Table I. Initial Nucleotide Transport Rates (k_T) for Carriers **2** and **4**

carrier[a]	Aq I pH[b]	Aq II	(10^{-9} mol/cm^2·h)[c] k_T(CMP)	k_T(GMP)	k_T(AMP)	k_G/k_A	k_G/k_C
2	6.15	H_2O	0.12	12.0	1.57	7.6	100
2	7.05	H_2O	0.0005	0.011	0.001	11	22
2	6.70	10 mM NaOH	0.30	12.3	2.82	4.4	41
2	7.05	10 mM NaOH	0.16	7.08	0.74	9.6	44
4	6.15	H_2O	0.16	1.01	0.73	1.4	6.3
4	7.05	10 mM NaOH	0.049	1.15	0.36	3.2	24
none	6.15	H_2O	$<10^{-4}$	$<10^{-4}$	$<10^{-4}$	*d*	*d*
sap.[e]	7.0	10 mM NaOH	$<10^{-4}$	$<10^{-4}$	0.004		

[a] 0.1 mM in dichloromethane. [b] The source phase, Aq I, contained a 1:1:1 ratio of AMP, CMP, and GMP at a 10 mM concentration in each. The initial pH was adjusted by the careful addition of NaOH(aq). [c] Transport experiments were performed in a manner similar to those reported in refs 5 and 7. Values reported are the average of three independent measurements; estimated error <5%. [d] Not determined. [e] Control experiment using 3,8,12,13,17,22-hexaethyl-2,7,18,23-tetramethylsapphyrin (0.1 mM) as the putative carrier.

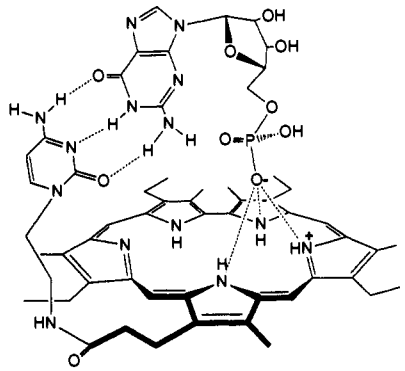

Figure 1. Possible structure for the proposed supramolecular complex formed between conjugate **2** and monobasic GMP.

AMP or CMP[14]) than its congener **4**. Further, better through-transport efficiency is always observed when the receiving phase (Aq II) is kept highly basic. Finally, a significant drop-off in efficiency, for both **2** and **4**, is observed as the initial pH of Aq I is increased from 6.15 to 7.05.

The above results are considered consistent with a model wherein complexation between the monoprotonated form of receptor **2** and the monobasic ($[ROPO_3H]^-$) form of GMP takes place at the Aq I–CH_2Cl_2 interface to produce a neutral, organic-soluble, supramolecular complex such as that depicted in Figure 1. This model, which is in accord with recent X-ray diffraction data,[15] provides a simple rationale for the experimental findings: First, decreased selectivity would be expected upon the introduction of "extra" cytosine-chelating subunits (as in, for example, **4**) since this would result in an increase in the number of possible hydrogen-bonding interactions and an incumbent loss in required substrate specificity. Second, higher through-transport rates would be observed in those cases where the receiving phase is kept basic since sapphyrin deprotonation and facilitated product release at the CH_2Cl_2–Aq II interface would necessarily be favored. Finally, a decrease in the through-transport rate is predicted since a lower concentration of the putative substrate, monobasic GMP (the $[ROPO_3H]^-$ form) in Aq I, would be expected as the second phosphate-centered ionization constant of GMP (pK_a = ca. 6.7[16]) is first approached and then surpassed.[17] That some transport occurs even at pH 7.05 is thus considered a reflection of the fact that, under the conditions of the experiment, binding of monobasic GMP is enhanced relative to that of the dibasic ($[ROPO_3]^{2-}$) form and that this binding enhancement, in turn, serves to augment the effective concentration of this monanionic (and hence readily neutralizable) species in the organic membrane phase.[17]

Although the model of Figure 1 is by no means proved, it is clear from the present study that the transport of a normally organic-insoluble species, namely GMP, can be effected by preparing and using an appropriate nucleobase-expanded porphyrin conjugate. This leads us to suggest that a similar designed receptor approach could be used to achieve the into-cell delivery of Xylo-GMP and other nucleotide drugs in vivo. We are currently exploring this possibility.

Acknowledgment. This work was supported by the Texas Advanced Research Program, the National Science Foundation, the Camille and Henry Dreyfus Foundation, and the Sloan Foundation.

Supplementary Material Available: Listings of synthetic experimental data and time plots for nucleotide transport studies (13 pages). Ordering information is given on any current masthead page.

(15) The 2:1 complex formed between monobasic phenyl phosphate and diprotonated sapphyrin has been analyzed in the solid state by X-ray diffraction. One phenyl phosphate is bound on the "top" face of the macrocycle to each of three pyrroles, while the other phosphate is bound to two pyrroles on the "bottom" side. Furuta, H.; Sessler, J. L.; Lynch, V. Unpublished results.

(16) Phillips, R.; Eisenberg, P.; George, P.; Rutman, R. J. *J. Biol. Chem.* **1965**, *240*, 4393-4397.

(17) Charge neutralization as a requirement for efficient carrier-mediated transport is known as Fick's first law. See ref 12, p 78.

1,5- and 1,9-Hydrogen Atom Abstractions. Photochemical Strategies for Radical Cyclizations

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Received June 22, 1992

The use of radical reactions in organic synthesis is now well established.[1] Current topics of research in radical chemistry include the development of nonreductive radical cyclization reactions,[2] the study of acyclic stereochemical control in radical reactions,[3] and the development of new methods for the generation of radicals.[4] Although the reaction of halides or selenides with tributylstannyl radicals is still the predominantly used method for generating radicals, the expense, toxicity, and operational difficulties associated with the organotin reagents have prompted the evaluation of alternate methods. Photochemistry has long been used to generate biradical intermediates; however, few of these reactive biradicals are useful in the generation of new radicals. Notable exceptions include the biradicals derived from benzophenones and certain quinones, which undergo efficient intermolecular hydrogen atom abstraction reactions.[5] The trapping of 1,4-biradicals (whose short lifetimes necessitate intramolecular

(1) For a timely review, see: Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

(2) Snider, B. B.; Buckman, B. O. *J. Org. Chem.* **1992**, *57*, 322 and references therein.

(3) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296.

(4) Giese, B.; Thoma, G. *Helv. Chim. Acta* **1991**, *74*, 1143. Newcomb, M.; Ha, C. *Tetrahedron Lett.* **1991**, *32*, 6493. Inokuchi, T.; Kawafuchi, H.; Torii, S. *J. Org. Chem.* **1991**, *56*, 4983.

(5) Kraus, G. A.; Kirihara, M. *J. Org. Chem.* **1992**, *57*, 3256. Hicks, D. R.; Anderson, R. C.; Fraser-Reid, B. *Synth. Commun.* **1976**, *6*, 417 and references therein.

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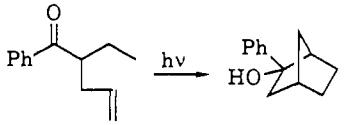
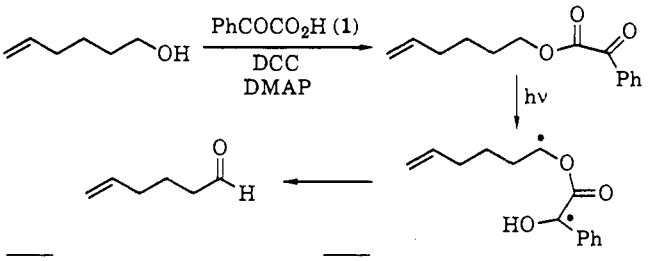
traps) to generate new biradicals which can cyclize is almost unknown. In a classic experiment, Wagner and co-workers irradiated 2-allylpropiophenone and isolated only 4% of 2-phenyl-2-norbornanol.[6]

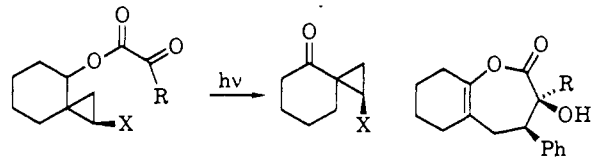


4%

In the context of developing new radical cyclization methods, we examined the interception of the biradicals produced by the photolysis of α-keto esters. The photolysis of α-keto esters has been well studied and has been employed in a mild procedure for the oxidation of alcohols by Binkley.[7] We initially examined the interception of the 1,4-biradicals derived from the photolysis of α-keto esters with an alkene. Acylation of 5-hexen-1-ol with benzoylformic acid (**1**) and DCC followed by irradiation afforded a good yield of 5-hexenal. We did not isolate any products resulting from the intramolecular trapping of the biradical by the alkene.



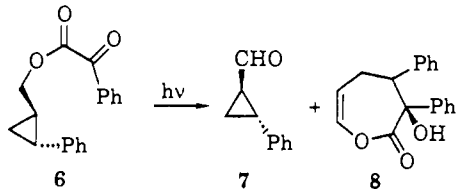
We next examined the cyclopropyl carbinyl radical rearrangement as a way to intercept the biradical. Compound **2a** was synthesized from cyclohexanone by the method of Murai.[8] Irradiation of **2a** provided a quantitative yield of ketone **3** (X = H) with no trace of products resulting from cleavage of the cyclopropane. Newcomb has demonstrated that phenyl substitution



2a: X = H, R = Ph
2b: X = R = Ph
2c: X = Ph, R = Me

3

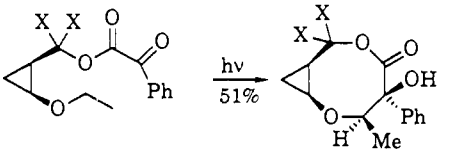
4: R = Ph
5: R = Me



6 **7** **8**

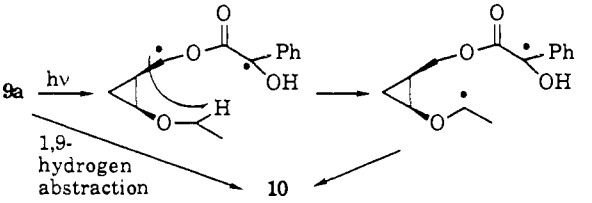
on a methylene carbon of the cyclopropane increases the rate of the cyclopropyl carbinyl radical opening by a factor of 100.[9] Irradiation of **2b** afforded a 30% yield of the seven-membered-ring lactone **4** and a 38% yield of the ketone **3** (X = Ph). The trans relationship of the two phenyl groups in **4** was proven by an X-ray structure determination. Irradiation of **2c** (R = Me, X = Ph) generated lactone **5** in 36% yield and ketone **3** (X = Ph) in 9% yield. Irradiation of the conformationally more flexible ester **6** provided trace amounts of aldehyde **7** and a 25% yield of lactone **8**. As in the previous experiments, the remainder of the material comprised decomposition products. Lactone **8** was a labile compound, both to column chromatography and, to a lesser extent, to the irradiation conditions.

In order to extend the scope of the cyclopropyl carbinyl opening, ester **9** was prepared by reduction of the known cyclopropyl ester[10] with LAH in ether at 0 °C followed by esterification with **1**. Surprisingly, irradiation of **9a** afforded only the eight-membered-ring lactone **10** in 51% yield. Lactone **10** may have been formed from the 1,4-biradical shown below by a 1,5-hydrogen transfer followed by cyclization.



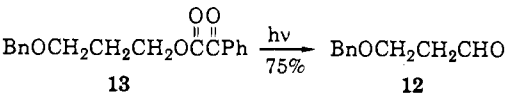
9a: X = H
9b: X = D

10: X = H
11: X = D

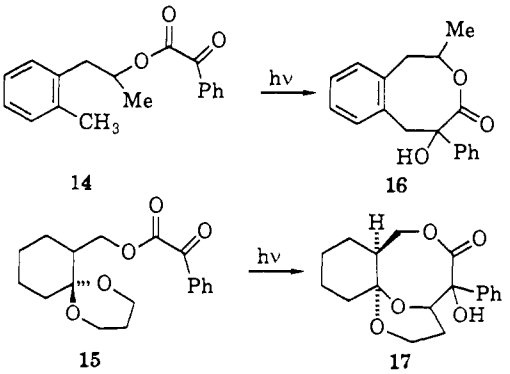


However, lactone **10** could also have been formed from a direct 1,9-hydrogen atom abstraction. Such long-range hydrogen atom abstractions are rare. All of the cases involve amino ketones, amino imides, or sulfide imides and proceed via an electron-transfer reaction.[11] In order to differentiate between the two mechanisms, the deuterated ester **9b** was prepared and subjected to the photolysis conditions. *Lactone **11** was isolated in 62% yield, demonstrating that in this case a 1,9-hydrogen abstraction reaction had indeed occurred.* The NMR spectrum of the product from photolysis of **9b** before purification showed no trace of product derived from the 1,5-hydrogen atom abstraction followed by a 1,5-hydrogen transfer. This remarkable selectivity may reflect photoreaction via the favored syn rotamer of the ester. The 1,5-hydrogen abstraction must occur from the anti rotamer.[12]

Several systems have been evaluated to identify structural features necessary for the formation of eight-membered-ring lactones. The production of aldehyde **12** from keto ester **13** indicates that some degree of conformational rigidity is required.



13 **12**



14 **16**

15 **17**

Both the aromatic analog **14** and the ketal **15** provided eight-membered-ring lactones **16** and **17** in 74% and 22% yields, respectively. Lactone **16** was a single stereoisomer as evidenced by

(6) Wagner, P. J.; Park, B.-S. *Org. Photochem.* **1991**, *11*, 227.
(7) Binkley, R. W. *Synth. Commun.* **1976**, *6*, 281.
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(9) Newcomb, M.; Manek, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 9662.
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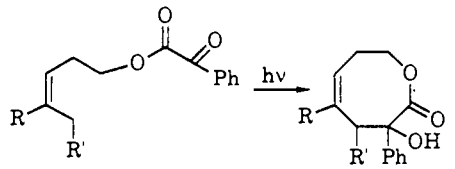
(11) Kraus, G. A.; Chen, L. *Tetrahedron Lett.* **1991**, *32*, 7151. Hasegawa, T.; Miyata, K.; Ogawa, T.; Yoshihara, N.; Yoshioka, M. *J. Chem. Soc., Chem. Commun.* **1985**, 363.
(12) This phenomenon may be related to the observation by Gellman that certain dipeptides have conformations with 10-membered hydrogen-bonded rings. See: Liang, G.-B.; Rito, C. J.; Gellman, S. H. *J. Am. Chem. Soc.* **1992**, *114*, 4440. We thank a referee for bringing this paper to our attention.

proton NMR and TLC. Lactone **17** was a mixture of stereoisomers at the newly-generated stereogenic center α to the carbonyl group.

Keto ester **18** cyclized to hydroxy lactone **19** in 49% yield. The cyclization of keto ester **18** to an eight-membered-ring lactone rather than a six-membered-ring lactone was unexpected. A 1,9-hydrogen atom abstraction reaction via the syn rotamer of the ester followed by rapid closure of the proximate biradical nicely rationalizes this result. Similarly, keto ester **20** cyclized exclusively to the eight-membered-ring lactone **21** in 31% yield.



18: R=H, R'=Me **19**: R=H, R'=Me
20: R=Me, R'=H **21**: R=Me, R'=H

The results presented herein demonstrate the potential of using either photochemically generated 1,4-biradicals or 1,9-hydrogen abstractions for ring-forming reactions. Extension to other photochemical reactions that proceed by way of 1,4-biradicals is in progress. Although the synthetic utility of this strategy remains to be determined, seven- and eight-membered oxacyclic rings are common subunits in certain families of marine natural products.[13]

(13) Faulkner, D. *Nat. Prod. Rep.* **1986**, *3*, 1.

Regioselective and Endo-Stereoselective [3 + 2] Cycloaddition of Dipolar Trimethylenemethane to Electron-Deficient Olefin

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Received July 13, 1992

Stereoselective synthesis of five-membered carbocycles continues to attract the interest of organic chemists.[1,2] We report that the thermal [3 + 2] cycloaddition of a substituted dialkoxy trimethylenemethane (TMM, **2**) to an electron-deficient olefin proceeds endo-stereoselectively with retention of the olefin geometry, providing a single-step synthesis of substituted cyclopentanes (Scheme I). Some examples of successful regiocontrol in the cycloaddition to unsymmetrical olefins are also described. The present cycloaddition of a 4π-electron TMM to an olefin[3] shares an important characteristic with the Diels–Alder reaction in that the reaction proceeds under predictable regio- and stereocontrol.

We have previously shown[4] that thermolysis of (*E*)-ethylidenecyclopropane **1a** at 60–100 °C reversibly and stereospecifically generates a dipolar, 4π-electron (*E*)-TMM **2a**, which is stereochemically stable under the conditions of its [3 + 2] cycloaddition to olefins (vide infra).[5] In order to investigate the stereochemical behavior of **2a** in the cycloaddition, we examined its reaction with dimethyl maleate. When a 1 M C_6D_6 solution of an equimolar mixture of **1a** and the maleate was heated at 80 °C for 24 h under nitrogen, the ketene acetals (**4a** and **5a**) were formed in 88% yield with a ratio of 95:5. By ^{1}H NMR analysis ($^3J_{HH}$, NOE, and COSY) combined with chemical derivatization,[6] the major isomer was assigned to be **4a**. In no case did we note isomerization of either the starting olefin or the product under the reaction conditions. The stereochemsitry of the product in conjunction with the *E* geometry of **2a** strongly suggested that the major cycloaddition pathway involves an endo transition state (**3**), wherein the acetal and the ester groups are located close to each other.[7] Various other observations (vide infra) are also consistent with the endo transition state. The stereoisomer **5a** may be due to an alternative exo transition state.

Several important observations were made. The endo:exo isomer ratio (**4a**:**5a**) exhibited notable dependence on the solvent polarity (Table I, entry 1), decreasing dramatically from 97:3 to 73:27[8] as the polarity of the solvent was increased from octane (ϵ = 1.9) to DMSO-d_6 (ϵ = 46.6). The results suggest that polar interactions between the directing groups control the stereochemistry. This solvent dependency stands in contrast to the very small solvent effects in the Diels–Alder reaction.[9] Polar solvent also accelerated the cycloaddition, which may be in part due to accelerated cycloaddition and in part due to accelerated TMM formation, which is about 100 times faster in DMSO than in an alkane solvent.[4] The product yield was little influenced by the solvent variation, however. The cycloadditions to methyl *trans*-crotonate (entry 2) and methacrylate (entry 3) proceeded with virtually complete endo selectivity, but with poor regioselectivity. However, a high level of regiocontrol was achieved with the aid of substituent steric effects. Thus, the isopropyl TMM **1b** reacted with methyl *trans*-crotonate to give a single endo adduct, with other isomers accounting for only 4% of the cycloadducts (entry 4). On the other hand, a cis olefin reacts regio-randomly even with **1b** (entry 5), and a bulky cis substituent on the olefin acceptor severely retards the cycloaddition (entry 7). These observations are also in agreement with the endo transition state **3**. Alternatively, methyl (*E*)-4,4-dimethyl-2-pentenoate, bearing a bulky olefinic substituent, reacted with **1a** to give a single cycloadduct (>97% isomeric purity, entry 6). In general, an olefin substituent trans to the ester group appears to ensure high endo selectivity

(1) [3 + 2] construction of five-membered carbocycles: (a) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163. (b) Becker, D. A.; Danheiser, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 389 and references therein. (c) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. (d) Cekovic, Z.; Saicic, R. *Tetrahedron Lett.* **1986**, *27*, 357. Curran, D. P.; Chen, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 6558. (e) Herndon, J. W.; Wu, C.; Harp, J. J.; Kreutzer, K. A. *Synlett.* **1991**, 1. (f) Beak, P.; Wilson, K. D. *J. Org. Chem.* **1987**, *52*, 3826. (g) Gray, B. D.; McMillan, J. A.; Moore, M. *Tetrahedron Lett.* **1987**, *28*, 689. (h) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695. Boger, D. L.; Brotherton-Pleiss, C. E. *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, pp 147–219. (i) Marino, J. P.; Laborde, E. *J. Am. Chem. Soc.* **1985**, *107*, 734. (j) Beal, R. B.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1986**, *51*, 4391. (k) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 3825. (l) Rosenblum, M.; Watkins, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 6322 and references therein. (m) Eidenschink, R.; Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 292. (n) Boche, G.; Martens, P. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 724. (o) Tokuyama, H.; Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.*, in press.

(2) (a) Reviews on TMM: Little, R. D.; Masjedizadeh, M. R.; Moeller, K. D.; Dannecker-Doerig, I. *Synlett* **1992**, 107. Berson, J. A. *Acc. Chem. Res.* **1978**, *11*, 486. Dowd, P. *Acc. Chem. Res.* **1972**, *5*, 242. (b) Metal-mediated TMM chemistry: Noyori, R.; Yamakawa, M.; Takaya, H. *Tetrahedron Lett.* **1978**, 4823 and references cited therein. Binger, P.; Buchi, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. Aumann, R.; Uphoff, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 357. Lewis, R. T.; Motherwell, M. B.; Shipman, M. J. *J. Chem. Soc., Chem. Commun.* **1988**, 948. Yamago, S.; Nakamura, E. *J. Chem. Soc., Chem. Commun.* **1988**, 1112. Yamago, S.; Nakamura, E. *Tetrahedron* **1989**, *45*, 3081. (c) Reviews on [3 + 2] cycloadditions: Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley & Sons: New York, 1984; Vols. 1 and 2. Little, R. D. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 239–270.

(3) Review: Nakamura, E. *Organic Synthesis in Japan, Past, Present, and Future*; Noyori, R., Ed.; Tokyo Kagaku Dozin: Tokyo, 1992; pp 273–282.

(4) Nakamura, E.; Yamago, S.; Ejiri, S.; Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1991**, *113*, 3183.

(5) Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* **1989**, *111*, 7285. Yamago, S.; Nakamura, E. *J. Org. Chem.* **1990**, *55*, 5553.

(6) Stereochemistry in Table I was unequivocally established by NMR and/or chemical correlation, except in entries 3 and 5 (partially assigned and assigned by analogy, respectively). See the supplementary material for details.

(7) Note that the structure of **3** is not meant to represent the exact geometry of the transition state, which may well be quite flexible.

(8) Product ratios in Table I were determined by capillary GC and by ^{1}H NMR.

(9) Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297. Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, Germany, 1988. Cf. Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1989**, *111*, 5469.

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