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Synthesis of 3-Alkyl-2-benzamido-4-hydroxybut-2-enoic Acid γ-Lactones from Alkyl Cuprates. Attempted Transformation to 2,3-Diamino Carboxylic Acids by Hydrogenation and Curtius Rearrangement

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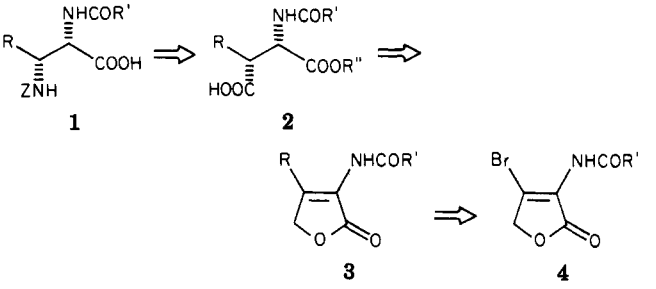
The reaction of lithium dialkylcuprate reagents with 2-benzamido-3-bromo-4-hydroxybut-2-enoic acid γ-lactone (**8**) gave the corresponding 3-alkylbut-2-enoic acid γ-lactone derivatives **3**. With lithium dimethylcuprate, a low yield of product was obtained; however, use of a new combined cuprate reagent, $(CH_3)_2CuLi$–CH_3Li–BF_3, provided 3-methylbut-2-enoic acid γ-lactone (**10**) in good yield. Reaction with lithium di-*n*-butylcuprate, and subsequent oxidative quenching with nitrobenzene, furnished in good yield the 3-*n*-butyl derivative **11**. The cuprate prepared from the acetonide of (*S*)-4-chlorobutane-1,2-diol, when coupled by the same procedure, gave the chiral lactone **15**; product **15** is of interest as a synthetic precursor to streptolutine, the amino acid component of the dioxopiperazine antibiotic 593A. Two key steps, reduction and Curtius rearrangement, were studied for the conversion of 2-(acylamino)but-2-enoic acid γ-lactones to 2,3-diamino carboxylic acids. The unsaturated lactone **10** underwent reduction with palladium on carbon at 80 °C and 300 psi of hydrogen; under these conditions the benzamido aromatic ring also was reduced. The Curtius rearrangement was studied for conversion of the aspartic acid monoamide **18** and related compounds to the corresponding 2,3-diamino carboxylic acids. The effect of selected amino and carboxyl protecting groups on the course of the rearrangement reaction was determined.

A general, stereocontrolled synthetic route to 2,3-diamino carboxylic acids is of interest. Such diamino carboxylic acids are natural constituents of amphomycin,[1] aspartocin,[2] the edeines,[3] the tuberactinomycins,[4] bleomycin,[5] and antibiotic 593A.[6] The penicillins and cephalosporins are a class of well-known antibiotics that contain a 2,3-diamino carboxylic acid unit incorporated into the penam and cephem structures. A synthesis of the *erythro*- and *threo*-2,3-diaminobutyric acids has been reported,[7a] while various routes to L-2,3-diaminopropanoic acid are known.[7b-f] Hydrolysis of a β-lactam has been employed for the preparation of L-2,3-diaminopropanoic acid;[7f] therefore, the current interest[8] in stereospecific carbon-carbon functionalization at C-4 of monocyclic β-lactams provides a potential entry to this class of amino acids.

Scheme I. Retrosynthesis of *threo*-2,3-Diamino Carboxylic Acids



An approach to the threo series of various 3-alkyl-substituted 2,3-diamino carboxylic acids **1** from 2-(acylamino)-3-bromo-4-hydroxybut-2-enoic acid γ-lactone (**4**)

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(4) Yoshioka, H.; Aok, T.; Goko, H.; Nakatsu, K.; Noda, T.; Sakakibara, H.; Take, T.; Nagata, A.; Abe, J.; Wakamiya, T.; Shiba, T.; Kaneko, T. *Tetrahedron Lett.* **1971**, 2043.

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Table I. Substitution Reactions of Dialkylcopper-Lithium Reagents with *N*-Benzoyl-3-bromo-2,3-didehydrohomoserine γ-Lactone (8)

8 **10**, R = Me; **11**, R = *n*-Bu

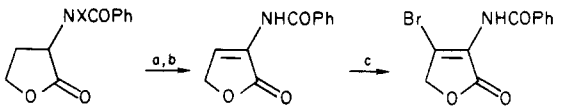
entry	alkyl cuprate (equiv)	reaction conditions	quenching	product	yield,[a] %
1	Me_2CuLi (1.5)	THF, 0 °C, 2 h	3 N HCl, 0 °C	**10**	26-29
2	Me_2CuLi (1.5)	THF, −30 °C, 1.5 h	3 N HCl, −30 °C	**10**	19
3	Me_2CuLi (1.5)	THF, −50 °C, 1.5 h	3 N HCl, −50 °C	**10**	30
4	Me_2CuLi (1.5)	THF, −78 °C, 1.5 h	3 N HCl, −78 °C	**10**	25
5	Me_2CuLi (1.5)	THF, 0 °C, 2 h	MeI, 0 °C	**10**	23
6	Me_3CuLi_2 (1.5)	THF, 0 °C, 2 h	MeI, 0 °C	*b*	*b*
7	Me_2CuLi, $MeBF_3Li$ (1.5)	THF, 0 °C, 2 h	3 N HCl, 0 °C	**10**	57
8	$MeBF_3Li$ (2.0) + **8**; then add Me_2CuLi (2.0)	THF, 0 °C, 30 min	3 N HCl, 0 °C	**10**	78
9	$(n\text{-Bu})_2CuLi$ (1.5)	THF, −66 °C, 1 h	3 N HCl, −78 °C	**7**	37[c]
				8	8
				11	55
10	$(n\text{-Bu})_2CuLi$ (1.5)	THF, −66 °C, 1.5 h	3 N HCl, −78 °C	**7**	30[c]
				11	70
11	$(n\text{-Bu})_2CuLi$ (1.5)	THF, −66 °C, 1.5 h	$PhNO_2$, −40 °C	**11**	78[a]
12	**14** (1.5)	THF, −66 °C, 1.5 h	$PhNO_2$, −40 °C	**15**	91

[a] Yields reported are for isolated, purified product. [b] Complex mixture formed. [c] As analyzed by NMR.

(or *N*-acyl-3-bromo-2,3-didehydrohomoserine γ-lactone) is envisioned, as outlined in a retrosynthetic analysis in Scheme I. The 3-amino function is introduced, with retention of configuration, by Curtius rearrangement[9] of a dicarboxylic acid monester **2**. Compound **2** is derived from a dehydrohomoserine derivative, **3**, by a sequence of reduction, occurring with cis stereochemistry, followed by opening of the lactone ring and oxidation of the primary alcohol to the carboxylic acid. The 3-alkyl group is introduced by coupling of a dialkylcopper–lithium reagent with the 3-bromo-2,3-didehydrohomoserine **4**.[10,11] The nature of these reactions will afford adequate stereocontrol, leading to the threo configuration. Indeed, if asymmetric reduction of the carbon–carbon bond in **3** is achieved, this would lead to a synthesis of **1** in an enantiomerically enriched form. In principle, this method can lead directly to derivatives having two different protecting groups on the amino functions and, thus, allowing differentiation between these sites.

Cuprate Coupling Reaction. *N*-Benzoyl-2,3-didehydrohomoserine γ-lactone (**7**) was prepared from **5**[12] by a sequence involving N-chlorination to give **6**, followed by elimination–isomerization.[13] The N-chlorination of **5** occurred readily, the reaction being complete within minutes, with *tert*-butyl hypochlorite catalyzed by sodium tetraborate;[14] in contrast, catalysis of this reaction by sodium methoxide[13] was inefficient, with hours to days being required for a reasonable conversion of **5** to **6**. The elimination reaction leading to **7** (Scheme II), formed in 50% yield, also led to formation of an approximately equal amount of **5** and a minor amount (2%) of a product identified as the 3-chlorodehydrohomoserine γ-lactone **9**.[15]

Scheme II[a]



5, X = H; **6**, X = Cl **7** **8** **9** (Br replaced with Cl)

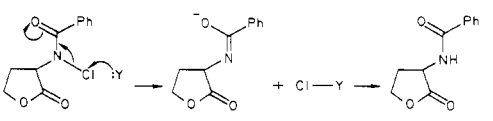
[a] (a) *t*-BuOCl, $Na_2B_4O_7$, MeOH; (b) Dabco, CH_2Cl_2; (c) Br_2 in CH_2Cl_2 and then Dabco.

Bromination of **7** and subsequent elimination[11,16] furnished the required *N*-benzoyl-3-bromo-2,3-didehydrohomoserine γ-lactone (**8**).

The substitution[11] of the vinyl bromide in **8** by reaction with different dialkylcopper–lithium reagents has been studied; the results of these studies are given in Table I. Lithium dimethylcuprate ($LiMe_2Cu$) upon reaction with **8** gave rather low yields (19–30%) of **10** regardless of variations in the reaction conditions or quenching methods used (entries 1–5). In contrast, $Li(n\text{-Bu})_2Cu$ provided **11** in good yield, with the yield being maximized by use of nitrobenzene to oxidatively quench[17] the reaction (entries 9–11).

Reinvestigation of the dimethylcuprate coupling reaction was undertaken. The reportedly more reactive Me_3CuLi_2[18] was investigated; however, a complex mixture of products

(15) The formation of **5** can be rationalized by attack of a nucleophile, Y (Y = Dabco or Cl^-), at chlorine of the *N*-chloro amide **6**. When the nucleophile is Cl^-, the molecular chlorine formed can lead to **9** by addition to the dehydro compound **7**, followed by elimination. We thank Professor D. A. Lightner for suggesting this to us.



6 **5**

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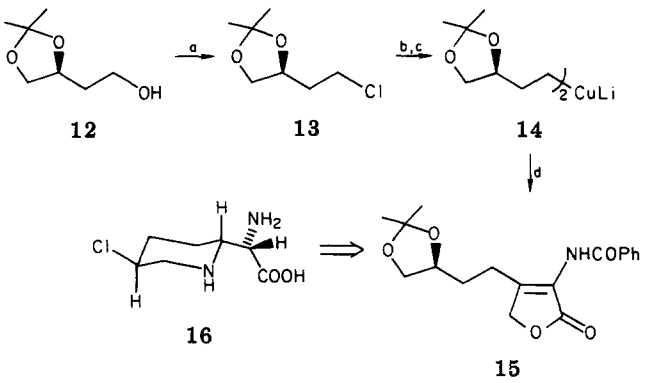
(18) Macdonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *9*, 5280.

Scheme III [a]



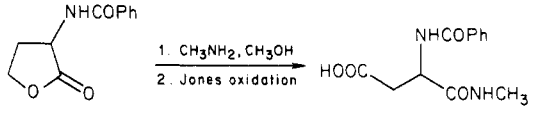
[a] (a) Ph_3P, CCl_4 (80%); (b) Li (1% Na), pentane; (c) CuI; (d) **8**.

was observed (entry 6). The reported[19] use of boron-modified alkylcuprates led us to study these reagents. To a solution of $LiMe_2Cu$ was added an equivalent of boron trifluoride etherate, which resulted in the formation of a dense yellow precipitate. Addition of 1 equiv of CH_3Li furnished a clear solution. To this solution was added the 3-bromohomoserine derivative **8**; after an acid workup of the reaction mixture, a 57% yield of **10** was obtained (entry 7).

We next studied the coupling reaction by the addition of **8** to a solution containing equal equivalents of CH_3Li and BF_3-Et_2O.[20] No reaction occurred, and **8** remained unchanged after a period of 30 min at 0 °C. A solution of 2 equiv of $LiMe_2Cu$ was prepared and added dropwise to the above reaction mixture. The coupling reaction occurred rapidly, and TLC analysis established the reaction to be complete following the addition of the cuprate. An acid quench, followed by workup of the reaction mixture, provided **10** in 78% yield (entry 8). This new, combined cuprate is an effective reagent for coupling a methyl group with **8** and is a superior combination for this reaction compared to $LiMe_2Cu$. A boron-mediated conjugate addition of a methyl cuprate to a hindered enone recently has been reported.[21]

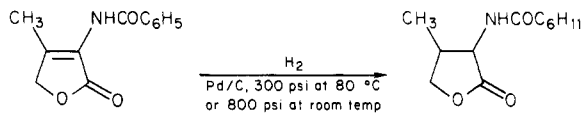
The chiral cuprate **14** was prepared from the known[22] triol acetonide **12** (Scheme III). Coupling of **14** with **8**, followed by oxidative workup by the addition of nitrobenzene, furnished the desired product **15**, isolated following chromatography in 93% yield. The increased yield in the coupling of **14** may be attributable to internal ligand stabilization.[23] Interest in **15** resulted from our plan for **15** to serve as a synthetic precursor to streptolutine (**16**), the amino acid component of the dioxopiperazine antibiotic 593A.[6] Transformation of **15** by the above-described sequence involving reduction of the carbon–carbon double bond followed by oxidation and Curtius rearrangement at C-4 of the lactone ring would give a 2,3-diamino carboxylic acid containing all of the carbons and suitably functionalized for conversion to streptolutine.[24]

Scheme IV



Reduction Studies. Reduction of 2-(acylamino)acrylic or cinnamic acid derivatives is well-known[25] and has been used, as mediated by use of chiral phosphine–rhodium catalysts, for preparation of α-amino acids of high enantiomeric purity.[26]

The parent dehydrohomoserine **7**, which lacks a 3-alkyl group, readily underwent catalytic reduction with Pd/C at 2–3 atm and ambient temperatures. We anticipated that the 3-methyl derivative **10**, being a tetrasubstituted alkene, would be more resistant to hydrogenation.[27] Reduction of **10** required rather forcing conditions, with reduction occurring at 300 psi and 80 °C with H_2 over Pd/C; reduction also occurred at 800 psi at room temperature. The benzene ring and the alkene function both were reduced under these conditions to yield a product whose ^1H NMR spectrum was consistent with that of γ-lactone **17**. We planned to study the reduction of **10**



with a chiral phosphine–rhodium homogeneous catalyst;[26] however, the known[28] decrease in enantioselectivity with increased hydrogen pressures for these catalysts caused us not to pursue this approach.[29]

Curtius Rearrangement Model Studies. 2,3-Diaminopropanoic acid has been prepared by the Curtius, Hofmann, and Schmidt reactions[7b–d] and, recently, from asparagine by reaction with bis[(trifluoroacetoxy)-phenyl]iodine.[7e] We have studied, as a model system, the Curtius rearrangement of N^1-methyl-2-benzamido-DL-aspartamide (**18**).

The aspartic acid derivative **18** was prepared from *N*-benzoylhomoserine γ-lactone **5** by a sequence involving amination and Jones oxidation (Scheme IV). Treatment of **18** with diphenylphosphoryl azide[30] (DPPA) at reflux in benzene, followed by addition of benzyl alcohol, gave a complex mixture of products. Amide and urethane functions are known to undergo intramolecular addition to the intermediate isocyanate formed in the rearrangement process.[31] Since **18** contained two amide groups, it was anticipated that this may be the case. β-Alanine and succinic acid derivatives were studied to more fully understand the effect of various amide and carboxyl functions on the course of the reaction (Table II).

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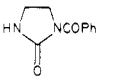
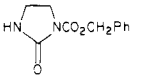
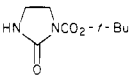
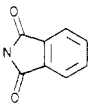
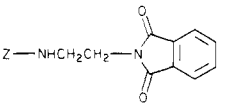
Table II. Curtius Rearrangement of β-Alanine and Succinic Acid Derivatives by Reaction with Diphenylphosphoryl Azide (DPPA)

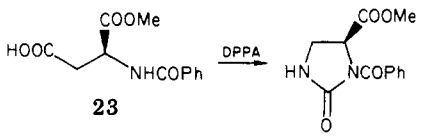
$$HOOCCH_2CH_2Y \xrightarrow[2.\ PhCH_2OH]{1.\ DPPA,\ PhH} \text{product (21 or 22)}$$

19 or 20

entry	reactant	Y	product	structure [a]	
1	19a	NHCOPh	21a		74
2	19b	$NHCO_2CH_2Ph$	21b		55
3	19c	$NHCO_2$-t-Bu	21c		27
4	19d		22a		65
5	20a	$COOCH_3$	22b	$Z\text{-}NHCH_2CH_2COOCH_3$	80
6	20b	$CON(CH_3)_2$	22c	$Z\text{-}NHCH_2CH_2CON(CH_3)_2$	60
7	20c	$CONHCH_3$	mixture of products		

[a] Z = $PhCH_2OCO$. [b] Yields reported are for purified product.

The results of the above study show that an amide or urethane function (entries 1–3, Table II), when properly situated, does react with the isocyanate intermediate to form the respective 1-acyl-2-imidazolidinones. In contrast, the methyl ester, phthalimido, and dimethylamido groups do not react with the isocyanate, which then undergoes reaction with benzyl alcohol to furnish the corresponding *N*-benzyloxycarbonyl derivatives (entries 4–6). However, the mono-*N*-methylsuccinamide (entry 7) gave a complex mixture of products, thus implicating the *N*-methyl carboxamide group as having a deleterious effect on the Curtius rearrangement in the two cases studied, i.e., entry 7 and compound **18**. As a final example, *N*-benzoyl-L-aspartic acid α-methyl ester (**23**) underwent smooth rearrangement to the imidazolidinone **24** in 60% yield.



23 24

Summary and Conclusions. A synthesis of 3-alkyl derivatives of *N*-benzoyl-2,3-didehydrohomoserine γ-lactone has been accomplished via coupling of the corresponding 3-bromo compound with lithium dialkylcuprates. This procedure likely will prove to be a reasonably general route to these compounds.

Studies on dehydrohomoserine derivatives involving hydrogenation and Curtius rearrangement as a potential route for the preparation of 2,3-diamino carboxylic acids have defined certain problems and limitations of the method. These limitations originate in the fairly stringent conditions for hydrogenation of the tetrasubstituted carbon–carbon double bond and in participation and side reactions by proximate amide functions during the Curtius rearrangement. Modification by use of more appropriate amino and carboxyl protecting groups, which we have shown not to trap the intermediate isocyanate, should prove beneficial. Likewise, application of bis[(trifluoroacetoxy)phenyl]iodine, a reagent shown to effect a Hofmann-like rearrangement without trapping by neighboring urethane or carboxamide functions,[7e] may be a more applicable procedure.

Experimental Section

All reactions involving organometallic reagents were run under a positive preessure of dry deoxygenated nitrogen or argon as indicated. Both gases were purified by being passed successively through a solution of triphenylmethyl anion in pyridine and concentrated sulfuric acid. ^1H NMR spectra were recorded on a Varian EM-360 or a JEOLCO MH-90 spectrometer. Chemical shifts are reported in δ units (parts per million relative to tetramethylsilane) in the indicated solvent. Coupling constants are reported in hertz. Mass spectra were obtained on a Bromma LKB 2091 GC-Ms or a Hitachi Perkin-Elmer RMU-6E at an ionizing voltage of 70 eV. IR spectra were recorded on a Perkin-Elmer 701B spectrophotometer. Optical rotations were recorded on a Perkin-Elmer 241 automatic polarimeter. Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Thin-layer chromatography was performed on a commerically prepared silica gel (PF-254) on glass plates. Visualization of compounds was performed with an ultraviolet light and iodide stain. Thick-layer preparative plates were prepared from silica gel 60 PF-254 on 20 cm × 20 cm glass plates. Column chromatography was accomplished by a medium-pressure system[32] using columns packed with silica gel (0.040–0.063 mm). Solvents used for elution are indicated in the text and are reported as volume percent. All solvents used were distilled in glass. For reactions requiring dry solvents, tetrahydrofuran was distilled from sodium benzophenone ketyl and transferred via syringe. Pentane, hexane, and dichloromethane were distilled from phosphorous pentoxide and stored over activated 3A molecular sieves. Methanol, pyridine, and polar solvents were dried over activated 3A molecular sieves for more than 48 h. Acetone was distilled from potassium permanganate. Boron trifluoride etherate and phosphorous oxychloride were distilled under vacuum (10 mm) and stored in Teflon-sealed glass vials under an inert atmosphere. All other reagents were used as purchased from the supplier. Glassware for experiments requiring anhydrous conditions were dried by a flame under a stream of the indicated purified inert gas. Reactions requiring the exclusion of light were conducted in flasks tightly wrapped with aluminum foil.

***N*-Benzoyl-*N*-chloro-DL-homoserine γ-Lactone (6).** *N*-Benzoyl-DL-homoserine γ-lactone (**5**) was prepared by the pro-

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cedure of Ohta[12] except that the reaction mixture was heated at reflux for 1 h before the workup. An ice-cold solution of 8.2 g (40 mmol) of **5** and 1.52 g (4 mmol) of sodium tetraborate in 52 mL of dry methanol was protected from light and treated with 8.2 mL (67 mmol) of *tert*-butyl hypochlorite. After 20 min, the methanol and excess *tert*-butyl hypochlorite were evaporated in vacuo at a bath temperature less than 35 °C. The residue was slurried in dry dichloromethane (75 mL) and quickly filtered through a medium-porosity fritted-glass filter to remove the insoluble sodium salts. The filtrate contained **6** and a small amount of starting material (<5%) and was used without further purification. The yield of **6** was approximately 95%: ^{1}H NMR ($CDCl_3$) δ 1.3 (s, *t*-BuOH), 2.5–2.95 (2 H, m), 4.1–4.8 (2 H, m), 5.4 (1 H, t), 7.3–7.9 (5 H, m); TLC R_f 0.24 ($CHCl_3$), 0.6 (EtOAc).

***N*-Benzoyl-2,3-didehydrohomoserine γ-Lactone (7).** To a chilled (0 °C), stirred solution of the crude *N*-chloro derivative **6** (9.58 g, 40 mmol) in dichloromethane (50 mL) was added 4.70 g (40 mmol) of 1,4-diazabicyclo[2.2.2]octane (Dabco) in 20 mL of dry dichloromethane. After stirring for 25 min at 0 °C, the cold solution was filtered. The filtrate was washed successively with 2 N hydrochloric acid and brine, dried over magnesium sulfate, filtered, and evaporated to dryness. The crude product contained approximately 49:49:2 mixture of **5/7/9**. Repeated crops of **7** were crystallized from acetone until **5** began to cocrystallize. The residual mixture was separated by medium-pressure liquid chromatography (MPLC) with silica gel 60 (230–400 mesh, E. Merck) and chloroform as the eluent. The small amount of the 3-chloro derivative **9** was not separated from **7**. The total yield of **7** was 4.1 g (50%); 3.8 g of **5** was recovered. The yield of **7** based on unrecovered **5** was 90%: mp 159–160 °C; ^{1}H NMR ($CDCl_3$) δ 5.05 (2 H, d), 7.3–8.6 (1 H + 1 H + 5 H, m, both vinyl and amide protons overlap aromatic region); TLC R_f 0.17 ($CHCl_3$), 0.7 (EtOAc), 0.5 (70:30 hexane–acetone). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.91. Found: C, 65.25; H, 4.47; N 6.91.

***N*-Benzoyl-3-bromo-2,3-didehydrohomoserine γ-Lactone (8).** To a stirred solution of 4.06 g (20 mmol) of **7** in 50 mL of dry dichloromethane was added dropwise over a period of 30 min 20 mL of 1.0 M bromine in dichloromethane. The solution was cooled to 0 °C and treated sequentially with a trace of hydroquinone and 2.31 g (20 mmol) of Dabco in 15 mL of dry dichloromethane. One minute after the addition of Dabco, the solution was filtered and washed with 1 N hydrochloric acid and brine. The solution was dried over magnesium sulfate and evaporated. Recrystallization from dry methanol yielded **8**: 4.0 g (70%); mp 163–165 °C. An analytical sample melted at 164.5–166 °C. Anal. Calcd for $C_{11}H_8BrNO_3$: C, 46.83; H, 2.86; N, 4.97. Found: C, 46.84; H, 2.79; N, 4.80.

The 3-chloro analogue **9** was similarly prepared in 40% yield; mp 166–165 °C. Anal. Calcd for $C_{11}H_8ClNO_3$: C, 55.6; H, 3.39; N, 5.89. Found: C, 55.3; H, 3.44; N, 5.92.

The spectral and TLC data for compounds **8** and **9** were identical: ^{1}H NMR (Me_2SO-d_6) δ 4.95 (2 H, s), 7.16–7.48 (3 H, m), 7.6–7.84 (2 H, m); TLC R_f 0.13 ($CHCl_3$), 0.69 (EtOAc).

General Procedure for R_2CuLi Coupling Reactions. Ultrapure CuI was added to a rigorously flame-dried flask under a dry inert gas. The flask and contents were gently flame dried again. Dry THF (30 mL/g of CuI) was added and the slurry cooled to the appropriate temperature for formation of the cuprate (i.e., 0 °C for dimethyl cuprate, −40 °C for di-*n*-butyl cuprate, and −30 °C for the chiral cuprate **14**). The appropriate organolithium reagent was added and stirred for approximately 30 min, and then the reaction mixture was cooled, if necessary, to a lower temperature for the coupling reaction. A tetrahydrofuran solution of the 3-bromo derivative **8** was added dropwise over 20–40 min and the reaction mixture stirred for the indicated time. The reactions were quenched as indicated (Table I) and worked up by pouring the mixture into 3 N hydrochloric acid or brine. The product was extracted with chloroform, treated with Norit, and dried over $MgSO_4/K_2CO_3$. After filtration through a Celite pad, the solution was evaporated and purified by MPLC on silica gel 60 with chloroform or hexane–acetone (90:10) as eluants.

Preparation of *N*-Benzoyl-3-methyl-2,3-didehydrohomoserine γ-Lactone (10) by Coupling with Me_2CuLi–MeLi–BF_3. A rigorously flame-dried, 50-mL, three-necked round-bottomed flask, equipped with a stirring bar, a gas inlet, a constant-flow dropping funnel with a gas outlet, and a serum cap was cooled to 0 °C under a positive pressure of argon. The cooled flask was then charged with 10 mL of dry THF, 0.25 mL of purified boron trifluoride etherate (2 mmol), and 1.7 mL of 1.2 M methyllithium in ether (2 mmol), and the mixture was stirred for 10 min. A solution of 0.28 g (1 mmol) of *N*-benzoyl-3-bromo-2,3-didehydrohomoserine γ-lactone (**8**) in 8 mL of dry THF was added, and the solution was stirred for 30 min. The dropping funnel was then charged with a solution of 3 mmol of lithium dimethylcuprate in THF–ether [prepared from cuprous iodide (0.28 g, 3 mmol), THF (7 mL), and methyllithium (2.5 mL of a 1.2 M solution in ether)]. The cuprate solution was added dropwise over 20 min to the cold reaction mixture. The reaction was quenched after 1 h by dropwise addition of 2.5 mL of 3 N hydrochloric acid. The reaction mixture was added to 50 mL of 3 N hydrochloric acid and extracted three times with 20-mL portions of dichloromethane. The combined extracts were treated with Norit and dried over magnesium sulfate. After filtration through a Celite pad and evaporation, the crude residue (210 mg) was chromatographed on a 20 cm × 20 cm preparative TLC plate with two developments by 70:30 hexane–acetone. The product was isolated to yield 170 mg (78%) of **10**. Recrystallization from ether produced an analytical sample: mp 177–178 °C; ^{1}H NMR ($CDCl_3$) δ 2.3 (3 H, s), 4.86 (2 H, s), 7.4–8.2 (6 H, m); TLC R_f 0.09 ($CHCl_3$), 0.57 (EtOAc), 0.5 (70:30 hexane–acetone). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.32; H, 5.14; N, 6.30.

***N*-Benzoyl-3-*n*-butyl-2,3-didehydrohomoserine γ-Lactone (11).** To a rigorously flamed out, 50-mL, three-necked, round-bottomed flask, equipped as described above for the preparation of **10**, was added 500 mg (2.64 mmol) of cuprous iodide under a rapid flow of nitrogen gas, and the apparatus was gently flame dried. The reaction flask was cooled to −40 °C (dry ice/acetone), and 15 mL of dry THF was injected via syringe. *n*-Butyllithium in hexane (3.3 mL, 1.6 M solution, 5.28 mmol) was added dropwise via syringe to the cuprous iodide slurry and stirred for 20 min. The cuprate solution was cooled to −66 °C, a solution of 500 mg (1.77 mmol) of **8** in 10 mL of dry THF was added dropwise, via the addition funnel, over 30 min, and the dropping funnel was rinsed with an additional 5 mL of dry THF. The reaction mixture was maintained at −66 °C for 1.5 h and then allowed to slowly (approximately 1 h) warm to −40 °C before being oxidatively quenched by the addition of 0.68 mL of nitrobenzene. After warming to room temperature, the reaction mixture was poured into 125 mL of 3 N hydrochloric acid or 125 mL of half-saturated aqueous sodium chloride. The aqueous solution was extracted three times with 50-, 25-, and 25-mL portions of chloroform. Filtration of the insoluble copper salts was accomplished as found necessary. The combined chloroform extracts were treated with Norit and dried over magnesium sulfate. After evaporation of the solvent, the crude reaction mixture was chromatographed by MPLC on a 15 mm × 100 cm column (silica gel 60, 230–400 mesh, E. Merck, with chloroform as the eluant) to yield 320 mg (74%) of **11**. Recrystallization of the product from water produced an analytical sample: mp 111–112 °C; ^{1}H NMR (acetone-d_6) δ 0.76–0.98 (3 H, m), 1.12–1.7 (4 H, m), 2.60 (3 H, t, J = 7 Hz), 4.92 (2 H, s), 7.34–7.62 (3 H, m), 7.88–8.08 (2 H, m); TLC R_f 0.09 ($CHCl)_3$, 0.73 (EtOAc), 0.30 (80:20 hexane/acetone). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.60; N, 5.40. Found: C, 69.42; H, 6.70; N, 5.10.

(*S*)-4-Chloro-1,2-*O*-isopropylidine-1,2-butanediol (13). A stirred solution of 9.89 g (67.6 mmol) of (*S*)-1,2-*O*-isopropylidine-1,2,4-butanetriol (**12**)[22] and 17.94 g (67.7 mmol) of triphenylphosphine in 20 mL of carbon tetrachloride[33] was heated to a gentle reflux at which time external heating was discontinued. After the reaction had subsided (approximately 20 min total reflux time), external heat was again applied and a gentle reflux maintained for 10 min. On cooling, the resultant solid mass of triphenylphosphine oxide was slurried in pentane, filtered, and washed with pentane. Evaporation in vacuo left a pale yellow oil. Kugelrohr distillation [50–60 °C (0.5 torr)] of the oil yielded 8.9 g (80%) of **13** as a clear oil; ^{1}H NMR ($CDCl_3$) δ 1.35 (3 H, s), 1.40 (3 H, s), 1.8–2.3 (2 H, m), 3.55–4.0 (3 H, m), 4.0–4.5 (2 H,

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m); TLC R_f 0.5 (80:20 hexane/acetone).

(S)-1,2-O-Isopropylidine-4-lithio-1,2-butanediol. A 50-mL three-necked flask, equipped as described above for preparation of **10** and containing 585 mg (25 mmol) of a 30% lithium (1% sodium) dispersion in mineral oil, was flame dried under a rapid flow of argon. After the flask cooled, the metal powder was washed free of mineral oil by two 10-mL portions of dry pentane. The residual metal powder was slurried in 10 mL of pentane, and 658 mg (4 mmol) of (S)-4-chloro-1,2-O-isopropylidine-1,2-butanediol (**13**) was added. The reaction mixture was refluxed gently for 30 min, cooled to room temperature, and filtered. The filtrate containing the above alkyllithium was used directly to form the corresponding cuprate.

(S)-N-Benzoyl-3-(3,4-O-isopropylidine-3,4-dihydroxybutyl)-2,3-didehydrohomoserine γ-Lactone (15). To a slurry of 282 mg (1.5 mmol) ultrapure copper(I) iodide in 10 mL of dry tetrahydrofuran cooled to −30 °C under argon was added 7.3 mL (approximately 3 mmol) of a freshly prepared solution of (S)-1,2-O-isopropylidene-4-lithio-1,2-butandiol in pentane. After 30 min at −30 °C, the resultant pale red solution was cooled to −65 °C, and a solution of 280 mg (1 mmol) of **8** in 8 mL of dry tetrahydrofuran was added dropwise over 45 min. The reaction was stirred for an additional 15 min at −65 °C and warmed slowly to −40 °C, and 0.34 mL of nitrobenzene was added to quench the reaction. After warming to room temperature, the reaction mixture was poured into dichloromethane (50 mL) and half-saturated brine (75 mL). The solution was filtered and the aqueous layer extracted twice more with 25-mL portions of dichloromethane. The combined dichloromethane solutions were treated with Norit and dried ($MgSO_4/K_2CO_3$, 1:1). After evaporation, the product was chromatographed (silica gel with chloroform as the eluant) to yield 300 mg (91%) of **15** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.33 (3 H, s), 1.4 (3 H, s), 1.5–2.1 (2 H, m) 2.83 (2 H, t), 3.4–3.8 (1 H, m), 3.95–4.4 (2 H, m), 4.93 (2 H, s), 7.4–8.13 (5 H, m), 8.35 (1 H, br s); TLC R_f 0.1 ($CHCl_3$), 0.5 (EtOAc). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.13; H, 6.50; N, 4.11.

Catalytic Reduction of N-Benzoyl-3-methyl-2,3-didehydrohomoserine γ-Lactone (10). To a solution of 96 mg (0.44 mmol) of **10** in 30 mL of absolute ethanol contained in a Parr high-pressure reaction vessel was added 50 mg of 10% palladium-on-charcoal. The vessel was twice purged with hydrogen and then pressurized to 800 psi at 25 °C. Periodic sampling revealed the slow consumption of starting material and concurrent production of a non-UV-active compound. After 35 h the reaction had gone to completion, and the excess hydrogen pressure was slowly released. The catalyst was filtered and the solution evaporated to dryness. The ^{1}H NMR of the white solid residue (100 mg) confirmed the loss of aromaticity in the product, and was consistent for compound **17**: ^{1}H NMR ($CDCl_3$) δ 0.8–2.3 (13 H, m), 2.86–3.33 (1 H, m), 3.33–3.8 (1 H, m), 3.97–5.0 (3 H, m), 6.2–6.7 (1 H, m); TLC R_f 0.30 (hexane/acetone, 70:30).

N^1-Methyl-N^2-benzoylhomoserinamide. Into an ice cold solution of 2.05 g (10 mmol) of N-benzoylhomoserine γ-lactone (**5**) in 20 mL of dry dichloromethane was slowly introduced 50–100 mmol of dry methylamine over 1 h. The solution was evaporated, and the residue was taken up in dichloromethane, washed successively with 1 N hydrochloric acid, saturated aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was recrystallized from absolute ethanol to give 2.26 g (96%) of product: mp 154–155 °C (lit.[34] mp 152 °C); ^{1}H NMR (Me_2SO-d_6) δ 1.8–2.2 (2 H, m), 2.65 (3 H, d), 3.4–3.75 (1 H, m, + 2 H, m), 4.4–4.8 (1 H, m, + 1 H, m), 7.4–8.2 (5 H, m), 8.58 (1 H, br d).

N^1-Methyl-N^2-benzoyl-DL-aspartamide (18). N^1-Methyl-N^2-benzoylhomoserinamide (473 mg, 2 mmol) was suspended in 80 mL of acetone. The solution was cooled to 10 °C, and 1.12 mL of Jones reagent (prepared by diluting 6.68 g of chromium trioxide and 5.75 mL of concentrated sulfuric acid to 25 mL with water) was added. The reaction mixture was stirred overnight at room temperature, following which excess oxidant was decomposed by addition of 10 drops of 2-propanol. After 30 min, the solution was filtered through Celite and evaporated to dryness. The residue was dissolved in a minimum amount of 1 N aqueous potassium hydroxide and reprecipitated by dropwise addition of 3 N hydrochloric acid. The white solid was collected, washed with ether, and air-dried to yield 460 mg (92%) of **18**: mp 187–189 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.4–3.0 (5 H, m), 4.6–5.1 (1 H, m), 7.4–8.15 (6 H, m), 8.5–8.9 (1 H, br d).

Curtius Rearrangement of β-Alanine and Succinic Acid Derivatives. The reactant β-alanine and succinic acid derivatives were prepared according to reported literature procedures: N-benzoyl-β-alanine (**19a**),[35] N-carbobenzoxy-β-alanine (**19b**),[36] N-[(*tert*-butyloxy)carbonyl]-β-alanine (**19c**),[37] N,N-phthaloyl-β-alanine (**19d**),[38] methyl succinate (**20a**),[39] N,N-dimethylsuccinamic acid (**20b**),[40] N-methylsuccinamic acid (**20c**),[41] N-benzoyl-*dl*-aspartic acid α-methyl ester (**23**).[42]

To a solution of the appropriate β-alanine (**19**) or succinic acid (**20**) (1 mmol) and 102 μL (1 mmol) of triethylamine in 3 mL of dry benzene was added a solution of 283 mg (1 mmol) of diphenylphosphoryl azide[30] in 2 mL of dry benzene. The reaction mixture was heated at reflux for 30 min after which 230 μL (2 mmol) of benzyl alcohol was added and the solution refluxed overnight. The solution was cooled, and the solvent was evaporated in vacuo. The residue obtained was purified by preparative TLC. The product, the development solvent, yield, and physical and spectral data are listed below.

N-Benzoyl-2-imidazolidinone (21a): EtOAc; 74%; mp 158–161 °C; mass spectrum, *m/e* (relative intensity) 190 (M^+), 105 (100), 85, 77; ^{1}H NMR ($CDCl_3$) 3.50–3.80 (2 H, t), 3.90–4.40 (2 H, t), 5.60–6.10 (1 H, br s), 7.10–7.90 (5 H, m); IR 1650, 1740 cm^{-1}.

N-Carbobenzoxy-2-imidazolidinone (21b): EtOAc; 55%; mp 113–114 °C; mass spectrum, *m/e* (relative intensity) 220 (M^+), 108, 91, 90, 86 (100), 85; ^{1}H NMR ($CDCl_3$/Me_2SO-d_6, 5:1) δ 3.10–3.70 (3 H, m), 3.80–4.20 (2 H, m), 5.30 (2 H, s), 7.47 (5 H, s); IR 1800, 1740 cm^{-1}.

N-(*tert*-Butoxycarbonyl)-2-imidazolidinone (21c): hexane/acetone (70:30); 27%; mp 107–110 °C; mass spectrum, *m/e* (relative intensity) 186 (M^+), 176, 86 (100), 85, 57; ^{1}H NMR ($CDCl_3$) δ 1.55 (9 H, s), 3.37–3.73 (2 H, m), 4.80–5.20 (2 H, m), 6.70–6.97 (1 H, br s).

N-Carbobenzoxy-N′,N′-phthaloyl-1,3-diaminoethane (22a). Compound **22a** was not purified by chromatography but was obtained by dilution of the reaction mixture with benzene, followed by washing the solution with saturated aqueous sodium bicarbonate, 0.5 N hydrochloric acid, and water and evaporation of the solvent in vacuo. The residue was recrystallized from hexane to give **22a**: 68%; mp 161–162 °C; ^{1}H NMR ($CDCl_3$) δ 3.46–3.72 (2 H, m), 3.79–4.06 (2 H, m), 5.10 (2 H, s), 7.40 (5 H, s), 7.70–7.94 (4 H, m).

N-Carbobenzoxy-β-alanine Methyl Ester (22b). Compound **22b** was not chromatographically purified but was worked up as for **22a**: 80%; oil, ^{1}H NMR ($CDCl_3$) δ 2.52 (2 H, t, J = 6 Hz) 3.46 (2 H, q, J = 6 Hz), 3.68 (3 H, s), 5.10 (2 H, s), 5.4 (1 H, br s), 7.33 (5 H, s); IR 1540, 1730 cm^{-1}.

N′,N′-Dimethyl-N-carbobenzoxy-β-alaninamide (22c): EtOAc; 60%; oil; ^{1}H NMR ($CDCl_3$) δ 2.40–2.67 (2 H, t, J = 6 Hz), 2.98 (6 H, s), 3.30–3.78 (2 H, m), 5.14 (2 H, s), 7.43 (5 H, s).

N^1-Benzoyl-5-(methoxycarbonyl)-2-imidazolidinone (24):[8a] EtOAc; 60%; mp 121–123 °C; mass spectrum, *m/e* (relative intensity) 248 (M^+), 189, 105 (100), 77; ^{1}H NMR ($CDCl_3$) δ 3.28–3.70 (2 H, m), 3.87 (3 H, s), 5.07 (1 H, dd), 6.17 (1 H, br s), 7.33–7.87 (5 H, m); IR 1760, 1740, 1680 cm^{-1}.

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Registry No. (±)-**5**, 82977-33-1; (±)-**6**, 82933-10-6; **7**, 82933-11-7; **8**, 82933-12-8; **9**, 82933-13-9; **10**, 82933-14-0; **11**, 82933-15-1; (*S*)-**12**, 32233-43-5; (*S*)-**13**, 69985-24-6; (*S*)-**15**, 82933-16-2; **17**, 82933-17-3; (DL)-**18**, 82933-18-4; **19a**, 3440-28-6; **19b**, 2304-94-1; **19c**, 3303-84-2; **19d**, 3339-73-9; **20a**, 3878-55-5; **20b**, 2564-95-6; **20c**, 56269-39-7; **21a**, 27034-77-1; **21b**, 55150-34-0; **21c**, 82933-19-5; **22a**, 82933-20-8; **22b**, 54755-77-0; **22c**, 23159-09-3; (L)-**23**, 82933-21-9; (*S*)-**24**, 82933-22-0; $MeBF_3Li$, 82977-34-2; Me_2CuLi, 15681-48-8; $(Bu)_2CuLi$, 24406-16-4; Me_3CuLi_2, 61278-42-0; DPPA, 26386-88-9; (*S*)-*N'*-methyl-*N*^{2}-benzoylhomoserinamide, 82933-23-1.

Synthesis of the Bottom Half of Chlorothricolide

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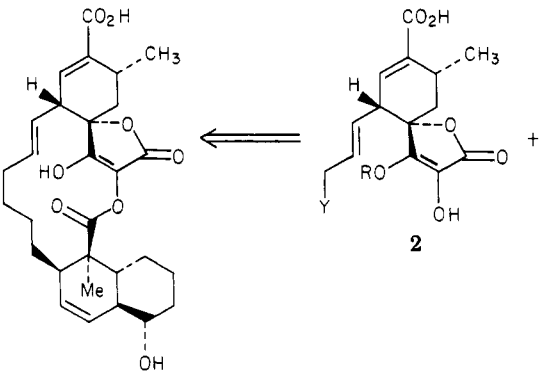
An efficient, stereoselective synthesis of lactone **5**, a synthetic equivalent of the bottom half of chlorothricolide (**1**) is described. The key steps of this synthesis are (i) the intramolecular Diels–Alder reaction of diene acetylene **13**, (ii) the dissolving metal reduction of unsaturated acid **34**, and (iii) the stereoselective alkylation of lactone enolate **44**. The overall yield of **5** is 15% for the 14-step sequence.

Introduction

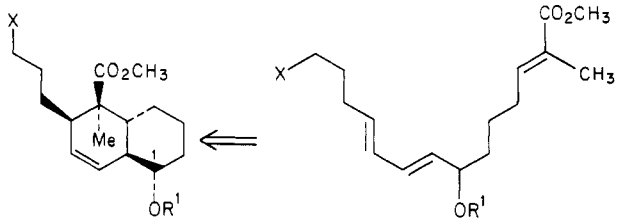
Chlorothricolide (**1**) is the aglycon of the antibiotic chlorothricin, which was isolated from *Streptomyces antibioticus* in 1969.[1] Chlorothricin is an inhibitor of pyruvate carboxylase and maleate dehydrogenase and is active against gram-positive bacteria.[2] Chlorothricolide methyl ester, produced by methanolysis of the natural product, retains some of the biological activity of chlorothricin itself.[3] Our original plan for the synthesis of **1** involved construction of the bottom half **3** by the intramolecular Diels–Alder reaction of **4**.[4] We recently reported a study of the intramolecular Diels–Alder reactions of a series of trienes in this structural series.[5] We found, however, that trienes of this type cyclize preferentially to cis- rather than trans-fused cycloadducts.[6] These results prompted us to explore a modified synthetic approach to the lower half of **1** (Scheme I).

We envisioned that hexahydronaphthalene **7**, a product of an intramolecular Diels–Alder reaction of diene acetylene **6**, might undergo a dissolving metal reduction to afford the desired trans-fused ring system **8**. Subsequent alkylation of this intermediate would afford the lower half **3** of chlorothricolide. Ideally, the two latter transformations would be accomplished in a single step via a reductive alkylation sequence.

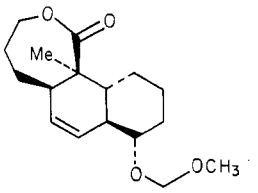
It seemed to us at the outset that the success of this plan would not be critically dependent on the protecting groups selected for **6** nor on the choice of the functionality present within the C-11 side chain. This assumption proved, however, to be incorrect, a conclusion which necessitated that two approaches to **3** be pursued. We describe herein



1 **2**



3 **4**



5

the results of these studies which culminated in an efficient, stereoselective synthesis of **3** (X = OH, R^1 = CH_2OCH_3) via lactone **5**.

Synthesis and Cyclizations of Diene Acetylenes 13 and 18. Condensation of 4-(benzyloxy)butyraldehyde **9**[8] with the lithium anion of 1-methoxybut-1-en-3-yne fol-

(1) (a) Keller-Schierlein, W.; Muntwyler, R.; Pache, W.; Zähner, H. *Helv. Chim. Acta* **1969**, *52*, 127. (b) Muntwyler, R.; Widmer, J.; Keller-Schierlein, W. *Ibid.* **1970**, *53*, 1544. (c) Muntwyler, R.; Keller-Schierlein, W. *Ibid.* **1972**, *55*, 2071. (d) Brufani, M.; Cerrini, S.; Fedeli, W.; Mazza, F.; Muntwyler, R. *Ibid.* **1972**, *55*, 2094.

(2) (a) Schindler, P. W.; Zähner, H. *Arch. Microbiol.* **1972**, *82*, 66; *Eur. J. Biochem.* **1973**, *39*, 591. (b) Pache, W.; Chapman, D. *Biochim. Biophys. Acta* **1972**, *255*, 348. (c) Schindler, P. W. *Eur. J. Biochem.* **1975**, *51*, 579.

(3) Schindler, P. W.; Scrutton, M. C. *Eur. J. Biochem.* **1975**, *55*, 543.

(4) Ireland and co-workers have recently reported their progress on the total synthesis of **1**: (a) Ireland, R. E.; Thompson, W. J.; Srouji, G. H.; Etter, R. *J. Org. Chem.* **1981**, *46*, 4863. (b) Ireland, R. E.; Thompson, W. J. *Ibid.* **1979**, *44*, 3041. (c) Ireland, R. E.; Thompson, W. J. *Tetrahedron Lett.* **1079**, 4705. (d) Ireland, R. E.; Thompson, W. J.; Mandel, N. S.; Mandel, G. S. *J. Org. Chem.* **1979**, *44*, 3583.

(5) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200.

(6) The endo/exo selectivity observed in these cyclizations was virtually independent of dienophile stereochemistry, a result previously observed in the thermal cyclizations of trienes in the perhydroindene series.[7]

(7) (a) Roush, W. R. *J. Org. Chem.* **1979**, *44*, 4008. (b) Roush, W. R.; Ko, A. I.; Gillis, H. R. *Ibid.* **1980**, *45*, 4264. (c) White, J. D.; Sheldon, B. G. *Ibid.* **1981**, *46*, 2273. (d) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269.

(8) Hurd, R. N.; Shah, D. H. *J. Org. Chem.* **1973**, *38*, 607. See also Wilson, C. L. *J. Chem. Soc.* **1945**, *87*, 45. Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1948**, *15*, 197.

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