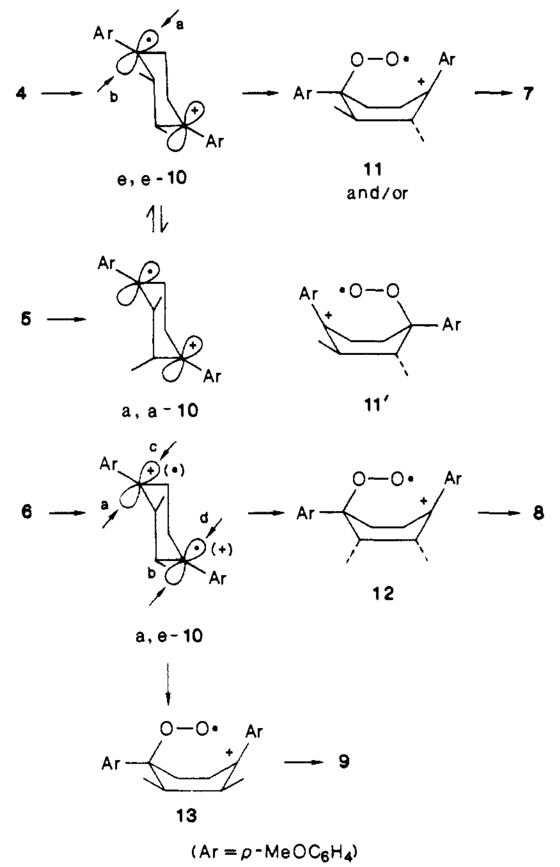
Scheme III



acetonitrile under the DCA-sensitized conditions **1a** and **1b** gave **3a**[12] and **3b**[12] in 6% and 72% yields, respectively. The yield of **3a** was increased to 48% by the addition of $Mg(ClO_4)_2$.[13]

If the initial cyclization occurs in a stereospecific manner, its stereochemical integrity should be conserved in the oxygenation product. In order to test this, the direct molecular oxygen trapping of intermediates was further applied for (*Z*,*Z*)-, (*E*,*E*)-, and (*E*,*Z*)-3,6-bis(*p*-methoxyphenyl)-2,6-octadienes (**4**), (**5**), and (**6**).[14] Observed stereochemical consequences were shown in Scheme II. Upon irradiation under similar oxygenation conditions, both the symmetrical **4** and **5** gave rise to the trans adduct **7**[12] in 72% and 80% yields, respectively, while a mixture of the *exo–cis*-**8** (58%)[12] and *endo–cis*-**9** (14%)[12] was obtained from **6**. The structure of **8** was determined by X-ray crystallographic analysis, and the unequivocal stereochemical assignments for **7** and **9** were obtained by comparisons of the ^1H NMR spectrum of **8** with those of **7** and **9** and by the observations of the NOE between the exo-C_5–CH_3 and exo-C_8–H for **7** and **8** but not for **9**. The stereospecific formations of those oxygenation products well rationalize the initial stereospecific formations of the chair cyclohexane-1,4-radical cations as shown in Scheme III.

The initial cyclizations of $4^{\bullet+}$ and $5^{\bullet+}$ give e,e-**10** and a,a-**10**, respectively. The oxygenation occurs at two sites, i.e., a and/or b in the more stable e,e-**10**. The subsequent recyclization through **11** and/or **11′**, thus, can afford the trans adduct **7**. On the other hand, oxygen can capture a,e-**10** from **6** at four different sites. Peroxyradical cation **12** captured at the less hindered site, i.e., a and/or b, recyclizes to afford **8** as a major product. The minor cis adduct **9** can be derived in a similar way from peroxyradical cation **13** captured at the more hindered site, i.e., c and/or d. Finally, it is of interest to note that the results of the Ce^{IV}-catalyzed reaction of 2,5-diphenyl-1,5-hecadiene[16] significantly differ from those of our photosensitized reactions.

Supplementary Material Available: X-ray experimental details for **8**, ^1H and ^{13}C NMR spectral data of 3,6-diaryl-2,6-octadienes and oxygenation products (**3a**, **3b**, and **4–9**), and listings of atomic positional parameters, anisotropic temperature factors, mean square displacement tensors, and bond lengths and bond angles (10 pages); listing of observed and calculated structure factors (18 pages). Ordering information is given on any current masthead page.

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[11] Guo, Q.-X.; Qin, X.-Z.; Wang, J. T.; Williams, F. *J. Am. Chem. Soc.*, in press. We thank Professor Williams for his generous offer of their EPR results before publication.

[12] Satisfactory elemental analyses and correct mass spectral data were obtained for all new compounds in this report, **3a** (mp 188–193 °C dec), **3b** (mp 198–204 °C dec), **4** (mp 55–56 °C), **5** (mp 86–87 °C), **6** (mp 52–54 °C), **7** (mp 197–199 °C), **8** (mp 195–196 °C), and **9** (mp 181–182 °C). **3a** was independently synthesized by the diimide reduction of 1,4-diphenyl-2,3-dioxabicyclo[2.2.2]oct-5-ene prepared by the dye-sensitized oxygenation of 1,4-diphenylcyclohexa-1,3-diene. The structures and stereochemical assignments of those compounds were unequivocally determined by the ^1H and ^{13}C NMR.

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[14] **4**, **5**, and **6** were prepared by the Wittig reaction of 1,4-bis(*p*-methoxyphenyl)butane-1,4-dione and ethyltriphenylphosphonium iodide by using *t*-BuOK in tetrahydrofuran in 42% 5%, and 17% yields, respectively. Stereochemical assignments are in agreement with those in previous reports.[15]

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Absence of a Common Ion Effect on the Hydrolysis of an α-Azido Ether of an Aliphatic Aldehyde[1]

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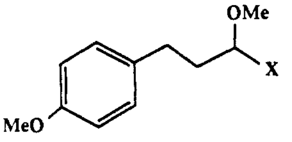
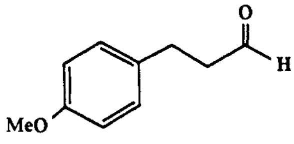
Hydrolysis of simple aliphatic acetals[2] and of the corresponding enol ethers[3] is widely believed to proceed via an oxocarbonium ion intermediate that reacts with water to give, ultimately, a common aldehyde product. Estimates of the stability of this intermediate have given rate constants for its reaction with water[4-6] ranging from $<5 \times 10^6$ to $\sim 10^{11}$ s^{-1}. We report here that there is no detectable trapping of an oxocarbonium ion intermediate, $RCH{=}OMe^+$, by 1 M azide ion, as determined by two different techniques. Added azide ion at constant ionic strength has little or no effect on the observed rate of solvolysis in aqueous solution of the α-azido ether **2**, and we use this fact to set an upper limit of 5×10^{-11} s for the lifetime of the putative oxocarbonium ion intermediate.



1 X = OAc
2 X = N_3



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A rate constant for the addition of water to protonated acetaldehyde of $<5 \times 10^6$ s^{-1} was estimated from the observed rate

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[1] Supported in part by grants from the National Institutes of Health (GM 20888) and the National Science Foundation (PCM 8117816).

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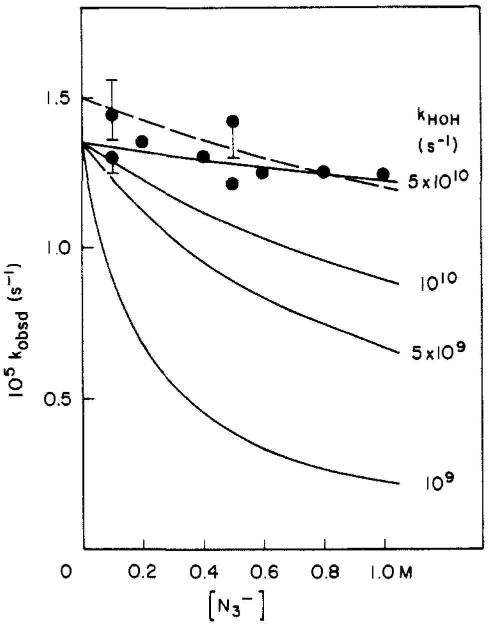
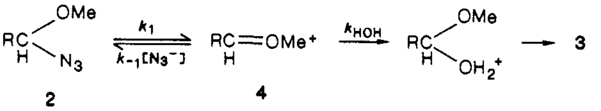


Figure 1. Dependence of k_{obsd} on the concentration of azide ion for the hydrolysis of **2** at 25 °C and ionic strength 1.0 M ($NaClO_4$). Less certain determinations are shown with attached error bars. The solid lines are theoretical curves derived from eq 2 with $k_1 = 1.35 \times 10^{-5}$ s^{-1}, $k_{-1} = 5 \times 10^9$ M^{-1} s^{-1}, and various values of k_{HOH}. The dashed line illustrates the fit of the data to eq 2 with $k_1 = 1.5 \times 10^{-5}$ s^{-1} and a limiting value of $k_{HOH} = 2 \times 10^{10}$ s^{-1}.

constant for the acid-catalyzed hydration of acetaldehyde and an estimated pK_a of −3.8 for protonated acetaldehyde.[6,7] However, Salomaa and Kankaanperä[4,8] suggested a rate constant of $\geq 10^{10}$ s^{-1} for the addition of water to $CH_3CH{=}OEt^+$, and the addition of methanol to a similar intermediate is at least as fast as bond rotation in the oxocarbonium ion.[9] Young and Jencks[5] predicted a rate constant of $\sim 10^{11}$ s^{-1} for addition of water to such an intermediate from the extrapolation of a linear free-energy relationship between rate constants for attack of water on the oxocarbonium ion intermediate derived from acetophenone dimethyl ketals, in the range 7×10^6–4×10^8 s^{-1}, and for the attack of sulfite dianion on the corresponding ketones.

The lifetime of such an intermediate can be obtained directly by exploiting the effect of added azide as a common ion; any nucleophilic substitution by azide ion is then a degenerate reaction. The azido compound **2** was generated in water from the bimolecular reaction of azide ion with the 150-fold more reactive acylal **1**[10] at 25 °C and ionic strength 1.0 M ($NaClO_4$).[11] At 1 M NaN_3 the yield of **2** from **1** is 48%,[12] and the rate[13] increases 1.8-fold, which predicts a yield of 45%. The remaining portion of **1** undergoes hydrolysis to yield the aldehyde **3**. These facts and the lesser effects of other nucleophilic reagents show that the reaction of **1** with azide ion is bimolecular and that there is no detectable trapping of any intermediate by azide ion. The ensuing hydrolysis of **2** was monitored by HPLC analysis,[14] which yielded first-order rate constants, k_{obsd}, for its breakdown to **3**.

Figure 1 shows that there is little or no inhibition of the hydrolysis of **2** by 0–1 M azide ion. Theoretical curves for the observed rate constants calculated from eq 2 based on the reaction scheme of eq 1 are drawn with $k_1 = 1.35 \times 10^{-5}$ s^{-1},[15] a value[16]



(1)

$$k_{obsd} = k_1 k_{HOH}/(k_{-1}[N_3^-] + k_{HOH}) \qquad (2)$$

of $k_{-1} = 5 \times 10^9$ M^{-1} s^{-1}, and various values of k_{HOH} (solid lines). These illustrate the expected rate depressions caused by azide ion for an intermediate **4** of varying reactivity toward water.

The best fit to the data is obtained with a value of $k_{HOH} = 5 \times 10^{10}$ s^{-1} (Figure 1), which corresponds to a partitioning ratio between diffusional trapping by azide ion and trapping by solvent water of $k_{-1}/k_{HOH} = 0.1$ M^{-1}. The dashed line represents a slightly higher value of k_1 combined with the lower limit of $k_{HOH} = 2 \times 10^{10}$ s^{-1}. Therefore, the upper limit on the lifetime of the putative oxocarbonium ion intermediate **4** in aqueous solution is ≤ 2–5×10^{-11} s. This agrees surprisingly well with the earlier predicted value.[5]

It is unlikely that a specific salt effect is responsible for the lack of inhibition of the hydrolysis of **2** or for the observed rate increase on the reaction of azide with **1**, since no effect on the rate of solvolysis of **1** was found in the presence of 0–2 M $NaClO_4$. Thus we can say that no oxocarbonium ion intermediate with a lifetime long enough to allow diffusion up to added solutes is formed in the hydrolysis of simple acetal derivatives.

It appears, then, that simple protonated aldehydes are $>10^4$-fold less reactive toward water than the oxocarbonium ions described here. This may result in part from use of an erroneous pK_a for protonated acetaldehyde, but it is unlikely that this could account for such a large effect. The acid-catalyzed ketonization of simple enols is 15–150-fold faster than ketonization of the corresponding methyl or ethyl enol ethers.[20-22] The inductive effects of H and CH_3 are similar,[23] so that the remarkably large ratio of $>10^4$ for

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(7) Levi, A.; Modena, G.; Scorrano, G. *J. Am. Chem. Soc.* **1974**, *96*, 6585–6588.

(8) This estimate is based on an elegant thermodynamic analysis of ground-state and transition-state energies for the hydrolysis of diethyl acetal and ethyl vinyl ether, which is based on a "first approximation" that the ratio of susceptibility to structural variation in the reactants, $\partial \Delta G_1^{\neq}/\partial \Delta G_2^{\neq}$, in the two reaction series is equal to $\Delta G_1^{\neq}/\Delta G_2^{\neq}$ for the reaction of the cation.[4] However, the estimate is uncertain because it is based on data for hydrolysis of substituted formals, not acetals, and no account is taken of the difference in entropy that arises from partially bonded ethanol in one and free ethanol in the other transition state. A similar estimate obtained from a correlation of carbocation stabilities with estimated rate constants for their formation[4] is also uncertain because substituent effects on the stabilities are much larger than on the rate constants.[17b]

(9) Gupta, R. B.; Franck, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 5393–5403.

(10) The acylal was synthesized by reaction of the corresponding α-chloro ether with 1 equiv of silver acetate in acetonitrile at room temperature. The α-chloro ether was prepared by the action of boron trichloride on the dimethyl acetal derived from **3**: Goff, D. A.; Harris, R. N., III; Bottaro, J. C.; Bedford, C. D. *J. Org. Chem.* **1986**, *51*, 4711–4714. **3** was prepared by pyridinium dichromate oxidation of 3-(4-methoxyphenyl)-1-propanol: Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.

(11) Solvolysis to generate **2** was carried out in solutions of NaN_3 at various concentrations with ~0.1–0.5 mM **1** and ca. 0.08 mM 3-(4-methoxyphenyl)-1-propanol, which was present as an injection standard for HPLC analysis.

(12) Determined by conversion of the aldehyde **3** to the semicarbazone followed by HPLC analysis with a Waters Associates reverse-phase octadecylsilane chromatography column (Nova-Pak™ C_{18} 4μ) and elution with $MeCN/H_2O$.

(13) The reaction of **1** was monitored spectrophotometrically by following proton release with phenolate as an indicator and ~0.1 mM substrate.

(14) For reactions in which **3** constituted a large proportion of the product mixture the 0.2-mL aliquots were treated with ca. 2 μL of 1 M sulfite buffer, 80% dianion, just prior to analysis in order to convert **3** to the anionic α-hydroxysulfonate and prevent interference of the analysis by aldehyde.

(15) Intercept of the line obtained by linear least-squares analysis of the data.

(16) Several lines of evidence suggest that the reaction of azide ion with unstable carbocations is diffusion controlled,[17,18] and the value of $k_{-1}/k_{HOH} = 0.1$ M^{-1} is much smaller than that ($\sim 10^6$ M^{-1}) for the activation-limited reactions of the more stable triarylmethyl carbocations.[19]

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addition of water to the two oxocarbonium ions, **4** and the protonated aldehyde, represents a lower limit for stabilization of the protonated intermediate by a strong hydrogen bond to solvent water. This will increase the O–H distance and decrease the positive charge on the carbonyl oxygen.

We conclude that the hydrolysis of acetal derivatives does not proceed via diffusionally equilibrated oxocarbonium ions. At this point, however, it is not possible to rule out an intermediate with a lifetime of less than ca. 10^{-11} s^{-1} or the possibility that the reaction with solvent is concerted with no oxocarbonium ion intermediate.[24]

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(23) The σ_I values for H and Me are 0 and −0.04, respectively; Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; Wiley-Interscience: New York, 1975; p 98.

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The First Fluorinated Cyclams

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Cyclam (1,4,8,11-tetraazacyclotetradecane) (**10**) has long been the most useful and versatile prototype in macrocyclic ligands for fundamental as well as applied coordination chemistry.[1] Recently, functionalization of its basic structure by incorporation of carbonyl group(s) adjacent to its amines, e.g., dioxocyclam (5,7-dioxo-1,4,8,11-tetraazacyclotetradecane) (**6**),[2] or by attachment of pendant donors such as phenol,[3,4] catechol,[5] pyridine,[6] and imidazole[7] to its carbon skeleton have added new dimensions to cyclam chemistry.

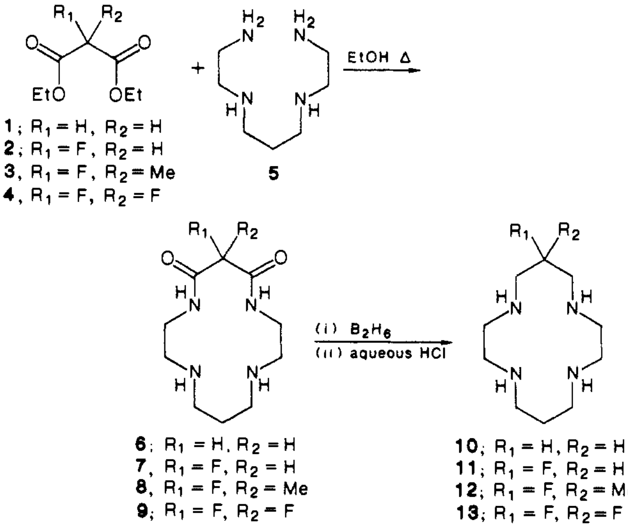
Now, for the first time, we report fluorine-containing cyclams **11–13** and dioxocyclams **7–9**. Their easy synthesis and novel properties indeed indicate the fluorination to be a new strategy for further extension of macrocyclic polyamines.

Table I. pK_a Values at I = 0.1 M ($NaClO_4$) and 25 °C and Infrared Spectra Data of Free Ligands

ligand	pK_1	pK_2	pK_3	pK_4	$\nu_{C=O}{}^a$ cm^{-1}
6	9.63	5.85			1660
7	9.37	5.65			1685
8	9.56	5.53			1680
9	9.22	5.18			1710
10	11.78	10.55	<2	<1	
11	10.96	9.41	<2	<1	
12	11.34	9.69	<2	<1	
13	10.78	7.52	<2	<1	

[a] Nujol.

6-Fluoro-(**7**), 6-fluoro-6-methyl-(**8**), and 6,6-difluoro-5,7-dioxo-1,4,8,11-tetraazacyclotetradecane (**9**) were synthesized by condensation of **5** with each corresponding fluorine-substituted malonic ester[8] (**2**,[9] **3**, and **4**) in refluxing ethanol. The cyclization becomes faster as more F is substituted, completing within 30 min with difluorinated **4** as compared to 3 days with nonfluorinated **1**,[10] with yields of 39% (for **7**), 54% (**8**), and 33% (**9**).[11] The dioxocyclams **7**, **8**, and **9** were reduced with diborane in tetrahydrofuran to the corresponding cyclams, 6-fluoro-(**11**), 6-fluoro-6-methyl-(**12**), and 6,6-difluoro-1,4,8,11-tetraazacyclotetradecane (**13**) in yield of 45%, 34%, and 54%, respectively,[12]



The protonation constants pK_a (Table I) for these new macrocycles (**7–9** and **11–13**) were determined by pH-metric titrations, to prove weakened amine basicities upon F substitution. The diminution in the amine basicities is most dramatic at the second stage of protonation (pK_2), in particular for cyclams series **10–13**. In the light of the remote location of the basic nitrogens from fluorines in dioxocyclams, the observed basicity-weakening effect by the F atoms may indirectly occur through the strengthened hydrogen bondings between the acidified (due to the electron-withdrawing effect of F) proximal amide hydrogens[13] and the distal

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(1) For recent articles: (a) Beley, M.; Collin, J.-P.; Ruppert, R.; Sauvage, J.-P. *J. Chem. Soc., Chem. Commun.* **1984**, 1315–1316. *J. Am. Chem. Soc.* **1986**, *108*, 7461–7467, and references cited therein. Grant, J. L.; Goswami, K.; Spreer, L. O.; Otvos, J. W.; Calvin, M. *J. Chem. Soc., Dalton Trans.* **1987**, 2105–2109. (b) Tsukube, H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 615–619. (c) Taniguchi, I.; Nakashima, N.; Yasukouchi, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1814–1815. (d) Loncin, M. F.; Desreux, J. F.; Merciny, E. *Inorg. Chem.* **1986**, *25*, 2646–2648. (e) Kunitake, T.; Ishikawa, Y.; Shimoumura, M. *J. Am. Chem. Soc.* **1986**, *108*, 327–328. (f) Ram, M. S.; Espenson, J. M.; Bakač, A. *Inorg. Chem.* **1986**, *25*, 4115–4118. (g) Blake, A. J.; Gould, R. O.; Hyde, T. I.; Schröder, M. *J. Chem. Soc., Chem. Commun.* **1987**, 431–433. (h) Bond, A. M.; Khalita, M. A. *Inorg. Chem.* **1987**, *26*, 413–420. (i) Koora, J. D.; Kochi, J. K. *Inorg. Chem.* **1987**, *26*, 908–916. (j) Takiguchi, T.; Nonaka, T. *Chem. Lett.* **1987**, 1217–1218. (k) Collin, J.-P.; Sauvage, J.-P. *J. Chem. Soc., Chem. Commun.* **1987**, 1075–1076.

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(11) **7**: mp 194.0–194.5 °C (from CH_3CN); ^1H NMR (90 MHz, $CDCl_3$) δ 1.5–1.9 (m, 2 H), 1.90 (br, 2 H), 2.4–3.0 (m, 8 H), 3.2–3.8 (m, 4 H), 5.23 (d, J = 48 Hz, 1 H), 7.45 (br, 2 H, amide NH). **8**: mp 179.5–180.0 °C (from CH_3CN); ^1H NMR (90 MHz, $CDCl_3$) δ 1.4–1.8 (m, 2 H), 1.77 (d, J = 24 Hz, 3 H), 2.4–3.0 (m, 10 H), 3.0–3.4 (m, 2 H), 3.4–3.8 (m, 2 H), 7.35 (br, 2 H, amide NH). **9**: dec 194–196 °C (from CH_3CN); ^1H NMR (90 MHz, $CDCl_3$–CD_3OD) δ 1.5–1.9 (m, 2 H), 2.5–2.9 (m, 4 H), 3.0–3.6 (m, 8 H).

(12) **11**: mp 170.0–172.0 °C (from CH_3CN); ^1H NMR (90 MHz, $CDCl_3$) δ 1.5–1.9 (m, 2 H), 2.1 (br, 4 H), 2.6–2.9 (m, 12 H), 2.9–3.2 (m, 4 H), 4.70 (d m, J = 45 Hz, 1 H). **12**: mp 112.0–113.0 °C (from CH_3CN); ^1H NMR (100 MHz, $CDCl_3$–CD_3OD) δ 1.44 (d, J = 22 Hz, 3 H), 1.8–2.1 (m, 2 H), 2.8–3.8 (m, 16 H). **13**: mp 148.5–149.0 °C (from CH_3CN); ^1H NMR (90 MHz, $CDCl_3$) δ 1.6–1.8 (m, 2 H), 2.0 (br, 4 H), 2.5–2.9 (m, 12 H), 2.8–3.3 (m, 4 H).

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