Table II. Variance of Reactant Ratios[a]

reactants	ratio	% composition[b] 2	3	4
(MeOH)				
NCS/LiBr	1:1	18.8	22.4	58.8
NCS/LiBr	1.5:1	17.2	28.4	54.4
NCS/LiBr	1:1.5	17.7	42.7	39.6
NCS/LiBr/LiCl	1:1:1	32.1	17.2	50.7
(THF)				
NCS/LiBr	1:1	75.6	22.3	
NCS/LiBr	1.5:1	79.2	20.8	
NCS/LiBr	1:1.5	44.2	55.8	
NCS/LiBr/LiCl	1:1:1	85.9	14.1	

[a] All reactions are with cyclohexene at concentration of $\sim 6 \times 10^{-1}$ M. [b] Only percent of 2:3:4 is shown here for comparison purposes; some starting material remained and some unidentified products were present.

heterocycles. An association of bromide ion with BrCl could potentially produce Br_2 in solution (eq 4), but irre-

$$2BrCl \rightleftarrows Br_2 + Cl_2 \quad (1)$$

$$BrCl + Cl^- \rightleftarrows BrCl_2^- \quad (2)$$

$$BrCl + Br^- \rightleftarrows Br_2Cl^- \quad (3)$$

$$Br_2Cl^- \rightleftarrows Br_2 + Cl^- \quad (4)$$

spective of the electrophilic brominating species the most likely reaction path for the formation of dibromide product is attack of bromide ion on a bromonium ion intermediate. The amount of dibromide product 3 observed should therefore be dependent upon the concentration of bromide ion in solution.

To further investigate the participation of halide ions in the product ratios obtained, we carried out several reactions in which the stoichiometry of reagents was no longer unity and in which 1 equiv of lithium chloride had been added (Table II). The results of these experiments clearly indicate that the anion concentration can drastically alter the product composition. Importantly, no significant change in the ratio of products was observed when the amount of NCS was increased, while additional LiBr increased the amount of dibromo product, 3, and addition of LiCl increased the quantity of bromine chloride adduct 2.

Experimental Section

All chemicals used were at least analytical reagent grade and were used as obtained. Reaction mixtures were analyzed by GLC performed on a Varian 3700 gas chromatograph using FID detection coupled to a Spectra Physics 4100 integrator/plotter. Separations were accomplished on a 50-m SE-30 capillary column (J&W), using a temperature program of 40 °C (3 min) to 210 °C at 20 °C/min. Analysis of peak composition was accomplished on a Hewlett-Packard 5984 GC/MS DS system with a 30-m SE-30 capillary column (J&W) using a temperature program of 80 °C (2 min) to 250 °C at 16 °C/min. The following m/e values were observed: 2, 196 (1.2), 198 (1.4), 200 (0.3); for 3, 240 (0.7), 242 (1.5), 244 (0.7); for 4 (MeOH), 192 (11.2), 194 (11.4); and for 4 (EtOH), 206 (11.4), 208 (11.3).

Acknowledgment. We thank Dr. Dale Spall for his assistance in obtaining GC/MS data. The financial support by the Department of Energy is gratefully acknowledged.

Registry No. 1, 110-83-8; bromine chloride, 13863-41-7; NCS, 128-09-6; Br^-, 24959-67-9.

A-Ring Bromination of Estradiol and 17α-Ethynylestradiol with *N*-Chlorosuccinimide and Bromide Ion. Possible Evidence for Hypobromite Intermediates

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A-ring radiobrominated estrogens may have applications in the detection and/or choice of therapy for some types of tumors.[1,2] A preliminary evaluation of radiobrominated steroids can be obtained through competitive receptor-binding studies,[3] using the stable brominated compounds. We, therefore, sought to obtain purified samples of two different estrogens brominated in the A ring. Although methods of brominating in the A ring of estrogens[4-6] have been described in the literature, we chose to employ a method that would convert bromide ion directly to an electrophilic brominating agent in situ. Such a method could be used for subsequent radiobrominations of these compounds.[7] Studies in this laboratory have demonstrated that mixing *N*-chlorosuccinimide (NCS) and bromide ion forms an electrophilic brominating species in situ.[8] We now report on the bromination of estradiol 1 and 17α-ethynylestradiol 5 with this combination of reagents.

Results and Discussions

Reaction of estradiol 1 with NCS/NaBr in ethanol at room temperature yielded a mixture of three brominated compounds. The brominated products were separated and purified by preparative high-performance LC (HPLC) and subsequently identified (Table III) as 2-bromoestradiol (2), 4-bromoestradiol (3), and 2,4-dibromoestradiol (4). Reaction of 17α-ethynylestradiol 5 with NCS/NaBr under the same reaction conditions also yielded three brominated products. The brominated products, 2-bromo-17α-ethynylestradiol (6), 4-bromo-17α-ethynylestradiol (7), and 2,4-dibromo-17α-ethynylestradiol (8), were subsequently separated, purified, and characterized (Table IV).

The A-ring bromination of estradiol 1 with NCS/Br^- was compared to brominations with *N*-bromoacetamide (NBA), *N*-bromosuccinimide (NBS), pyridinium bromide perbromide (PBPB), and Br_2 to see if the ratios of brominated products, 2–4, were the same (Table I). Indeed, all brominations carried out in ethanol gave nearly identical ratios of products by analytical HPLC. However, it was interesting to note that changing the solvent had a dramatic change in the ratio of 2:3 for PBPB but apparently not for NCS/Br^-.

When the reactions of 1 and 5 with NCS/Br were followed by reverse-phase HPLC, a transient species was observed.[9] Within a 40-min reaction time essentially all

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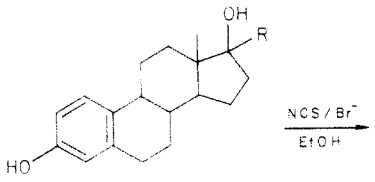
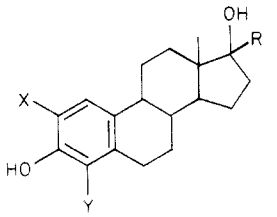
(7) Wilbur, D. S.; Bentley, G. E.; O'Brien, H. A., Jr. *J. Labelled Compd. Radiopharm.*, in press.
(8) See preceding note.
(9) A similar intermediate was also observed in the reaction of estrone under identical conditions.



1, R = H
5, R = C≡CH



2, R = H; X = Br; Y = H
3, R = H; X = H; Y = Br
4, R = H; X = Br; Y = Br
6, R = C≡CH; X = Br; Y = H
7, R = C≡CH; X = H; Y = Br
8, R = C≡CH; X = Br; Y = Br

of the starting material disappeared to yield a new, more lipophilic species (98% by UV detection).[10] As the reaction continued to completion (5–7 h), the relative proportions of the intermediate and the brominated products continually changed until only the brominated species **2–4** or **6–8** were present.

It was possible to isolate the intermediates observed in the reaction of both **1** and **5**. The intermediates were faint yellow solids which could be stored for several days in the refrigerator (~7 °C) with little apparent decomposition (by HPLC analysis). The presence of bromine in the intermediates was confirmed by radiobrominations[7] and chemical transformations of the isolated solids. For example, the solids reacted with themselves when stored (covered from light) at room temperature for 2 weeks to yield the brominated products. Furthermore, reintroduction of the isolated intermediates into the reaction medium (ethanol) yielded the brominated products; however, the reaction rate was slower than normal and the product ratios of 2-bromo/4-bromo were observed to be approximately 1:1. Cointroduction of either succinimide or sodium chloride with the isolated intermediates into ethanol resulted in the reactions occurring in the normal reaction time, with nearly the same product ratios as observed when the reactions were uninterrupted. Additionally, introduction of the isolated intermediate from the reaction of **1** into an ethanol solution of phenol yielded *o*- and *p*-bromophenol along with the brominated estradiols **2–4**.

Attempts to obtain proton and carbon NMR data on the isolated intermediates were unsuccessful.[11] However, it was possible to follow the reaction of **1** with NCS/LiBr in EtOH-d_6 by proton NMR. After 30 min from the time of addition of NCS (a time that one observes 98+% of intermediate by HPLC), the chemical shifts for the aromatic protons of the mixture of **1** and LiBr had changed dramatically (Table II). Interestingly, even though the aromatic protons were shifted a great deal, the overall coupling pattern (i.e., H(1) and H(2) doublet annd H(4) singlet) had not changed appreciably. A dramatic change in the UV spectrum was also observed when following the reaction of **1** with NCS/NaBr in ethanol. During the reaction a new absorbance pak at 252 nm ($\epsilon \simeq 7000$) grew in and disappeared.

Table I. Brominated Estradiol Product Ratios

reagent[a]/solvent[b]	% 2[c]	% 3[c]	% 4[c]
NCS/NaBr/EtOH	24	69	7
NBA/EtOH	25	69	6
NBS/EtOH	23	69	8
PBPB/EtOH	28	69	3
PBPB/THF	42	51	7
PBPB/HOAc	54	46	trace
Br_2/HOAc	40	51	9
NCS/LiBr/THF	21	50	29

[a] One equivalent of each reagent was used; all reactions were run at room temperature. [b] Reactions were run at an approx. concentration of 2×10^{-2} M. [c] Relative UV response factors measured at 254 nm for 2:3:4 were 1.2:1.0:2.1.

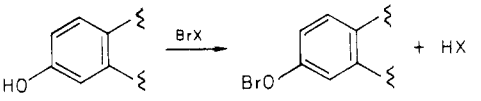
Table II. Aromatic Proton Chemical Shifts

	H(1)	H(2)	H(4)
estradiol, 1[a]	7.02, d, J = 9 Hz	6.51, d, J = 9 Hz	6.47, s
1[b]	6.98, d, J = 9 Hz	6.47, d, J = 9 Hz	6.41, s
intermediate of 1[a]	7.38, d, J = 10 Hz	6.03, d, J = 10 Hz	5.98, s
phenoxide of 1[b]	6.81, d, J = 9 Hz	6.19, d, J = 9 Hz	6.15, s

[a] EtOH-d_6, δ. [b] THF-d_8, δ.

Similar eluting intermediates could be observed by HPLC for the reaction of **1** and **5** with NCS alone, but the formation of the intermediates was very slow (~85% after 5 days) as were the subsequent A-ring chlorinations (~2% reaction in 5-days reaction time). In contrast to this, NBS reacted with **1** and **5** to produce the same intermediates (by HPLC retention times) within the same reaction times. While this does not necessarily indicate the formation of NBS in the reaction of NCS/Br^-, it does suggest that there may be a common pathway for the electrophilic bromination of phenolic steroids in ethanol.

One possible structure for the intermediate is that of a phenoxy hypobromite **10**. Such an intermediate might arise from the acid–base interaction of the electrophilic brominated species generated in situ and the phenolic A ring. Hypohalites are postulated as reaction intermediates



10

in NBS oxidations of alcohols[12] and have been previously proposed to explain the ortho selectivity observed for some brominating agents reacting with phenol.[13] Evidence which tends to support a hypobromite intermediate might seemingly be gained from the fact that no intermediate was observed in the corresponding reaction with estradiol 3-methyl ether under identical reaction conditions. Additional evidence might be obtained from the ^{1}H NMR and UV spectra recorded during the reaction of **1** with

(10) The UV data show that the extinction coefficients at 254 nm for the isolated intermediates are very much larger than those for either **1** or **5** or their brominated products at that wavelength; thus the actual proportions may be different.

(11) Dissolving the intermediates appeared to change them enough that they were no longer suitable to obtain spectra which contained only the intermediates. Attempts to prepare concentrated solutions for carbon NMR resulted in deep yellow solutions, in which the subsequent bromination reactions occurred very rapidly.

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Table III. Characterization of A-Ring Brominated Estradiols

	2	3	4
mp,[a] °C	191-193 (lit.[4] 156-157 (lit.[6] 197-198)	207-208.5 (lit.[4] 207-208), (lit.[6] 213.5-215)	225-226 (lit.[4] 218-219), (lit.[6] 223-226)
UV (EtOH), λ_{max} (ϵ)	210 (16 300), 286 (3400)	210 (17 100), 282 (2200), 287 (2200)	212 (22 500), 292 (3200)
^{1}H NMR[b] aromatic protons	7.15 (1 H, s) 6.52 (1 H, s)	6.99 (1 H, d, J = 9 Hz)	7.26 (1 H, s)
^{13}C NMR aromatic carbons			
C-1	130.5[b]	125.4[c]	128.5[c]
C-2	107.7	112.6	104.4
C-3	152.7	150.0	147.1
C-4	117.4	113.6	113.2
C-5	138.1	136.3	136.6
C-10	133.9	134.2	135.6
mass spectra (parent peaks)	352 (26) 350 (29)	352 (98) 350 (100)	432 (56) 430 (100) 428 (58)

[a] Uncorrected. [b] Me_2SO-d_6, δ. [c] $CDCl_3$, δ.

NCS/bromide. Although it is difficult to interpret the spectral changes with respect to a hypohalite intermediate, it is clear that they did arise from the formation of some intermediate. The ^{1}H NMR spectra show that the aromatic protons in the intermediate are affected greatly by the nature of the intermediate, but because the splitting pattern of the aromatic protons is retained, it might be concluded that the bromine atom has not addedc to the aromatic ring itself. As a potential model system, the phenoxide of estradiol, 1, was prepared in THF by reaction with NaH[14] and the ^{1}H NMR and UV spectra were recorded. Indeed, a new absorbance band at λ_{max} 248 nm was observed in the UV spectrum; however, an additional absorbance at λ_{max} 311 nm was also observed which was not present in the intermediate. Likewise, contrary to the ^{1}H NMR shifts observed for the reaction of 1, when the phenoxide was prepared in THF-d_8, all of the aromatic protons were shifted upfield (Table II). Because of the difficulty in interpreting the UV and ^{1}H NMR spectra, perhaps the most compelling evidence for the phenoxy hypobromite intermediates is that of the bromination of phenol with the isolated intermediate.

Experimental Section

Estradiol and 17α-ethynylestradiol were purchased from Sigma Chemical Co. and were used as obtained. *N*-Chlorosuccinimide was obtained from Aldrich and was used as obtained. Sodium bromide was obtained from Mallincrodt and was finely pulverized prior to use.

Proton NMR Data. Proton NMR spectra were obtained on a Varian EM-360 or JEOL FX-90 with the solvents shown (Tables II, III, and IV) referenced to Me_4Si equal to 0 ppm. Proton chemical shifts are noted only for the aromatic regions as they are the only ones of interest in this study.

Carbon NMR Data. Carbon-13 spectra were obtained on either a Varian CFT-20 or a JEOL FX-90. The chemical shifts are referenced to the center peak of the deuterated solvent used. Only the A-ring chemical shifts were recorded as with ^{1}H NMR. The assignments are not unequivocal and are based on those reported in the literature.[15]

(14) Allcock, H. R.; Fuller, T. J.; Matsumura, K. *J. Org. Chem.* **1981**, *46*, 13-22.

Table IV. Characterization of A-Ring Brominated 17α-Ethynylestradiols

	6	7	8
mp,[a] °C	227-228	178.5-179	185-187
UV (EtOH), λ_{max} (ϵ)	211 (16 000), 286 (3600)	209 (15 300), 287 (2100)	211 (18 800), 292 (3000)
^{1}H NMR[b] aromatic protons	7.35 (1 H, s) 6.70 (1 H, s)	7.17 (1 H, d, J = 9 Hz) 6.81 (1 H, d, J = 9 Hz)	7.45 (1 H, s)
^{13}C NMR[b] aromatic carbons			
C-1	130.5	126.0	129.6
C-2	107.6	114.1	108.0
C-3	152.3	152.6	149.2
C-4	117.2	113.7	114.7
C-5	138.3	137.6	137.6
C-10	134.4	134.3	136.3
anal. calcd (found)	C, 64.08; H, 6.18 (C, 63.96; H, 6.19)	(C, 64.09; H, 6.29)	C, 52.88; H, 4.84 (C, 53.10; H, 4.99)

[a] Uncorrected. [b] Acetone-d_6, δ.

UV Spectral Data. UV spectra were obtained on a Hewlett-Packard 8450A UV/visible spectrophotometer. Samples were $\sim 1.5 \times 10^{-4}$ M in absolute ethanol and were measured in cells of 1-cm path length.

Mass Spectral Data. Mass spectra were obtained on a Hewlett-Packard 5984 GC/MS DS system. The samples were introduced by GLC on a 6-ft 3% OV-101 column at 250 °C.

High-Performance Liquid Chromatography. Analyses of reaction mixtures were performed with Waters Associates 6000A pumps, UK6 injector, Model 450 UV detector (at 254 nm), system controller, and data module. Reaction progress was followed by reverse-phase analysis on a radial compression module, using a Radial Pak C-18 column, eluting with 1:1 CH_3CN/H_2O. In order to obtain an accurate percentage of dibromo derivatives, we determined the reaction product ratios on a μ-Porasil column, eluting with 100:1 $CHCl_3/CH_3CN$. Preparative HPLC was performed by a Waters Associates Prep LC/System 500A, using a reverse-phase column, eluting with 2:3 CH_3CN/H_2O.

NCS/NaBr Brominations. To a solution of 0.7 mmol of 1 or 5 dissolved in 30 mL of absolute EtOH were added 0.7 mmol of NaBr and 0.7 mmol of NCS. The solution was rapidly stirred at room temperature for 5–7 h (reaction progress was followed by HPLC). The reaction mixture was diluted to a volume of ~125 mL by addition of ice/H_2O to the ethanol solution. The white precipitate was collected and dried under vacuum to give nearly a quantitative yield based on the monobrominated product. The solid contained four species, three brominated and some starting material. Pure samples were obtained by preparative HPLC (Tables III and IV).

Isolation of Intermediates. The reactions were set up with the proportions as described above. After an ~30-min reaction time, the reaction progress was checked by HPLC (usually 98+% by UV) and the reaction solution was added to ~100 mL of crushed ice. The solid white precipitate was collected by vacuum filtration in a sintered glass funnel. It was observed that the best results were obtained when ice was present throughout the filtration. The solid was then placed in a small round-bottom flask, covered with light, and was dried under high vacuum (~10 μm) for about 3 h. The intermediate from 1 was a faint yellow solid: yield of 246 mg (96% based on monobromo); melting point, softened at 60 °C, melted at 145–152 °C with gas evaluation. The intermediate of 5 was also a faint yellow solid: yield of 201 mg (79%); mp 85–98 °C.

Acknowledgment. We appreciate the assistance of Dr. Don Ott and Dr. Dale Spall in obtaining NMR and mass spectral data. We gratefully acknowledge the financial

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support given by the Department of Energy.

Registry No. 1, 50-28-2; 1 3-hypobromite derivative, 79769-51-0; 1 3-phenoxy derivative, 79746-28-4; 2, 15833-07-5; 3, 1630-83-7; 4, 19590-55-7; 5, 57-63-6; 6, 79746-29-5; 7, 79746-30-8; 8, 79769-52-1; NCS, 128-09-6; Br^-, 24959-67-9.

MIRC Reactions. 3. Use of Doubly Activated Substrates

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We recently reported the formation of three-, five-, six-, and seven-membered-ring esters bearing β-heteroatom substituents, through the utilization of what we have termed a MIRC (Michael Initiated Ring Closure) reaction.[1] Herein, we provide (1) a rationale for the use of geminate doubly activated ω-halo α,β-unsaturated esters rather than monoactivated systems as substrates for the MIRC reaction and (2) evidence which demonstrates that the doubly activated substrates constitute more desirable starting materials, in that both five- and six-membered-ring diesters can be prepared in fair to excellent yields by using a number of different nucleophiles, *including those which do not afford MIRC products when monoactivated systems are utilized.*

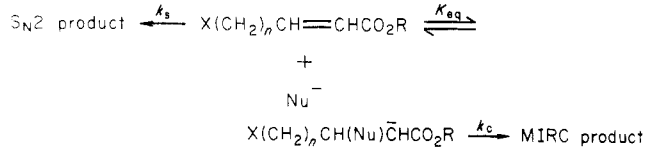
From our previous studies, we were aware that three-membered rings could be formed from the addition of lithium alkylthiolates to methyl 4-bromocrotonate in THF at 0 °C.[1] Five-, six-, and seven-membered rings were formed from the addition of lithium diisopropylamide (LDA) to the requisite ω-bromo α,β-unsaturated ester in THF at −78 °C (five- and six-membered ring) or at room temperature (seven-membered ring). However, attempts to close to five-, six-, and seven-membered rings by using alkylthiolates were thwarted by competitive S_N2 displacement reactions.[1b]

While this difference in behavior between nucleophiles was interesting to note, it was at the same time annoying, from the point of view that it appeared to point to a practical limitation upon the scope of the MIRC reaction. From the outset, we were particularly interested in being able to utilize a wide range of nucleophiles in order to take advantage of the chemistry associated with the carbon–nucleophile bond in the product and thereby modify it in a variety of potentially useful ways.[2] With this objective in mind, we initiated the study described below.

From an examination of Scheme I it is clear that the amount and the rate of formation of the MIRC product is dependent upon the enolate concentration and the rate constant for ring closure, k_c, while the amount and the rate of formation of the competing S_N2 product is dependent upon the concentration of the starting ester, the concentration of the nucleophile, and the rate constant for substitution, k_s. Obviously, the relative concentrations of the starting ester, the nucleophile, and the enolate are related to the equilibrium constant, K_{eq}.[3]

To gain an appreciation for the factors which influence the magnitude of K_{eq}, one can use the thermodynamic

Scheme I



Scheme II. Thermodynamic Cycle to Estimate K_{eq}

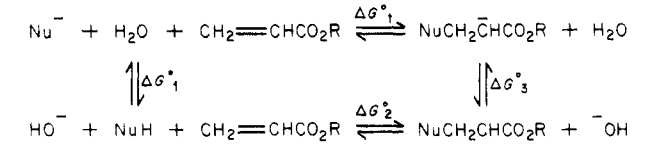
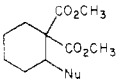
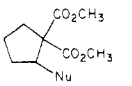


Table I[a]

% yield		
		nucleophile
46	65	L-Selectride
80	73	KCN
78	88	$NaCH(CO_2CH_3)_2$
94	82-94	*t*-BuSNa or Li

[a] See the Experimental Section for details. Yields refer to chromatographically pure compounds and are not optimized.

cycle which is illustrated in Scheme II. The individual steps associated with the cycle include two acid–base equilibria (steps one and three) for which, at 25 °C, $\Delta G°_1 = -1.37\Delta pK_a$ and $\Delta G°_3 = -1.37\Delta pK_a'$, where $\Delta pK_a = pK_a(NuH) - pK_a(H_2O)$ and $\Delta pK_a' = pK_a(H_2O) - pK_a(R'CH_2CO_2R)$, while for step two, $\Delta G°_2 = [\Delta H°(NuH) - \Delta H°(NuC)] + [\Delta H°(C{=}C) - \Delta H°(CH)] - T\Delta S°$. Thus, it follows that overall $\Delta G°_{total} = \Delta G°_t = \sum \Delta G°_i = [-1.37[pK_a(NuH) - pK_a(R'CH_2CO_2R)]] + [[\Delta H°(NuH) - \Delta H°(NuC)] + [\Delta H°(C{=}C) - \Delta H°(CH)] - T\Delta S°]$.

From these simple considerations, one can clearly see the role played by the pK_a difference between the conjugate acids of the nucleophile and the ester enolate upon the position of the overall equilibrium. Our objective was to make a reasonably minor perturbation to the original monoactivated substrate which would lead to a decrease in $\Delta G°_t$ relative to the monoactivated Michael acceptor system. To achieve this goal, we elected to utilize a doubly activated unsaturated ester (an alkylidene malonate) as the substrate since the pK_a of the conjugate acid of the enolate resulting after the conjugate addition is substantially lower than that of the monoactivated system and ought to thereby lead to a favorable shift in the equilibrium. Of course, simply shifting the equilibrium to the right does not guarantee the formation of a larger amount of the MIRC product, since changing from a less to a more highly stabilized enolate could lead to a reduction in the rate of ring closure, thereby still allowing the S_N2 process to compete favorably with the MIRC reaction.

*Fellow of the Alfred P. Sloan Foundation.

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(2) (a) Cooke, M. P., Jr. *Tetrahedron Lett.* **1979**, 2199–2202. (b) Ghera, E.; Ben-David, Y. *Ibid.* **1979**, 4603–4604. (c) Mpango, G. B.; Mahalanbis, K. K.; Mahdavi-Damghani, Z.; Snieckus, V. *Ibid.* **1980**, 4823–4826. (d) Mpango, G. B.; Snieckus, V. *Ibid.* **1980**, 4827–4830. (e) Ponton, J.; Helquist, P.; Conrad, P. C.; Fuchs, P. L. *J. Org. Chem.* **1981**, *46*, 118–122.

(3) For an excellent and thorough discussion which presents a general equation which represents the relationship between product ratio and equilibrium see: Zefirov, N. *Tetrahedron* **1977**, *33*, 2719–2722.

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