spectrum, m/e (relative intensity) 255 (parent, weak), 195 (25), 135 (100), 107 (12), 82 (25).

(-)-Hastanecine (1). To a suspension of 1.00 g (26.3 mmol) of lithium aluminum hydride in 60 mL of tetrahydrofuran was added 1.05 g (4.11 mmol) of diacetate **54** in one portion. The mixture was heated under reflux for 30 min and cooled to room temperature. To the mixture was added sequentially 1.5 mL of tetrahydrofuran, 500 mL of water, 500 μL of 6% aqueous sodium hydroxide, and 500 μL of water. The resulting slurry was stirred for 5 min and filtered through Celite. The filtrate was concentrated in vacuo to give 1.09 g of a white solid which was chromatographed over 50 g of silica gel (methanol–concentrated ammonium hydroxide, 50:1) to give 582 mg (90%) of (-)-hastanecine (1): mp 112.5–113.5 °C (lit.[28] mp 113–114 °C); $[\alpha]^{25}_D$ -9.72° (*c*, 1.15 methanol), $[\alpha]^{25}_D$ -10.0° (*c*, 0.725 ethanol) [lit.[25] $[\alpha]^{20}_D$ -10.0° (*c*, 0.43 ethanol), $[\alpha]_D$ -9.1° (*c*, 0.43 methanol)]; IR (CH_2Cl_2) 3300 (br) cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 1.58–1.80 (m, 1 H), 1.86–2.05 (m, 2 H), 2.05–2.22 (m, 1 H), 2.45–2.58 (m, 4 H, NCH, OH and CH), 2.60–2.75 (m, 1 H, NCH), 3.19–3.35 (m, 3 H, NCH and NCH_2), 3.59 (dd, J = 10.6, 7.6 Hz, 1 H, OCH_2), 3.86 (dd, J = 10.8, 4.2 Hz, 1 H, OCH_2), 4.08–4.17 (m, 1 H, OCH); mass spectrum, m/e (relative intensity) 157 (parent, 8), 113 (18), 82 (100); exact mass calcd for $C_8H_{15}NO_2$ m/e 157.1103, found, m/e 157.1108. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.11; H, 9.62. Found: C, 61.11; H, 9.47.

1(*R*)-Acetoxy-7-(acetoxymethyl)-1,2,5,7a(*S*)-tetrahydro-3*H*-pyrrolizin-3-one (55). To 370 mg (0.97 mmol) of iodo amide **52** in 30 mL of dry benzene was added 190 mg (1.25 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in one portion. The solution was stirred at room temperature until TLC analysis showed no **52** was left (3.5 h) and diluted with 30 mL of dichloromethane. The mixture was concentrated in vacuo and the residual dark brown oil (598 mg) was chromatographed over 60 g of silica gel (ethyl acetate–hexane, 3:2 gradually increased to 2:1) to give 201 mg (81%) of diacetate **55** as a yellow oil: IR(CH_2Cl_2) 1745, 1705, 1240 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 2.03 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3), 2.76 (dd, J = 9, 3 Hz, 2 H, CH_2CO), 3.50–4.23 (m, 1 H, NCH), 4.25–4.90 (m, 4 H, NCH and OCH_2), 5.00–5.40 (m, 1 H, OCH), 5.87 (br s, 1 H, =CH).

(-)-Heliotridine (2). To a solution of 101 mg (0.40 mmol) of diacetate **55** in 6 mL of dry tetrahydrofuran was added 99 mg (2.6 mmol) of lithium aluminum hydride in one portion. The mixture was heated at reflux for 30 min followed by dilution with 15 mL of tetrahydrofuran and sequential addition of 100 μL of water, 70 μL of 6% aqueous sodium hydroxide, and 100 μL of water. The resulting slurry was stirred for 5 min and filtered through Celite. The filtrate was concentrated in vacuo to give 49 mg of a yellow oil which was chromatographed over 15 g of silica gel (methanol–concentrated ammonium hydroxide, 50:1) to give 38 mg (62%) of **2** as a pale yellow crystalline solid: mp 116–117 °C (lit.[28] mp 117.5–118 °C); $[\alpha]^{18}_D$ -31.9° (*c*, 0.35 methanol), $[\alpha]^{18}_D$ -32.1° (*c*, 0.35 ethanol) [lit.[28] $[\alpha]^{18}_D$ +32.0° (*c*, 10.0 methanol)]; IR (CH_2Cl_2) 3300 (br) cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.55–2.00 (m, 2 H, CH_2), 2.50–2.80 (m, 1 H, NCH), 3.05–3.45 (m, 2 H, NCH), 3.55–4.25 (m, 5 H, OCH_2, NCH and OCH), 5.15 (br s, 2 H, OH), 5.45 (br s, 1 H, =CH); mass spectrum, m/e (relative intensity) 155 (20, parent), 110 (55), 93 (16), 79 (100), 67 (15); exact mass calcd for $C_8H_{13}NO_2$ m/e 155.0946, found m/e 155.0950.

Acknowledgment. We thank Richard Weisenberger for recording mass spectra at The Ohio State University Chemical Instrument Center. Financial support from the National Institutes of Health is gratefully acknowledged. We also thank the NIH for a grant (GM-27431) to Ohio State University in support of the acquisition of a Bruker WM-200 MHz NMR spectrometer used during the course of this research.

Supplementary Material Available: Experimental procedures for the preparation of **6a**, **6b**, **7**, **8**, **9**, **11b**, **11c**, **12b**, **12c**, **13**, **14a**, **15**, **26a**, **26b**, **26c**, **27a**, **27b** (11 pages). Ordering information is given on any current masthead page.

2-Siloxy-Substituted Methyl Cyclopropanecarboxylates as Building Blocks in Synthesis: Efficient One-Pot Conversion to γ-Butyrolactones

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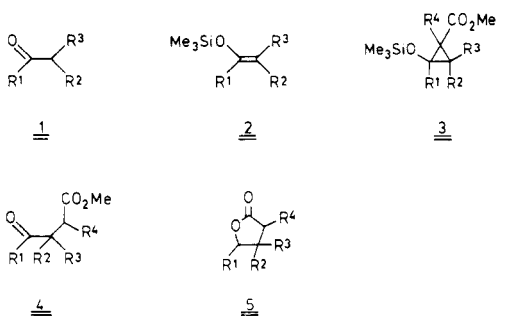
A high-yield one-pot transformation of the easily available 2-siloxy-substituted methyl cyclopropanecarboxylates **3** to γ-butyrolactones **5** is described. According to the regioselective preparation of **3**, isomeric lactones **5** can be synthesized without problems. Modified procedures delivering α-deuterated or side-chain functionalized lactones are disclosed.

Due to the occurrence in natural products and other biologically active molecules,[1] γ-butyrolactones (dihydro-2(3*H*)-furanones) are highly desirable targets in organic synthesis.[2] In addition, they can be versatile starting materials for other important compound classes (e.g., furans, cyclopentenones, etc.).[3]

Chart I



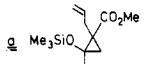
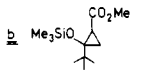
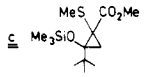
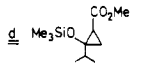
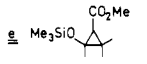
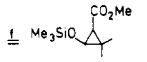
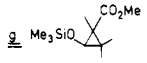
1 2 3 4 5

(1) Nakanishi, K.; Goto, T.; Ito, S.; Nalori, S.; Nozoe, S. "Natural Products Chemistry"; Kodansha Ltd: Tokyo, 1974.

(2) Reviews: (a) Kröper, H. "Methoden der Organischen Chemie"; Houben-Weyl-Müller, Ed.; Thieme: Stuttgart, 1963; Vol VI/2, p 561. (b) Boyd, G. V.; Wolfe, J. F.; Ogliaruso, M. A. "The Chemistry of Acid Derivates"; Patai, S., Ed.; Wiley: New York, 1979. For some very recent methods, see: (c) Giese, B.; Hasskerl, T.; Lünig, U. *Chem. Ber.* **1984**, *117*, 859. (d) Hoppe, D.; Lichtenberg, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 241. (e) Costisella, B.; Gross, H.; Schick, H. *Tetrahedron* **1984**, *40*, 733. (f) Tamaru, Y.; Mitzutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079. For an enantioselective synthesis of γ-butyrolactones, see: (g) Roder, H.; Helmchen, G.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Angew. Chem.* **1984**, *96*, 895.

0022-3263/85/1950-0242$01.50/0

Table I. Conversion of Methyl 2-Siloxycyclopropanecarboxylates 3 to γ-Butyrolactones 5

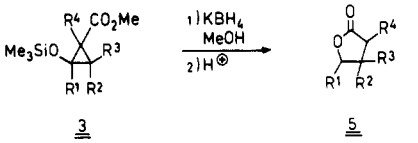
entry	starting material 3	γ-butyrolactone 5	yield
a			78 % [a]
b			91 %
c			90 % [b]
d			95 %
e			95 %
f			92 %
g			89 %

[a] 1.7:1 mixture of stereoisomers. [b] 1:1 mixture of stereoisomers.

Recently we described the very efficient and flexible synthesis of methyl 2-siloxycyclopropanecarboxylates **3** (R^4 = H) by [2 + 1]-cycloaddition of (methoxycarbonyl)carbenoid (from methyl diazoacetate) to silyl enol ethers **2** (obtained from **1**).[4] Even large-scale preparations (up to 0.5 mol) of **3** have been performed in high yield. A fourth substituent R^4 can be introduced by a newly developed deprotonation–alkylation sequence (Chart I).[5] Various modes of ring cleavage lead to 4-oxoalkanoate derivatives, e.g., **4**, in good to excellent yields, thus establishing **3** as very versatile building blocks in organic synthesis.[6] Here we want to present the results of our efforts in converting **3** into γ-butyrolactones **5**.[7]

Results

After some experimentation we found that treatment of **3** with potassium borohydride[8] in methanol for 16 h at room temperature and acidic workup[9] affords the desired γ-butyrolactones **5** by a very simple one-pot procedure in excellent yields and with high purity (eq 1, Table I).

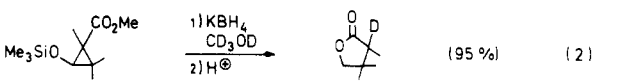


(1)

3 **5**

The multistep reaction very likely starts with desilylation of **3** by potassium methylate (generated in situ from KBH_4 and MeOH) and ring opening to the methyl 4-oxoalkanoate **4**. Reduction forming the corresponding methyl 4-hydroxyalkanoate is followed by lactonization to **5**. In accordance with this mechanism, no reaction occurs if tetrahydrofuran instead of methanol is used as solvent. Therefore the direct attack of the hydride reagent at C-2 of **3** is unlikely.[10]

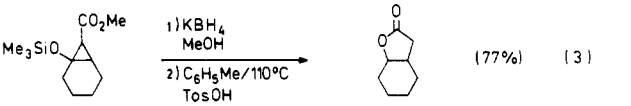
Corresponding to the regioselective synthesis of **3**[4,5] from **1** via **2**, isomeric γ-butyrolactones **5** can easily be constructed (entries d, e, and g). The simple preparation of α-propenyl- or α-(methylthio)-substituted γ-butyrolactones is promptly achieved (entries a and c). Other functionalities should be introducible by this protocol. Where the ring opening/reduction of **3g** is performed in CD_3OD, a 95% yield of α-deuterated γ-butyrolactone **5g'** is obtained (eq 2). Thus, a shortcut way to prepare specifically labeled compounds **5** is established.



(95 %) (2)

3g **5g'**

With **3h** complete conversion into the bicyclic lactone **5h** cannot be realized by the standard one-pot procedure. A mixture of **5h** and the corresponding hydroxy ester is isolated. However, changing the workup and refluxing in toluene with a catalytic quantity of *p*-toluenesulfonic acid cleanly gives **5h** in satisfying yield (eq 3). Since prolonged

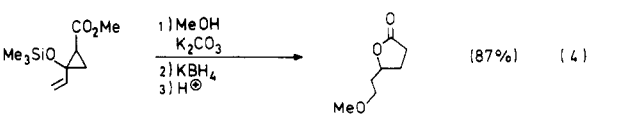


(77%) (3)

3h **5h** (cis : trans = 1:1.5)

heating of **5h** under the acidic cyclization conditions does not alter the cis/trans ratio, the 1:1.5 distribution reflects the stereoselectivity of the reduction step.[11]

Not surprisingly cyclopropane **3i** gives a complex mixture of products if the standard procedure is used.[12] As **3i** can be cleaved into **4i** followed by addition of suited nucleophiles to give functionalized 4-oxoalkanoic esters,[7] we made use of this quality to prepare γ-butyrolactone **6** with a methoxy-substituted γ-side chain. This modified one-pot method consists of subsequent treatment of **3i** in methanol with a trace of potassium carbonate and potassium borohydride, which delivers after acidic workup a 87% overall yield of **6** (eq 4).



(87%) (4)

3i **6**

(3) See ref 2a and 2b. For some recent uses of γ-butyrolactones: (a) Jalali, M.; Boussac, G.; Lallemand, J.-Y. *Tetrahedron Lett.* **1983**, *24*, 4307. (b) Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130. (c) Cavicchioli, S.; Savoia, S.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1984**, *49*, 1246.

(4) Kunkel, E.; Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, *512*.

(5) Reichelt, I.; Reissig; H.-U. *Liebigs Ann. Chem.* **1984**, 531.

(6) (a) Kunkel, E.; Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 802. (b) Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 820. (c) Reissig, H.-U. *Tetrahedron Lett.* **1981**, *22*, 2981. (d) Reichelt, I.; Reissig, H.-U. *Synthesis* **1984**, 786. (e) Reichelt, I.; Reissig, H.-U. *Tetrahedron Lett.*, in press.

(7) Grimm, E. Diploma Thesis, University of Würzburg, 1984.

(8) Use of $NaBH_4$ in the same manner also delivers γ-butyrolactones **5**; however, yields are lower and products are contaminated with varying amounts of **4** and the corresponding 1,4-diols.

(9) In several examples we also got good yields of **5** by neutralizing the reaction mixture instead of acidifying (e.g., 90% **5b**). However, occasionally this workup procedure gave less clean products containing traces of trimethylsilylated compounds. Nevertheless γ-butyrolactones with acid-sensitive functional groups should become available by using this less harsh modification.

(10) Ring cleavage of cyclopropanes by nucleophiles: Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

(11) Isomerization to the thermodynamically more stable *cis*-lactone is possible under acid catalysis: Klein, J. *J. Am. Chem. Soc.* **1959**, *81*, 3611.

(12) Synthesis of **5i** from **3i** might be possible by addition of $CeCl_3$. Compare: Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

Since nucleophiles different from methanol can easily be introduced (e.g., amines, nitroalkanes)[7] and since other vinylcyclopropanes of type **3i** are available, this one-pot multistep conversion should be of special interest for the efficient synthesis of γ-functionalized γ-butyrolactones.

Conclusion

There are some drawbacks of the method described here, if high stereoselectivity (entries a, c, eq 3) and disubstitution in α- and γ-position in **5** is required. However, the easy availability of the 2-siloxy-substituted methyl cyclopropanecarboxylates **3**, the cheapness of the reagents used, and the simplicity of the one-pot procedure should make our method very well suited for constructing γ-butyrolactones even in moderate to large scale. Since functional groups are introduceable by different modes, our regioselective overall transformation **1** → **5** using **3** as crucial intermediates should broaden existing synthetic methodology.

Experimental Section

Infrared spectra (IR) were recorded on a Beckman-Acculab 4 spectrometer in CCl_4. Nuclear magnetic resonance spectra (NMR) were obtained on a Varian T-60 or EM 390 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. Boiling points (bp) reported correspond to the oven temperature of a Büchi-Kugelrohr apparatus. Methanol was dried over 4-Å molecular sieves. Starting materials **3b,d,e,f,h,i** are from ref 4, and **3a,c,g** are from ref 5.

General Procedure. KBH_4 (0.54 g, 10.0 mmol) (EGA-Chemie) was gradually added to a solution of 10.0 mmol of **3** in 10 mL of dry MeOH at 0 °C. The ice bath was removed after 1 h, and the suspension was stirred for 16 h at 20 °C, then cooled to 0 °C, treated with 8 mL of 50% aqueous sulfuric acid, and diluted with water to give a clear solution. Standing overnight, the mixture was then extracted with 20 mL of CH_2Cl_2 3 times. The organic layers were dried (anhydrous $MgSO_4$) and concentrated, and the resulting **5** was Kugelrohr distilled.

Dihydro-5-methyl-3-(2-propenyl)-2(3*H*)-furanone (5a): 78% (bp 100 °C (1 mm)) as a 1.7:1 mixture of stereoisomers; ^1H NMR δ 1.1–3.0 (m, 5 H), 1.36, 1.41 (2 d, 3 H, 5-Me, J = 6.5 Hz), 4.3–4.8 (m, 1 H, 5-H), 4.9–5.3, 5.5–6.2 (2 m, 2 H, 1 H, H_2C=CH);[13] IR 1785 (C=O), 1645 (C=C).

5-*tert*-Butyldihydro-2(3*H*)-furanone (5b): 91% (bp 95 °C (4 mm), 74 °C (2 mm)[14]); ^1H NMR δ 0.95 (s, 9 H, 5-C_4H_9), 1.85–2.7 (m, 4 H, CH_2CH_2), 4.15 (t, 1 H, 5-H, J = 7 Hz); IR 1775 (C=O).

5-*tert*-Butyldihydro-3-(methylthio)-2(3*H*)-furanone (5c): 90% (bp 90 °C (0.2 mm)) as a 1:1 cis:trans mixture; ^1H NMR δ 0.88 (br s, 9 H, 5-C_4H_9), 2.20 (br s, 3 H, SMe), 1.4–2.9 (m, 2 H, CH_2), 3.3–3.8 (m, 1 H, 3-H), 4.0–4.45 (m, 1 H, 5-H); IR 1775 (C=O). Anal. Calcd for $C_9H_{16}O_2S$: C, 57.41; H, 8.70; Found: C, 57.87; H, 8.89.

Dihydro-5-isopropyl-2(3*H*)-furanone (5d): 95% (bp 100 °C (4 mm), 106–108 °C (20 mm)[15]); ^1H NMR δ 0.88, 1.10 (2 d, 2 × 3 H, Me, J = 6 Hz), 1.6–2.7 (m, 5 H, CH_2CH_2, CH), 3.95–4.3 (m, 1 H, 5-H); IR 1775 (C=O).

Dihydro-4,4,5-trimethyl-2(3*H*)-furanone (5e): 95% (bp 100 °C (4 mm), 88–89 °C (10 mm)[16]); ^1H NMR δ 0.96, 1.10 (2 s, 2 × 3 H, 4-Me), 1.22 (d, 3 H, 5-Me, J = 7 Hz), 2.30 (s, 2 H, 3-H), 4.20 (q, 1 H, 5-H, J = 7 Hz); IR 1785 (C=O).

Dihydro-4,4-dimethyl-2(3*H*)-furanone (5f): 92% (bp 100 °C (12 mm), 89 °C (10 mm)[17]); ^1H NMR δ 1.28 (s, 6 H, 4-Me), 2.38 (s, 2 H, 3-H), 4.00 (s, 2 H, 5-H); IR 1785 (C=O).

Dihydro-3,4,4-trimethyl-2(3*H*)-furanone (5g): 89% (bp 100 °C (4 mm); ^1H NMR δ 0.92, 1.08 (2 s, 2 × 3 H, 4-Me) 1.02 (d, 3 H, 3-Me, J = 7.5 Hz), 2.23 (q, 1 H, 3-H, J = 7.5 Hz), 3.80, 3.93 (AB signal, 2 H, 5-H, J = 12 Hz); IR 1770 (C=O). Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.43; Found: C, 65.32; H, 9.30.

3-Deuteriodihydro-3,4,4-trimethyl-2(3*H*)-furanone (5g′). Conditions were like the general procedure except CD_3OD was used, however, instead of MeOH: 95% (bp 100 °C (4 mm)); ^1H NMR δ 0.78, 0.95 (2 s, 2 × 3 H, 4-Me), 0.88 (s, 3 H, 3-Me), 3.70, 3.78 (AB signal, 2 H, 5-H, J = 12 Hz), no signal at ≈2.25 ppm corresponding to **5g**.

Hexahydrobenzo-2(3*H*)-furanone (5h). According to the general procedure **3h** was reacted with KBH_4 in MeOH. After 16 h, the mixture was brought to pH 5 by 2 N hydrochloric acid and extracted with 150 mL of toluene (3 portions). The extract was heated in a water separator for 8 h with 50 mg of *p*-toluenesulfonic acid, then cooled down, mixed with 50 mg of K_2CO_3, filtered, and concentrated. Kugelrohr distillation afforded 1.08 g (77%) of **5i** (100 °C (6 mm)) as a 1:1.5 cis:trans mixture; ^1H NMR δ 0.8–2.7 (m, 11 H), 3.5–3.9 (m, 0.6 H, 5-H, trans isomer), 4.43 (q, 0.4 H, 5-H, cis isomer J = 4 Hz);[18] IR 1790 (C=O).

5-(2-Methoxyethyl)dihydro-2(3*H*)-furanone (6). **3i** (1.05 g, 5.00 mmol) was dissolved in 5 mL of CH_3OH and mixed with 15 mg of K_2CO_3 at 5 °C. After being stirred for 16 h at room temperature, the solution was cooled to 0 °C and 0.27 g (5.00 mmol) of KBH_4 were added. Then the general procedure was followed, providing 623 mg (87%) of **6** (bp 100 °C (5 mm)): ^1H NMR δ 1.7–2.7 (m, 6 H), 3.37 (s, 3 H, OMe), 3.41 (t, 2 H, OCH_2, J = 6 Hz), 4.5–4.9 (m, 1 H, 5-H); IR 1785 (C=O). Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39; Found C, 58.49; H. 8.64.

Acknowledgment. Generous support of this work by the Deutsche Forschungsgemeinschaft is gratefully appreciated.

Registry No. **3a**, 93781-84-1; **3b**, 77903-42-5; **3c**, 90288-81-6; **3d**, 90288-80-5; **3e**, 90288-87-2; **3f**, 77903-45-8; **3g**, 77903-55-0; **3h**, 79646-62-1; **3i**, 90288-82-7; *cis*-**5a**, 93757-77-8; *trans*-**5a**, 93757-78-9; **5b**, 21175-44-0; *cis*-**5c**, 93757-79-0; *trans*-**5c**, 93757-80-3; **5d**, 38624-29-2; **5e**, 23461-76-9; **5f**, 13861-97-7; **5g**, 1679-56-7; **5g**, 93757-81-4; *cis*-**5h**, 24871-12-3; *trans*-**1h**, 27345-71-7; **6**, 93757-82-5.

(13) Frochaux-Zeidler, E. L.; Testa, B. *Pharm. Acta Helv.* **1979**, *54*, 229.
(14) Loewen, P. C.; Mukhuba, L. P.; Brown, R. K. *Can. J. Chem.* **1972**, *50*, 1502.
(15) Raphael, R. *J. Chem. Soc.* **1947**, 805.
(16) Ruzicka, L. *Helv. Chim. Acta* **1942**, *42*, 188.
(17) Krishnamurty, S.; Vreeland, W. B. *Heterocycles* **1982**, *18*, 265.
(18) Herz, W.; Glick, L. A. *J. Org. Chem.* **1963**, *28*, 2970.