Synthesis of 1,2,3-Triazole-containing Bile Acid Dimers and Properties of Inverse Micellar Mimic

Zhen Zhang,[1] Yong Ju,*[1,2] and Yufen Zhao[1]
[1]*Key Laboratory of Bioorganic Phosphorous Chemistry & Chemical Biology, Ministry of Education, Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China*
[2]*State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China*

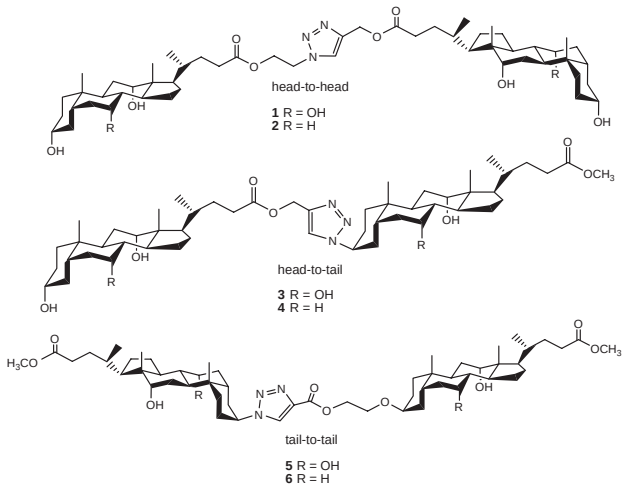
(Received July 18, 2007; CL-070755; E-mail: juyong@mail.tsinghua.edu.cn)

Six new 1,2,3-triazole-containing bile acid dimers, involving head-to-tail, head-to-head, and tail-to-tail three types of steroidal derivatives, have been synthesized via Cu^{I}-catalyzed 1,3-dipolar cycloaddition reaction "click chemistry" in high yields. The inverse micellar properties of these compounds were also investigated through hydrophilic dye solubilization studies in nonpolar media.

"Click chemistry," optimized by Sharpless and co-workers, is the Cu^{I}-catalyzed 1,3-dipolar cycloaddition between azides and terminal alkynes.[1] The mild reaction conditions, high yielding, simple reaction and purification performance, and exclusive 1,4-disubstituted 1,2,3-triazole products as well as being stable to various solvents including water, have promoted it as a unique organic synthetic modular approach widely applied in biomedical science, organic synthesis, and material chemistry during the past several years.[2]

Bile acids are naturally occurring compounds in the steroid family which are essential for many physiological functions. Currently, bile acids, due to their inexpensive availability, the rigid steroid framework, unique facial amphiphilicity, and together with viability of being chemically modified on C3, C7, C12, and even C24, have attracted considerable interest for diverse significant applications, involved in pharmacology, asymmetric synthesis, molecular recognition, and also polymeric materials.[3]

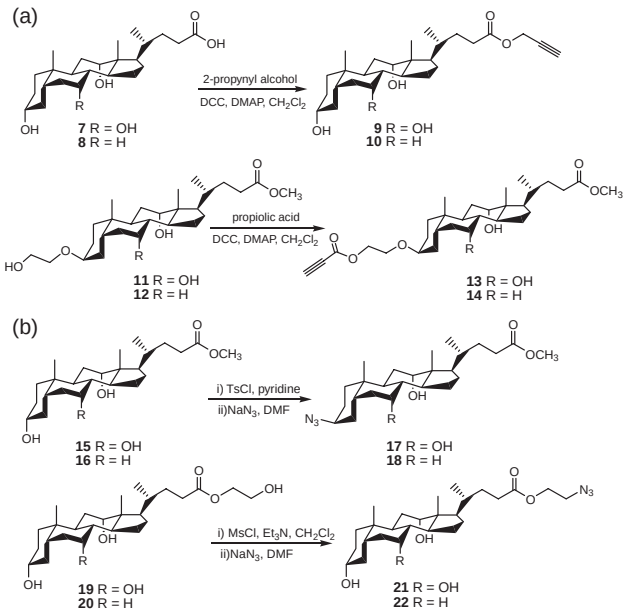
Many useful alterations have exhibited with the replacement of one or more carbon atoms of a steroid molecule by a heteroatom. Azasteroids especially feature numerous biological activities.[4] Besides that, more recently, 1,3-disubstituted imidazolium groups have been introduced to bind anions.[5] Consequently, the azole group which is often found in biologically active compounds and π-conjugated functional materials, because of the aromaticity and lone-pair electrons, may have great potential for applications in supramolecular chemistry. To the best of our knowledge, up to now, there are only few published reports using 1,3-dipolar cycloaddition for the synthesis of 1,2,3-triazole-containing steroidal derivatives.[6] Furthermore, the in situ generated triazole unit was revealed as a very active pharmacophore instead of just a passive linker.[7] As continuous our previous work[8] and to further develop a facile method to offer various useful bile acid–triazole conjugates, herein, we report the design and synthesis of six new bile acid dimers linked with 1,2,3-triazole ring containing head-to-head, head-to-tail, and tail-to-tail three types of steroidal compounds via Cu^{I}-catalyzed 1,3-dipolar cycloaddition (Scheme 1). The initial mimic inverse micellar properties of these molecules are investigated in an organic solvent. It might be interesting to concerning the functional difference of these molecules.



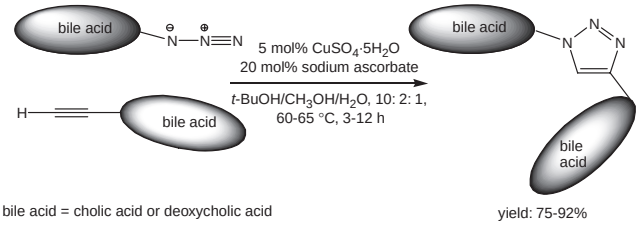
Scheme 1. Structures of six bile acid dimers.

2-Propynyl esters **9**, **10**, **13**, and **14** were synthesized by esterification in the presence of DCC with a catalytic amount of 4-dimethylaminopyridine. Formation of alcohols **11** and **12** was carried out by nucleophilic displacement of 3α-mesylate bile acids with ethylene glycol.[9] The azido groups at both C3 and the side chain were introduced through double nucleophilic displacement.[6b,10] Tosylation or mesylation on the hydroxy group of the corresponding steroidal derivatives followed by treatment with NaN_3 in DMF gave the desired azides **17**, **18**, **21**, and **22**. And compounds **15**, **16**, **19**, and **20** were easy to obtain by acid-catalyzed esterification (Scheme 2).[11] Synthesis of the bile acid–triazole conjugates was described in Scheme 3 and was undertaken as the following general procedure: a solution of equimolar azide and 2-propynyl ester, 5 mol % $CuSO_4 \cdot 5H_2O$ and 20 mol % sodium ascorbate in *t*-BuOH–CH_3OH–H_2O (10:2:1) was stirred at 60–65 °C for 3–12 h (Scheme 3). The pure dimeric compounds were obtained after column chromatographic purification in 75–92% yield (Table 1).[12]

Due to flexible conformation and facial amphiphilicity, these molecules probably adopt an inverse-micelle-like conformation in a nonpolar solvent and hydrophobic faces turn toward the solvent.[13] Such dimers may have the ability to solubilize hydrophilic substances in nonpolar solvents. We investigated the solubilization of cresol red sodium (CR), a hydrophilic dye (inset, Figure 1) by dimers in $CHCl_3$ based on solid–liquid extraction measurement.[13b] The dye solubilized by the dimers varied, while negligible solubility was observed without any additive (Figure 1). Generally, the amount of dye extracted increased linearly with the concentration of dimers. These studies



Scheme 2. Synthesis of steroidal (a) terminal alkynes and (b) azides.



Scheme 3. Synthesis of bile acid dimers via "click chemistry."

Table 1. Dimeric compounds containing 1,2,3-triazole prepared by the Cu^{I}-catalyzed synthesis

Entry	Alkyne	Azide	Compds.	Yield/%
1a	**9**	**21**	**1**	92
1b	**10**	**22**	**2**	88
2a	**9**	**17**	**3**	84
2b	**10**	**18**	**4**	80
3a	**13**	**17**	**5**	77
3b	**14**	**18**	**6**	75

indicated that compound **1** led to the best encapsulation of the dye, which may result from possessing more hydroxy groups and more flexible linkage and therefore the strongest binding. It is due to the sandwich-type amphiphile conformation with the better hydrophilic and more space cavity inside (Figure 2).

In conclusion, facile synthesis of six new bile acid dimers containing 1,2,3-triazole ring was fulfilled by "click chemistry." The solubility of a hydrophilic dye in a nonpolar solvent may promote these molecules interesting candidates for biological and drug delivery applications. Further work is in progress.

This work was supported by the NSFC (No. 20772071), SRFDP (No. 20050003104) and PCSIRT (IRT0404).

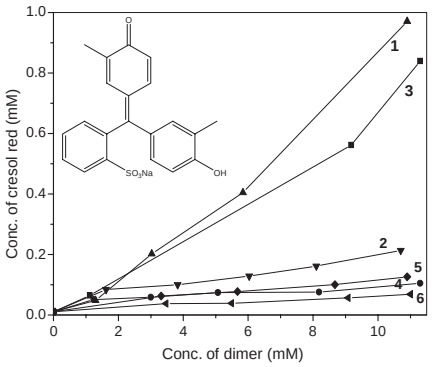


Figure 1. Solubilization of CR (inset) by synthetic dimers.

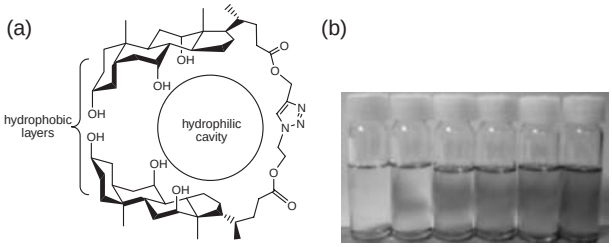


Figure 2. (a) Possible amphiphile conformation of **1**; (b) Extraction of CR by increasing concentrations of **1**. Left to right: [**1**] = 0–2.7 mM.

References and Notes

1 V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
2 a) W. H. Binder, R. Sachsenhofer, *Macromol. Rapid Commun.* **2007**, *28*, 15. b) W. H. Binder, C. Kluger, *Curr. Org. Chem.* **2006**, *10*, 1791. c) Q. Wang, S. Chittaboina, H. N. Barnhill, *Lett. Org. Chem.* **2005**, *2*, 293.
3 a) D. B. Salunke, B. G. Hazra, V. S. Pore, *Curr. Med. Chem.* **2006**, *13*, 813. b) A. Iuliano, S. Facchetti, G. Uccello-Barretta, *J. Org. Chem.* **2006**, *71*, 4943. c) A. P. Davis, *Coord. Chem. Rev.* **2006**, *250*, 2939. d) X.-X. Zhu, M. Nichifor, *Acc. Chem. Res.* **2002**, *35*, 539.
4 J. Burbiel, F. Bracher, *Steroids* **2003**, *68*, 587.
5 a) V. K. Khatri, S. Upreti, P. S. Pandey, *Org. Lett.* **2006**, *8*, 1755. b) M. Chahar, S. Upreti, P. S. Pandey, *Tetrahedron* **2007**, *63*, 171.
6 a) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210. b) N. G. Aher, V. S. Pore, *Synlett* **2005**, (14), 2155. c) V. S. Pore, N. G. Aher, M. Kumar, P. K. Shukla, *Tetrahedron* **2006**, *62*, 11178.
7 Y. Bourne, H. C. Kolb, Z. Radic, K. B. Sharpless, P. Taylor, P. Marchot, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 1449.
8 a) S. H. Ji, Q. Xiao, Y. Ju, Y. F. Zhao, *Chem. Lett.* **2005**, *34*, 944. b) P. Y. Jin, K. Liu, S. H. Ji, Y. Ju, Y. F. Zhao, *Synthesis* **2007**, *(3)*, 407. c) D. M. Wu, S. H. Ji, Y. Wu, Y. Ju, Y. F. Zhao, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2983. d) Y. Li, Z. Zhang, Y. Ju, C. O. Zhao, *Lett. Org. Chem.* **2007**, *4*, 414.
9 G. Wess, W. Kramer, W. Bartmann, A. Enhsen, H. Glombik, S. Müllner, K. Bock, A. Dries, H. Kleine, W. Schmitt, *Tetrahedron Lett.* **1992**, *33*, 195.
10 M. J. Sofia, R. Kalarla, N. Kogan, R. Dulina, Y. W. Hui, N. T. Hatzenbuhler, D. Liu, A. Chen, T. Wagler, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2251.
11 X. Hu, Z. Zhang, X. Zhang, Z. Li, X. X. Zhu, *Steroids* **2005**, *70*, 531.
12 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
13 a) Y. Zhao, E.-H. Ryu, *J. Org. Chem.* **2005**, *70*, 7585. b) N. Vijayalakshmi, U. Maitra, *J. Org. Chem.* **2006**, *71*, 768. c) S. Ghosh, U. Maitra, *Org. Lett.* **2006**, *8*, 399.

Published on the web (Advance View) November 10, 2007; doi:10.1246/cl.2007.1450