Table I. Effect of Buffer Composition on the Endo- and Exovesicular Rates of Hydrolysis of DTNB[c]

buffer composition[a]	pH	DODAC (M) × 10^5	k_1[b] (s^{-1}) × 10^3	k_2[b] (s^{-1}) × 10^3	$\frac{k_2}{k_1}$
borate 5 mM, NaCl 2.5 mM	9.2	5.3	2.0	5.6	2.8
borate 5 mM, NaBr 2.5 mM	9.2	5.3	1.8	3.7	2.1
NaOH 1 mM, NaCl 4 mM	10.9	5.3	2.0	180	90
NaOH 1 mM, NaBr 4 mM	10.8	5.3	3.3	44	13.3
triethylammine·HCl 5 mM	9.7	5.3	7.8	13	1.7
triethylammine·HBr 5 mM	9.7	5.3	6.2	3.9	0.6
triethylammine·HCl 10 mM	10.8	13	72	160	2.2
triethylammine·HBr 10 mM	10.9	13	98	63	0.6

[a] All buffer, vesicle, and salt solutions contained erythritol (90 mM). [b] Observed pseudo-first-order rate constants for the endovesicular (k_1) and exovesicular (k_2) reactions, respectively. [c] DTNB concentration was 2.0 × 10^{-6} M for both endo- and exovesicular reactions. The second-order rate constant for the alkaline hydrolysis of DTNB, calculated from ref 3, was 0.818 M^{-1} s^{-1} (30 °C).

hydrolysis at high pH in the absence of buffer may be attributed to rate-limiting $^-$OH permeation. Endovesicular rates limited by $^-$OH diffusion have been reported.[5c] Buffers containing neutral species can accelerate the rate of $^+$H/$^-$OH permeation across bilayers.[5b,12] The similarity of endo and exovesicular rates in this system can be understood in terms of similar reactivities at the inner and outer surfaces and of faster permeation rates for $^-$OH with buffers.

Addition of bromide produced a decrease in the rate of the exovesicular reaction, not affecting the endovesicular process (Figure 1A, Table I). The ratio between the exo- and endovesicular rate constants (k_2/k_1) can even be reversed by the addition of external salts (Table I). The inhibitory effect at the outer surface was attributed to a $^-$OH/$^-$Br exchange.[13] The permeability of halide ions is (at least) 1000 times less than $^+$H/$^-$OH for the same bilayer.[14] Therefore a bromide inhibitory effect on the endovesicular reaction was not to be expected since the (externally) added ion did not penetrate during reaction.

The DODAC concentration-dependence of the exovesicular reaction was identical with that previously reported[3] (Figure 1C). The endovesicular rate constant decreased slightly with [DODAC] irrespective of the buffer (Figure 1C). These results were rationalized by using the pseudophase ion-exchange formalism.[13] Thus, an increase in [DODAC] leads exclusively to a displacement of the externally bound $^-$OH since the concentration of free $^-$Cl increases with [DODAC] only in the external aqueous compartment. Since the concentration of free $^-$Cl in the internal aqueous compartment does not change with [DODAC] the local concentration of (internally) bound $^-$OH was not a sharp function of [DODAC]. The small decrease of the exovesicular rate constant with [DODAC] can be attributed to the lower local concentration of externally bound $^-$OH and thus a lower $^-$OH penetration rate.

In conclusion, we have demonstrated that the effects of the internal and external surfaces of DODAC vesicles on the alkaline hydrolysis of DTNB are similar. Moreover these results show that the rate of the endo- and exovesicular reactions can be controlled by the rate of reagent permeation and also by the nature (and concentration) of the ions present in both inner and outer aqueous compartments. Since vesicles prepared with synthetic amphiphiles are extremely efficient catalysts,[1-6] the control of both site and rate of reaction opens new perspectives in the understanding and use of these and other microreactors.

Acknowledgment. This work was partially supported by grants from FAPESP, FINEP, and CNPq. We thank Dr. M. Armelin for her help with this manuscript.

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(12) Bramhal, J. *Biochim. Biophys. Acta* **1984**, *778*, 393.

(13) Quina, F. H.; Chaimovich, H. *J. Phys. Chem.* **1979**, *83*, 1844.

(14) (a) Papahadjopoulos, D.; Jacobson, K.; Nir, S.; Isaac, T. *Biochim. Biophys. Acta* **1975**, *311*, 330. (b) Bramhall, J.; Hofmann, J.; DeGuzman, R.; Montestruque, S.; Schell, R. *Biochemistry* **1987**, *26*, 6330. (c) Bramhall, J. *Biochemistry* **1987**, *26*, 2848.

Double Alkylation of α,β-Unsaturated Acetals. An Inverse Polarity Approach

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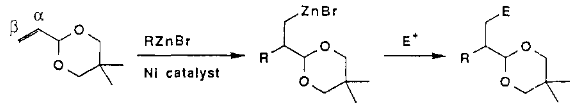
Regiochemistry of enolate formation-alkylation sequence (double alkylation) can often be controlled very effectively via Michael additions:[1] Noyori's prostaglandin synthesis immediately comes to mind.[2] Reported herein is an umpolung[3] version of the process, and the general scheme is illustrated below.

We have found that an α,β-unsaturated acetal undergoes rapid metalation upon treatment with allylzinc in the presence of nickel catalyst. Allylzinc reagent, as a nucleophile, attacks at α carbon of the acetal **1**, and then the resulting carbanion at β-position reacts with a variety of electrophiles to afford α,β-dialkylated acetal effectively, eq 1.



1

(1)

Copper-[4] or nickel-[5]catalyzed reaction of the Grignard reagent with α,β-unsaturated acetals was reported to produce only the corresponding Michael-type addition (β-alkylation) products in moderate yields. In some cases, the more reactive allylic Grignard reagent reacts with nonactivated double bonds.[6] Allylic zinc reagents, in contrast, are relatively unreactive toward alkenic bonds.[6b,7]

Treatment of 1 equiv of α,β-unsaturated acetal with a solution of allylzinc bromide (3.5 equiv) in CH_2Cl_2[8] under the influence

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(1) Stork, G.; Rosen, P.; Goldman, N. L. *J. Am. Chem. Soc.* **1961**, *83*, 2965. Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275. Posner, G. H. *Org. React.* **1972**, *19*, 1. Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.

(2) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847.

(3) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.

(4) Normant, J. F.; Commercon, A.; Bourgain, M.; Villieras, J. *Tetrahedron Lett.* **1975**, 3833. See also: Commercon, A.; Bourgain, M.; Delaumeny, M.; Normant, J. F.; Villieras, J. *Tetrahedron Lett.* **1975**, 3837.

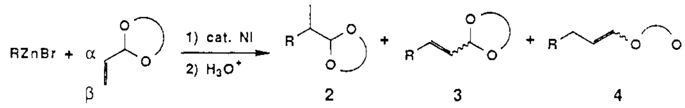
(5) Wenkert, E.; Ferreira, T. W. *Organometallics* **1982**, *1*, 1670. See, also: Menicagli, R.; Malanga, C.; Finato, B.; Lardicci, L. *Tetrahedron Lett.* **1988**, *29*, 3373.

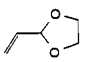
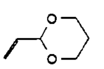
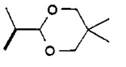
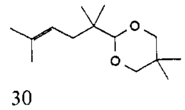
(6) (a) Lehmkuhl, H.; Reinehr, D. *J. Organomet. Chem.* **1970**, *25*, C47; **1972**, *34*, 1; **1973**, *57*, 29. Lehmkuhl, H.; Reinehr, D.; Henneberg, D.; Schroth, G. *J. Organomet. Chem.* **1973**, *57*, 49. Lehmkuhl, H.; Reinehr, D. Schomburg, G.; Henneberg, D.; Damen, H.; Schroth, G. *Liebigs Ann. Chem.* **1975**, 103. Lehmkuhl, H.; Reinehr, D.; Henneberg, D.; Schomburg, G.; Schroth, G. *Liebigs Ann. Chem.* **1975**, 119. Lehmkuhl, H.; Bergstein, W.; Henneberg, D.; Janssen, E.; Olbrysch, O.; Reinehr, D.; Schomburg, G. *Liebigs Ann. Chem.* **1975**, 1176. Lehmkuhl, H.; Janssen, E. *Liebigs Ann. Chem.* **1978**, 1854. (b) Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1. Lehmkuhl, H. *Bull. Soc. Chim. Fr. II* **1981**, 87.

(7) A substitution reaction between phenylzinc chloride and α,β-unsaturated acetals or ortho esters in the presence of a Pd catalyst was known, see: Chatterjee, S.; Negishi, E. *J. Org. Chem.* **1985**, *50*, 3406.

0002-7863/89/1511-0366$01.50/0

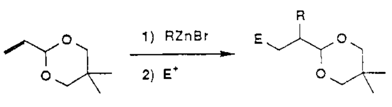
Table I. Regioselective Alkylation of α,β-Unsaturated Acetals[a]

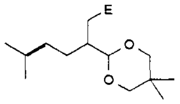
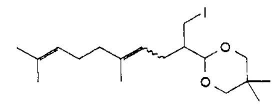
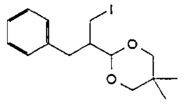


entry	RZnBr[b]	acetal	product (% yield)[c] α-adduct **2**	β-adduct **3**	 **4**
1	$PhCH_2ZnBr$	**1**	51	13	26
2[d]	$PhCH{=}CH{-}CH_2ZnBr$	**1**	46[e]	0	26
3	$CH_2{=}CH{-}CH_2ZnBr$	**1**	<2	0	0
4	$(CH_3)_2C{=}CH{-}CH_2ZnBr$		28[e]	0	43
5	$(CH_3)_2C{=}CH{-}CH_2ZnBr$		35[e]	2[e]	22
6	$(CH_3)_2C{=}CH{-}CH_2ZnBr$	**1**	60[e]	4[e]	26
7	$(CH_3)_2C{=}CH{-}CH_2ZnBr$		 30	0	0
8	geranylzinc bromide	**1**	62[e]	6[e]	26

[a] Unless otherwise specified, alkylation was carried out by adding an acetal (1 equiv) to a mixture of alkylzinc bromide (3.5 equiv) and $NiBr_2(PBu_3)_2$ (0.1 equiv) in CH_2Cl_2 at 40 °C for 30–40 min. [b] Prepared by treatment of activated zinc powder with the corresponding alkyl bromide in THF at 10–15 °C for 30–60 min. [c] Isolated yield. [d] The reaction was carried out at 40 °C for 2 h. [e] The allylic zinc reagent reacted at the primary carbon.

Table II. One-Pot Double Functionalization of α,β-Unsaturated Acetals[a]



entry	RZnBr	electrophile	condition, (°C, h)	product	yield[b] (%)
1	$(CH_3)_2C{=}CH{-}CH_2ZnBr$	D_2O	15, 0.5	 E = D	41
2	$(CH_3)_2C{=}CH{-}CH_2ZnBr$	I_2[c]	0, 0.3	E = I	60
3	$(CH_3)_2C{=}CH{-}CH_2ZnBr$	CH_3I/HMPA[d]	25, 16	E = CH_3	50
4	$(CH_3)_2C{=}CH{-}CH_2ZnBr$	$H_2C{=}CH_2CH_2I$/ CuCN·2LiCl[e]	-20, 0.3 25, 14	E = $CH_2{-}CH{=}CH_2$	45
5	$(CH_3)_2C{=}CH{-}CH_2ZnBr$	$HC{\equiv}CCH_2Br$/ CuCN·2LiCl[f]	-20, 1 0, 2	E = $CH{=}C{=}CH_2$	30
6	geranylzinc bromide	I_2[c]	0, 0.2		60
7	$PhCH_2ZnBr$	I_2[c]	0, 0.3		49

[a] Unless otherwise noted, the reaction was carried out by using an alkylzinc bromide, acetal, and $NiBr_2(PBu_3)_2$ (3.5, 1, and 0.1 equiv each) at 40 °C for 40 min followed by addition of the electrophile. [b] Isolated yield. [c] 2 equiv of I_2 were used. [d] Methylation was carried out by using 10 equiv of CH_3I and a large excess of HMPA. [e] Allylation was carried out by using an allyl iodide, CuCN, and LiCl (10, 1, and 2 equiv each). [f] Allenylation was carried out by using a propargyl bromide, CuCN, and LiCl (8, 1, and 2 equiv each).

of catalytic $NiBr_2(PBu_3)_2$ (10 mol %) at 40 °C for 30 min gave a mixture of the α-adduct **2** and the β-adducts **3** and **4** in fair to good combined yields (Table I).[9] The new process disclosed herein exhibited the following characteristic features: (1) Choice of acetal is crucial for obtaining the α-alkylated acetal **2** selectively, and the acetal derived from 2,2-dimethyl-1,3-propanediol is effective for this purpose (entries 4–6). (2) Various types of reactive zinc reagents are applicable to this process. Unfortunately, however, allylzinc bromide is less effective for the alkylation process (entry 3). (3) The reaction between the α-alkylated α,β-unsaturated acetal and 3-methyl-2-butenylzinc bromide afforded the α-adduct exclusively (entry 7).

The in situ generated zinc homoenolate was trapped efficiently with D_2O or I_2 to afford the corresponding deuteriated or halogenated products (Table II, entries 1, 2, 6, and 7). Similarly, treatment of β-zincioacetal with an excess of iodomethane in HMPA (25 °C, 16 h) furnished the methylated product (entry 3).[10,11] Transmetalation with CuCN·2LiCl according to the

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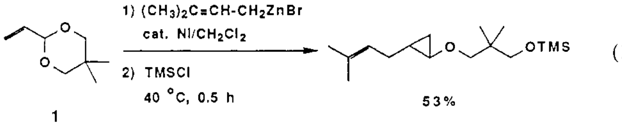
[8] A solution of 3-methyl-2-butenylzinc bromide in CH_2Cl_2 was prepared as follows: A suspension of zinc dust (73.9 mg, 1.13 mmol) in 2 mL of THF containing 47.0 mg (0.25 mmol) of 1,2-dibromoethane was heated to reflux for a few minutes, and cooled to 25 °C, and 0.103 mL (0.88 mmol) of 1-bromo-3-methyl-2-butene was added at 0 °C. After the mixture was stirred at 0 °C for 40 min, most of the THF was removed by concentration in vacuo. The remaining sticky gray solid was dissolved with dry CH_2Cl_2 (2 mL). The resulting greenish gray solution was ready to use.

[9] Without a Ni catalyst no addition reaction proceeds below 100 °C.

procedure of Normant[12] followed by allylation or allenylation proceeds smoothly (entries 4 and 5).

Upon heating, the zinc homoenolate was eliminated to give the α-alkylated α,β-unsaturated acetal. Such dehydrometalation could be suppressed completely below room temperature. Noteworthy is the fact that an additive TMSCl facilitates an intramolecular alkylation to afford exclusively the corresponding cyclopropanol derivative (eq 2).



(2)

Acknowledgment. Partial financial support from the Ministry of Education, Japanese Government, is gratefully acknowledged.

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(10) For alkylation of zinc homoenolate, see: (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368. Oshino, H.; Nakamura, E.; Kuwajima, I. *J. Org. Chem.* **1985**, *50*, 2802. Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 83. Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056. (b) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5559. Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955. Ochiai, H.; Tamaru, Y.; Tsubaki, K.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4418. Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1157. Ochiai, H.; Nishihara, T.; Tamaru, Y.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 1343. Tamaru, Y.; Nakamura, T.; Sakaguchi, M.; Ochiai, H.; Yoshida, Z. *J. Chem. Soc., Chem. Commun.* **1988**, 610. For similar reactions, see: (c) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, 2395. Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(11) A representative experimental procedure is given by the prenylation–methylation sequence of 5,5-dimethyl-2-vinyl-1,3-dioxane (**1**) (entry 3 in Table II). To a solution of 3-methyl-2-butenylzinc bromide (0.88 mmol)[8] in CH_2Cl_2 (2 mL) was added catalytic $NiBr_2(PBu_3)_2$ (15.6 mg, 0.025 mmol) at 25 °C. After 10 min, 5,5-dimethyl-2-vinyl-1,3-dioxane (**1**) (35.6 mg, 0.25 mmol) was added at 25 °C, and the resulting mixture was stirred at 40 °C for 40 min. Zinc homoenolate, thus obtained, was methylated by adding a mixture of CH_3I (0.156 mL, 2.5 mmol) and HMPA (1.04 mL, 6 mmol) at 25 °C for 16 h. The mixture was poured into saturated NH_4Cl aqueous solution and extracted with ether. The combined extracts were dried and concentrated, and the product was purified by column chromatography on silica gel (AcOEt/hexane = 1:20) to give 5,5-dimethyl-2-(1′-ethyl-4′-methyl-3′-pentenyl)-1,3-dioxane (28.3 mg, 50% yield) as a colorless oil.

(12) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 4427, 4431, 5727.

Photochemical Generation of Bicyclo[4.2.2]decapentaene from [4.2.2]Propella-2,4,7,9-tetraene. Preference of [4]Paracyclopha-1,3-diene Structure over Bicyclo[4.2.2]deca-1,3,5,7,9-pentaene Structure

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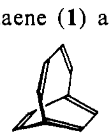
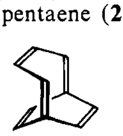
Geometrically distorted unsaturated compounds have attracted considerable attention in recent years. The hitherto unknown bicyclo[4.2.2]decapentaene is of particular interest because at least two unique alternative structures, namely, bicyclo[4.2.2]deca-1(8),2,4,6,9-pentaene (**1**) and -1,3,5,7,9-pentaene (**2**), are conceivable. The former is [4]paracyclophadiene,[1] whereas the latter may be viewed as 1,6-etheno bridged *cis,trans,cis,trans*-cyclooctatetraene.[2] Both structures feature two bridgehead double bonds and are expected to be highly reactive. In this communication we report that the photochemical transformation of [4.2.2]propella-2,4,7,9-tetraenes, **3a**[3] and **3b**,[4] leads to bicyclo[4.2.2]decapentaenes which are best represented by the structures **1a** and **1b**, respectively.

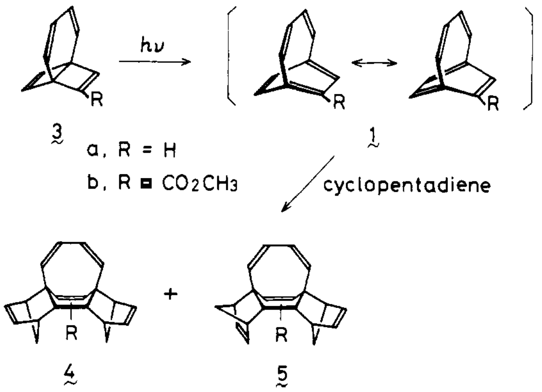


1



2

Irradiation of a mixture of **3a** and cyclopentadiene in hexane with a high pressure mercury lamp through Pyrex at 0 °C led to the formation of two 2:1 adducts of cyclopentadiene to **3a** (63% yield) in a ratio of ca. 1:2. The minor and major products were assigned as **4a** and **5a**, respectively, on the basis of their spectral data.[5] Thus, the cleavage of the central σ bond of **3a** and the subsequent Diels–Alder addition of two molecules of cyclopentadiene to the bridgehead double bonds of resultant **1a** were unambiguously established primarily by the following observations: (1) the ^{1}H NMR spectra of **4a** and **5a** each consisted of ten olefinic and ten aliphatic proton absorptions, (2) ^{1}H NMR signals characteristic of a norbornene ring, and (3) the very similar UV spectra of **4a** and **5a** showing λ_{max} at ca. 270 nm (ϵ ~4000) which indicated the intactness of the conjugated diene moiety of **3a**. The simple ^{1}H and ten line ^{13}C NMR spectra of the minor product were compatible only with a symmetrical structure, and close examination of the ^{1}H NMR permitted the assignment of **4a** as a diexo adduct. Virtually no volatile products other than **4a** and **5a** were detected in the product mixture. The photochemical reaction of **3b** with cyclopentadiene similarly afforded a mixture of **4b** and **5b** together with their secondary products[6] in a combined yield of 40%. In no case was any adduct derived from **2** detected.[7]



In addition to the aforementioned trapping experiments, the formation of **1** was supported by a spectroscopic study. When **3a** in an EPA[9] glass was irradiated with a low-pressure mercury lamp (254 nm) at 77 K, an absorption showing λ_{max} at 274 and 347 nm appeared (Figure 1a).[10,11] The species generated was stable at 77 K in the dark but underwent complete decomposition when the frozen glass was thawed below −100 °C. The transient was also photochemically susceptible, and, upon irradiation with

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(1) Generation of [4]paracyclophane as a transient was very recently confirmed. (a) Tsuji, T.; Nishida, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1189. *J. Am. Chem. Soc.* **1988**, *110*, 2157. (b) Kostermans, G. B. M.; Bobeldijk, M.; De Wolf, W. H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1987**, *109*, 2471.

(2) *cis,trans,cis,trans*-Cyclooctatetraene is not yet known.

(3) Tsuji, T.; Nishida, S. *Tetrahedron Lett.* **1983**, *24*, 3361.

(4) Tsuji, T.; Komiya, Z.; Nishida, S. *Tetrahedron Lett.* **1980**, *21*, 3583.

(5) See Supplementary Material.

(6) Products via di-π-methane rearrangement and intramolecular [2 + 4] cycloaddition.[5]

(7) Examination of molecular models (FMM; Prentice-Hall: Englewood Cliffs, NJ) indicates that addition of two molecules of cyclopentadiene to the bridgehead double bonds of **2** is not sterically hindered and effectively relieves the steric strain inherent in **2**. It should also be pointed out that a bridgehead olefin of a related structure undergoes ready cycloaddition with cyclopentadiene.[8]

(8) Wiberg, K. B.; Matturro, M. G.; Okarma, P. J.; Jason, M. E. *J. Am. Chem. Soc.* **1984**, *106*, 2194.

(9) A 5:5:2 mixture of ether, isopentane, and ethanol.

(10) The absorption spectra of the transients in Figure 1 were obtained by correcting difference spectra (before and after the 254-nm light irradiation) for the consumption of **3**. The conversion of **3a** determined by GLC using decane as an internal standard was 8% and that of **3b** using tetraglyme as an internal standard was 22%.

(11) Molar absorptivity at 274 nm was estimated to be ca. 5000.

0002-7863/89/1511-0368$01.50/0