM), and CD data, compounds **8**, **13**, and **17** showed the presence of secondary structure. Other compounds failed to self-aggregate under the conditions that were tried (see *Exper. Part*).

Conclusions. – We synthesized a set of bolaamphiphiles and analogues with hydrophobic head groups and studied self-assembly of them. We observed that the amides **5** and **8** had a selectivity to self-assemble over the alkanediyl-linked derivative **20**. Esters **13** and **17** too formed gels which were less prominent when compared to amides **5** and **8**. The presence of a hydrophilic head initiated self-assembly through H-bonding, whereas hydrophobic heads failed to form any secondary structures (in our case norbornene derivatives **6** and **7**). Therefore, by this study we emphasize that the basic requirements for self-assembly/secondary-structure formation of a bolaamphi-

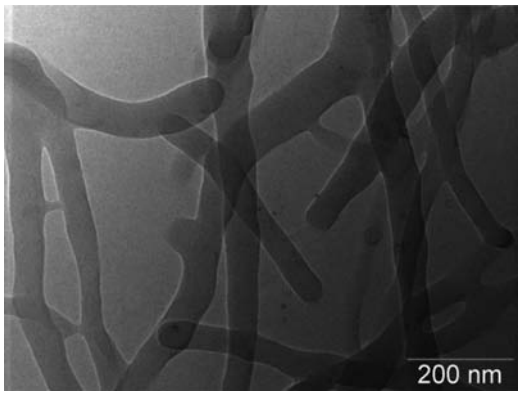


Fig. 4. *TEM of bolaamphiphile* **5**

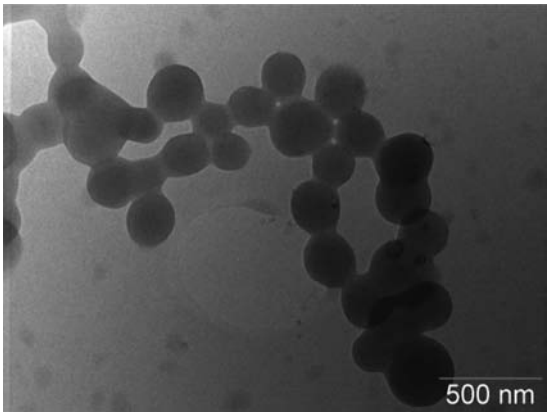


Fig. 5. *TEM of bolaamphiphile* **8**

phile are the presence of a hydrophilic head which can initiate H-bonding, and the presence of amide or ester bonds to strengthen the structure, which we demonstrated by using bolaamphiphiles **8**, **13**, and **17**, derived from a nucleoside-based amino acid.

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Experimental Part

1. *General.* All commercially available reagents and solvents (*Fluka*, *Aldrich*, *Rankem*) were used without further purification. For reactions requiring anh. conditions, dry solvents were bought (*Rankem*). Technical grade AcOEt and petroleum ether used for CC were distilled prior to use. TLC: silica gel *60* F_{254} plates (SiO_2; *Merck*); detection with UV light, *Molish* reagent (H_2SO_4, EtOH, H_2O, $C_{10}H_8O$), or phosphomolybdic acid ($H_3PMo_{12}O_{40}$, EtOH). Column chromatography (CC): silica gel *60*

(SiO_2, 70–230 mesh; *Merck* No. 107734). Optical rotations: *Anton paar MCP 200* polarimeter at 25°; [α] values in 10^{-1} deg cm^2 g^{-1}. IR Spectra: *Perkin-Elmer-Paragon Spectrum-400-FTIR/FT-NIR* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Avance-Bruker-300* and *Varian-Innova-500* spectrometer; at 300 or 500 (^{1}H) and 75 and 125 MHz (^{13}C); δ(H) in ppm rel. to Me_4Si as internal standard, *J* in Hz; δ(C) in ppm rel. to residual solvent signal ($CDCl_3$, δ(C) 77; (D_6)DMSO, δ(C) 39.51). ESI-Q-MS: *Agilent-Technologies-LC/MSD-Trap-SL* instrument; in *m*/*z*. HR-ESI-MS: *Agilent-Technologies-6510 Q-TOF* LC/MS instrument; in *m*/*z*.

2. *General Procedure for TEM Studies.* In a typical procedure, a compound (5 mg) was mixed with 100 µl of H_2O and 30 µl of MeOH at r.t. and heated to 60° to get a clear soln. Upon cooling to r.t., the bolaamphiphiles **5**, **8**, **13**, and **17** began to precipitate, others remained in soln. The turbid mixture was subjected to TEM studies. TEM samples were prepared by placing sample-mixture drops directly on the polymer-coated grids by means of a micropipette. The bolaamphiphiles present in the H_2O/MeOH mixture were allowed to settle, and the extra solvent was subsequently removed by placing the TEM grid on a neat filter paper and drying at r.t. for half a day. The morphology and size and shape distribution of the bolaamphiphiles were recorded with the TEM instrument operating at 120 keV. In each image, more than 150 particles were analyzed with the SIS imaging software to create size-distribution histograms. The diffraction patterns were recorded at a selected area to determine the crystal structure and phases of crystals at 660 mm camera length.

3. *Amide Bolaamphiphiles: General Procedure.* To a stirred soln. of eicosanedioic acid (**9**; 1.8 mmol) in dry CH_2Cl_2/DMF 1:1 (15 ml) was added sequentially HOBt (3.7 mmol) and EDCI (5.2 mmol) at 0° under N_2. After 15 min, free amine (3.7 mmol) in dry CH_2Cl_2/DMF 1:1 (10 ml) was added. The mixture was allowed to reach r.t. and stirred further for 12 h under N_2. After dilution with CH_2Cl_2, the mixture was washed with 1N HCl (10 ml), H_2O, 5% aq. $NaHCO_3$ soln. (15 ml), and brine, the combined org. layer dried (Na_2SO_4) and concentrated, and the residue purified by CC (SiO_2 *60–120*, AcOEt/hexane 1:2): diamide.

*(3a*R,*3′a*R,*5*S,*5′*S,*6*R,*6′*R,*6a*R,*6′a*R*)-Dimethyl 6,6′-[(1,20-Dioxoeicosane-1,20-diyl)diimino]bis[tetrahydro-2,2-dimethylfuro[2,3-*d*][1,3]dioxole-5-carboxylate]* (**5**): Yield 98 mg (70%). White solid. M.p. 82–84°. $[\alpha]_D^{25} = +43$ (*c* = 1.2, MeOH). IR (neat): 3307, 2989, 2920, 2850, 1745, 1654, 1080, 1035. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.09 (*d*, *J* = 9.5, 2 H); 5.94 (*d*, *J* = 3.4, 2 H); 4.73 (*d*, *J* = 4.1, 2 H); 4.58 (*dd*, *J* = 4.2, 9.4, 2 H); 4.42 (*d*, *J* = 3.4, 2 H); 3.58 (*s*, 6 H); 2.04–1.99 (*m*, 4 H); 1.42 (*s*, 6 H); 1.25–1.23 (*m*, 38 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.8; 168.7; 112.7; 104.7; 83.8; 76.7; 56.5; 52.4; 36.4; 29.5; 29.3; 29.2; 29.1; 26.5; 26.0; 25.5. HR-ESI-MS: 763.4363 ($[M+Na]^+$, $C_{38}H_{64}N_2NaO_{12}^+$; calc. 763.4351).

*(1*S,*1′*S,*2*S,*2′*S,*3*R,*3′*R,*4*R,*4′*R*)-Dimethyl 3,3′-[1,20-Dioxoeicosane-1,20-diyl)diimino]bis[bicyclo[2.2.1]hept-5-ene-2-carboxylate]* (**6**): Yield 281 mg (72%). White solid. M.p. 120–125°. $[\alpha]_D^{25} = +110.5$ (*c* = 1, MeOH). IR (neat): 3411, 2978, 1654, 1537, 1365, 1171. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.46 (*d*, *J* = 8.8, 2 H); 6.30–6.23 (*m*, 2 H); 6.22–6.16 (*m*, 2 H); 4.22–4.11 (*m*, 2 H); 3.68 (*s*, 6 H); 2.95 (*s*, 2 H); 2.71 (*s*, 2 H); 2.12 (*t*, *J* = 7.3, 4 H); 1.95 (*d*, *J* = 9.27, 4 H); 1.67–1.46 (*m*, 8 H); 1.6 (br. *s*, 28 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 174.0; 171.5; 137.3; 136.6; 52.2; 51.0; 48.8; 46.8; 46.0; 44.6; 37.4; 30.2; 30.0; 29.9; 29.7; 26.3. HR-ESI-MS: 663.4343 ($[M+Na]^+$, $C_{38}H_{60}N_2NaO_6^+$; calc. 663.4344).

*(1*S,*1′*S,*2*R,*2′*R,*3*R,*3′*R,*4*R,*4′*R*)-Dimethyl 3,3′-[1,20-Dioxoeicosane-1,20-diyl)diimino]bis[bicyclo[2.2.1]hept-5-ene-2-carboxylate]* (**7**): Yield 270 mg (70%). White solid. M.p. 118–120°. $[\alpha]_D^{25} = -62$ (*c* = 1, MeOH). IR (neat): 3411, 2978, 1654, 1537, 1365, 1171. ^{1}H-NMR(300 MHz, $CDCl_3$): 6.19–6.16 (*m*, 2 H); 6.06–6.03 (*m*, 2 H); 5.80 (*d*, *J* = 6.3, 2 H); 3.96 (br. *s*, 2 H); 3.60 (*s*, 6 H); 3.10 (*s*, 2 H); 2.80 (*s*, 2 H); 2.54 (*t*, *J* = 3.4, 6.9, 2 H); 2.15–2.10 (*m*, 4 H); 1.62–1.52 (*m*, 8 H); 1.21 (br. *s*, 28 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.0; 171.7; 135.2; 134.6; 54.1; 52.7; 52.0; 49.0; 47.2; 45.2; 37.2; 30.1; 30.0; 29.9; 29.8; 26.3. HR-ESI-MS: 663.4343 ($[M+Na]^+$, $C_{38}H_{60}N_2NaO_6^+$; calc. 663.4344).

*(2*S,*2′*S,*3*S,*3′*S,*5*R,*5′*R*)-Dimethyl 3,3′-[1,20-Dioxoeicosane-1,20-diyl)diimino]bis[5-[3,4-dihydro-5-methyl-2,4-dioxopyrimidin-1(2*H*)-yl]tetrahydrofuran-2-carboxylate]* (**8**): Yield 520 mg (72%). White solid. M.p. 124–126°. $[\alpha]_D^{25} = +37$ (*c* = 0.5, MeOH). IR (neat): 3300, 3071, 2924, 2853, 1748, 1698, 1539, 1469, 1275. ^{1}H-NMR(500 MHz, $CDCl_3$): 11.18 (*s*, 2 H); 8.41 (*d*, *J* = 5.0, 2 H); 7.95 (*s*, 2 H); 6.4 (*t*, *J* = 5.0, 2 H); 4.58–4.42 (*m*, 2 H); 4.28 (*d*, 2 H); 3.79 (*s*, 6 H); 2.24–1.98 (*m*, 8 H); 1.83 (*s*, 6 H); 1.58–1.42 (*m*, 4 H); 1.21 (*s*, 28 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.8; 168.7; 112.7; 104.7; 83.8; 76.7; 56.5; 52.4; 36.4; 29.5; 29.3; 29.2; 29.1; 26.5; 26.0; 25.5. HR-ESI-MS: 845.4661($[M+H]^+$, $C_{42}H_{65}N_6O_{12}^+$; calc. 845.4655).

4. *Ester Bolaamphiphiles: General Procedure.* To a stirred soln. of acid (0.49 mmol) in anh. CH_2Cl_2 (10 ml) was added (catalytic) DMAP (3 mg) and dodecane-1,12-diol (**14**; 0.23 mmol). Then DCC (0.59 mmol) was added at 0°, and the mixture was stirred for 5 min at 0° and 3 h at 20°. Precipitated urea was then filtered off, and the filtrate was evaporated *in vacuo*. The residue was taken up in CH_2Cl_2 and again filtered to remove any further precipitated urea. The CH_2Cl_2 soln. was washed with 0.5N HCl (2 ×) and sat. $NaHCO_3$ soln., dried ($MgSO_4$), and concentrated and the residue purified by CC (SiO_2 *60–120*; AcOEt/hexane 1:3): diester.

*(3a*R,*3′a*R,*5*S,*5′*S,*6*R,*6′*R,*6a*R,*6′a*R*)-Dodecane-1,12-diyl Bis[6-{[(1,1-Dimethylethoxy)carbonyl]amino}tetrahydro-2,2-dimethylfuro[2,3-*d*][1,3]dioxole-5-carboxylate]* (**12**): Yield 0.147 g (75%). White solid. M.p. 75–78°. $[\alpha]_D^{25} = +93.5$ ($c = 1$, MeOH). IR (neat): 3411, 3347, 2924, 2850, 1762, 1723, 1247, 1058. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.90 (*d*, *J* = 3.3, 2 H); 4.8 (*d*, *J* = 8.3, 2 H); 4.75 (*d*, *J* = 3.8, 2 H); 4.53 (*d*, *J* = 3.5, 2 H); 4.4 (*dd*, *J* = 3.7, 8.5, 2 H); 4.20 (*t*, *J* = 8.3, 4 H); 1.51 (*s*, 6 H); 1.41 (*s*, 30 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.2; 154.6; 112.0; 104.0; 84.0; 80.2; 77.1; 65.9; 58.2; 30.2; 30.0; 30.0; 29.7; 29.0; 28.8; 27.2; 26.7; 26.3. HR-ESI-MS: 795.2309 ($[M + Na]^+$, $C_{38}H_{64}N_2NaO_{14}^+$; calc. 795.4283).

*(2*S,*2′*S,*3*S,*3′*S,*5*R,*5′*R*)-Dodecane-1,12-diyl Bis{5-[3,4-dihydro-5-methyl-2,4-dioxopyrimidin-1(2*H*)-yl]}-3-{[(1,1-dimethylethoxy)carbonyl]amino}tetrahydrofuran-2-carboxylate}* (**13**): Yield 83 mg (68%). White solid. M.p. 160–162°. $[\alpha]_D^{25} = +25.8$ ($c = 1$, MeOH). IR (neat): 3322, 2931, 2853, 1698, 1520, 1473, 1273, 1167. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.19 (*s*, 2 H); 7.71 (*s*, 2 H); 7.42 (*d*, *J* = 6.3, 2 H); 6.16–6.03 (*m*, 2 H); 4.16–3.91 (*m*, 8 H); 2.19–2.01 (*m*, 4 H); 1.66 (*s*, 6 H); 1.54–1.36 (*m*, 4 H); 1.26 (*s*, 9 H); 1.10 (*s*, 16 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.0; 162.1; 153.4; 149.0; 134.8; 108.4; 84.5; 80.8; 77.9; 64.7; 36.0; 29.0; 28.9; 28.7; 28.2; 28.0; 25.3; 12.6. HR-ESI-MS: 877.4560 ($[M + H]^+$, $C_{42}H_{65}N_6O_{14}^+$; calc. 877.4553).

5. *Alcohol-Derived Bolaamphiphiles* **17** *and* **20**. *1,1-Dimethylethyl* N-*{(2*S,*3*S,*5*R*)-5-[3,4-Dihydro-5-methyl-2,4-dioxopyrimidin-1(2*H*)-yl]tetrahydro-2-(hydroxymethyl)furan-3-yl}carbamate* (**16a**). To a soln. of AZT azide (**15**; 50 mg, 0.107 mmol) in dry MeOH (5 ml), 20% $Pd(OH)_2$/C (7 mg) was added, and the mixture was stirred under H_2 for 3 h. Then Boc_2O (0.029 ml, 0.128 mmol) was added to the mixture. After 1 h, the mixture was filtered through a pad of *Celite*, the pad washed with MeOH (20 ml), the filtrate concentrated, and the residue purified by CC (AcOEt/hexanes 3:2): **16a** (30 mg, 75%). White solid. M.p. 115–118°. R_f (30% AcOEt/hexanes) 0.2. $[\alpha]_D^{25} = +93.5$ ($c = 1$, MeOH). IR (neat): 3445, 2977, 1652, 1506, 1168. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.65 (*s*, 1 H); 7.74 (*s*, 1 H); 6.09–6.06 (*m*, 1 H); 5.07–5.05 (br. *s*, 1 H); 4.23–4.05 (*m*, 2 H); 3.93–3.72 (*m*, 2 H); 2.32–2.28 (*m*, 3 H); 1.91 (*s*, 3 H); 1.44 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.1; 156.1; 150.7; 135.9; 110.9; 85.9; 84.2; 80.5; 61.5; 49.4; 37.7; 28.2; 12.5. HR-ESI-MS: 342.3219 ($[M + H]^+$, $C_{15}H_{24}N_3O_6^+$; calc. 342.3217).

*Bis{{(2*S,*3*S,*5*R*)-5-[3,4-dihydro-5-methyl-2,4-dioxopyrimidin-1(2*H*)-yl]-3-{[(1,1-dimethylethoxy)carbonyl]amino}tetrahydrofuran-2-yl}methyl} Eicosanedioate* (**17**). To a soln. of AZT-derived carbamate **16a** (100 mg, 0.29 mmol), benzoyl chloride (41 mg, 0.29 mmol), and eicosanedioic acid (**9**, 50 mg, 0.14 mmol) in dry THF (5 ml), Et_3N (0.1 ml, 0.58 mmol) was added slowly, followed by DMAP (9 mg, 25 mol-%). The mixture was stirred until the reaction was complete and then quenched with 10% HCl soln. (10 ml). The soln. was extracted with AcOEt (2 × 10 ml), the combined org. phase washed with sat. $NaHCO_3$ soln. (2 × 20 ml), dried, and concentrated, and the residue purified by CC (SiO_2, AcOEt/hexane 3:7): **17** (123 mg, 85%). White solid. M.p. 118–120°. $[\alpha]_D^{25} = +13.7$ ($c = 1$, MeOH). IR (neat): 3338, 2926, 2853, 1772, 1710, 1466. ^{1}H-NMR (300 MHz, $CDCl_3$): 11.4 (*s*, 2 H); 7.43 (*s*, 2 H); 7.25 (*d*, *J* = 7.5, 2 H); 6.15 (*t*, *J* = 6.7, 2 H); 4.30–4.01 (*m*, 6 H); 3.81–3.79 (*m*, 2 H); 2.35–2.22 (*m*, 8 H); 1.79 (*s*, 6 H); 1.45 (*m*, 4 H); 1.39 (*s*, 18 H); 1.22 (br. *s*, 28 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.2; 163.6; 155.4; 150.6; 134.6; 111.4; 84.8; 83.5; 80.2; 64.0; 51.3; 37.7; 34.1; 33.9; 29.5; 29.3; 29.1; 29.0; 28.3; 24.8; 12.5. HR-ESI-MS: 989.5825 ($[M + H]^+$, $C_{50}H_{81}N_6O_{14}^+$; calc. 989.5825).

*1-{(2*R,*4*S,*5*S*)-4-Azido-5-{[[(1,1-dimethylethyl)dimethylsilyl]oxy}methyl}tetrahydrofuran-2-yl}-5-methylpyrimidine-2,4(1*H,*3*H*)-dione* (**18**). To a soln. of **15** (7.0 g, 23.4 mmol) in DMF (30 ml) were added 1*H*-imidazole (2.39 g, 35.1 mmol) and ^{t}BuMe$_2$SiCl (4.58 g, 30.4 mmol). After being stirred at r.t. under N_2 for 15 h, the mixture was diluted with H_2O and extracted with AcOEt (2 × 100 ml). The combined org. phase was washed with brine (100 ml), dried (Na_2SO_4), and concentrated and the residue subjected to FC (SiO_2, hexanes/AcOEt 20:1): **18** (8.7 g, 90%). White solid. M.p. 99–102°. $[\alpha]_D^{25} = +93.5$ ($c = 1$, MeOH). IR (neat): 3445, 2977, 1652, 1506, 1168. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.12 (*s*, 1 H); 7.40 (*s*, 1 H);

6.18 (*t*, *J* = 6.7, 1 H); 4.27–4.19 (*m*, 1 H); 4.03–3.9 (*m*, 2 H); 3.86–3.79 (*m*, 1 H); 2.50–2.40 (*m*, 1 H); 2.30–2.19 (*m*, 1 H); 1.93 (*s*, 3 H); 0.97 (*s*, 9 H); 0.16 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 150.2; 134; 111.0; 84.4; 84.3; 62.8; 60.4; 37.9; 25.8; 18.3; 12.5; −5.3; −5.4. HR-ESI-MS: 382.2909 ($[M+H]^+$, $C_{16}H_{28}N_5O_4Si^+$; calc. 382.1968).

*3,3′-(Dodecane-1,12-diyl)bis[1-{(2*R*,4*S*,5*S*)-4-azido-5-{{[(1,1-dimethylethyl)dimethylsilyl]oxy}methyl}tetrahydrofuran-2-yl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione]* (**18a**). AZT-Derived siyl ether **18** (250 mg, 0.65 mmol), 1,12-dibromododecane (106 mg, 0.32 mmol), and K_2CO_3 (270 mg, 1.94 mmol) were added to dry acetone at 20°. The mixture was heated to reflux overnight. After completion of the reaction (TLC minotoring), the mixture was cooled to r.t. and the solvent evaporated. After addition of H_2O, the mixture was extracted with AcOEt (2 × 20 ml), the org. layer dried ($MgSO_4$) and concentrated, and the residue purified by CC (SiO_2; *60–120*, AcOEt/hexane 1:5): **18a** (198 mg, 65%). White solid. M. p. 56–58°. $[\alpha]_D^{25} = +45.5$ (*c* = 1, MeOH). IR (neat): 3445, 2977, 1652, 1506, 1168. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.29 (*d*, *J* = 1.08, 2 H); 6.14 (*t*, *J* = 6.4, 2 H); 4.16–4.10 (*m*, 2 H); 3.88–3.79 (*m*, 8 H); 3.73–3.68 (*m*, 2 H); 2.40–2.32 (*m*, 2 H); 2.18–2.11 (*m*, 2 H); 1.84 (*d*, *J* = 0.92, 3 H); 1.53–1.43 (*m*, 2 H); 1.22–1.16 (*m*, 16 H); 0.85 (*s*, 9 H); 0.04 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 162.2; 149.8; 132.1; 127.6; 109.7; 85.0; 84.2; 62.9; 60.5; 49.8; 38.5; 30.1; 29.8; 28.1; 27.5; 26.5; 19.0; 14.0; −4.3; −4.5. HR-ESI-MS: 929.5476 ($[M+H]^+$, $C_{44}H_{77}N_{10}O_8Si_2^+$; calc. 929.5458).

*3,3′-(Dodecane-1,12-diyl)bis[1-[(2*R*,4*S*,5*S*)-4-azidotetra hydro-5-(hydroxymethyl)furan-2-yl]-5-methylpyrimidine-2,4(1*H*,3*H*)-dione]* (**20**). A soln. of **18a** (1.4 g, 2.06 mmol) in THF (15 ml) was treated with 1M Bu_4NF in THF (3.09 ml, 3.09 mmol) at 0° and stirred for 2 h at r.t. The mixture was diluted with H_2O and extracted with AcOEt (2 × 50 ml). The combined org. layer was washed with brine (50 ml), dried (Na_2SO_4), and concentrated and the residue purified by CC (SiO_2, 40% AcOEt/hexane): **20** (1.1 g, 95%). Semi-solid. R_f (50% AcOEt/hexanes) 0.2. $[\alpha]_D^{25} = +35.5$ (*c* = 1, MeOH). IR (neat): 3411, 2978, 1654, 1537, 1365, 1171. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.34 (*d*, *J* = 1.06, 2 H); 6.16 (*t*, *J* = 6.3, 2 H); 4.23–4.18 (*m*, 2 H); 3.96–3.76 (*m*, 6 H); 3.37 (*t*, *J* = 6.8, 4 H); 2.47–2.39 (*m*, 2 H); 2.26–2.19 (*m*, 2 H); 1.91 (*d*, *J* = 0.87, 6 H); 1.87–1.80 (*m*, 2 H); 1.66–1.52 (*m*, 4 H); 1.36–1.24 (*m*, 16 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 162.3; 149.7; 133.7; 109.6; 86.4; 84.3; 61.8; 60.8; 50.7; 41.8; 37.9; 30.1; 29.9; 29.7; 28.0; 27.4; 13.9. HR-ESI-MS: 701.3739 ($[M+H]^+$, $C_{32}H_{49}N_{10}O_8^+$; calc. 701.3729).

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