protons[7] (Table I) on the linked carbons (C-8, 9, 12 and 13 in Figure 1). No couplings was observed between H-11 and H-12 as the dihedral angle is close to 90°. The NOE between the proton at 1-H and 3-Me(16-H) and one of the *gem*-dimethyls (19-H) indicated the locations of three methyls on the transoid diene system. 2D-NOE[8] of **1** (3-Me/1-H, 19-H(Me)/1H, 2-H/13-H, 13′-H/20-H(Me), 13′-H/7-Me) revealed the gross conformation which is similar to that of its oxidation product **2**.[9] The location of the *sec*-methyl was suggested from the NOE between the 20-Me and 11-H of **2**. ^{13}C NMR (25 MHz) data (C_6D_6) also indicated a bicyclic structure with three trisubstituted double bonds (Table I); the assignments are based on the (INEPT)[10] method, selective decoupling, and the comparison with the data of **2**.

Compound **2**, $C_{20}H_{32}O$ (*m/z* 288.2452, calcd 288.2498) was isolated from the stored (6 years at −20 °C) hexane extract of *C. ugandensis* soldier heads by column chromatography using 10:1 hexane/EtOAc over SiO_2. The tricyclic nature of compound **2** was disclosed from the ^{13}C NMR data, which showed the presence of one trisubstituted double bond, an exocyclic disubstituted double bond, and a strongly shielded triplet carbon (19.0 ppm, C-13; shielded by the 7,17-ene) (Table I). The ^{13}C NMR assignments are based on heteronuclear chemical shift correlation spectroscopy (CSCM).[11] ^1H NMR (360 or 300 MHz) with COSY,[6] 2D-NOE,[8] sequential additions of lanthanide shift reagent [Eu(fod)$_3$-d_{27}], extensive homonuclear difference decoupling, and NOE measurements allowed for complete proton assignments (Table I) and also established the relative configurations **2**. A possible biogenesis[12] of cubugene **1** together with the co-occurring irregular cubitene **3**[2] is shown in Figure 1.

Acknowledgment. We are grateful to Dr. Darlington for the second collection of *Cubitermes ugandensis*. We also thank the grants from the NSF, the A. P. Sloan Foundation, and the Camille and Henry Dreyfus Foundation.

Registry No. 1, 89890-83-5; 2, 89890-84-6; 3, 66723-19-1; bifloratriene, 69636-81-3; cembrene A, 31570-39-5.

(7) The present numbering is based on biogenetic considerations, even though the cubugene skeleton does not follow a regular head-to-tail biogenesis. The numbering differs from that employed earlier for the cooccurring cubitene **3**.[2]

(8) Kumar, A.; Wagner, G.; Ernst, R. R.; Wuthrich, K. *Biochem. Biophys. Res. Commun.* **1980**, *96*, 1156. We thank Dr. LeRoy F. Johnson of Nicolet Instrument, Freemont, CA, for the improved 2D-NOE pulse sequence.

(9) The compound **2** was obtained as the major oxidation product by treatment of **1** with *m*-chloroperbenzoic acid in CH_2Cl_2. The initial epoxidation is stereoselective, since the exo face of the 2,3-ene (the *re,re* face) is more readily accessible.

(10) Morris, G. A.; Freeman, R. *J. Am. Chem. Soc.* **1979**, *101*, 760. Morris, G. A. *Ibid.* **1980**, *102*, 428. Burum, D. P.; Ernst, R. E. *J. Magn. Reson.* **1980**, *39*, 163.

(11) Mandsley, A. A.; Kumar, A.; Ernst, R. R. *J. Magn. Reson.* **1977**, *28*, 463. Bax, A. "Two-dimentional Nuclear Magnetic Resonance in Liquids"; Kluwer Boston Inc.: Hingham, MA, 1981; p 61.

(12) We are grateful to a referee who suggested revision of a previous biogenetic scheme to the one shown.

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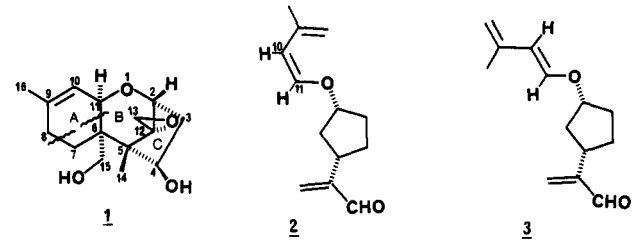
A Novel Type of Intramolecular Diels–Alder Reaction Involving Dienol Ethers: An Unusual Preference for a Boat Transition State in the Incipient Ring Formation

Summary: Cis and trans dienol ethers **2** and **3** have been stereospecifically synthesized and their intramolecular Diels–Alder reactions studied. While **3** did not cyclize upon prolonged heating, the cis dienol ether **2** underwent smooth cyclization through an unusual boat transition state to provide a novel trichothecane-like skeleton **13**.

Sir: Notwithstanding the extensive efforts directed at understanding the stereochemical outcome in the intramolecular Diels–Alder reaction, there have been few comparative studies reported on the reactivity and stereoselection imposed by the configuration at the diene moiety.[1,2] Furthermore, while 1-oxygenated dienes have been widely employed in the intermolecular Diels–Alder reaction,[3] there are virtually no examples known for the intramolecular version of this reaction.[2] As part of a synthetic approach toward a trichothecane skeleton such as verrucarol (**1**),[4] we had occasion to examine these aspects in the



1 **2** **3**

thermal cyclization using the two stereospecifically synthesized dienol ethers **2** and **3**. In the following, we report that while the latter did not change upon prolonged heating, the former underwent cyclization, involving a unique boat-like transition state during the formation of the incipient B ring, to provide a novel trichothecane-like skeleton.

The synthesis of the two stereoisomeric dienol ethers **2** and **3** commenced from the *exo*-methylene lactone **4**,[5,6] as summarized in Scheme I. Deprotonation of the α-alkoxy ester **5** with LDA followed by treatment with methacrolein afforded a 29:71 mixture of threo and erythro β-hydroxy esters **6a** and **6b**, respectively, in 87% yield.[7] These threo

(1) Reviews: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (b) Oppolzer, W. *Synthesis* **1978**, 793. (c) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63.

(2) After the completion of this manuscript, we learned that in a recent paper Burke et al. (*Tetrahedron Lett.* **1984**, *25*, 19) studied the configurational effect on the stereochemical outcome of the intramolecular Diels–Alder reaction using the 1-(silyloxy)-1,3-butadiene system (isomeric at the 3-ene).

(3) Reviews: (a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. (b) Petrzilca, M.; Grayson, J. I. *Synthesis* **1981**, 753.

(4) For the synthesis of the trichothecanes, see the following and references cited therein: (a) Trost, B. M.; McDougal, P. G.; Haller, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 383. (b) Roush, W. R.; D'Ambra, T. E. *Ibid.* **1983**, *105*, 1058.

(5) All new compounds reported herein have spectral (360-MHz ^1H and 90.56-MHz ^{13}C NMR, IR, UV, and MS) and microanalytical data consistent with the assigned structure.

(6) Obtained from norcamphor in five steps in 73% overall yield. The transformation involves: (i) MCPBA (1.4 equiv), $(CH_2Cl)_2$, reflux, 2 h (96%); (ii) LDA (1.2 equiv), THF, −78 °C, 1 h; Me_3SiCl (2.1 equiv). −78 °C to −20 °C, 2 h; (iii) $PhSCH_2Cl$ (1.2 equiv), $ZnBr_2$ (0.01 equiv), 20 °C, 16 h [88% overall yield for (ii) and (iii)]; (iv) $NaIO_4$ (1.3 equiv), $MeOH/H_2O/PhH$, 20 °C, 16 h; (v) PhH, reflux, 2 h [86% overall yield for (iv) and (v)].

(7) This result is in accord with the low stereoselection normally observed for the condensation of ester enolates with carbonyl compounds. For a recent review on the subject, see: Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521.

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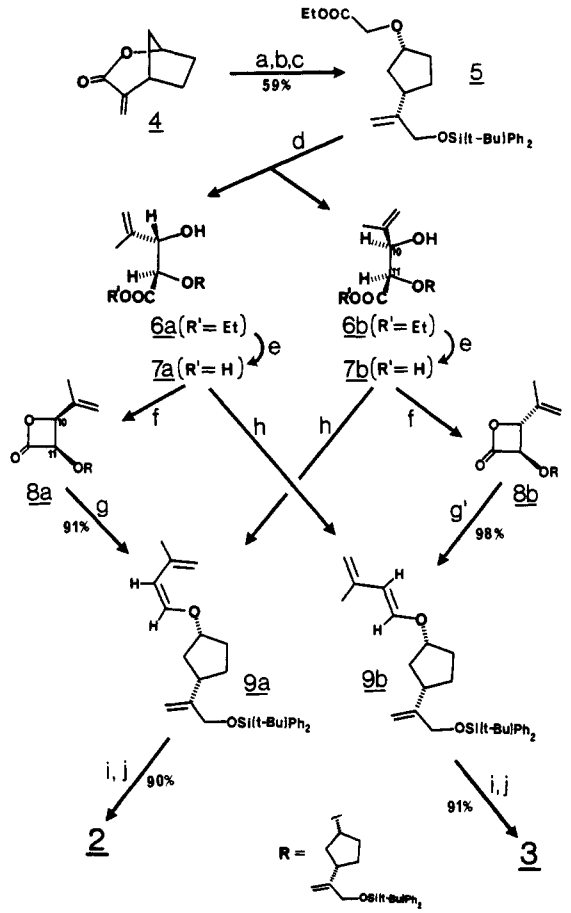
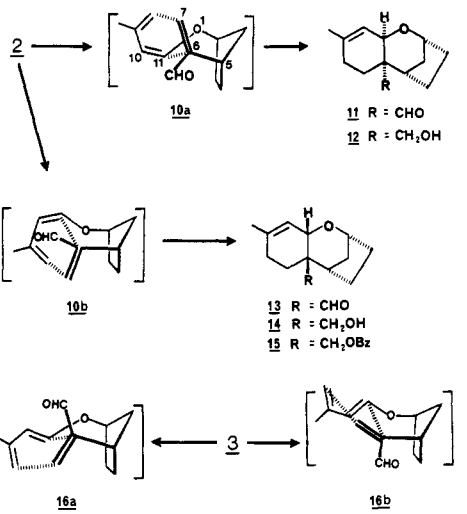
Scheme I[a]



[a] Conditions: (a) DIBAL (3 equiv), toluene, 20 °C, 2 h (89%); (b) $(t\text{-Bu})Ph_2SiCl$ (1.2 equiv), imidazole (2.6 equiv), DMF, −42 °C, 15 min (81%); (c) $N_2CHCOOEt$ (5 equiv), HBF_4 (0.1 equiv), CH_2Cl_2, 0 °C, 2 h (82%); (d) LDA (1.5 equiv), THF, −78 °C, 10 min; methacrolein (2.3 equiv), −78 °C, 1 h (87%); (e) LiOH (2.5 equiv), $MeOH/H_2O$, 20 °C, 8 h; (f) $PhSO_2Cl$ (5 equiv), pyridine, 0 °C, 1.5 h; (g) 190 °C (neat, sealed tube, anhydrous K_2CO_3), 5 min; (g') 140 °C (neat, sealed tube), 40 min; (h) DMF dineopentyl acetal (5.5 equiv), CH_2Cl_2, 20 °C, 5 h; (i) $(n\text{-Bu})_4N^+F^-$ (2 equiv), THF, 20 °C, 2 h; (j) Ag_2CO_3/Celite (16 equiv), benzene, reflux, 30 min.

and erythro isomers, each obtained as an equimolar mixture of diastereomers originating from the cyclopentyloxy moiety, were readily separated by silica gel flash column chromatography, or, more conveniently, by preparative HPLC.[8] The 360-MHz ^1H NMR showed $^3J_{10,11}$ of 5.8 (**6a**) and 5.5 Hz (**6b**), thus preventing unambiguous stereochemical assignments at this stage. Elaboration of the two dienol ethers **9a** and **9b** was accomplished from β-hydroxy acids **7a** and **7b** by two stereospecific decarboxydehydration methods as illustrated in Scheme I. Thus, treatment of **7a** and **7b** with $PhSO_2Cl$/pyridine provided β-lactones **8a** (cis, $^3J_{10,11}$ = 6.0 Hz) and **8b** (trans, $^3J_{10,11}$ = 3.8 Hz) in 77% and 72% yields from their corresponding β-hydroxy esters, respectively.[9] Thermolysis of **8a** and **8b** cleanly gave rise to cis and trans dienol ethers **9a** ($^3J_{10,11}$ = 7.1 Hz) and **9b** ($^3J_{10,11}$ = 12.8 Hz), respectively, in excellent yields. On the other hand, exposure of β-hydroxy acids **7a** and **7b** to DMF dineopentyl acetal led to the stereospecific formation of trans and cis dienol ethers **9b** (86% from **6a**) and **9a** (91% from **6b**), respectively.[10] When these two methods were combined, each of the dienol ethers **9a** and **9b** was obtained over 98% stereochemically pure in 63% and 68% overall yields, respectively, from the ester **5**.[11]

Scheme II



The possible transition states for the thermal cycloaddition of the two dienol ether aldehydes **2** and **3**[12] are shown in Scheme II. All the exo transition states,[13] two each for **2** and **3**, were excluded from considerations, as they were deemed either infeasible (for those from **2**) or unfavorable due to severe nonbonding interactions between the hydrogens at C-10 and those on the cyclopentyl ring (for those from **3**). The two endo transition states from the trans dienol ether **3**, **16a** and **16b**, did not appear to involve obvious serious steric repulsions and would have led to the isomeric *trans*-tetrahydrochromane systems. In contrast, the cis dienol ether **2** was expected to produce, via endo transition states, two isomeric *cis*-tetrahydrochromanes **11** and **13** upon thermal cyclization.

In an intramolecular Diels-Alder reaction leading to a 6,6-carbocyclic ring system, the carbon atoms connecting the diene and the dienophile moieties are expected to adopt the more stable cyclohexane conformation in the transition state.[14] Electron diffraction studies[15] of the hydrocarbon bicyclo[3.2.1]octane revealed that the chair conformation i is the only detectable disposition of the

i ii

molecule. In addition, the boat form ii has been calculated to be 6.45 kcal/mol less stable than the chair form i.[16]

(8) A 57 mm × 30 cm Waters Prep PAK-500 silica cartridge was used on a Waters Prep 500 instrument with an 88:12 hexanes/ethyl acetate mixture as an eluent.

(9) (a) Adam, W.; Baeza, J.; Liu, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 2000. (b) Mulzer, J.; Pointner, A.; Chucholowski, A.; Brüntrup, G. *J. Chem. Soc., Chem. Commun.* **1979**, 52.

(10) (a) Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1975**, 1545. Ruttimann, A.; Wick, A.; Eschenmoser, A. *Helv. Chim. Acta* **1975**, *58*, 1450.

(11) This new, highly efficient, stereospecific synthesis of dienol ethers has been shown to be generally applicable. Details to be described as a separate account.

(12) The use of dienol ether aldehydes **2** and **3** was required for the cyclization reaction, since **9a** and **9b** did not cyclize even under forcing conditions (350 °C in decalin in a sealed tube under vacuum).

(13) Throughout the text, the terms endo and exo refer to the relative position of the aldehyde of the dienophile to the diene moiety.

(14) (a) Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 6289. (b) Taber, D. F.; Gunn, B. P. *Ibid.* **1979**, *101*, 3992.

(15) Mastryukov, V. S.; Osina, E. L.; Vilvok, L. V.; Hilderbrandt, R. L. *Zh. Strukt. Khim.* **1981**, *22*, 57.

These considerations led us to predict that the cycloadducts arising from the chair-like transition states **10a** and **16a** would be obtained preferentially upon thermolysis of the dienol ethers **2** and **3**.

Heating the cis dienol ether **2** at 170 °C (1.5 h, sealed tube) in decalin smoothly gave rise to the cycloadducts **13** and **11** with a high degree of stereoselectivity (ca. 60:1) in over 80% yield. However, unexpectedly, the major product proved to be **13** by comparison of the ^{1}H NMR spectra of the reduction products **12** and **14**[17] with that of authentic **12**.[18] The structure of **13** was further validated by a single-crystal X-ray analysis of the benzoate **15**.[19] Interestingly, the trans isomer **3** was found to be quite resistent to cyclization, even under much more drastic conditions (250 °C in decalin in a sealed tube for several hours).[20] The unexpected high stereoselectivity for the formation of **13** indicates a preference for the transition state possessing a boat conformation in the formation of the ring B. Efforts are currently underway in these laboratories to determine the factor(s) that favors this unusual boat transition state in the intramolecular Diels–Alder reaction.

Acknowledgment. We are grateful to the National Institutes of Health (ES-02851) for the support of this work and to the National Science Foundation for its contribution to the purchase of a Bruker 360-MHz NMR instrument. We thank Professor W. R. Roush for the authentic sample of **12** and its ^{1}H NMR spectrum. J.I.L. is grateful for a Rackham predoctoral fellowship during the course of this work.

(16) Maier, W. F.; Schleyer, P. von R. *J. Am. Chem. Soc.* **1981**, *103*, 1891.

(17) For **14**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.105 (ddd, 1 H, J = 2.2, 4.6, 12.7 Hz, 12β-H), 1.255 (t, 1 H, J = 4.3 Hz, OH), 1.42–1.67 (m, 5 H), 1.697 (s, 3 H, 16-H), 1.790 (m, 1 H, 3-H), 1.910 (m, 2 H, 8-H), 2.330 (d, 1 H, J = 12.7 Hz, 12α-H), 2.392 (dd, 1 H, J = 4.6, 6.5 Hz, 5-H), 3.357 (d, 2 H, J = 4.3 Hz, 15-H), 3.401 (d, 1H, J = 4.5 Hz, 11-H), 4.358 (s, 1 H, 2-H), 5.379 (dq, 1 H, J = 4.5 [d], 1.4 Hz [q], 10-H); ^{13}C NMR (90.56 MHz, $CDCl_3$) δ 22.71 (t), 23.19 (t), 23.61 (q), 27.65 (t), 30.20 (t), 34.32 (t), 38.00 (d), 42.36 (s), 64.18 (t), 65.64 (d), 75.45 (d), 120.65 (d), 138.80 (s).

(18) Roush, W. R.; D'Ambra, T. E. *J. Org. Chem.* **1980**, *45*, 3927.

(19) Performed by Dr. W. M. Butler (The University of Michigan).

(20) The fact that the cis dienol ether **2** is much more reactive than the trans isomer, contrary to the bimolecular case, is perhaps a reflection of the lower entropy of activation in the cycloaddition of **2** with respect to that of **3**, with higher population of conformers disposed for the cyclization.

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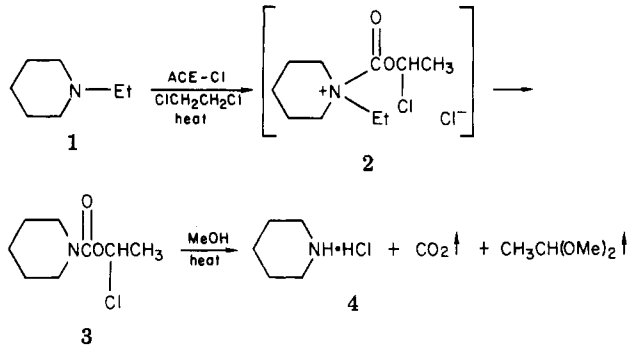
A New Reagent for the Selective, High-Yield N-Dealkylation of Tertiary Amines: Improved Syntheses of Naltrexone and Nalbuphine

Summary: Secondary amine hydrochlorides are obtained in high yield by reaction of tertiary amines with α-chloroethyl chloroformate followed by warming the intermediate carbamate in methanol.

Sir: We introduce here a new reagent, α-chloroethyl chloroformate (ACE-Cl), for the selective N-dealkylation of tertiary amines. While further development of the process is required (especially cleavage selectivity studies), we believe the initial results warrant bringing the new methodology to the early attention of synthetic chemists.

The new process is exemplified by the specific N-deethylation of *N*-ethylpiperidine (**1**) to give piperidine hydrochloride (**4**) in 99% yield. The reaction is performed



by adding ACE-Cl (1 equiv[1]) to **1** in $ClCH_2CH_2Cl$ at 0 °C (15 min) and then refluxing the mixture for 1 h. The intermediate ACE-piperidine **3** (bp 67–69 °C at 0.2 mm)[2] can be isolated but usually is de*ACE*ylated directly to **4** by evaporating the reaction mixture in vacuo and then heating the residue in MeOH (30–45 min at 50 °C to reflux).[1] Added H^+ is not needed to convert **3** to **4**. High-yield dealkylation with ACE-Cl is very surprising since other alkyl chloroformates (ROCOCl: R = Et, $PhCH_2$, Cl_3CCH_2) almost exclusively fragment to RCl + CO_2 in the presence of **1**.[3] Presumably the $CHClCH_3$ unit of **2** is too hindered to undergo competitive S_N2 attack by Cl^- and the related cation is too unstable to permit S_N1 substitution. In its reactivity toward **1**, ACE-Cl parallels the best previous chloroformate type N-dealkylation reagent, vinyl chloroformate (VOC-Cl).[3] However, ACE-Cl is much cheaper to make than VOC-Cl,[4] the yield of **4** is 99% (vs. 90% with VOC-Cl[3]), and in VOC removal,[3,5] HCl addition is required to convert VOC-piperidine to **3**. With ACE-Cl, this extra step is eliminated and the overall conditions are therefore much milder, thus expanding the list of functionalities permitted in the amine to be dealkylated.

With ACE-Cl (then MeOH), *N*-methylmorpholine is cleaved to morpholine·HCl in 96% yield and *N,N'*-dimethylpiperazine similarly is double N-demethylated to piperazine·2HCl in 96% overall yield. This selectivity is unexpected. In the mechanistically analogous von Braun dealkylation with BrCN, only ring scission products are obtained from both reactants.[6] However, as predicted benzyl cleavage is preferred over methyl loss: with ACE-Cl, glaucine (**5**) affords the ring-opened phenanthrene **6** (89% yield). Even dealkylation of aromatic amines occurs

(1) With complex amines, excess ACE-Cl is used. Reflux time is a function of amine complexity and difficulty of bond breaking; **1** is a simple amine with a very difficult bond to break. If the reaction medium is not dry, some starting amine is tied up as its HCl salt. If anhydrous conditions are unattainable, 0.05–0.2 equiv of H^+ scavenger (e.g., 1,8-bis(dimethylamino)naphthalene) can be included in the mixture. This should be protonated after reaction (with HCl gas) and removed from the reaction mixture (by filtration through silica) before methanolysis.

(2) Spectral and analytical data including high-resolution MS or combustion analyses are in accord with the structures proposed for all new compounds.

(3) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567.

(4) Liquid phosgene (1.1 equiv) is added to a stirred mixture of acetaldehyde (1.0 equiv) and $PhCH_2N^+(n\text{-}Bu)_3Cl^-$ (0.05 equiv., reusable) (dry ice condenser to mediate exothermic process). After 1 h, excess phosgene is removed by aspiration (in hood! through traps!). The ACE-Cl is distilled at room temperature and 4 mm into a −60 °C trap and then purified by reduced pressure distillation (96% yield of bp 77 °C at 180 mm). **Note:** Review phosgene safety precautions before repeating! Cagnon, G.; Piteau, M.; Senet, J.-P.; Olofson, R. A.; Martz, J. T. Eur. Pat. Appl. EP 40 153 [*Chem. Abstr.* **1982**, *96*, 142281y].

(5) Olofson, R. A.; Yamamoto, Y. S.; Wancowicz, D. J. *Tetrahedron Lett.* **1977**, 1563. Olofson, R. A.; Schnur, R. C. *Ibid.* **1977**, 1571.

(6) Hageman, H. A. *Org. React.* (*N.Y.*) **1953**, *7*, 198.

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