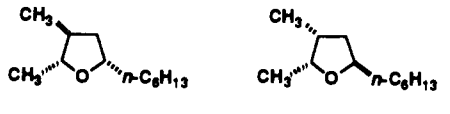

14

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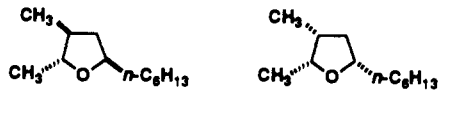
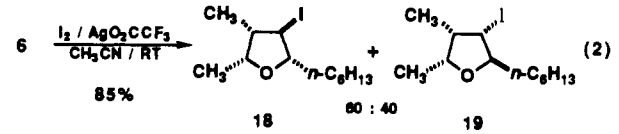


16

17

difference due to the diamagnetic shielding experienced by the proton syn to the two alkyl groups. Identical shift patterns have been observed by Semmelhack and Zhang for a series of 2,3,5-trialkyltetrahydrofurans.[7,9] A similar analysis of the cyclization products themselves is possible. The chemical shift of the proton on the carbon bearing selenium is influenced by the number of syn alkyl neighbors present in the structure. This resonance is centered at 2.8 ppm when both neighbors are syn (**10** and **12**), 3.5 ppm when there is a single syn alkyl group (**2**, **7**, **8**, **11**, and **13**), and 3.9 ppm when both syn neighbors are hydrogen (**9**). The numerous examples of phenylthio-substituted tetrahydrofurans, also by Williams,[8,9] show identical trends. Finally, we have prepared an authentic sample of **10** by independent synthesis using our previously described methodology.[1]

At this point, a paper by Lipshutz and Barton appeared[10] which reported the use of benzeneselenenyl chloride in acetonitrile to effect ring closures of substrates stereochemically analogous to those in our study. In particular, they claimed exclusive formation of single isomers from the *E*-olefin substrates. As shown in Table I, these conditions, when applied to **5** and **6**, did improve the stereoselectivity for the indicated major product. However, the stereochemical assignments reported by Lipshutz and Barton are incorrect.[11] Since their study also reported an unprecedented syn mode of addition in iodine-induced cyclizations, we have used their conditions (I_2, AgO_2CCF_3, CH_3CN) with olefinic alcohol **6** (eq 2). The resulting 60:40 mixture of **18**:**19**[4] is consistent with



(2)

the normal and expected anti addition pathway. Reduction of **18** (Bu_3SnH, AIBN, PhH) gave **17** while similar treatment of **19** provided **15**. Thus, for the examples that we have studied, we find significant errors in the stereochemical assignments made by Lipshutz and Barton.[12]

In conclusion, we can say that it is now possible to ring close the four isomeric homoallylic alcohols, **3**–**6**, with good to complete stereocontrol by the judicious choice of phenylselenation conditions.[13] In all cases the favored product has an anti relationship of the phenylseleno group to the adjacent methyl. Reduction then provides selective access to 2,3,5-trisubstituted tetrahydrofurans (e.g., **14**–**17**). These results now allow the rational planning of syntheses of natural and unnatural products wherein these stereochemical patterns are commonly sought.

Supplementary Material Available: Cyclization procedures, NMR spectra, and a complete discussion of the assignments for tetrahydrofurans **2** and **7**–**19** (17 pages). Ordering information is given on any current masthead page.

(10) Lipshutz, B. H.; Barton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 1084–1086.

(11) These authors based their stereochemical assignments exclusively on NOE measurements.

(12) Only in the formation of **8** from **4** do the results we have obtained with substrates **3**–**6** match the selenoetherification results of these authors.[10] Attempted iodoetherifications of **3**–**6** give no indication of a novel syn addition mode.

(13) Reaction of **6** with benzeneselenenyl chloride in acetonitrile at low temperature (<−30 °C) improved the **12**:**13** ratio to 92:8.

Facial Amphiphiles

Yuan Cheng, Douglas M. Ho, Craig R. Gottlieb, and Daniel Kahne*

Department of Chemistry, Princeton University Princeton, New Jersey 08544

Michael A. Bruck

Department of Chemistry, University of Arizona Tucson, Arizona 85721

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There is currently a great deal of interest in the design and study of novel amphiphiles. Evidence in the literature indicates that helical peptides with facial amphiphilicity have interesting effects on phospholipid membranes. In some contexts, they bind to the membrane interface and help target adjacent peptide sequences to membrane-bound receptors.[1] In other contexts they cause membrane fusion[2] or permeabilization.[3] The separation of polar and nonpolar domains along the long axis of the peptides to produce structures with a hydrophobic face and a hydrophilic face—what we call *facial amphiphilicity* to distinguish it from the head-to-tail amphiphilicity seen in typical polar lipids—is thought to be critical for the observed effects on membranes. Whether nonpeptidic molecules with a similar distribution of polar and nonpolar domains can mimic some of the effects of amphiphilic peptides is a question that has been raised but not addressed,[1b] in part because there are few natural examples of such molecules. We report herein the synthesis and crystallographic characterization of two nonpeptidic facial amphiphiles as a first step in answering this question.[4,5]

The synthetic amphiphiles are glycosylated derivatives of cholic acid (**4**) and *allo*-cholic acid (**5**). Cholic acid was chosen as a starting structure because it is rigid and has three hydroxyls oriented along one face. It is already moderately amphiphilic.[6] Glycosylation of the axial hydroxyls at C-7 and C-12 produces derivatives with a similar hydrophobic face but a much more hydrophilic polyhydroxylated face.[7] Compounds **4** and **5** were synthesized from the readily available C-3 protected cholic acid (**1**) and *allo*-cholic acid (**2**) methyl esters,[8] respectively, by the procedure outlined in Scheme I.[9] The key step is glycosylation of the hindered C7 and C12 hydroxyls using perbenzylated glycosyl sulfoxide **3**.[10] As far as we know, this is the only glycosylation

(1) (a) Kaiser, E. T.; Kezdy, F. J. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 1137. (b) Kaiser, E. T.; Kezdy, F. J. *Science* **1984**, *223*, 249. (c) Kaiser, E. T.; Kezdy, F. J. *Annu. Rev. Biophys. Biophys. Chem.* **1987**, *16*, 561.

(2) (a) Terwilliger, T. C.; Weissman, L.; Eisenberg, D. *Biophys. J.* **1982**, *37*, 353. (b) Lear, J. D.; DeGrado, W. F. *J. Biol. Chem.* **1987**, *262*, 6500. (c) Suenaga, M.; Lee, S.; Park, N. G.; Aoyagi, H.; Kato, T.; Umeda, A.; Amako, K. *Biochim. Biophys. Acta* **1989**, *981*, 143. (d) Takahashi, S. *Biochemistry* **1990**, *29*, 6257.

(3) (a) Hall, J. E.; Vodyanoy, I.; Balasubramanian, T. M.; Marshall, G. R. *Biophys. J.* **1984**, *45*, 233. (b) Lear, J. D.; Wasserman, Z. R.; DeGrado, W. F. *Science* **1988**, *240*, 1177. (c) Tosteson, M. T.; Alvarez, O.; Hubbell, W.; Bieganski, R. M.; Attenbach, C.; Caporales, L. H.; Levy, J. J.; Nutt, R. F.; Rosenblatt, M.; Tosteson, D. C. *Biophys. J.* **1990**, *58*, 1367. (d) Oiki, S.; Madison, V.; Montal, M. *Proteins: Struct. Funct., Genet.* **1990**, *8*, 226.

(4) Another type of facial amphiphile was recently reported: Stein, T. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1992**, *114*, 3943. This paper also contains a good summary of different types of amphiphiles and leading references.

(5) For other unnatural amphiphiles see, for example: (a) Menger, F. M.; Whitesell, L. G. *J. Org. Chem.* **1987**, *52*, 3793. (b) Menger, F. M.; Littau, C. A. *J. Am. Chem. Soc.* **1991**, *113*, 1451.

(6) (a) Armstrong, M. J.; Carey, M. C. *J. Lipid Res.* **1982**, *23*, 70. (b) Roda, A.; Hofmann, A. F.; Mysels, K. J. *J. Biol. Chem.* **1983**, *258*, 6362. (c) Hofmann, A. F.; Mysels, K. J. *Colloids Surf.* **1988**, *30*, 145.

(7) Others have modified cholic acid to make host molecules. See, for example: (a) Burrows, C. J.; Sauter, R. A. *J. Incl. Phenom.* **1987**, *5*, 117. (b) Bonar-Law, R. P.; Sanders, J. K. M. *J. Chem. Soc., Chem. Commun.* **1991**, 574.

(8) Zhu, X.; Amouzou, E.; McLean, S. *Can. J. Chem.* **1987**, *65*, 2447.

(9) All new compounds were characterized by ^1H and ^{13}C NMR and FAB MS.

(10) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

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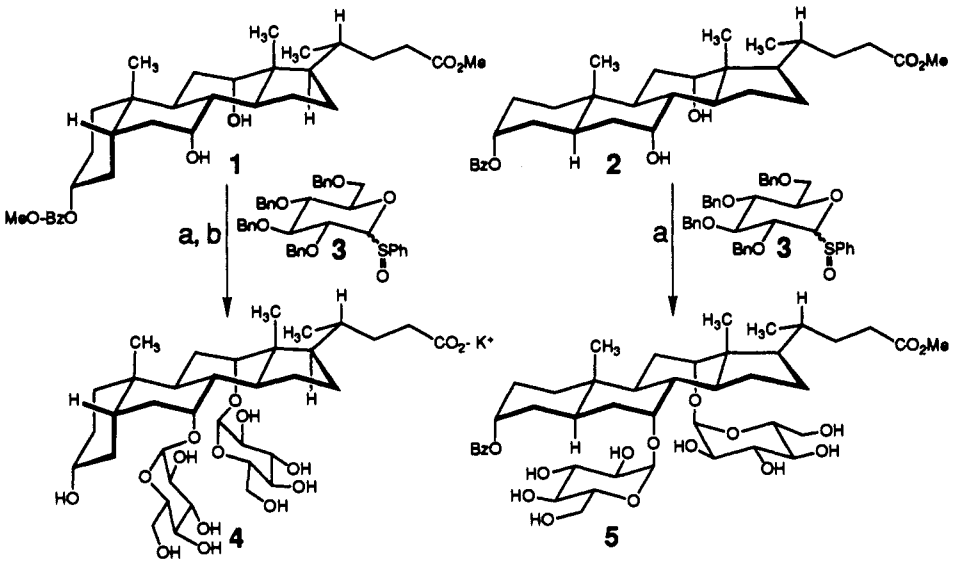
Scheme I[a]



[a] (a) 1. Tf_2O (4.0 equiv), toluene, 2,6-di-*tert*-butyl-4-methylpyridine (2.4 equiv), −78 °C, **3** (4.0 equiv); 2. sterol (**1** or **2**, 1.0 equiv), −78 °C, 30 min, then warm to room temperature; 3. $NaHCO_3$ (aqueous); 4. $Pd(OH)_2/C$, MeOH/benzene 8:1, 50 psi, 24 h. (b) K_2CO_3 (saturated), MeOH, reflux, 3 h.

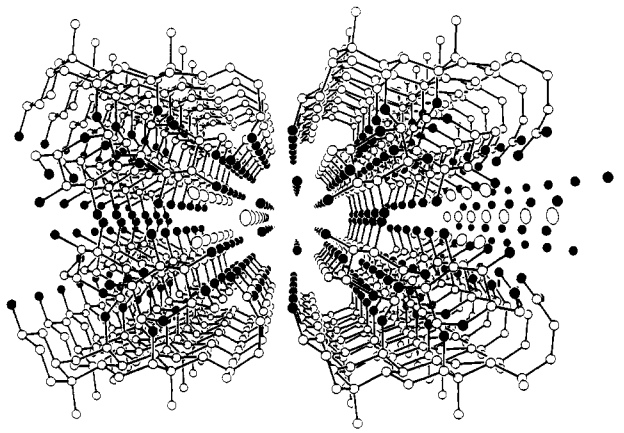


Figure 1. Crystal packing of compound **4**. Oyxgen atoms are represented by blackened circles (●); the isolated oxygens are water molecules. Partially occupied potassium ion sites in the lattice are depicted by open ellipsoids (0).

method capable of attaching sugars to both hindered oxygens.

Crystallization of **4** from methanol/dioxane (1:1) and **5** from H_2O/methanol (2:1) gave crystals suitable for X-ray diffraction.[11] The glycosylated bile acid derivatives crystallize in amphipathic, nearly planar bilayers (Figures 1 and 2). In both structures, pairs of glycosteroids are held together by hydrogen bonds between hydroxyls on opposing sugars. The pairs are parallel for compound **4** and antiparallel for compound **5**. The side chain in **4** adopts an unusual bent conformation (C17–C20–C22–C23 torsion = 66° and C20–C22–C23–C24 torsion = −88°, for a perpendicular bend) as a result of favorable electrostatic interactions between the

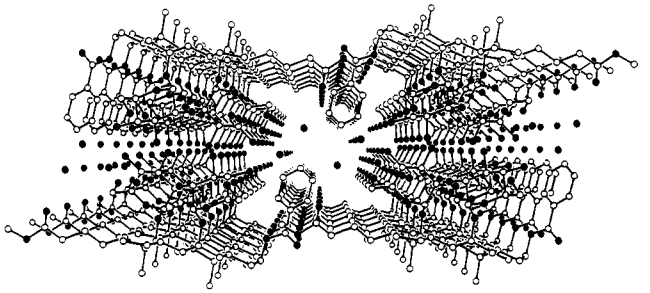


Figure 2. Crystal packing of compound **5**. Oxygen atoms are represented by blackened circles (●); the isolated oxygens are water molecules which display only partial occupancy at the indicated positions in the lattice.

carboxylate and polar groups on the polyhydroxylated surface. Most interesting, however, are the large channels containing organized water molecules between adjacent pairs of glycosteroids.[12]

The organization of the glycosylated bile acids in the solid state is consistent with our original goal of designing molecules with facial amphiphilicity.[13] Studies on the behavior of these novel facial amphiphiles in solution and in the presence of membranes are underway.

Acknowledgment. This work was supported by the Office of Naval Research and Interneutron Pharmaceuticals, Inc.

Supplementary Material Available: ^1H and ^{13}C NMR data, structural drawings, and tables of crystal data, refinement parameters, atomic coordinates, isotropic and anisotropic displacement coefficients, hydrogen atom coordinates, and bond lengths and angles for compounds **4** and **5** (49 pages). Ordering information is given on any current masthead page.

(11) (a) **4**: $K^+C_{36}H_{59}O_{15}^-\cdot 2H_2O$, MW = 807.0; orthorhombic, space group $C222_1$; a = 8.993 (1) Å, b = 24.625 (2) Å, c = 35.386 (3) Å, V = 7836 (1) Å^3, D_c = 1.37 g cm^{-3}, Z = 8; $R(F)$ = 0.0761, $wR(F)$ = 0.0816 for anisotropic refinement with 3239 observed reflections [$F > 3\sigma(F)$] and 493 parameters. (b) **5**: $C_{44}H_{66}O_{16}\cdot 2.5H_2O$, MW = 896.0; monoclinic, space group $C2$; a = 35.861 (8) Å, b = 8.377 (2) Å, c = 16.853 (4) Å, β = 111.41 (2)°, V = 4713 (2) Å^3, D_c = 1.26 g cm^{-3}, Z = 4; $R(F)$ = 0.1160, $wR(F)$ = 0.1368 for isotropic refinement with 2225 observed reflections [$F > 3\sigma(F)$] and 244 parameters. Structures were solved by fragment search (PATSEE) and structure expansion (XS:TEXP) and refined by full-matrix least-squares (XLS). (c) PATSEE: A program for the location of a fragment of known geometry by integrated Patterson, packing, and direct methods. Egert, E.; Sheldrick, G. M. *Acta Crystallogr.* **1985**, *A41*, 2262. SHELXTL PLUS 4.11 for R3/V and R3m/V crystallographic systems, G. M. Sheldrick, University of Goettingen, Germany, and Siemens Analytical X-ray Instruments, Inc., Madison, WI, 1990.

(12) Some cholic acid crystals also contain channels. Usually the channels are hydrophobic, and included guests are organic molecules: (a) Miki, K.; Masui, A.; Kasai, N.; Miyata, M.; Shibakami, M.; Takemoto, K. *J. Am. Chem. Soc.* **1988**, *110*, 6594. (b) Miyata, M.; Shibakami, M.; Chirachanchai, S.; Takemoto, K.; Kasai, N.; Miki, K. *Nature* **1990**, *343*, 446. (c) Miki, K.; Kasai, N.; Shibakami, M.; Takemoto, K.; Miyata, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1757.

(13) Cholic acid tends to crystallize in a nonplanar bilayer array, often with individual molecules interleaved, apparently so that contact of nonpolar surfaces is maximized. (a) Miki, K.; Kasai, N.; Shibakami, M.; Chirachanchai, S.; Takemoto, K.; Miyata, M. *Acta Crystallogr.* **1990**, *C46*, 2442. (b) Cobbledick, R. E.; Einstein, F. W. B. *Acta Crystallogr.* **1980**, *B36*, 287. (c) Cheng, Y.; Ho, D. M.; Kahne, D. Unpublished results.