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Asymmetric Hydrogenation of Amino Acid Precursors Promoted by a New Type of Cholesterol Amphiphiles: Investigation of Aggregation Behaviour and Stereoselective Effects

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Abstract. Reaction of 2-hydroxyethanesulfonic acid sodium salt, 3-hydroxypropanesulfonic acid sodium salt or 2-amino-ethanesulfonic acid sodium salt with cholest-5-en-3β-ol-3-chloroformate yields the chiral amphiphilic compounds 2-(cholest-5-en-3β)oxy-carbonyloxy-ethanesulfonic acid sodium salt **1**, 2-(cholest-5-en-3β)oxy-carbonyloxy-propanesulfonic acid sodium salt **2** and 2-(cholest-5-en-3β)oxy-carbonylamino-ethanesulfonic acid sodium salt **3**, respectively. Another chiral amphiphile 2-(cholest-5-en-3β)oxy-carbonylethanesulfonic acid sodium salt **4** was synthesized by treating cholest-5-en-3β-ol with sulfopropionic acid anhydride. The surfactants form vesicles in aqueous solutions, as shown by electron microscopy. Stepwise destruction of these vesicles by addition of ethanol or methanol was proved by Circular Dichroism (CD) measurements. Especially compound **3** shows pronounced induced CD effects with the achiral dye 3,6-diamino-acridine-sulfate (proflavine). The synthesized chiral amphiphiles were used in the asymmetric hydrogenation reaction of methyl (*Z*)-α-acetamidocinnamate. In the case of an achiral rhodium complex as catalyst the prepared surfactants **1**, **2**, and **4** are able to provide an enantiomer excess by themselves. The best ee-value reached was 8.5% methyl (*R*)-*N*-acetylphenyl-alaninate in connection with compound **4**.

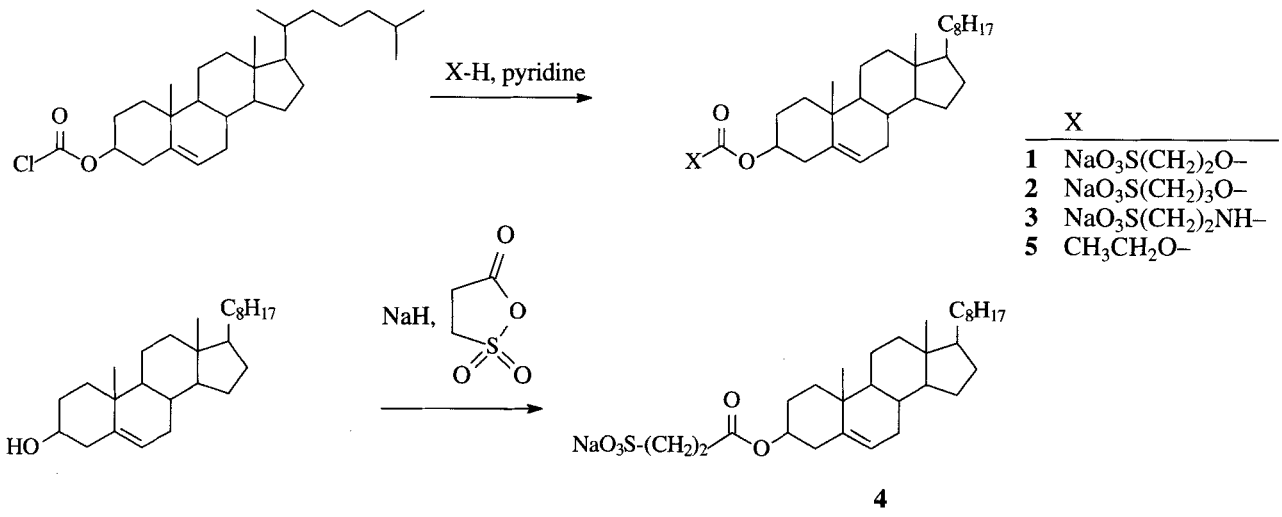
Cholesterol and other steroid derivatives, for instance bile acids, play an important role in membrane building processes. Chemists, biochemists and pharmaceutical research groups dealing with bilayer membrane systems and liposomes show a continuous interest in this type of compounds [1]. Various derivatization methods, e. g. ethoxylation [2], [3], glycosylation [4] or esterification [5], were used to yield amphiphilic cholesterol derivatives. Bolaamphiphile-like sterol polyethers [6] were synthesized as well as polymerizable vesicle forming quaternary ammonium derivatives of cholesterol [7]. Surfactants built up from the cholesterol skeleton can form vesicles although they are single chain amphiphiles. This special aggregation behaviour is connected with the strongly hydrophobic steroidal building block. Amphiphiles containing a rigid segment prefer to form bilayer aggregates [8].

In the case of chiral surfactants special bilayer structures like fibers or helices could be found [9, 10]. It became a matter of high interest to use such assemblies for chiral recognition and chiral induction processes.

In the present paper we investigate a new type of cholesterol derivatives as amphiphiles in the stereoselective hydrogenation of aminoacid precursors with respect to the morphology of assemblies in water.

Results and Discussion

In connection with investigations of asymmetric reactions in assembled amphiphiles [11] we synthesized the new amphiphilic cholesterol derivatives **1**, **2** and **3** by treating cholest-5-en-3β-ol-3-chloroformate with 2-hydroxyethanesulfonic acid sodium salt, 3-hydroxypropanesulfonic acid sodium salt, and 2-amino-ethanesulfonic acid sodium salt, respectively, in pyridine. Reaction of cholest-5-en-3β-ol, activated by sodium hydride, with sulfopropionic acid anhydride gave 2-(cholest-5-en-3β)oxy-carbonylethanesulfonic acid sodium salt **4**. Because of the different solubilities of the reaction



	X
1	$NaO_3S(CH_2)_2O$–
2	$NaO_3S(CH_2)_3O$–
3	$NaO_3S(CH_2)_2NH$–
5	CH_3CH_2O–

Scheme 1

partners all reactions run heterogeneous resulting in only low to moderate yields. The compounds were characterized by elemental analysis, ^{13}C NMR spectroscopy and mass spectrometry. They showed typical amphiphilic properties in aqueous solution like foam formation and solubilisation of water insoluble dyes, although their solubility in water is limited.

The turbid aqueous dispersions of **1**, **2**, **3** and **4** were treated in an ultrasonic bath for 15 min at room temperature and then investigated by electron microscopy. In all solutions we found vesicles in a wide range of sizes (Figure 1). Table 1 shows the vesicle diameter range for the amphiphiles described here. Compound **4** forms remarkably larger aggregates than the other surfactants. Sonication of aqueous dispersions of **1** and **3** with a needle probe tip results in quite uniform unilamellar vesicles with diameters around 20 nm.

Vesicles can be destroyed by thermal influences, by addition of electrolytes or by addition of organic solvents [12]. We studied the changes in the aggregation behaviour of the cholest-5-en-3β-ol derivatives by varying the ratio of water to alcohol (ethanol or methanol) in the solvent-amphiphile-mixture by means of CD measurements [13]. The dispersions investigated were prepared in the following way: $4 \cdot 10^{-5}$ mol of the solid compound and the calculated amount of water were placed in a 100 ml volumetric flask and treated for 15 min in an ultrasonic bath at room temperature followed by the addition of ethanol or methanol to fill the remaining volume of the flask. It is impossible to dissolve the solid in previously prepared water-alcohol-mixtures or in pure alcohol because of its low solubility.

Table 1 Vesicle diameter range for the synthesized amphiphile compounds as indicated by electron microscopy

compound	diameter range of vesicles
1	20 nm–1 μm
2	20 nm–1 μm
3	20 nm–1 μm
4	100 nm–2 μm

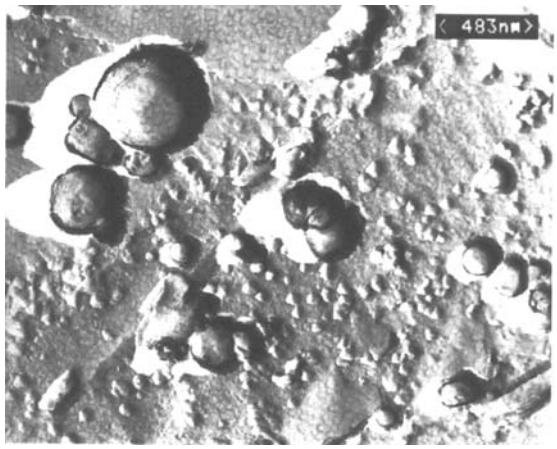


Fig. 1 Electron micrograph of a freeze fractured sample of **1** in water (0.5 mg ml^{-1}) after treating the sample in an ultrasonic bath for 15 min at room temperature

As shown in Figure 2 the CD method proves very clearly and better than other methods the stepwise degradation of the aggregates by addition of alcohol. The vesicles withstand a certain amount of organic solvent depending on the structure of the amphiphile and on the kind of solvent. Vesicles of compound **1** and **3** resist 20% of ethanol and 40% of methanol, aggregates of amphiphile **2** show a more sudden degradation. These lysis experiments could not be performed with com-

pound **4** because of its very low solubility in water.

By the example of Figure 2 we want to explain the aggregation behaviour in water-alcohol-mixtures for the synthesized amphiphiles:

Figure 2 shows the CD spectra of compound **1** in pure water and in mixtures of water and ethanol from a ratio water:ethanol = 9:1 to 4:6 (v/v). The CD spectrum of **1** in pure water with the negative peak at 203 nm does not change remarkably up to 20% ethanol content in the solvent mixture. A further increase of ethanol above 20% results in a continuous change of the CD spectra up to a water to ethanol ratio of 5:5. The typical spectrum in water with the negative band at 203 nm changed into a spectrum with a positive maximum at 198 nm. Spectra of solutions from compound **1** containing more than 50% ethanol look quite similar to the 5:5 spectrum.

This behaviour can be explained by assuming a stepwise degradation (lysis) of the vesicular aggregates by addition of ethanol. Up to an ethanol content of ca. 20% the vesicles remain intact but swell as shown by electron microscopy. By addition of further ethanol the vesicles start to break up by osmotic pressure resulting in an equilibrium between the aggregated and the monomeric form of **1**. The interchromophoric interactions which are responsible for the shape of the CD spectrum of the aggregates in water diminish continuously until the ethanol content reaches 50%, where the small residue of vesicular aggregates play no further role in the spectrum. From that point the overwhelming amount of molecules occurs in the monomeric form showing the CD effects of the single molecularly dispersed species. This hypothesis is strongly supported by two additional facts:

a) compound **5** contains the same molecular framework and the same chromophores as compound **1**, but no sulfonate group responsible for the aggregation properties. As expected, this compound shows a CD spectrum very similar to the spectrum of compound **1** in solutions with high ethanol content (Figure 3).

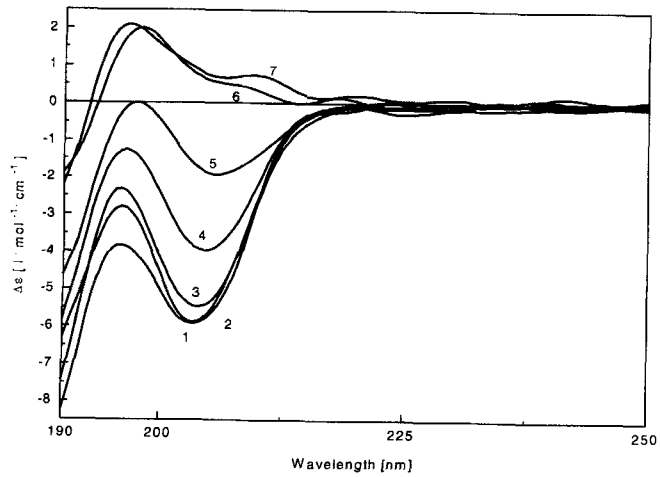


Fig. 2 Compound **1** ($c = 4\times10^{-4}$ mol l^{-1}) in 1: water; 2 to 7: mixtures of water/ethanol; 2: 9/1; 3: 8/2; 4: 7/3; 5: 6/4; 6: 5/5; 7: 4/6 (all mixtures as v/v-ratios)

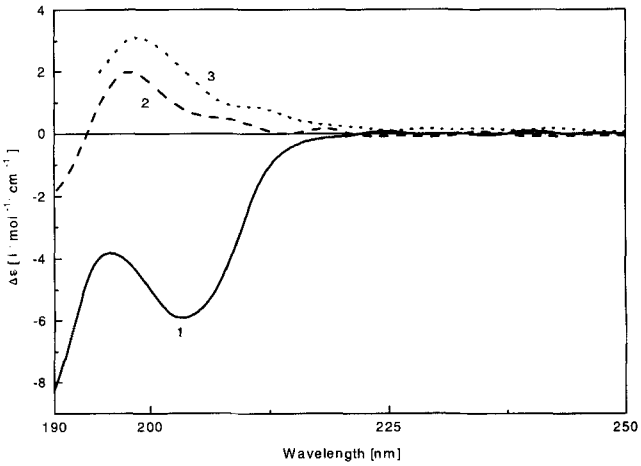


Fig. 3 Spectrum 1: compound **1** in water, $c = 4\times10^{-4}$ mol l^{-1}; Spectrum 2: compound **1** in water/ethanol 5:5 (v/v), $c = 4\times10^{-4}$ mol l^{-1}; Spectrum 3: compound **5** in ethanol, $c = 4\times10^{-4}$ mol l^{-1}

b) Induced CD effects which are explained in the following section do not occur in solutions with more than 50% ethanol content.

By performing the experiments with the more polar methanol instead of ethanol the destruction of the vesicles occurs at a higher organic solvent content. The lysis of vesicles of **1** is completed at a water to methanol ratio of 3:7. This means that the CD spectrum does not change with further addition of methanol.

We made the same observations with compound **3** in a set of water–ethanol- and water–methanol-mixtures. For compound **2** the equilibrium region between aggregated molecules and monomers is smaller than in the case of **1** or **3**, the CD spectra do not change remarkably up to an ethanol (or methanol) content of 40% and the resulting CD spectrum of **2** in the mixture with a water-to-alcohol ratio of 5:5 shows already the positive maximum at 198 nm.

Chiral bilayers or monolayers are able to induce Circular Dichroism effects in the absorption bands of achiral molecules [14]. In these systems the Induced Circular Dichroism (ICD) is closely associated to a liquid-crystalline order of the layer components [15]. ICD can also be observed in host-guest-complexes, e. g. with azo dyes in cyclodextrins [16] or other cage-type host molecules [17]. In biochemistry, the dyes proflavine, methylene blue and similar platelet-shaped dyes are used for specific staining of DNA samples [18]. These dyes form dimers in aqueous solution [19] and are able to intercalate between the base pairs of the DNA helix.

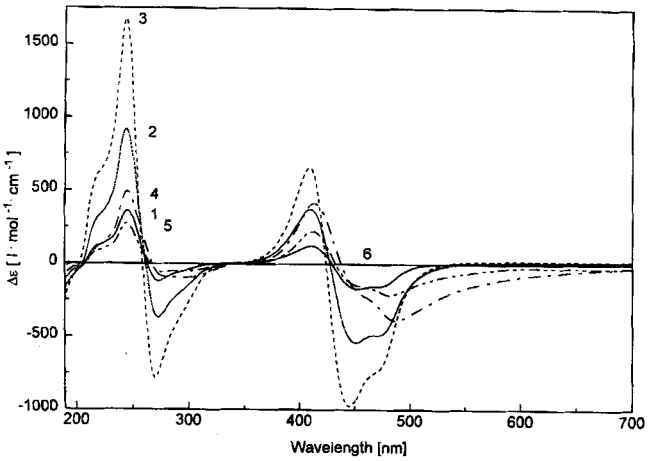
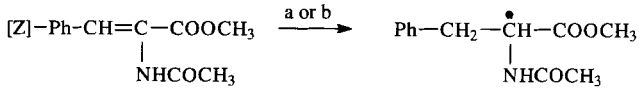


Fig. 4 CD spectra of mixtures of compound **3** (5×10^{-4} mol l^{-1}) and proflavine (2×10^{-4} mol l^{-1}) in 1: water; 2 to 6: mixtures of water/ethanol; 2: 9/1; 3: 8/2; 4: 7/3; 5: 6/4; 6: 5/5 (spectrum identical with baseline above 200 nm); (all mixtures as v/v- ratios)

We used achiral dyes to perform ICD experiments with the chiral amphiphiles **1**, **2** and **3** in pure water at the beginning. Especially compound **3** induces large CD effects in the spectrum of proflavine. The ICD spectra show split band CD curves in the UV bands of the dye attributable to electronic transitions polarized along the long axis of the dye molecules [20]. This fact and the magnitude of the effects show that the ICD spectra probably are caused by exciton-type interaction between the single dye molecules [21]. It is very likely that the charged dye assumes a helical or otherwise chiral suprastructure on the surface or in the bulk of the oppositely charged vesicular aggregates.

In comparison with **3** 2-(cholest-5-en-3β)oxy-carbonyloxy-propanesulfonic acid sodium salt **2** gives smaller ICD effects, whereas **1** shows almost no Induced CD signals with proflavine. An explanation for that could be a higher ordered surface of the aggregates of compound **3** because of the possibility to form NH···O hydrogen bonds. Small ICD effects were observed with compound **2** and **3**, respectively, and methylene blue. As we expected no Induced Circular Dichroism was found with the negatively charged dye methylorange. In accordance to this observation Kunitake et al. found ICD with cationic chiral vesicles in presence of methylorange [15].

Especially in the case of amphiphile **3** with proflavine or methylene blue the Induced CD effects increase enormously by addition of ethanol. They attain a maximum at a water to ethanol ratio of 8:2 and decrease after that down to zero by increasing the ethanol amount in the solvent mixture to more than 50% (Figure 4). We showed in this way that the Induced Circular Dichroism is really connected with chiral vesicular aggregates



a: $[Rh(COD)_2]BF_4$, BPPM, chiral amphiphile, water, H_2 (0.1 MPa)
BPPM: (2S,4S)-*N*-*tert*-Butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethyl-pyrrolidine
b: $[Rh(COD)_2]BF_4$, BDPB, chiral amphiphile, water, H_2 (0.1 MPa)
BDPB: $(Ph)_2P\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}P(Ph)_2$

Scheme 2

which are destroyed in solutions with a high ethanol content. A possible explanation for the occurence of a maximum of the ICD at an ethanol content of 20% could be a better accessibility of the vesicles by the dye molecules due to the aforementioned swelling of the aggregates.

As described in recent reports [22] the asymmetric hydrogenation of amino acid precursors catalyzed by rhodium complexes could be effected in water as medium in presence of micelle-forming amphiphiles. The basis reaction performed in our laboratory is shown in Scheme 2: methyl (*Z*)-α-acetamidocinnamate has been hydrogenated in the presence of the synthesized chiral amphiphiles with an optically active rhodium(I)-phosphine complex and an achiral rhodium(I)-phosphine complex, respectively, to yield methyl *N*-acetylphenylalaninate.

The chiral complex with BPPM leads to high enantiomeric excesses in the presence of the investigated amphiphiles **1**, **2**, **3** and **4** and shows high activities (Table 2). In comparison, the *ee*-value and activity for this complex in pure water is given, too. If the chiral ligand is replaced by the achiral BDPB-ligand then still small

Table 2 Hydrogenation of methyl (*Z*)-α-acetamidocinnamate in water with the catalytic system $[Rh(COD)_2]BF_4$ and BPPM or BDPB as ligands. Effect of the synthesized chiral surfactants. Hydrogenation conditions: Solvent (15 ml H_2O), surfactant, methyl (*Z*)-α-acetamidocinnamate (1 mmol), rhodium complex (0.01 mmol) and phosphine (0.011 mmol) (in situ preparation of catalyst)

Amphiphile (A)	Ligand	Rh:A mol/mol	*t*/2 min	%*ee* (*R*) (± 1%)
without in H_2O	BPPM		90	78.0
in MeOH			2	90
1	BPPM	1:10	12	94.0
	BDPB	1:10	10	3.0
2	BPPM	1:10	16	93.0
	BDPB	1:20	9	4.5
3	BPPM	1:10	11	94.5
	BDPB	1:10		rac.
4	BPPM	1:10	11	95.0
	BDPB	1:20	11	8.5

enantiomeric excesses were found when the reaction was performed in the presence of the synthesized chiral surfactants **1**, **2** and **4**. In these cases the highest *ee*-value reached was 8.5% methyl (*R*)-*N*-acetylphenylalaninate in connection with compound **4** (Table 2). That means there occurs a chiral induction during the reaction caused by the vesicular chiral environments built up by the amphiphiles only. Substance **3** containing the carbonylamino group does not influence the reaction to give a preferential enantiomer. Experiments to propose a possible mechanism for this effects are just under way.

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Experimental

Reagents and Chemicals. CD spectra were recorded on a JASCO J-710 spectropolarimeter at 25 °C. ^{13}C NMR spectra were measured on a Bruker AC 250 in DMSO-D_6 at 70 °C, 90 °C or 110 °C and are reported in ppm(δ). Melting points were determined on a Cambridge Instruments apparatus and are uncorrected. Column chromatography was performed with MERCK silica gel 60 (230–400 mesh ASTM). TLC was performed with MERCK TLC aluminium foils coated with silica gel 60 F_{254}, layer thickness 0.2 mm. Elemental analyses were obtained on a Leco CHNS-932. Mass spectra were measured using an Intectra AMD 402; relative intensities are given in parenthesis. All reagents were the highest quality commercially available and were used without further purification.

2-(Cholest-5-en-3β)oxy-carbonyloxy-ethanesulfonic acid sodium salt (**1**)

In a 250 ml flask dry 2-hydroxyethanesulfonic acid sodium salt (3 g, 20.25 mmol), cholest-5-en-3β-ol-3-chloroformate (9 g, 20.04 mmol) and absolute pyridine (100 ml) were stirred under argon for 20 h at room temperature to give a yellow gel. Suction filtration of this gel yielded a colourless residue which was placed in a 100 ml flask with 40 ml of ethanol and refluxed for 1h. The fine colourless crystals were removed by filtration, suspended in the eluent ($CHCl_3$: MeOH = 3:1 v/v) and chromatographed at silica gel. The compound with the R_f-value 0.35 (TLC with $CHCl_3$: MeOH = 3 : 1 v/v) was isolated. Evaporation and drying *in vacuo* gave **1** as colourless powder. Yield 2.4 g, 4.3 mmol (21%); *m.p.* 285 °C (dec.). – ^{13}C NMR(DMSO-D_6,70 °C): 153.45 (OC(O)O), 49.95 (NaO_3S-CH_2), 63.93 ($\underline{C}H_2$-OC(O)O), 76.85 (OC(O)O-$\underline{C}H$)). – $C_{30}H_{49}NaO_6S$ (560.77); calcd.: C 64.28%; H 8.75%; S 5.71%; found: C 64.22%; H 9.04%; S 5.52%. – MS (FAB) *m/z* (%): 537 (M – Na^+, 48); 306 (52).

2-(Cholest-5-en-3β)oxy-carbonyloxy-propanesulfonic acid sodium salt (**2**)

In a 100 ml flask dry 3-hydroxypropanesulfonic acid sodium salt (1.62 g, 10.0 mmol), cholest-5-en-3β-ol-3-chloroformate (4.5 g, 10.0 mmol) and absolute pyridine (50 ml) were stirred under argon for 20 h at 55 °C. After evaporation of the pyridine the brown residue was stirred with a mixture of 20 ml water and 20 ml ethanol for 1 h. The resulting precipitate was removed by filtration and then dispersed in $CHCl_3$. The organic phase was washed with water, concentrated to 5 ml and chromatographed at silica gel (eluent $CHCl_3$:EtOH = 1:1 v/v). The substance with the R_f-value 0.4 (TLC with $CHCl_3$:EtOH = 1:1 v/v) was isolated. Evaporation and drying *in vacuo* gave **2** as colourless powder. Yield 1.5 g, 2.6 mmol (26%); *m.p.* 230 °C (dec.). – ^{13}C NMR (DMSO-D_6, 90 °C): 153.59 (OC(O)O), 49.40 (NaO_3S-CH_2), 66.52, ($\underline{C}H_2$-OC(O)O), 76.75 (OC(O)O-CH). – $C_{31}H_{51}NaO_6S$ (574.80); calcd.: C 64.80%; H 8.88%; S 5.57%; found: C 64.58%; H 8.88% S, 5.29%. – MS (FAB) *m/z* (%): 551 (M–Na^+, 25); 385 (9).

2-(Cholest-5-en-3β)oxy-carbonylamino-ethanesulfonic acid sodium salt (**3**)

In a 100 ml flask dry 2-amino-ethanesulfonic acid sodium salt (1.47 g, 10.0 mmol), cholest-5-en-3β-ol-3-chloroformate (4.5 g, 10.0 mmol) and absolute pyridine (50 ml) were stirred under argon for 20 h at room temperature to give an orange solution. After evaporation of the pyridine the brown residue was refluxed with 30 ml of ethanol for 0.5 h. The resulting colourless precipitate was removed by filtration of the hot solution. The ethanolic mother liquid was concentrated to 5 ml and chromatographed at silica gel (eluent $CHCl_3$: MeOH = 3 : 1 v/v). The substance with the R_f-value 0.4 (TLC with $CHCl_3$: MeOH = 3 : 1 v/v) was isolated. Evaporation and drying *in vacuo* gave **3** as colourless powder. Yield 3.4 g, 6.1 mmol (60%); *m.p.* 289 °C (dec.). – ^{13}C NMR (DMSO-D_6,90 °C): 154.97 (NC(O)O), 50.36 (NaO_3S-CH_2), 39.01 ($\underline{C}H_2$-NHC(O)O), 72.85 (NHC(O)O-$\underline{C}H$). – $C_{30}H_{50}NNaO_5S$ (559.79); calcd.: C 64.40%; H 8.95%; N 2.50%;S 5,72%; found: C 63.64%; H 9.24%; N 2.71%; S 5.45%. –MS (FAB) *m/z* (%): 536 (M–Na^+, 100); 306 (42).

2-(Cholest-5-en-3β)oxy-carbonylethanesulfonic acid sodium salt (**4**)

0.3 g (12 mmol) NaH, 50 ml absolute toluene and cholest-5-en-3β-ol (3.86 g, 10 mmol) were stirred in a 250 ml flask under argon at room temperature for 24 h. Then sulfopropionic acid anhydride (2.53 g, 19 mmol) was added, followed by stirring the dispersion for 20 min. Now 100 ml of further toluene were added and 2.5 ml water were dropped slowly into the mixture. After that the solution was evaporated to yield a dry residue, which was diluted in eluent and chromatographed at silica gel ($CHCl_3$: MeOH = 3 : 1 v/v). The substance with the R_f-value 0.33 (TLC with $CHCl_3$: MeOH = 3 : 1 v/v) was isolated. Evaporation and drying *in vacuo* gave **4** as colourless powder. Yield 1.2 g, 2.2 mmol (22%); *m.p.* >340 °C (dec.). – ^{13}C NMR (DMSO-D_6,110 °C): 170.73 (C(O)O), 46.43 (NaO_3S-CH_2), 35.31($\underline{C}H_2$-C(O)O), 72.95 (C(O)O-$\underline{C}H$). – $C_{30}H_{49}NaO_5S$ (547.77); calcd.: C 66.17%;

H 9.00%; S 5.88%; found: C 65.12%; H 9.05%; S 5.88%.– MS (FAB) *m/z* (%): 522 ($M-Na^+$, 74).

(Cholest-5-en-3β-ol) ethyl carbonate (**5**)

In a 100 ml flask NaH (0.095 g, 4.0 mmol), cholest-5-en-3β-ol-3-chloroformate (1.3 g, 3.0 mmol) and absolute ethanol (40 ml). were stirred under argon for 20 h at room temperature. The resulting colourless precipitate was collected by filtration, dissolved in the eluent (toluene : acetic acid ethyl ester = 10 : 1 v/v) and chromatographed at silica gel. The substance with the R_f-value 0.7 (TLC with toluene : acetic acid ethyl ester = 10 : 1 v/v) was isolated. Evaporation and drying *in vacuo* gave **5** as fine colourless crystals. Yield 0.7 g, 1.5 mmoles (50%); *m.p.* 102–111 °C. – ^{13}C NMR ($CDCl_3$): 154.54 (OC(O)O), 14.25 ($\underline{C}H_3$-CH_2-OC(O)O), 63.59 (CH_3-$\underline{C}H_2$-OC(O)O), 77.60 (OC(O)O-$\underline{C}$H).– $C_{30}H_{50}O_3$ (458.73); calcd.: C 78.60%; H 10.91; found: C 78.24%; H 10.76%.

Vesicle preparations from 1 and 3

A thermostatted vessel with argon insertion was charged with 20 mg of **1** or **3**, respectively, and 40 ml water. To get small unilamellar vesicles the resulting mixture was treated at 50 °C for 20 min with a Labsonic 2000 U sonicator using a titanium needle probe tip (output 46 W).

Electron micrographs

Droplets of the aqueous solutions of the synthesized amphiphiles were placed onto gold grids (7 μm, 400 mesh, Baltec). The samples were frozen with a jet freezing device (JFD 030, Bal-tec) in liquid propane, fractured and shadowed with platinum/carbon by a BAF 060 (Bal-tec). The resulting replicas were washed with warm water and dried in air. Electron micrographs were carried out on a Carl Zeiss TEM EM 912 OMEGA.

CD measurements

The solutions without dye were prepared as described in the main part of the text. For measurements of Induced CD, stock solutions of the dye in water were prepared and checked by UV-spectroscopy on the day of the measurement. Concentration of the proflavine stock solution: 2×10^{-2} mol l^{-1}. In all cases the dye solution was added as last admixture. The resulting solution was measured in standard cylindrical quartz cuvettes at 25 °C within 30 minutes after mixing. Molar Absorption and Molar Circular Dichroism of the dye-containing solutions were calculated using the concentration of the dye.

Hydrogenation

Hydrogenation was performed under normal pressure at 25 °C. Solvent (15 ml H_2O), surfactant, methyl (*Z*)-α-acetamidocinnamate (1 mmol), rhodium complex (0.01 mmol), and phosphine (0.011 mmol) were placed in a deaerated hydrogenation flask and stirred for 20 h before setting the flask under hydrogen atmosphere (0.1 MPa). The reaction was followed by volumetric measurement. When the reaction was complete, the mixture was extracted with chloroform (5 ml). In this extract the enantioselectivity was controlled by gas chromatography with a Hewlett Packard 5890 Series II using a 12.5 m×0.2 mm silica fused column coated with XE-60 L-valine *tert.*-butyl amide at 165 °C (detector: FID).

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