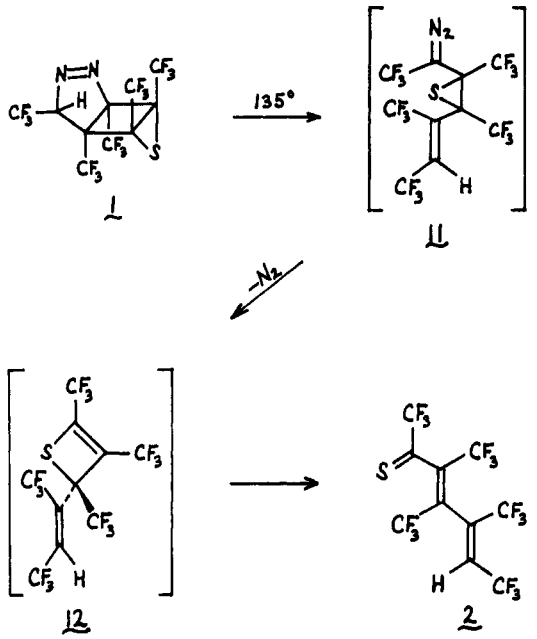
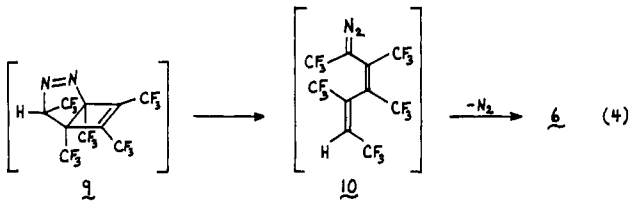
Scheme II



atoms lie in a single plane.[14] Both transition-state geometries are orbital symmetry allowed for diazo compounds.

Formation from **5** of a vinylcyclopropene can now be understood in terms of (1) base-catalyzed isomerization of **5** to its less stable tautomer **9**,[15] (2) 1,3-cycloelimination to produce acyclic diazo compound **10**, and (3) nitrogen loss to yield a vinylcarbene which cyclizes to **6** (eq 4).[16] The stereochemical assignments for the



(4)

hydrogen in **9** and **10** are surmised from the configuration of **6** and the fragmentation stereochemistry established in eq 3.

Thermal degradation of **1** presumably begins with a 1,3-cycloelimination, yielding diazothiirane **11**. Simultaneous or stepwise, nitrogen loss and ring expansion lead to thietene **12**, which ring opens to **2** under the reaction conditions (Scheme II). Though neither **11** nor **12** has been detected, this interpretation gains strong support from its correct prediction of the configuration at both double bonds of **2**. The *Z* configuration of the hydrogen-bearing double bond follows directly from the exo location of the hydrogen in **1**. At the other site, the lower energy configuration is to be expected since ring opening of thietene **12** can occur in either stereochemical sense. The observed *Z* (trans) configuration appears, in fact, to be the stabler one on steric grounds.

The 1,3-dipolar cycloeliminations described above[17] are doubtless facilitated by release of strain in the four-membered ring.[18] Within the constraint that such a driving force be built in, the diazo compound cycloaddition/cycloelimination sequence illustrated here should be quite general.

Acknowledgment. We thank Howard Hutchins for valuable assistance with ^{19}F NMR spectroscopy and the National Science Foundation for generous financial support.

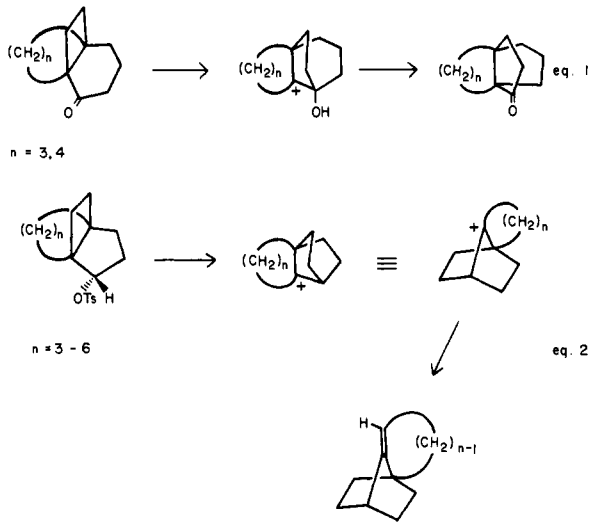
(14) Leroy, G.; Sana, M. *Tetrahedron* **1975**, *31*, 2091.
(15) For a review of pyrazoline thermolysis based on prior tautomerization, see: Müller, E. *Methoden Org. Chem.* (*Houben-Weyl*), **1971**, *4*, Part 3, 42-89.
(16) For examples of vinylcarbene cyclization, see: Hartzler, H. In "Carbenes"; Mass, R. A., Jones, M., Eds.; Wiley: New York, 1975; Vol. II, p 57 ff.
(17) Kobayashi has independently discovered 1,3-dipolar cycloeliminations in a series of compounds closely related to ours. Interestingly, he has isolated a thietene analogous to our postulated intermediate **12**: Kobayashi, Y.; Kumadaki, I.; Hanzawa, Y. *Yuki Gosei Kagaku Kyokaishi* **1979**, *37*, 183.
(18) There is evidence that 1,3-dipolar cycloelimination occurs as a side reaction in the photolysis of unstrained pyrazolines (ref 19) and even, to a very minor extent, in the pyrolysis of one such compound: Crawford, R. J.; Mishra, A. *J. Am. Chem. Soc.* **1966**, *88*, 3963.
(19) Buchwalter, S. L.; Closs, G. L. *J. Org. Chem.* **1975**, *40*, 2549, and references therein.
(20) Goodyear Fellow, 1978-1979. This report is based on the Ph.D. Dissertation of E.D.L., Dartmouth College, 1979.

Evan D. Laganis,[20] David M. Lemal*
Department of Chemistry, Dartamouth College
Hanover, New Hampshire 03755
Received February 26, 1980

Tricyclo[4.2.2.0^{1,6}]decane-Tricyclo[4.2.2.0^{1,5}]decane Interconversions. [4.2.2]Propellane Rearrangements and a Nonphotochemical Propellane Synthesis

Sir:

Propellanes containing one cyclobutane ring—the [*m.n.*2]-propellanes (*m*, *n* > 2)—are now fairly well-known.[1] Acid-catalyzed rearrangements of their derivatives have been studied



productively by Cargill[1c-g] and Tobe[1h] and their colleagues. As illustrated in eq 1 and 2, these reactions occur by way of 1,2 migration of an external bond of the cyclobutane component of the propellane. Alternate mechanisms based on 1,2 migration of the central propellane bond do not account reasonably for the observed products. We have found, however, that this is not the case for propellanes containing a second cyclobutane ring, the [*n*.2.2]propellanes.[2] These are very much more reactive, and now only migration of the strained central bond accounts satisfactorily

(1) (a) Ginsburg, D. "Propellanes, Structure and Reaction", Verlag Chemie: Weinheim, Germany, 1975. (b) Tobe, Y.; Kimura, K.; Odaira, Y. *J. Org. Chem.* **1979**, *44*, 639, and ref 2 therein. (c) Cargill, R. L.; Jackson, T. E.; Peet, N. P.; Pond, D. M. *Acc. Chem. Res.* **1974**, *7*, 106. (d) Cargill, R. L.; Bechham, M. E.; Siebert, A. E.; Dorn, J. *J. Org. Chem.* **1965**, *30*, 3647, and references therein. (e) Peet, N. P.; Cargill, R. L.; Bushey, D. F. *Ibid.* **1973**, *38*, 1218. (f) Cargill, R. L.; Crawford, J. W. *Tetrahedron Lett.* **1967**, 169. (g) Cargill, R. L.; Damewood, J. R.; Cooper, M. M. *J. Am. Chem. Soc.* **1966**, *88*, 1330. (h) Tobe, Y.; Hayauchi, Y.; Sakai, Y.; Odaira, Y. *Ibid.* **1980**, *45*, 637.
(2) (a) Eaton, P. E.; Nyi, K. *J. Am. Chem. Soc.* **1971**, *93*, 2786. (b) Eaton, P. E.; Temme, G. H., III *Ibid.* **1973**, *95*, 7508.

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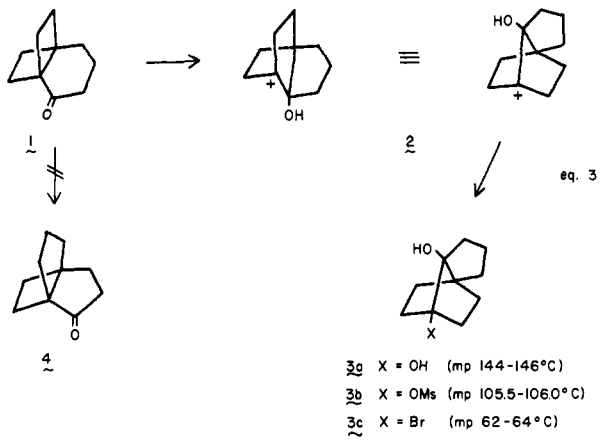
for the products. We report here on the [4.2.2]propellanes in particular.

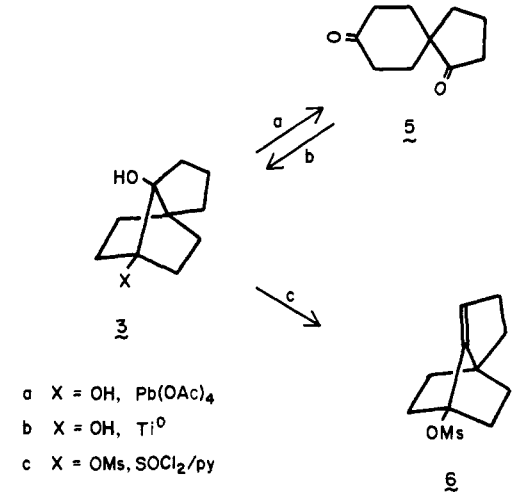
Treatment of the [4.2.2]propellane ketone **1**, tricyclo-[4.2.2.0^{1,6}]decan-2-one,[2] with one or another of a variety of acids leads quickly and cleanly to the corresponding 1:1 adduct **3a–c** (eq 3). In no case have we observed formation of **4**, the product



3a X = OH (mp 144-146°C)
3b X = OMs (mp 105.5-106.0°C)
3c X = Br (mp 62-64°C)

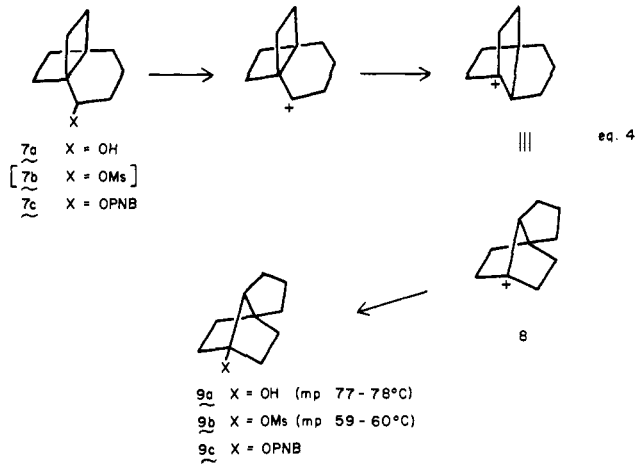
to be expected from an extension of eq 1. This compound is known[1g] and is stable under the mild reaction conditions used for the rearrangements of **1** (0.05–0.20 M solutions in ether, 10–30 min, room temperature, 1–3 equiv of acid). For comparison, we note that the conversions of eq 1 do not occur under such conditions and are slow even in boiling benzene.[1e]

Not much is known about the tricyclo[4.2.2.0^{1,5}]decane ring system of **3**; compounds of this skeleton have only been obtained very recently.[1h,3] For the cases here, the gross structure was deduced from analytical and spectroscopic considerations and was confirmed for vicinal diol **3a** by lead tetraacetate cleavage in high yield to **5**, spiro[4.5]decane-1,8-dione, itself available for comparison by direct synthesis.[4] The positions of the functionalities in the hydroxymesylate **3b** followed from dehydration of **3b** with thionyl chloride in pyridine to the symmetric ene mesylate **6**, characterized most usefully by ^{13}C NMR. The completed assignment was confirmed by an X-ray analysis of **3b** kindly undertaken by Engel at Bern.[5]



a X = OH, $Pb(OAc)_4$
b X = OH, Ti^{0}
c X = OMs, $SOCl_2$/py

The [4.2.2]propellane alcohol **7a** undergoes ready, clean rearrangement to **9a** on treatment with sulfuric acid or to **9b** on reaction with methanesulfonic acid (eq 4). These structures were derived directly via the synthesis of **9b** by hydrogenation of **6**. Even the most patient attempts to make the mesylate of **7** gave only the rearranged mesylate **9b**. It was possible, however, to prepare the unrearranged *p*-nitrobenzoate **7c**; its rearrangement in 60 vol



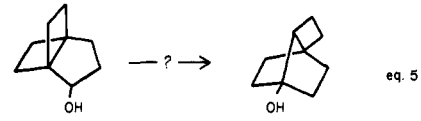
7a X = OH
[**7b** X = OMs]
7c X = OPNB

9a X = OH (mp 77-78°C)
9b X = OMs (mp 59-60°C)
9c X = OPNB

% acetone-d_6/D_2O at 100 °C is first order, $k_1 = 1.6 \times 10^{-4}$ s^{-1}. The product is a 4:1 mixture of the *p*-nitrobenzoate **9c** and the alcohol **9a**; the former, the product of internal return, predominates, but the fraction of product arising from solvent capture is significant.

We believe the rearrangements **1** → **3** and **7** → **9** occur, as illustrated, via the 1-norbornyl cation derivatives **2** and **8**, respectively.[6-8] Normally, access to a bridgehead norbornyl cation is prohibitively expensive energetically, but here the release of strain which accompanies the change of carbon skeleton (about 20 kcal/mol)[9] pays a significant fraction of the energy costs. To probe this further, we are now looking at the reactions of lower propellanes, e.g., for the possibility of a [3.2.2]propellane[2] rearrangement into the as yet unknown tricyclo[3.2.2.0^{1,4}]nonane system (eq 5); here the carbons skeletons are more nearly isoenergetic.

The functionalized tricyclo[4.2.2.0^{1,5}]decanes obtained so readily from the [4.2.2]propellane rearrangements are interesting. For



example, the hydroxybromide **3c** on short exposure to aqueous silver nitrate at room temperature gives diol **3a** in excellent yield. This reaction, which occurs so easily, seems to belie the usual strictures concerning the solvolysis of bridgehead bromides. Comfortingly, we can show that this apparent solvolysis really proceeds via a pinacol–pinacolone type rearrangement. This produces the [4.2.2]propellane ketone **1**, AgBr, and HNO_3. The acid so released then catalyzes the addition of water to **1**, as per

(3) (a) Schleyer, P. v. R.; Grubmuller, P.; Maier, W. F.; Vostrowsky, O. *Tetrahedron Lett.* **1980**, 921. (b) Jaggi, F. J.; Ganter, C. *Helv. Chim. Acta* **1980**, *63*, 214.
(4) Dave, V.; Whitehurst, J. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 393.
(5) Engel, P., private communication.

(6) There are very few similar cases known. 1-Bicyclo[2.2.0]hexane carbinyl mesylate rearranges into the norbornyl system.[7a] Ring expansions of cubane carbinyl systems to homocubanes are probably of similar genre.[7b,c]
(7) (a) Dauben, W. G.; Chitwood, J. L.; Scherer, K. V., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 1014. (b) Cole, T. W., Jr. Ph.D. Thesis, University of Chicago, 1966. Eaton, P. E.; Cole, T. W., Jr., unpublished data. (c) Stock, L. M.; Cole, T. W., Jr., private communication.
(8) The degree by which ionization precedes rearrangement is not yet well-defined. There is an indication that it is substantial; solvolysis of **7c**, a secondary *p*-nitrobenzoate, is 40 times faster under the same conditions than the related primary equivalent in the Dauben study.[7a]
(9) The strain energy of the [4.2.2]propellane is estimated as not less than 52 kcal/mol. This is 21 kcal/mol greater than that calculated for tricyclo-[4.2.2.0^{1,5}]decane; see: Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005.

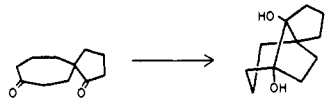
eq 3, to give the observed product. In a variant of the pinacol–pinacolone rearrangement, KO-*t*-Bu in HO-*t*-Bu converts the hydroxymesylate **3b** back to the propellane ketone **1**, isolable in good yield.

Observations of this sort suggest that if tricyclo[4.2.2.0^{1,5}]decanes functionalized like **3** could be obtained from nonpropellane precursors, we might develop a new approach to propellane synthesis. Indeed, we have done this successfully. Titanium(0) intramolecular reductive coupling[10] of spirodione **5** at high dilution gives diol **3a** (25%, nonoptimized).[11] Reaction of **3a** with mesyl chloride/triethylamine in CH_2Cl_2 forms only monomesylate **3b**. This with base (conveniently lithium aluminum hydride in ether) goes cleanly to [4.2.2]propellane alcohol **7a**. As spirodione **5** is fairly readily available by standard aldol reactions, etc. (40% overall from cyclopentanone),[13] this synthesis provides for the first time a "photochemistry-free" approach to highly strained propellanes. This should prove very useful, particularly for the preparation of more complexly substituted propellanes.

Acknowledgment. The research efforts of The Principal Investigator are supported generously by the National Science Foundation (CHE-78-07430) and the National Cancer Institute of the National Institutes of Health (CA-12961). The high-field NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and NCI via the University of Chicago Cancer Research Center (CA-14599). We thank G. H. Temme III for his contributions to the exploratory work.

(10) McMurry, J. F.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255, and references therein.

(11) We have found that expansion of **5** with ethyl diazoacetate gives, after standard manipulation, spiro[4.6]undecane-1,8-dione (i) which on reduction with Ti(0) gives tricyclo[4.3.2.0^{1,5}]undecane-5,6-diol (ii), the carbon skeleton of the tumor inhibitor quadrone.[12]



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(12) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, 499.

(13) By modification of the procedures in ref 4.

Philip E. Eaton,* Patrick G. Jobe, Kayson Nyi

Searle Chemistry Laboratory
Department of Chemistry, The University of Chicago
Chicago, Illinois 60637

Received June 18, 1980

Polymerized Vesicles[1]

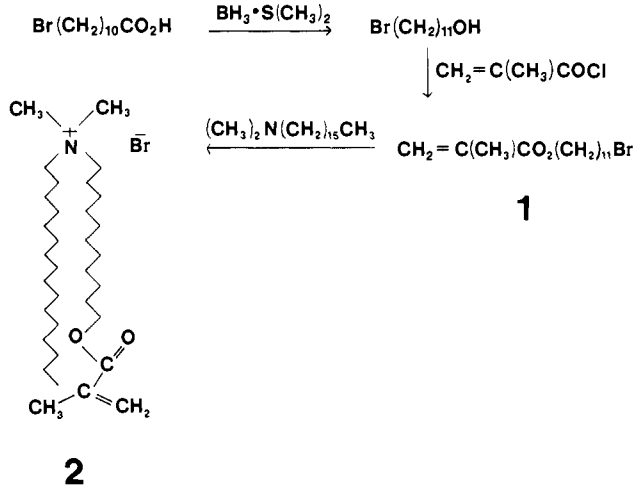
Sir:

In this communication, we introduce the concept of polymerized vesicles and report the synthesis of the first representative example.

Vesicles derived from naturally occurring phospholipids (liposomes) and synthetic surfactants are now being extensively investigated as carriers of drugs, models for biological membranes, and devices for photochemical solar energy conversion.[2-10] Because vesicles are thermodynamically unstable, however, all applications based on their long-term use are limited.[11] If vesicles could be prepared in polymerized forms, they should not only retain many of the key elements found in nonpolymerized analogues but should also be intrinsically more stable. In terms of drug delivery, they might serve as unique polydisperse, time-release carriers which, like liposomes, (1) promote the passage of drugs across cell membranes, (2) increase the plasma lifetime of the drug, (3) improve targeting prospects, and (4) retard drug catabolism.[4] They should, however, be less prone to in vivo (1) lipid-exchange processes, (2) direct removal and net transfer of lipids from vesicles, (3) uncontrolled leakage of entrapped drugs, and (4) vesicle–vesicle and vesicle–cell fusion.[12] Additionally, if polymerized vesicles promote the separation of charged photoproducts, they would be attractive candidates for practical solar energy devices.[7,9] We have been keenly interested in the concept of polymerized vesicles for these reasons and also because of the intriguing structural properties that these polymers would possess. In the following report, we present preliminary results which demonstrate the viability of our concept by showing that an ammonium surfactant can be polymerized in vesicle form and that the resulting vesicles *retain their spherical nature and aqueous interior while exhibiting enhanced stability.*

Ammonium salt **2** was synthesized by using the sequence of reactions shown in Scheme I.[13,14] Multilamellar vesicles were prepared by stirring 0.044 g (0.074 mmol) of **2** in 5 mL of D_2O at 58 °C for 10 min. Subsequent sonication (Branson LS-75, 75 W, 10 min, 58 °C, microtip probe) produced a clear stable solution, indicating the formation of small bilayer vesicles.[7] The Fourier transform ^{1}H NMR spectrum, while somewhat broadened, clearly showed the presence of the intact vinyl group (Figure 1A).

Scheme I



(1) Supported by the National Science Foundation (Grant CHE-77-28366).

(2) Bangham, A. D. *Prog. Biophys. Mol. Biol.* **1968**, *18*, 29. Bangham, A. D.; Hill, M. W.; Hill, N. G. *Methods Membr. Biol.* **1974**, *11*, 38.

(3) Papahadjopoulos, D. *Ann. N. Y. Acad. Sci.* **1978**, *308*, 1.

(4) Juliano, R. L. *Can. J. Physiol. Pharmacol.* **1978**, *56*, 683.

(5) Kunitake, T.; Okahata, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3860.

(6) Tran, C. D.; Klahn, P. L.; Romero, A.; Fendler, J. H. *J. Am. Chem. Soc.* **1978**, *100*, 1622.

(7) Fendler, J. H. *Acc. Chem. Res.* **1980**, *13*, 7.

(8) Mangel, M. *Biochim. Biophys. Acta* **1976**, *430*, 459. Toyoshima, Y.; Morino, M.; Sukigara, M. *Nature (London)* **1977**, *265*, 187. Stillwell, W.; Tien, H. T. *Biochim. Biophys. Acta* **1978**, *81*, 212. Ford, W. E.; Otvos, J. W.; Calvin, M. *Nature (London)* **1978**, *274*, 507; *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 3590.

(9) Infelta, P. P.; Gratzel, M.; Fendler, J. H. *J. Am. Chem. Soc.* **1980**, *102*, 1479. Nomura, T.; Escabi-Perez, J. R.; Sunamoto, J.; Fendler, J. H. *J. Am. Chem. Soc.* **1980**, *102*, 1484.

(10) Weinstein, J. N.; Magin, R. L.; Yatvin, M. B.; Zaharko, D. S. *Science (Washington, D.C.)* **1979**, *204*, 188.

(11) On prolonged standing, vesicles undergo fussion.[7]

(12) For an excellent review of vesicle–cell interactions, see: Poste, G.; Papahadjopoulos, D., ref 3, p 164.

(13) Procedures used for reduction of the carboxylic acid were identical with those previously described: Lane, C. F. *Aldrichimica Acta* **1975**, *8*, 20.

(14) **1**: ^{1}H NMR ($CDCl_3$) δ 6.08 (m, 1 H, vinyl), 5.50 (m, 1 H, vinyl), 4.13 (t, 2 H, $-OCH_2CH_2$), 3.39 (t, 2 H, CH_2Br), 1.94 (m, 3 H, $CH_3C=$), 2.0–1.1 (br m, 18 H, CH_2); anal. ($C_{15}H_{27}BrO$) C, H. **2**: ^{1}H NMR ($CDCl_3$) δ 6.08 (m, 1 H, vinyl), 5.52 (m, 1 H, vinyl), 4.15 (t, 2 H, $-OCH_2CH_2$), 3.65 (br m, 4 H CH_2^+N), 3.42 (s, 6 H, CH_3^+N), 1.95 (m, 3 H, $CH_3C=$), 2.0–1.1 (br m, 46 H, CH_2), 0.9 (m, 3 H, CH_3); anal. ($C_{33}H_{66}NO_2Br\cdot{}^1/_2H_2O$) C, H.

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