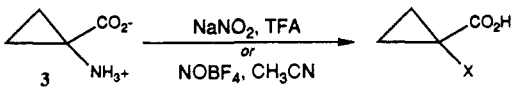
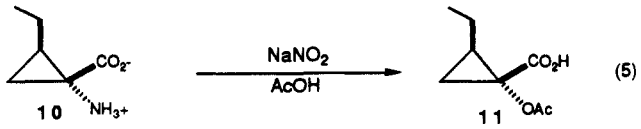
Table II

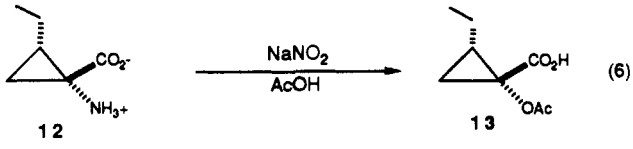


compd	nucleophile	yield, %
6	LiBr	73
14	KCl	75
15	EtOH	65
16	CH_3COSH	60
17	KCN	64
18	$CH_2{=}CHCH_2Si(CH_3)_3$	30

diazotization conditions, each produces a different diastereomeric acetoxy acid (75 and 78%, eqs 5 and 6). That these processes proceed with overall *retention* of stereochemistry was established by comparison with an authentic sample of **13** prepared by literature methods.[13]



(5)



(6)

The reactions of **1** in trifluoroacetic acid with other nucleophiles were examined. This solvent change eliminates competing nucleophilic trapping. Substitution can also be effected in acetonitrile with nitrosonium tetrafluoroborate[14] as the diazotizing agent. As summarized in Table II, halide, sulfur, and even carbon nucleophiles (allyltrimethylsilane, cyanide) provide substitution products in respectable yields. For comparison with bis(trifluoromethyl)acetolactone, the only α-lactone that reacts with ethanol via acyl-C–O cleavage (presumably due to decreased polarization of the alkyl-C–O bond), diazotization of **3** was conducted in the presence of ethanol. The exclusive formation of the α-alkoxy acid was observed.

Both kinetic and stereochemical studies imply the generation of oxaspiropentanone **1** in the deamination of ACC.[15] The reactivity of **1** with ethanol suggests greater α-alkyl-C–O bond polarization compared with bis(trifluoromethyl)acetolactone. Evidence from this reaction that **8** is the common intermediate and that ring-opening products cannot be derived from the α-lactone suggests that the rearrangements and racemization observed on diazotization of tertiary amino acids may be occurring not through opening of their α-lactones but via the diazonium ions.

These transformations provide ready access to substituted cyclopropanecarboxylic acid derivatives that are otherwise difficult to obtain, particularly because the enolate chemistry of cyclopropanecarboxylic acid is extremely limited.[16] Oxaspiropentanone is thus an umpolung synthon for **2**.[17]

Acknowledgment. Financial support from the National Institutes of Health (GM 38226) is gratefully acknowledged. NMR spectra were obtained on an instrument provided by NSF equipment grant CHE 84-14329. Mass spectra were obtained at the UCSF Bio-Organic, Bio-Medical Mass Spectrometry Resource, A. L. Burlingame, Director, supported by NIH Grant RR01614.

Supplementary Material Available: Experimental procedures for the syntheses of **4a,b**, **6**, **11**, and **13–18** and Table S1 containing spectral data (11 pages). Ordering information is given on any current masthead page.

(12) Pirrung, M. C.; McGeehan, G. M. *J. Org. Chem.* **1986**, *51*, 2103.
(13) Salaun, J.; Karkour, B. *Tetrahedron Lett.* **1987**, *28*, 4669. Heine, H.-G.; Wendisch, D. *Justus Liebigs Ann. Chem.* **1976**, 463. Comparison of the ^{13}C NMR spectra of the amino acids of known stereochemistry and the corresponding hydroxy acids (Table S1, supplementary material) gives further confidence in the stereochemical assignments. In particular, the observed shielding effect of a *syn*-alkyl group (γ-gauche) on the carboxyl resonance in **10** and **11** validate their structures.
(14) Olah, G. A.; Olah, J. A. *J. Org. Chem.* **1965**, *30*, 2386.
(15) The formation of a "hot" pyramidal carbonium ion **2** (Laali, K.; Olah, G. *Rev. Chem. Intermed.* **1985**, *6*, 237. Kirmse, W.; Schutte, H. *J. Am. Chem. Soc.* **1967**, *89*, 1284) which reacts within a solvent cage or ring-opens was suggested by a reviewer. While solvolyses of cyclopropyl halides (Roberts, J. D.; Chambers, V. C. *J. Am. Chem. Soc.* **1951**, *73*, 5034. DePuy, C. H.; Schnack, L. G.; Hausser, J. W. *J. Am. Chem. Soc.* **1966**, *88*, 3343. Schleyer, P. v. R.; Van Dine, G. W.; Schollkopf, U.; Paust, J. *J. Am. Chem. Soc.* **1966**, *88*, 2868. Hausser, J. W.; Uchic, J. T. *J. Org. Chem.* **1972**, *37*, 4087. Jefford, C. W.; Wojnarowski, W. *Tetrahedron* **1969**, *25*, 2089. Jefford, C. W.; Medary, R. T. *Tetrahedron* **1967**, *23*, 4123) with retention of configuration are known (Ledlie, D. B.; Nelson, E. A. *Tetrahedron Lett.* **1969**, 1175. Ledlie, D. B.; Barber, W.; Switzer, F. *Tetrahedron Lett.* **1977**, 607. Olah, G.; Liang, G.; Ledlie, D. B.; Costopoulos, M. G. *J. Am. Chem. Soc.* **1977**, *99*, 4196 and references therein), they are observed only in those systems that cannot undergo ring opening for geometric reasons (i.e., Bredt's rule violations). The data preclude a single intermediate such as **2** (or **1**) which can ring-open or react with external nucleophiles.
(16) Haner, D.; Seebach, D. *Chimia* **1985**, *39*, 356.
(17) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. Hase, T. *Umpoled Synthons*; Wiley: New York, 1986.

Simple One-Pot Syntheses of Spiroketals and Oxaspirolactones by Addition of γ- and δ-Cerioalkoxides to Lactones and Cyclic Anhydrides

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Department of Chemistry, University of Pittsburgh Pittsburgh, Pennsylvania 15260

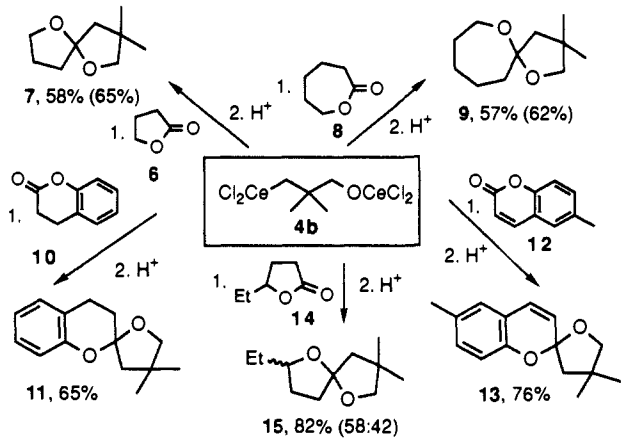
Received April 23, 1990

We present here a method of preventing the ring opening, leading to double addition, that often occurs when organometallics react with lactones, and the utility of this method is illustrated by novel one-pot syntheses of spiroketals, including two pheromones. Reactions of organolithium compounds or Grignard reagents with lactones are unpredictable, giving products derived from the addition of 1 or 2 equiv of the nucleophile to the carbonyl group.[1,2] Unsubstituted, saturated lactones tend to undergo double organometallic attack to give diols,[1-3] whereas polysubstituted lactones are somewhat more prone to monoaddition of organolithium compounds and Grignard reagents.[4,5] Lithium acetylides are widely employed since they give satisfactory yields of monoaddition products which are important intermediates in the synthesis of natural spiroketals.[8]

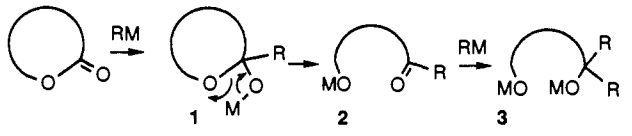
(1) Cavicchioli, S.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1984**, *49*, 1246 and references therein.
(2) Betancourt de Perez, R. M.; Fuentes, L. M.; Larson, G. L.; Barnes, C. L.; Heeg, M. J. *J. Org. Chem.* **1986**, *51*, 2039 and references therein.
(3) Belov, V. N.; Tarnopolskii, Y. I. *Zh. Org. Khim.* **1965**, *1*, 634. Cohen, N.; Banner, B. L.; Blount, J. F.; Tsai, M.; Saucy, G. *J. Org. Chem.* **1973**, *38*, 3229.
(4) Williams, D. R.; Barner, B. A. *Tetrahedron Lett.* **1983**, *24*, 427. Isobe, M.; Ichikawa, Y.; Masaki, H.; Goto, T. *Ibid.* **1984**, *25*, 3607. Bartlett, P. A.; Holm, K. H.; Morimoto, A. *J. Org. Chem.* **1985**, *50*, 5179. Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N.; Smith, A. B., III. *J. Am. Chem. Soc.* **1986**, *108*, 2662. Tobia, D.; Baranski, J.; Rickborn, B. *J. Org. Chem.* **1989**, *54*, 4253.
(5) Lithium enolates of esters[6] and 1,3-diketones,[7] which were found to efficiently yield monoaddition products with δ-valerolactone, represent special cases since the stabilization of the hemiketal via lithium chelation prevents the ring opening.
(6) Duggan, A. J.; Adams, M. A.; Brynes, P. J.; Meinwald, J. *Tetrahedron Lett.* **1978**, 4323.
(7) Attwood, S. V.; Barrett, A. G.; Florent, J.-C. *J. Chem. Soc., Chem. Commun.* **1981**, 556.

0002-7863/90/1512-6389$02.50/0

Scheme I



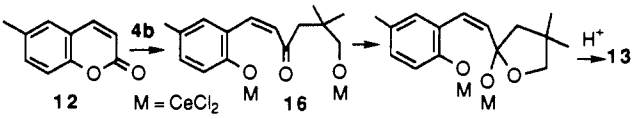
Double addition, leading to a metalated diol (**3**), is presumably caused by ring opening of hemiacetal salt **1**, the monoaddition product, followed by addition of the organometallic RM to the resulting ketone (**2**), which is more reactive toward organometallics than the original lactone. From analysis of the reaction mixtures, it was clear that this process, along with lactone deprotonation, was responsible for foiling our attempts to obtain acceptable yields of spiroketals by addition of lithium γ- and δ-lithioalkoxides to lactones followed by acid-induced ketalization.



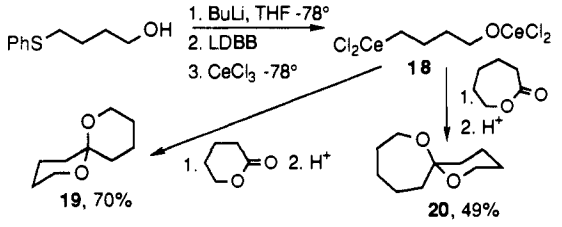
In an attempt to decrease the rate of this undesirable ring opening, we have studied the addition in cases in which M = $CeCl_2$. The work of Imamoto[9] and Luche[10] has indicated that Ce^{III} is extremely oxophilic, and we had hoped that the stronger Ce–O bond would cleave more slowly than the Li–O bond. The success of diisobutylaluminum hydride at delivering a single hydride ion to a lactone[11] is presumably due to the influence of the strong Al–O bond in slowing the rate of opening of **1** (R = H). We also anticipated that organoceriums would cause less enolization than the organolithiums.[9] We now report the success of this strategy.

During our studies on the synthetic applications of γ-lithioalkoxides generated by the reductive cleavage of oxetanes by lithium di-*tert*-butylbiphenylide (LDBB),[12] we examined lactones as electrophiles, focusing on a potentially short synthetic method to obtain spiroketals. The latter, especially [4.4], [4.5], and [5.5] spiroketal systems, are contained in important insect pheromones, polyether antibiotics, antiparasitic agents, and fungal toxins.[13,14] However, our initial efforts were discouraging, the yield of the model target molecule, 1,6-dioxaspiro[4.5]decane (**5**), from the

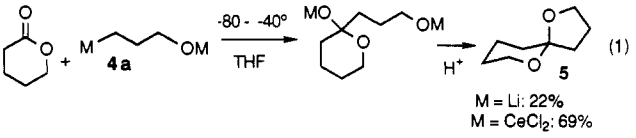
Scheme II



Scheme III

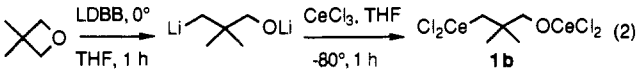


reaction of lithium 3-lithiopropoxide (**4a**; M = Li) and δ-valerolactone, averaging only 22% (eq 1). After exchange of the lithium ion in the salt **4a** with cerium(III),[9] the yield of **5** increased to 69%.



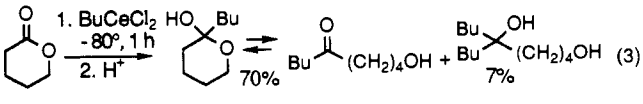
(1)

Furthermore, this type of reaction is effective for a variety of five-, six-, and even seven-membered lactones, making it a general, one-pot synthesis of [4.*n*] spiroketal systems (Scheme I; isolated yields are given with GC yields in parentheses).[15] For practical purposes, we chose lithium 2,2-dimethyl-3-lithiopropoxide, which can be produced from inexpensive 3,3-dimethyloxetane,[12] as the substrate for transmetalation to the dicerio analogue **4b** to be used for further reactions with lactones (eq 2).



(2)

Even dihydrocoumarin (**10**) and 6-methylcoumarin (**12**), lactones that should readily open upon nucleophilic attack due to the stability of the leaving groups, gave good yields of spiroketals **11** and **13**, respectively. It appears likely that these two lactones do indeed open upon reaction with organocerium compounds but that the resulting intermediate ketoalkoxides (e.g., **16**) are immediately internally protected by the formation of dichlorocerium lactolates which, after acidic workup, yield the desired spiroketals (Scheme II).[16] The crucial role of this novel protective cyclization is demonstrated by the results of the reaction of *n*-butylcerium dichloride or methylcerium dichloride with 6-methylcoumarin (**12**); the product mixture consisted of 50% of unreacted lactone, a large quantity of very polar material, presumably including double-addition products, and no detectable product of single addition.[17] In contrast, the less easily opened δ-valerolactone reacts with *n*-butylcerium dichloride to give 70% of monoaddition product, as a mixture of ring and open-chain isomers, and only 7% of double addition product (eq 3). The latter experiment also demonstrates the generality of the monoaddition of organoceriums to lactones.[18]



(3)

(8) Phillips, C.; Jacobson, R.; Abrahams, B.; Williams, H. J.; Smith, L. R. *J. Org. Chem.* **1980**, *45*, 1920. Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105. Baker, R.; Swain, C. J.; Head, J. C. *J. Chem. Soc., Chem. Commun.* **1986**, 874. Baker, R.; Herbert, R. H. *Ibid.* **1987**, 1123. Crimmins, M. T.; Bankaitis, D. M. *Tetrahedron Lett.* **1983**, *24*, 4551. Hannessian, S.; Ugolini, A.; Therien, M. *J. Org. Chem.* **1983**, *48*, 4427. Chabala, J. C.; Vincent, J. E. *Tetrahedron Lett.* **1978**, 937.

(9) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

(10) Luche, J.-L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976.

(11) Winterfeldt, E. *Synthesis* **1975**, 617.

(12) Mudryk, B.; Cohen, T. *J. Org. Chem.* **1989**, *54*, 5657.

(13) Recent review on spiroketals: Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

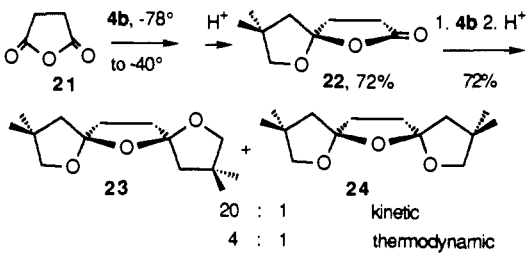
(14) Syntheses of 1,7-dioxaspiro[5.5]undecanes: Kluge, A. F. *Heterocycles* **1986**, *24*, 1699.

(15) Products were chromatographically pure and were characterized by ^1H NMR and HRMS.

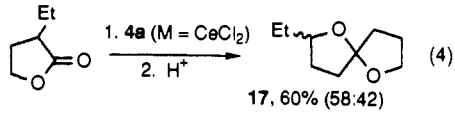
(16) This cyclization/ring opening is vaguely reminiscent of the reaction of lactones and cyclic anhydrides with di-Grignard reagents: Canonne, P.; Foscolos, G. B.; Bélanger, D. *J. Org. Chem.* **1980**, *45*, 1828. Canonne, P.; Bélanger, D.; Lemay, G.; Foscolos, G. B. *Ibid.* **1981**, *46*, 3091.

(17) Coumarin with $LiAlH_4$–$CeCl_3$, DIBAL, or trialkylaluminum also gives diols: Fukuzawa, S.; Fujinami, T.; Yamauchi, S.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1929. Alberola, A.; Ortega, A. G.; Pedrosa, R.; Bragado, J. L. P.; Amo, J. F. R. *J. Heterocycl. Chem.* **1983**, *20*, 715.

Scheme IV



Equation 4 presents one of the shortest and most convenient syntheses of racemic 2-ethyl-1,6-dioxaspiro[4.4]nonane (**17**) (chalcogran), a major pheromone component of the Norway spruce pest.[19] The latter was obtained in only 15% yield when the dilithio version of **4a** was employed.



(4)

Oxaspiroannulation of six-membered rings to lactones is also successful (Scheme III). The requisite lithium 4-lithiobutoxide can be generated by deprotonation of 4-(phenylthio)butanol by *n*-butyllithium followed by reductive lithiation[20] with LDBB in THF at −78 °C. Transmetalation with $CeCl_3$ provides the valuable organocerium species **18**, which reacts with lactones as shown. 1,7-Dioxaspiro[5.5]undecane (**19**) is a major component of the olive fruit fly pheromone,[14,21] and the reaction product (**20**) of **18** and ϵ-caprolactone is a ring system that is also found in nature.[22]

Finally, monoaddition of cerium 3-cerioproposide **4b** to cyclic anhydrides occurs in variable yields to provide, after acidic workup, oxaspirolactones, a rare type of compound.[23] The best yield was obtained with succinic anhydride (**21**, Scheme IV).[24] When the dilithio analogue of **4b** was used instead, only 13% of **22** could be obtained. Preliminary experiments indicate that both maleic and phthalic anhydrides also provide oxaspirolactones but in the reduced yields of 40 and 25%, respectively. Lactone **22** can be induced to undergo another addition of organocerium **4b** leading to a diastereoisomeric mixture of the 1,6,8-trioxadispiro-[4.1.4.2]tridecane system, **23** and **24**.[25,26]

Acknowledgment. We thank the National Science Foundation for financial support.

Supplementary Material Available: Sample procedures for additions of organocerium reagents to lactones and cyclic anhydrides and the spectral data for the products (3 pages). Ordering information is given on any current masthead page.

(18) Although the reaction of *n*-butyllithium and δ-valerolactone has been reported to give " an extremely complex mixture of products",[1] in our hands, 50% of monoaddition was observed.

(19) Isolation and characterization: Francke, W.; Heeman, V.; Gerken, B.; Renwick, J. A. A.; Vité, J. P. Naturwissenschaften **1977**, *64*, 590. Recent syntheses: Högberg, H.-E.; Hedenström, E.; Isaksson, R.; Wassgren, A.-B. *Acta Chem. Scand.* **1987**, *B41*, 694 and citations therein.

(20) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152.

(21) Baker, R.; Herbert, R.; Howse, P. E.; Jones, O. T. *J. Chem. Soc., Chem. Commun.* **1980**, 52. DeShong, P.; Waltermire, R. E.; Ammon, H. L. *J. Am. Chem. Soc.* **1988**, *110*, 1901.

(22) Kitching, W.; Lewis, J. A.; Perkins, M. V.; Drew, R.; Moore, C. J.; Schurig, V.; König, W. A.; Francke, W. *J. Org. Chem.* **1989**, *54*, 3893.

(23) See, for example: Fukuda, H.; Takeda, M.; Sato, Y.; Mitsunobu, O. *Synthesis* **1979**, 368. Yamamoto, M.; Yoshitake, M.; Yamada, K. *J. Chem. Soc., Chem. Commun.* **1983**, 991. Ousset, J. B.; Mioskowski, C.; Yang, Y.-L.; Falck, J. R. *Tetrahedron Lett.* **1984**, *25*, 5903.

(24) A solution of **4b** at −78 °C in THF is cannulated into a solution of the anhydride at −78 °C.

(25) Related systems are known: Ponomarev, A. A.; Markushina, I. A. *Zh. Obshch. Khim.* **1963**, *33*, 3955. Baker, R.; Brimble, M. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 125.

(26) The relative stereochemistry was surmised from the higher dielectric constant of **24**.

Relation of Surfactant Monomer Structure to Flip-Flop Dynamics in Surface-Differentiated Synthetic Bilayer Membranes†

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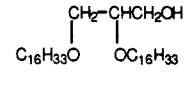
Received May 4, 1990

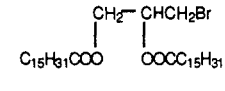
The transverse or "flip-flop" migration of a lipid molecule from one leaflet of a hydrated bilayer membrane to the other is an activated process that requires disruption of the membrane packing, as well as energetically costly transient interactions of the polar lipid head group with the bilayer's hydrocarbon interior, and of the lipid's hydrocarbon chains with water.[1,2] There is intense current interest in the dynamics of lipid flip-flop in biological membranes or liposomes created from naturally occurring lipids.[3] Recently, we showed that bilayer vesicles created from simple tetraalkylammonium ion surfactants could be chemically differentiated at their exovesicular and endovesicular surfaces, enabling us to visualize the dynamics of subsequent endovesicular/exovesicular exchanges.[4] Here we demonstrate that bilayer vesicles constructed of structurally diverse synthetic surfactants can be similarly studied, and that monomer structure can be readily related to flip-flop dynamics within the membrane.

The functional (**F**) and corresponding nonfunctional (**NF**) surfactants appear in Chart I. Surfactants **1-F** and **1-NF** were known.[4] For **2** or **3**, *N*-methyl-*N*,*N*-diethanolamine was either etherified or esterified to afford the precursor tertiary amines, which were then quaternized with GCH_2Br[4a] (**F** surfactants) or MeBr (**NF** surfactants).

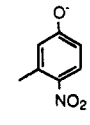
Surfactant **4-F** was prepared by quaternization with GCH_2Br of the tertiary amine obtained from the reaction of (2,2-diheptadecyl-1,3-dioxolan-4-yl)methyl bromide[5] with dimethylamine, whereas **4-NF** resulted directly from quaternization of the same bromide with Me_3N. In the **5** system, racemic glycerol dipalmityl ether (**7**)[6] was converted to the analogous bromide with CBr_4/Ph_3P; the bromide was then reacted with dimethylamine; and the resulting tertiary amine was quaternized with GCH_2Br or MeBr to afford **5-F** or **5-NF**. Surfactants **6** were derived from racemic bromide **8**,[7] which either was directly quaternized to **6-NF** with Me_3N or reacted with dimethylamine to give a tertiary amine that was converted to **6-F** by quaternization with GCH_2Br. All surfactants were crystalline solids that were purified by chromatography and recrystallization and characterized by NMR spectroscopy and elemental analysis.[8]



7



8



9 (G')

† Dedicated to Professor Clifford A. Bunton on the occasion of his "retirement".

(1) (a) Jain, M. K.; Wagner, R. C. *Introduction to Biological Membranes*; Wiley: New York, 1980; p 110f. (b) Fendler, J. H. *Membrane Mimetic Chemistry*; Wiley: New York, 1982; p 145f.

(2) Kornberg, R.; McConnell, H. M. *Biochemistry* **1971**, *10*, 1111. McNamee, M. G.; McConnell, H. M. *Ibid.* **1973**, *12*, 2951.

(3) Herrmann, A.; Zachowski, A.; Devaux, P. F. *Biochemistry* **1990**, *29*, 2023. Wimley, W. C.; Thompson, T. E. *Ibid.* **1990**, *29*, 1296. Hope, M. J.; Redelmeier, T. E.; Wong, K. F.; Rodrigueza, W.; Cullis, P. R. *Ibid.* **1989**, *28*, 4181.

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