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[f007]

Synthesis and characterization of new *tail-to-tail* dimers of bile acids with different spacers

Álvaro Antelo, Mercedes Álvarez Alcalde, Aida Jover, Francisco Meijide, and José Vázquez Tato

Departamento de Química Física, Facultad de Ciencias, Universidad de Santiago de Compostela, Avda. Alfonso X El Sabio s/n, 27002 Lugo, Spain,

Abstract

New dimeric steroid-based surfactants derived from 3α,7α,12α-trihydroxy-5β-cholan-24-amine (steroid residue) and isophthalic acid, 5,5'-biisobenzofuran-1,1',3,3'-carboxylic acid and succinic acid (spacers) were synthesized and structurally characterized by NMR techniques. The first spacer was also employed to synthesize the dimer corresponding to the 3α,12α-dihydroxy-5β-cholan-24-amine residue. In all cases the steroid residues are *tail-to-tail* linked through amide bonds with the spacers.

Introduction

Dimeric surfactants represent a very interesting type of tensioactive compounds that comprise two surfactant-like moieties connected by a bridge of varying nature (flexible or rigid) and length. When the linking is performed at or near their head groups, the resulting dimers are known as *gemini*. This kind of compounds has recently been object of increasing study in view of their enhanced tensioactive properties compared with those of monomeric surfactants, as well as their phase behaviour.[1,2]

Compared with typical alkyl-chain surfactants,[3] bile salts present different surface properties, a fact directly related to their structure, namely their facial amphiphilicity. Although the transference of this peculiar characteristic to the *gemini* structure could lead to new tensioactive properties and aggregation behaviours, only few examples of *gemini* surfactants formed by two bile acid residues linked in a *tail-to-tail*

[1] In, M.; Zana, R. *Journal of Dispersión Science and Technology* **2007**, 28, 143-57.
[2] Hait, S. K.; Moulik, S. P. *Curr. Sci.* **2002**, *82*, 1101.
[3] P.P. Nair, D. Kritchevsky, The Bile Acids; Physiology and Metabolism vol. 1, Plenum Press, New York, 1971 Chapt. 8.

way have been published.[4,5,6,7,8] In view of the results obtained by a previous study of the host-guest interactions between the *tail-to-tail* dimers presented here and ibuprofen which are published in other communication at *ECSOC13*, the new *gemini* surfactants were synthesized and are now available for experimental studies.

The natural bile acids (1 and 2), the precursors of the dimers (3-7) and the synthesized tensioactive derivatives (8-11) are compiled in figure 1.

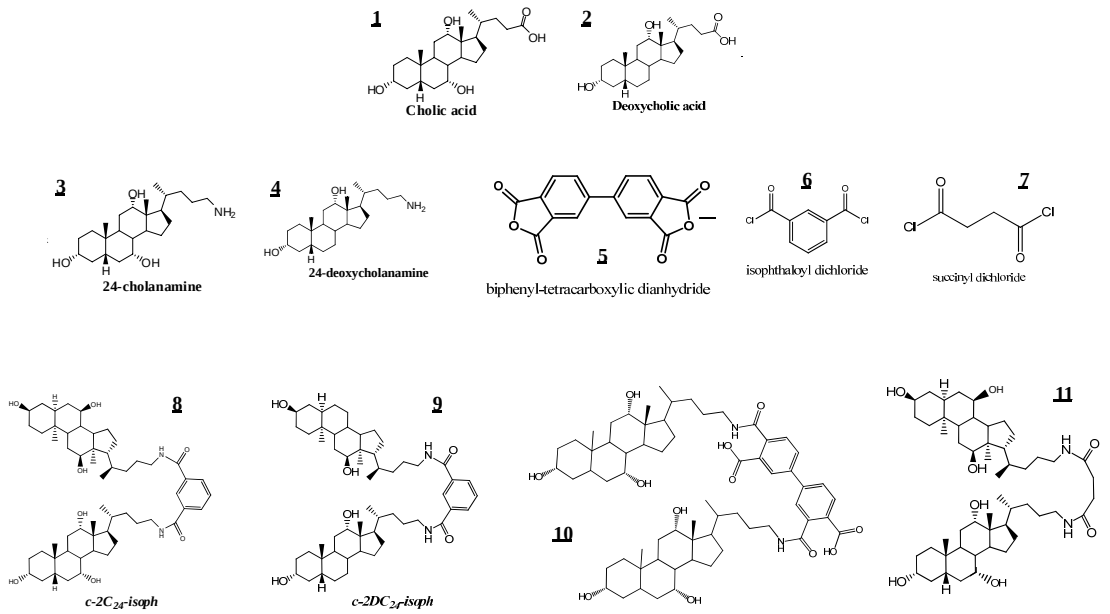


Figure 1.- Natural bile acids (1-2), precursors (3-7) and dimers synthesized (8-11).

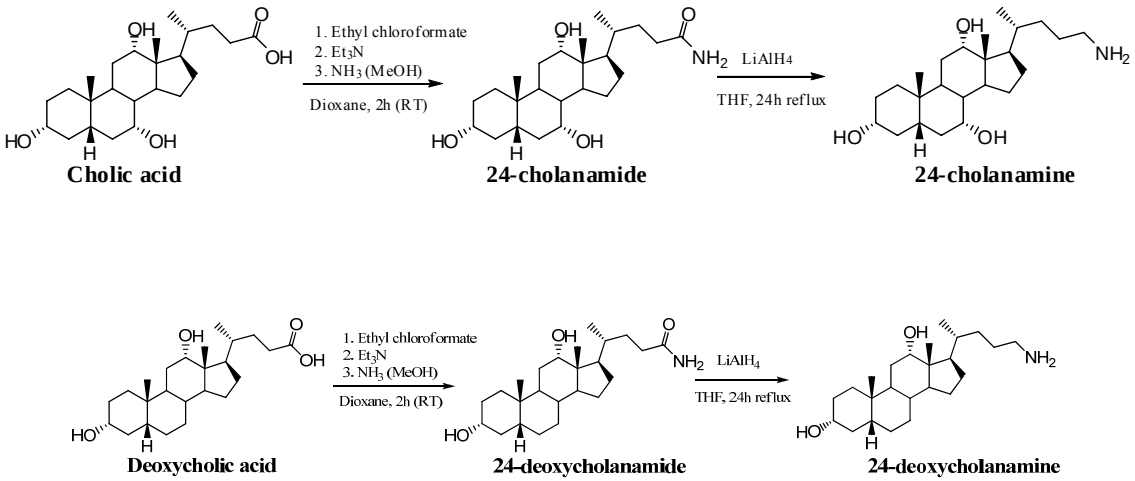
Experimental section

Synthesis.

The synthesis of the precursor steroid residues (24-cholanamine and 24-deoxycholanamine) from the corresponding natural bile acids are sketched in Scheme 1, following well described routes.[8,9]

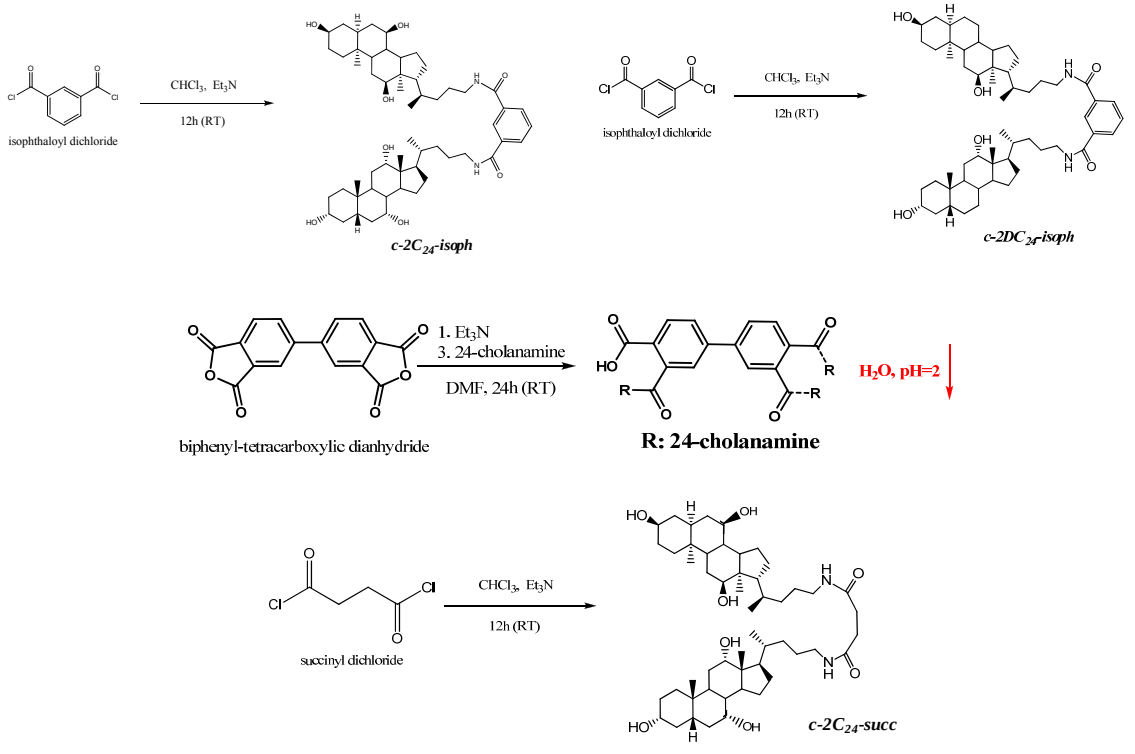
[4] McKenna, J.; McKenna, J. M.; Thornthwaite, D. W. *J. Chem. Soc., Chem. Commun.* **1977**, 809.
[5] Li, Y.; Dias, J. R. *Chem. Rev.* **1997**, *97*, 283.
[6] Ronsin, G.; Kirby, A. J.; Rittenhouse, S.; Woodnutt, G.; Camilleri, P. *J. Chem. Soc., Perkin Trans. 2* **2002**, 13026.
[7] M. Álvarez Alcalde, A. Jover, F. Meijide, L. Galantini, N. V. Pavel, A. Antelo and J, Vázquez Tato, *Langmuir*, **2008,** *24*, 6060.
[8] Alcalde, M. A.; Antelo, A.; Jover, A; Meijide, F., Tato, J. V. *12th INTERNATIONAL ELECTRONIC CONFERENCE ON SYNTHETIC ORGANIC CHEMISTRY.*
[9] Fini, A.; Fazio, G.; Roda, A.; Bellini, A. M.; Mencini, E.; Guarneri, M. *J. Pharm. Sci.* **1992**, *81*, 726.

Scheme 1



The synthetic strategies for obtaining the *gemini* surfactants are resumed in Scheme 2 and commented on in the following paragraphs.

Scheme 2



8 and 9.- 24-Cholanamine (0.5117 g, 1.3 mmol) or 24-deoxycholanamine (2.0 g, 5.4 mmol) were dissolved in a mixture of 25 mL of dried $CHCl_3$ and 1 mL of TEA. After 30 min, the solutions were cooled at 0ºC and a solution of isophthaloyl dichloride

(0.1188 g, 0.59 mmol) in 5 mL of dried $CHCl_3$ was added dropwise with stirring. After 90 min the ice bath was removed and the reaction was maintained for 12 h at r.t. (8) or at 50°C (9). The solvent was then evaporated under vacuum. Finally, the products were purified by column chromatography (silica gel 70-230 mesh; eluent 8:2 ethyl acetate:methanol, R_f = 0.5 and 0.72, respectively for 8 and 9). Overall yields: 50% (8), 75% (9).

10.- Biphenyl tetracarboxylic dianhydride (0.26 g, 1 mmol) was dissolved in 4 mL of dried DMF. Solution was cooled at 0ºC and a solution of 3α,7α,12α-trihydroxy-5β-cholan-24-amine (1.2 g, 3.1 mmol) and triethylamine (1.0 mL, 7.20 mmol) in 8 mL of dried DMF was added. After 15 min the ice bath was removed and the reaction was maintained for 24 h at r.t. The solvent was evaporated under vacuum. Then 5 mL of methanol were added and washed twice with water (pH=2) where the compound precipitates in its diacid form. Then the precipitate was filtered and dried in a vacuum oven. Finally the product was purified by column chromatography (silica gel 70-230 mesh; eluent 7:3 ethyl acetate:methanol, R_f=0.69). Overall yield 46%.

11.- 24-Cholanamine (0.4 g, 0.36 mmol) was dissolved in a mixture of 25 mL of dried $CHCl_3$ and 1 mL of TEA. After 30 min, the solution was cooled to 0ºC and a solution of succinyl dichloride (0.03 g, 0.17 mmol) in 5 mL of dried $CHCl_3$ was added dropwise with stirring. After 90 min the ice bath was removed and the reaction was maintained for 12 h at r.t. The solvent was evaporated under vacuum. Finally the product was purified by column chromatography (silica gel 70-230 mesh; eluent 8:2 ethyl acetate:methanol, R_f=0.56). Overall yield 70%.

Structural characterization.

Identity of compounds was confirmed by ^1H (300 MHz), ^{13}C (75 MHz) NMR and DEPT-135 (75MHz) experiments carried out in a Brucker AC 300 spectrometer (Figures 2-12).

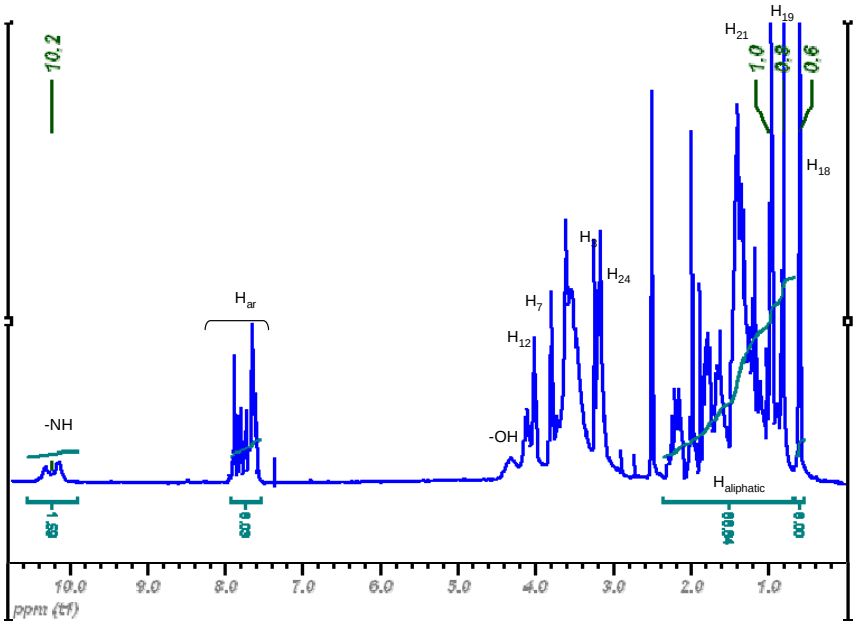


Figure 2.- ^{1}H spectrum of 10 in DMSO-d_6.

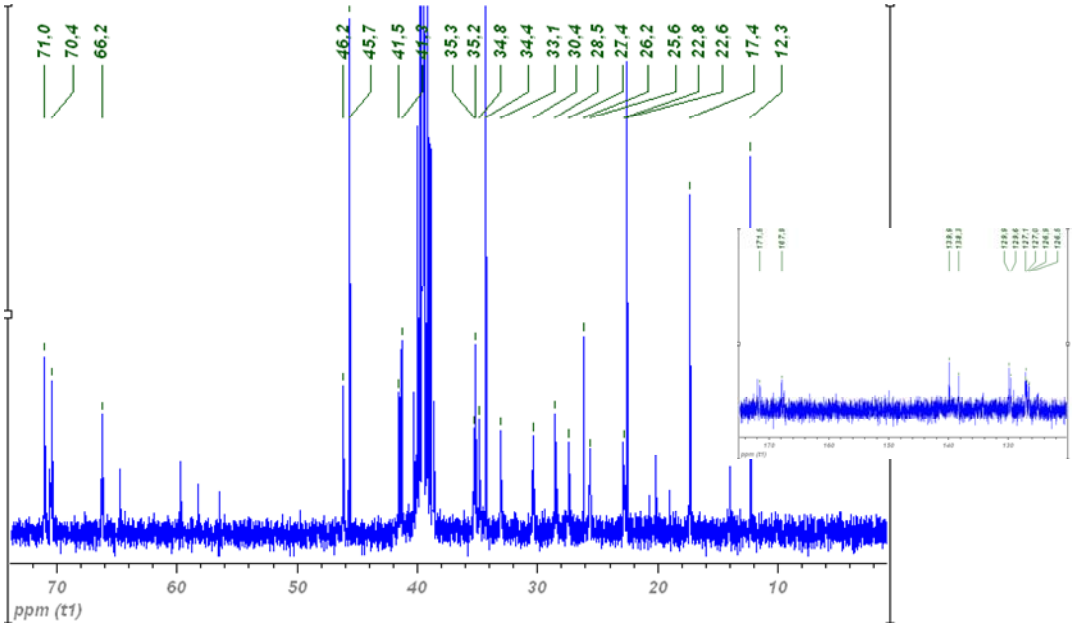


Figure 3.- ^{13}C spectrum of 10 in DMSO-d_6.

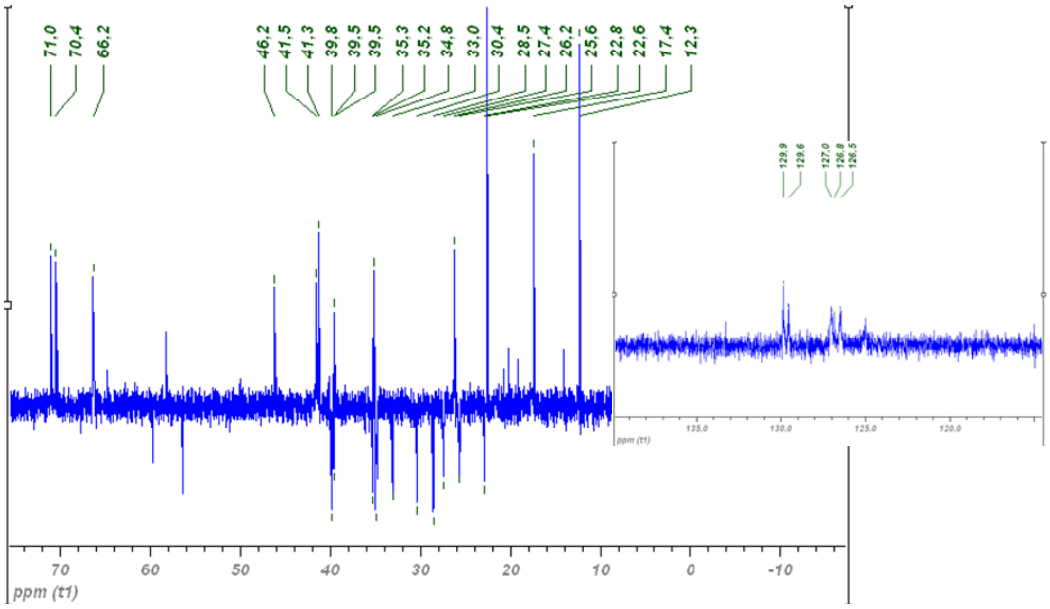


Figure 4.- DEPT-135 spectrum of <u>10</u> in DMSO-d_6.

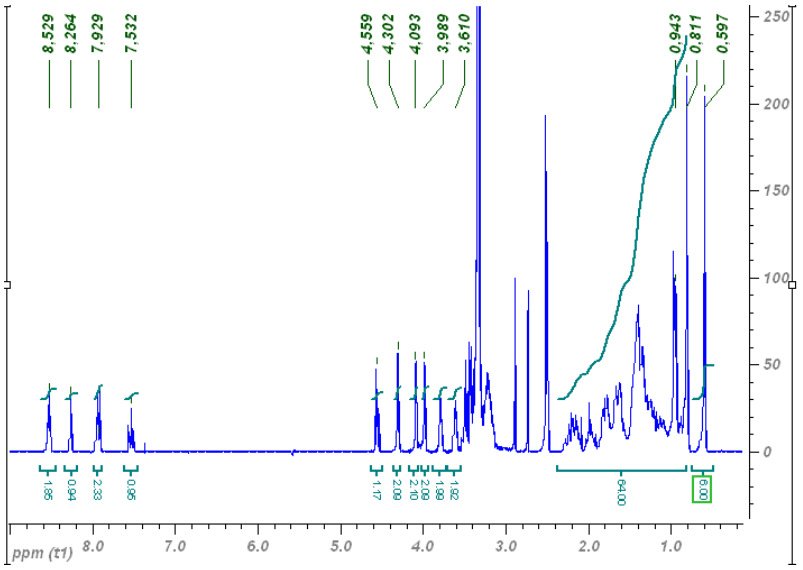


Figure 5.- ^{1}H spectrum of <u>8</u> DMSO-d_6.

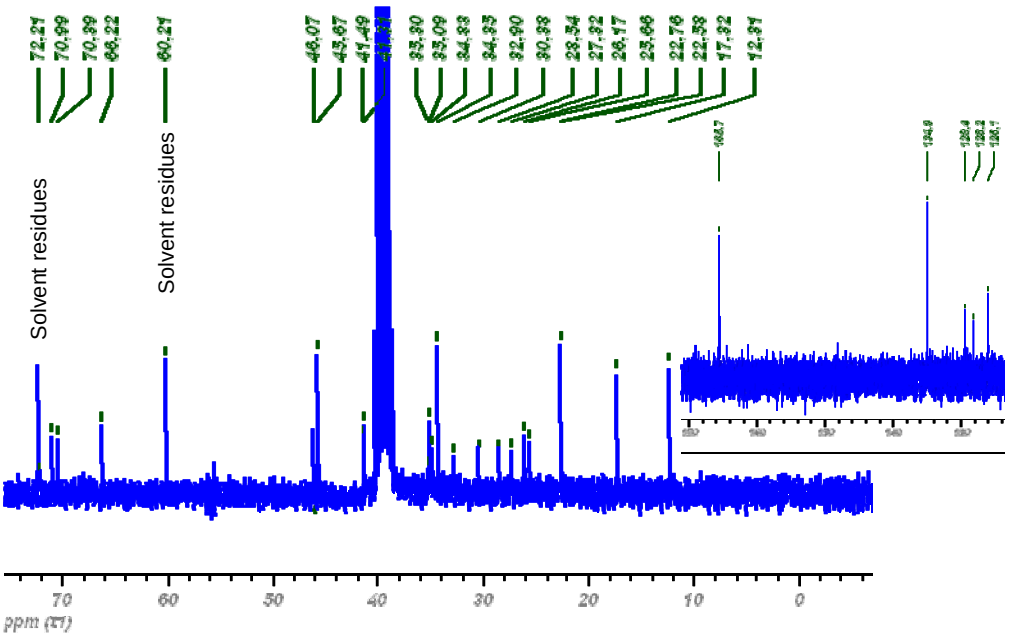


Figure 6.- ^{13}C-NMR spectrum of 8 in DMSO-d_6.

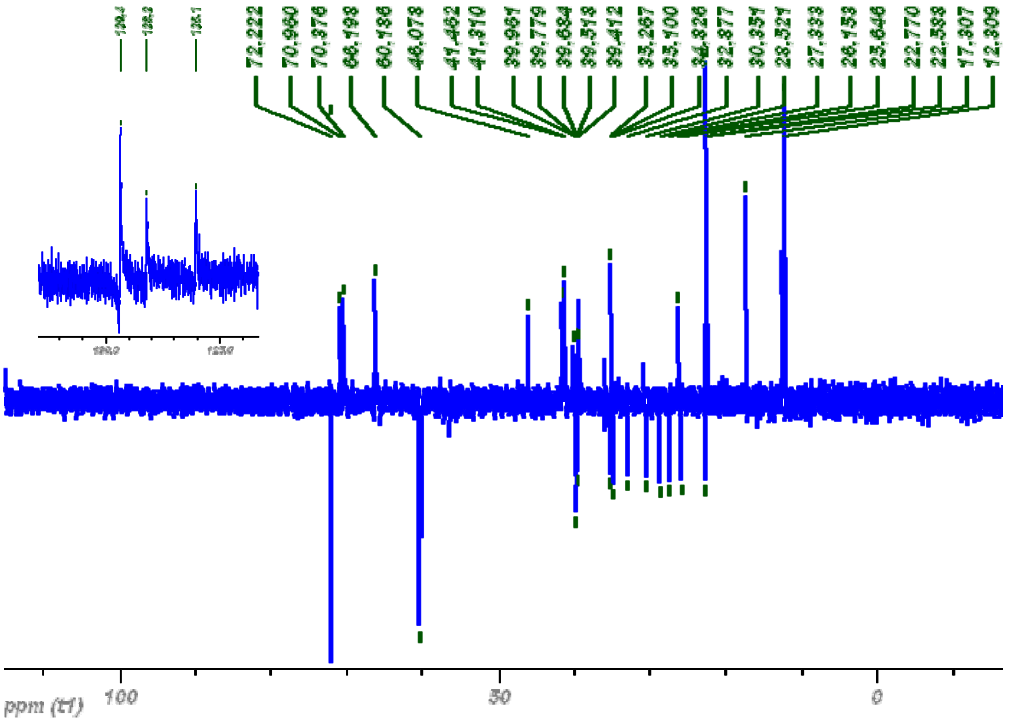


Figure 7.- DEPT-135 spectrum of 8 in DMSO-d_6.

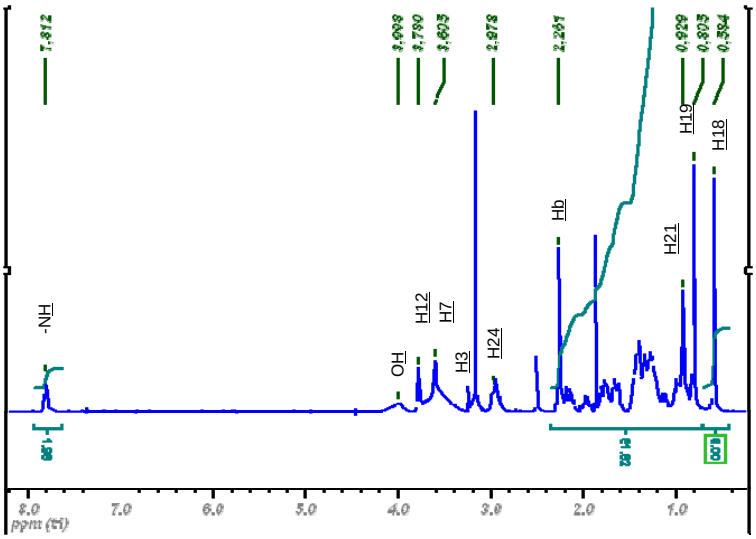


Figure 8.- ^{1}H-NMR spectrum of 11 in DMSO-d_6.

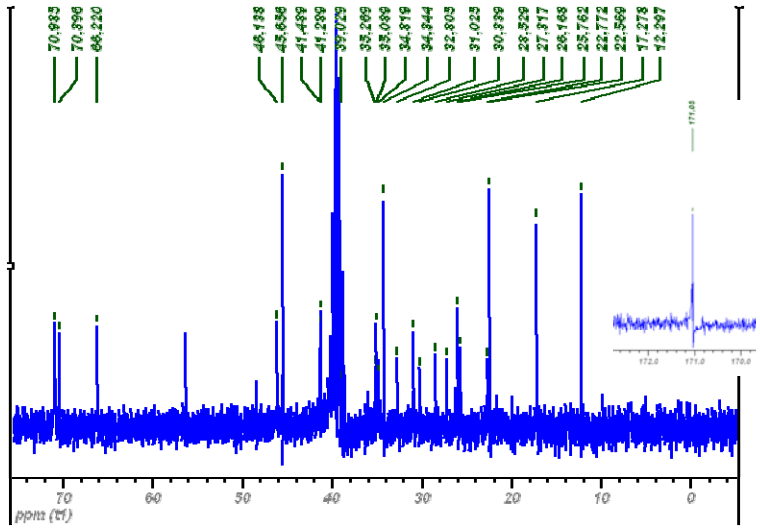


Figure 9.- ^{13}C-NMR spectrum of 11 in DMSO-d_6.

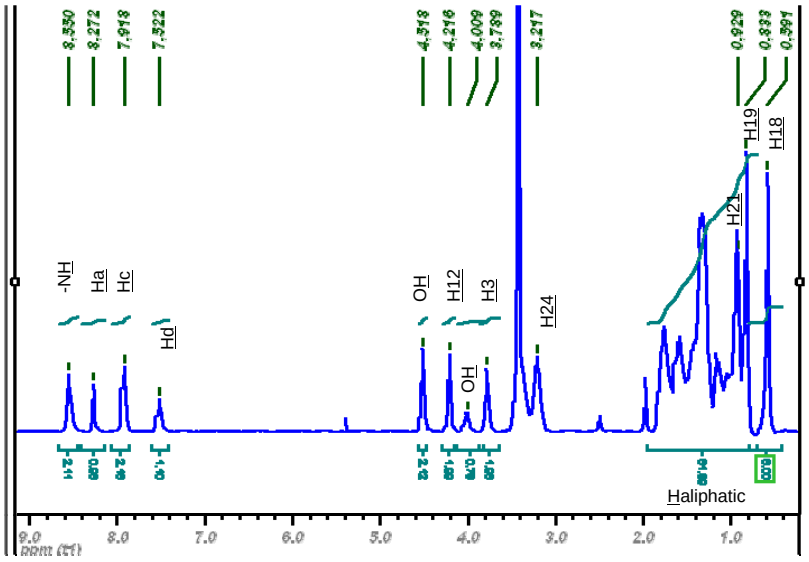


Figure 10.- ^{1}H-NMR spectrum of 9 in DMSO-d_6.

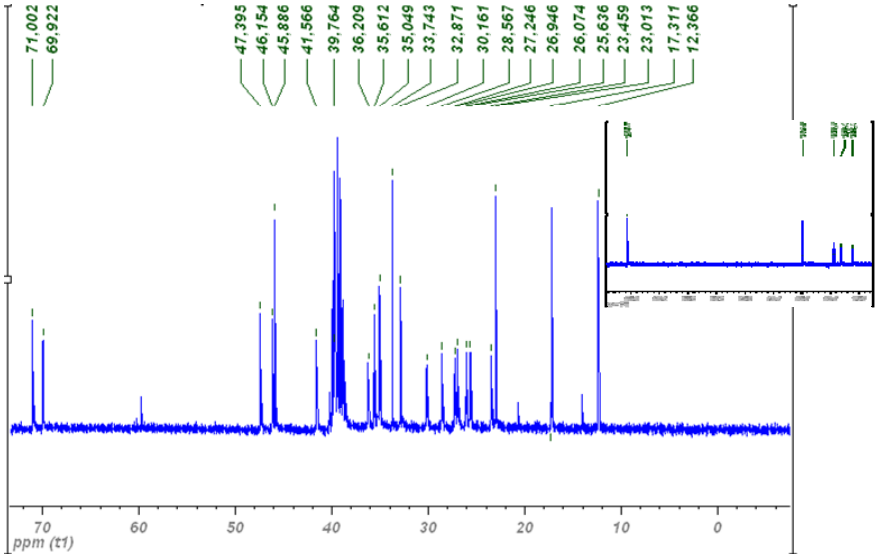


Figure 11.- ^{13}C-NMR spectrum of 9 in DMSO-d_6.

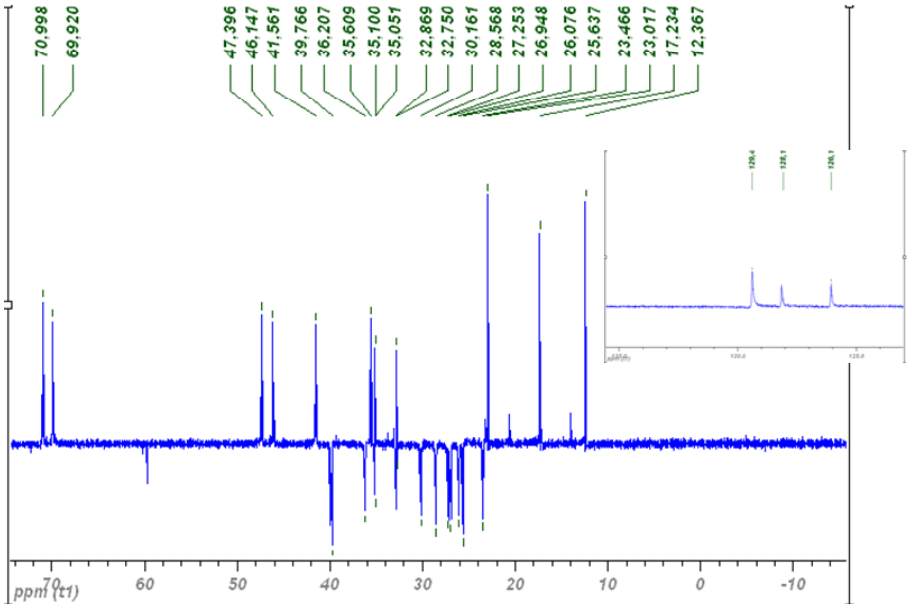


Figure 12.- DEPT-135 spectrum of 9 in DMSO-d_6.

Conclusions

Dimeric steroid-based surfactants 8-11 have been satisfactorily synthesized and structurally characterized by NMR techniques.

Acknowledgments. Authors thank the Ministerio de Ciencia y Tecnología (Project MAT2004-04606) and the Xunta de Galicia (PGIDIT05PXIC26201PN) for financial support.