Nucleophilic Displacements on an α-Chloro Thioether by Organocuprates: A Novel Synthesis of Desoxybiotin

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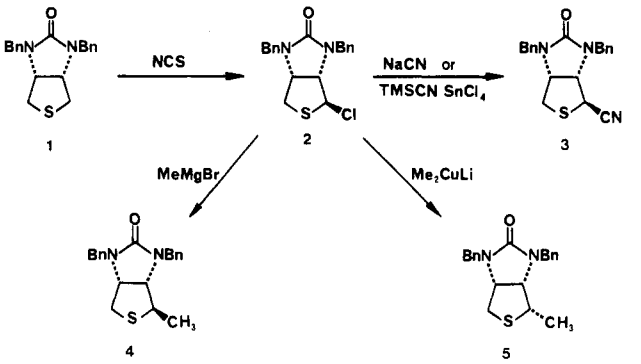
Reactions of organometallic reagents with α-chloro thioether **2**, which is readily prepared from thienoimidazolone **1**, have been investigated as an approach to the synthesis of biotin (**10**). Methyllithium and methylmagnesium bromide attack exclusively from the less hindered exo face, affording **4**, while lithium dimethylcuprate attacks from the endo face with inversion of configuration, affording **5**. Lithium dipentylcuprate affords predominantly exo isomer **6**, while halide-free lithium methylpentylcuprate affords predominantly endo isomer **7**. Debenzylation of **7** yields desoxybiotin (**9**) which can be microbially oxidized to biotin (**10**). Alternatively, **2** was hydrolyzed and oxidized to thiolactone **13**, a known precursor of biotin.

Recently we described an efficient synthesis of the biotin precursor, (3aα,6aα)-1,3-dibenzylhexahydro-1*H*-thieno-[3,4-*d*]imidazol-2(3*H*)-one (**1**) from abundantly available 2,5-dihydrothiophene 1,1-dioxide.[1,2] Conversion of **1** into the vitamin biotin (**10**) requires only stereospecific introduction of the pentanoate side chain and deprotection. The side chain has previously been appended stereospecifically to thienoimidazolone precursors by multistep transformations, such as reaction of thiolactone **13** with a Grignard reagent, followed by elimination and catalytic hydrogenation,[3] or alkylation of the anion of the exo sulfoxide derived from **1**.[4]

We decided to investigate a conceptually direct alternative route in which the side chain would be introduced by a formal nucleophilic displacement upon α-chloro thioether **2** by an organometallic reagent. In this approach, we planned to take advantage of the pronounced reactivity of α-halo thioethers toward nucleophiles and organometallic reagents.[5-7] In order to generate the required stereochemistry, an S_N2-like displacement on **2** with inversion from the highly hindered endo face was required. Although we recently observed that nucleophilic displacement by malonate on an α-chloro ether proceeded via an S_N2 mechanism with inversion of configuration,[8] the stereochemistry resulting from reaction of α-halo ethers or α-halo thioethers with organometallic reagents has received only scant attention.[9] Therefore our objective was to determine whether displacement upon α-chloro thioether **2** would occur with inversion via an S_N2-like mechanism as required or with retention of configuration via an S_N1 or single electron transfer mechanism.

Results and Discussion

N-Chlorosuccinimide readily chlorinates **1** α to the sulfur to produce **2** in essentially quantitative yield. Formation of **2** occurs via initial S chlorination, followed by migration analogous to the Pummerer rearrangement.[10,11] As expected, benzylic halogenation did not interfere.[13] When excess *N*-chlorosuccinimide was used, the symmetrical α,α′-dichloride accompanied the desired product. The 1.2-Hz ^1H NMR vicinal coupling constant of the anomeric proton in **2** demonstrates that chlorine occupies a pseudoaxial position exo to the ring as depicted.[14] Formation of the exo-chloro isomer was anticipated, based upon the greater steric accessibility of the exo face of **1** and the anomeric effect[11,15] which confers stability with respect to the endo-chloro isomer with which **2** is in potential equilibrium. In contrast to simple α-halo ethers and thioethers which are extremely labile,[10,11] **2** is stable for months and is not hydrolyzed in neutral aqueous media.



Initial experiments demonstrated that **2** was quite resistant to nucleophilic attack from the endo face. Thus treatment of **2** with dimethyl sodiomalonate under various conditions afforded only a low yield of a mixture of endo and exo malonates. Sodium cyanide in acetonitrile reacted with **2** to give a moderate yield of exo nitrile **3** formed via an S_N1 displacement. The stereochemistry of the exo nitrile **3** was obvious from the lack of vicinal coupling between the protons α and β to the nitrile. An authentic sample of **3** with identical properties was prepared by reaction of **2** with trimethylsilyl cyanide.[12] Formation of

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Table I. Reactions of 2 with Organometallic Reagents

reagent	equiv	mol LiX/ mol R_2CuLi[a]	temp, °C	time, h	solvent[b]	yield, %	prod ratio exo:endo
							4:5
MeMgBr	6.4	(0)	22	20	A	85	100:0
MeLi	2.5	(0)	−50 to −10	80	B	10	100:0
Me_2CuLi	5.0	3	−53	18	C	67	25:75
Me_2CuLi	3.4	1	−55 to 4	10	C	49	0:100
							6:7
$(pentyl)_2CuLi$	5.0	3	−78	30	A	72	60:40
$(pentyl)_2CuLi$	2.9	1	−60	13	A	58	50:50
pentyl(Me)CuLi	3.0	1	−60	11	A	53	40:60
pentyl(Me)CuLi	3.0	0	−60 to −55	12	A	42	35:65
$(pentyl)_2CNCuLi_2$	2.5	2	−78	12	B	21	100:0

[a] Moles of LiX per mol of organocuprate reagent. [b] Solvents: A = ether; B = THF; C = ether–THF (2:1).

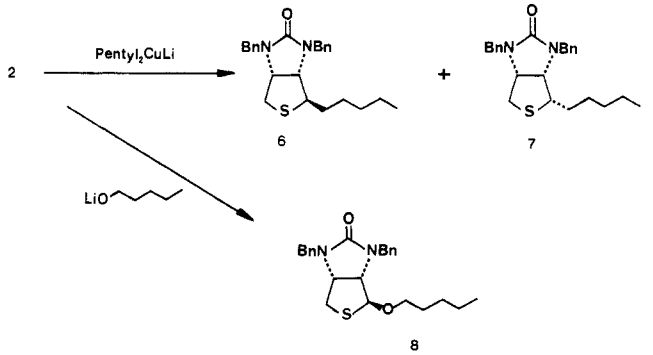
3 with NaCN in acetonitrile was accompanied by a curious reduction of 2 to 1 and a small amount of hydrolysis to thiolactol 12. Reaction of 2 with sodium cyanide in apparently anhydrous Me_2SO, followed by aqueous workup, afforded 12 exclusively.

Attention was now focused upon the reaction between α-chloro thioether 2 and organometallic reagents (Table I). As a model, 2 was treated with methyllithium and methylmagnesium bromide.[6] Methylmagnesium bromide reacted with 2 to produce a good yield of 4, the *undesired* product of exclusive attack from the less hindered exo face. Methyllithium also afforded 4, though in low yield. The stereochemistry of 4 was readily assigned by coupling constant analysis and by comparison with an authentic sample.[14] Formation of 4 by attack from the less hindered face presumably is the consequence of a single electron transfer mechanism of organometallic reactions and is consistent with previous observations that organometallic reagents react with optically active secondary alkyl halides to afford partially or totally racemic products.[16,17] A single electron transfer process is expected to be particularly favorable in the present case because a free radical at the carbon atom undergoing substitution can be stabilized by the adjacent sulfur atom.[13,18] Formation of 4 also indicates that chelation with the urea moiety does not direct approach of the organometallic from the endo face.

In order to achieve the desired displacement with inversion of configuration, we investigated the reactions of 2 with organocuprates (Table I). Organocuprates generally displace secondary halides with inversion of configuration.[19-22] To our knowledge, however, the reaction of an organocuprate with an α-halo ether or α-halo thioether has not been reported. We were concerned that the ability of the sulfur atom to stabilize an adjacent free radical[18] or carbonium ion[15] might preclude obtention of the desired inversion. In the event, however, when 2 was treated with lithium dimethylcuprate prepared from CuI and MeLi solution containing an equal concentration of LiBr (producing 1 mol of LiI and 2 mol of LiBr per mol of Me_2CuLi), a 25:75 mixture of exo isomer 4 and endo isomer 5 was formed. More gratifyingly, when 2 was treated with Me_2CuLi prepared from CuI and low-halide MeLi, completely stereoselective production of 5 via inversion of configuration resulted. The LiBr present in the former reaction may decrease stereoselectivity by attacking 2 with inversion, or by subtly changing the nature of the cuprate.[20]

The structure of 5 was unambiguously assigned by ^1H NMR and comparison with an authentic sample.[14] Several mechanisms for substitution reactions by organocuprates have been proposed which are consistent with the observed inversion of configuration. The available evidence does not allow a distinction to be made between an S_N2-like displacement, an oxidative displacement mechanism involving a formal copper(III) intermediate followed by a reductive elimination, or short-lived radicals.[19-23] Although accord concerning the mechanistic rationale for this inversion of configuration has not been reached, its utility for control of stereochemistry is of considerable significance.

We now turned our attention to the analogous displacement with lithium dipentylcuprate (Table I). Lithium dipentylcuprate prepared from a pentyllithium solution equimolar in LiBr reacted with 2 in ether at −78 °C to afford a 60:40 mixture of exo isomer 6 and endo isomer 7 in 72% yield. When the reaction was performed in a



mixture of THF and ether, a lower yield resulted. Use of lithium dipentylcuprate prepared from halide-free pentyllithium afforded a 50:50 mixture of 6 and 7. The stereochemistry of 7 was determined by coupling constant analysis[14] and by direct comparison with an authentic sample.[24,25] The stereoselectivity achieved in this dis-

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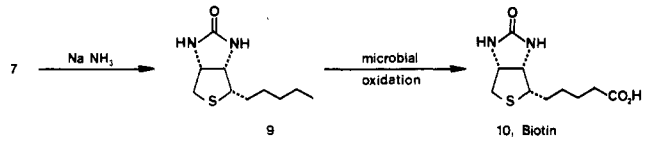
placement is apparently less dramatic than that achieved with lithium dimethylcuprate because of increased steric demand.[26] Therefore **2** was treated with the mixed lithium methylpentylcuprate which preferentially transfers pentyl rather than methyl.[20] This reagent gave a 40:60 ratio of **6** to **7** in the presence of 1 equiv of LiBr. A 35:65 ratio of **6** to **7**, the most favorable for our purposes, was obtained with halide-free lithium methylpentylcuprate.

Rigorously anaerobic conditions must be employed during the preparation of and use of cuprates from pentyllithium. Adventitious oxygen readily oxidizes pentyllithium to lithium pentyl oxide,[27] which reacts quite rapidly (1.5 h, −78 °C) with **2** to afford a high yield of **8**. Thus, lithium dipentylcuprate prepared from pentyllithium which had been stored for several weeks affords predominantly **8**, as does authentic lithium pentyl oxide. The structure of **8** was clear from its ^{1}H NMR and mass spectra and HCl-catalyzed hydrolysis to **12**. Carbon dioxide must also be excluded as it reacts with pentyllithium to produce 6-undecanone.[28]

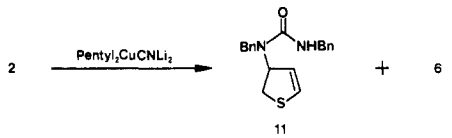
In order to complete the synthesis of biotin, **7** can easily be debenzylated with sodium in liquid ammonia or concentrated hydrobromic acid to afford desoxybiotin (**9**).[24]



9 10, Biotin

Transformation of the terminal methyl group into a carboxylic acid has been efficiently accomplished by microbial oxidation with various bacteria including *Corynebacterium* and *Pseudomonas* to yield biotin (**10**).[24]

An investigation of the reaction of **2** with the higher order mixed cyanocuprate $(pentyl)_2CuCNLi_2$ was made.



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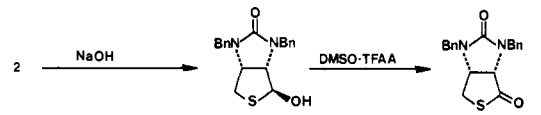
Higher order mixed cyanocuprates possess greater thermal stability than lower order organocuprates, generally display greater reactivity, and favor substitution over elimination and reduction.[20-22] Surprisingly, $(pentyl)_2CuCNLi_2$ at −78 °C afforded none of the desired endo product, **7**, but only a low yield of the exo product, **6**, as well as reduction to **1**, elimination to **11**, and further fragmentation to *N,N'*-dibenzylurea and (presumably) thiophene. A lower yield of **6** accompanied by more elimination resulted at higher temperature.

An alternative more conventional route to biotin was also pursued. α-Chloro thioether **2** was easily hydrolyzed to thiolactol **12**[3] with sodium hydroxide in dimethoxyethane and water. Interestingly, hydrolysis with sodium hydroxide in dioxane and water occurred 70 times slower. Thiolactol **12** was oxidized to the known thiolactone, **13**, with Me_2SO and trifluoroacetic anhydride.[29] The present synthesis of thiolactone **13** is more efficient and economical than previously reported syntheses.[3] Transformation of thiolactone **13** into biotin (**10**) can be accomplished via an eight-step reaction sequence which is employed in a commercial synthesis of biotin.[3]



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Experimental Section

NMR spectra were obtained on Varian HFT-80 (^{1}H NMR, 80 MHz, 5-mm probe), Varian CFT-20 (^{13}C NMR, 20 MHz, 8-mm probe), and Nicolet NT-300NB (^{1}H NMR, 300 MHz, 5-mm probe) (^{13}C NMR, 75 MHz, 5-mm probe) spectrometers. Low-resolution mass spectra were obtained on a Hewlett-Packard 5980A spectrometer with 70-eV electron impact ionization, and high-resolution mass spectra were recorded on a Kratos MS-30 spectrometer. Infrared spectra were recorded on a Unicam SP1000 spectrophotometer. Melting points are uncorrected. Analytical thin layer chromatography (TLC) was performed on EM 5539 silica gel 60 plates, and preparative flash chromatography was performed on EM silica gel 60 (0.040–0.063 mm).

All reactions were carried out under nitrogen and stirred magnetically unless otherwise stated. Reactions involving organometallic reagents were generally carried out under argon in glassware which was oven-dried and flushed with argon. Ether and THF were distilled from Na and benzophenone. Acetonitrile was distilled from CaH_2. Air- and moisture-sensitive reagents were transferred with gas-tight syringes or via cannulae. Organic phases were dried over anhydrous $MgSO_4$. Solvents were evaporated in vacuo on a rotary evaporator.

Lithium dialkylcuprates were prepared from alkyllithium and CuI. CuI (Aldrich) was purified by recrystallization from aqueous KI and washed with ether, and the resulting white powder was stored in vacuo over $CaSO_4$.[30,31] $(Pentyl)_2CNCuLi_2$ was prepared from pentyllithium and CuCN. CuCN (Aldrich) was dried by azeotropic removal of water with toluene and washed with ether, and the resulting grey powder was stored in vacuo. Methyllithium (low halide and complex with LiBr) was purchased from Aldrich.

(3aα,4α,6aα)-1,3-Dibenzyl-4-chlorohexahydro-1*H*-thieno-[3,4-*d*]imidazol-2(3*H*)-one (2). *N*-Chlorosuccinimide (1.09 g, 8.2 mmol, 105 mol %) (recrystallized from water, and dried in vacuo) was added over 5 min to a stirred solution of the thienoimidazolidone **1** (2.53 g, 7.8 mmol) in benzene (65 mL, dried over 4A sieves) at 15 °C. The mixture was pale yellow and heterogeneous. After 3 h the amount of starting material became constant (TLC) and was still detectable at the end of 5 h. After 6 h additional NCS (60 mg, 0.45 mmol, 6 mol %) was added. One hour later, the reaction was quenched with 40 mL of water and extracted three times with methylene chloride. The combined extracts were dried, and the solvent was evaporated to afford white crystalline **2** (2.79 g, 100% yield): mp 108–109 °C; IR ($CHCl_3$) 3020, 2980, 1700, 850 cm^{-1}; mass spectrum, *m/e* (relative intensity) 360 (13, M + 2), 358 (29, M$^+$), 325 (4), 91 (100); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.34 (10 H, m, Ar), 5.25 (1 H, d (J = 1.2), CH-Cl), 4.78, 4.61, 4.39, 4.21 (4 H, 4 d (J = 15.4), benzylic), 4.01 (1 H, ddd (J = 1.3, 3.6, 7.3), NCH), 3.96 (1 H, dd (J = 1.2, 7.3), NCH), 3.18 (1 H, dd (J = 3.6, 12.7), $CH_{exo}S$), 3.00 (1 H, dd (J = 1.3, 12.7), $CH_{endo}S$); ^{13}C NMR ($CDCl_3$) δ 159.0, 136.7, 136.6, 128.7, 128.2, 128.0, 127.9, 127.7, 72.7, 72.4, 60.0, 47.3, 46.2, 36.4.

Anal. Calcd for $C_{19}H_{19}N_2OSCl$: C, 63.59; H, 5.34; N, 7.81. Found: C, 63.70; H, 5.43; N, 7.92.

(3aα,4α,6aα)-1,3-Dibenzyl-4-cyanohexahydro-1*H*-thieno-[3,4-*d*]imidazol-2(3*H*)-one (3). A. A heterogeneous mixture of NaCN (>98% cyanide content, 26.1 mg, 0.533 mmol, 280 mol %), **2** (68 mg, 0.190 mmol), and acetonitrile (3 mL) were sealed in a flask and heated to 80 °C. After 12 h the solvent was evaporated. Addition of water and extraction into CH_2Cl_2 afforded crude product. Chromatography on silica gel eluted with hex-

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(25) An authentic sample of **7** was also prepared from **9** as described in the Experimental Section.

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ane–ethyl acetate (1:1) afforded **1** (30.7 mg, 50% yield) and **3** (26.4 mg, 40% yield).

B. To a solution of **2** (72 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) at 22 °C was added $SnCl_4$ (0.10 mL, 0.226 mg, 0.87 mmol, 434 mol %) dropwise. After 5 min trimethylsilyl cyanide (0.035 mL, 26 mg, 0.263 mmol, 130 mol %) was added. After 28 h, addition of water, extraction, and chromatography as above afforded **12** (24.5 mg, 36% yield) and **3** (31.4 mg, 45% yield): mass spectrum, *m/e* (relative intensity) 349 (4, M^+), 233 (19), 91 (100), 84 (20); ^1H NMR (300 MHz, $CDCl_3$) δ 7.19–7.3 (10 H, m, Ar), 4.72, 4.55, 4.41, 4.27 (4 H, d (J = 15), benzylic), 4.28 (1 H, d (J = 8.5), CHN), 4.24 (1 H, m, CHN), 3.62 (1 H, s, CHCN), 3.01 (1 H, dd (J = 3.8, 12.9), $CH_{exo}S$), 2.94 (1 H, d (J = 12.9), $CH_{endo}S$); ^{13}C NMR ($CDCl_3$) δ 158.6, 136.4, 129.1, 128.9, 128.7, 127.5, 117.5, 66.7, 61.0, 47.4, 46.4, 39.7, 37.5; HRMS calcd for $C_{20}H_{19}N_3OS$ *m/e* 349.1249, found 349.1243.

(3aα,4α,6aα)-1,3-Dibenzylhexahydro-4-methyl-1*H*-thieno-[3,4-*d*]imidazol-2(3*H*)-one (4). A solution of **2** (107.7 mg, 0.30 mmol) in benzene (1 mL) was treated with MeMgBr (0.4 mL, 2.40 M, 0.96 mmol, 320 mol %, in ether) at 10 °C for 1 h. Additional MeMgBr (320 mol %) was added, and the reaction was warmed to 22 °C and stirred for 20 h. After the normal extraction, the product was purified by chromatography to afford **4** (86.3 mg, 85% yield) identical in all respects with an authentic sample:[14] mass spectrum, *m/e* (relative intensity) 338 (9, M^+), 277 (14), 247 (13), 187 (13), 91 (100); IR ($CHCl_3$) 3050, 2970, 1690, 1450, 1360, 1250 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}N_2OS$: C, 70.97; H, 6.55; N, 8.31. Found: C, 70.61; H, 6.31; N, 8.16.

(3aα,4β,6aα)-1,3-Dibenzylhexahydro-4-methyl-1*H*-thieno-[3,4-*d*]imidazol-2(3*H*)-one (5). A. An ether solution of methyllithium (0.45 mL, 0.40 M, 0.18 mmol, 690 mol %, 0.05 M halide concentration) was added to CuI (16.6 mg, 0.087 mmol, 335 mol %) in THF (0.2 mL) at −60 °C to form lithium dimethylcuprate.[32] After 0.5 h, a solution of **2** (9.3 mg, 0.026 mmol) in THF (0.25 mL) was added while the bath temperature was maintained at −55 °C. The reaction was allowed to warm to −40 °C over 6 h, then to 4 °C over 4 h, then quenched with water, extracted three times with CH_2Cl_2, and purified by chromatography on silica gel (EtOAc–hexane, 67:33) to afford **5** (49% yield), identical in all respects with an authentic sample:[14] IR ($CHCl_3$) 3050, 2970, 1690 cm^{-1}; mass spectrum, *m/e* (relative intensity) 338 (9, M^+), 277 (12), 247 (8), 187 (8), 91 (100), 86 (26), 84 (32).

B. When **2** was treated under similar conditions with Me_2CuLi (496 mol %) prepared from MeLi containing an equal concentration of LiBr, a 1:3 mixture (67% yield) of **4** and **5** was obtained.

Pentyllithium Solution with LiBr.[31,33] 1-Bromopentane (2.0 g, 1.6 mL, 13 mmol) was added dropwise over 0.5 h to cleaned lithium containing 1% Na (0.512 g, 74 mmol, 224 mol %) in ethyl ether (15 mL) at 22 °C under argon. The cloudy reaction mixture was cooled to 4 °C, and additional 1-bromopentane (3.0 g, 2.51 mL, 20 mmol) was added dropwise over an additional 4 h. The resulting mixture was a cloudy white solution with slight residue of unreacted lithium. The solution was decanted with a cannula. Pentyllithium prepared in this manner was 1.5 M (diphenylacetic acid titration) and stable at room temperature for 1 week.

Low-Halide Pentyllithium Solution.[34] Lithium dispersion containing 1% Na (27.6 g dispersion in mineral oil, 1.0 mol, 220%) was washed with anhydrous ether under an argon atmosphere and suspended in anhydrous ether (200 mL). 1-Chloropentene (54.3 mL, 0.45 mol) was added dropwise over 3 h. After 2 h of further stirring, the precipitate was allowed to settle and the supernatant was removed through a cannula. After 3 days at 0 °C, additional LiCl precipitated and was removed by filtration through glass wool. Titration indicated 1.54 M pentyllithium and <0.05 M LiCl.

Reaction of 2 with Halide-Free Lithium Methylpentylcuprate. Methyl copper was prepared by the dropwise addition of methyllithium in ether (low halide, 1.6 M, 0.27 mL, 0.436 mmol, 309 mol %) to a suspension of CuI (83 mg, 0.436 mmol, 309 mol %) in diethyl ether (1 mL) under an argon atmosphere at −60 °C.[20] After 10 min stirring was stopped, and the yellow precipitate of polymeric methyl copper was allowed to settle. Halide-free methyl copper was obtained by removal of the supernatant through a cannula followed by an ether wash. Pentyllithium (low halide prepared above, 1.54 M, 0.29 mL, 0.447 mmol, 318 mol %) was added dropwise to the solid halide-free methyl copper prepared above at −60 °C. After 10 min, a solution of **2** (50.5 mg, 0.141 mmol) in ethyl ether (3 mL) was added slowly to the homogeneous colorless solution of lithium methylpentylcuprate. After 12 H at −55 °C the reaction was quenched by the addition of water (5 mL) and saturated ammonium chloride solution (3 mL) and allowed to warm to 22 °C. The resulting dark suspension was filtered. The deep blue filtrate was extracted with methylene chloride, dried, and evaporated in vacuo to afford crude **6** and **7** (66 mg).

(3aα,4α,6aα)-1,3-Dibenzylhexahydro-4-pentyl-1*H*-thieno-[3,4-*d*]imidazol-2(3*H*)-one (6). Flash chromatography (methylene chloride) afforded the exo isomer **6** (8 mg, 14% yield): mass spectrum, *m/e* (relative intensity) 394 (10, M^+), 347 (5), 303 (12), 277 (22), 265 (12), 187 (11), 91 (100); ^1H NMR (300 MHz, $CDCl_3$) δ 7.2–7.3 (10 H, m, Ar), 4.81, 4.80, 4.20, 4.14 (4 H, 4 d (J = 15.5), benzylic), 4.03 (1 H, ddd (J = 3.8, 5.4, 8.8), NCH), 3.67 (1 H, dd (J = 8.8, 2.5), NCH), 3.13 (1 H, m, SCH), 2.82 (1 H, dd (J = 12.5, 5.4), SCH_{exo}), 2.72 (1 H, dd (J = 12.5, 3.8), SCH_{endo}), 1.5 (2 H, m, $SCHCH_2$), 1.2 (6 H, m, $CH_2CH_2CH_2$), 0.86 (3 H, t (J = 7.0), CH_3); ^{13}C NMR ($CDCl_3$) δ 159.0, 137.3, 128.7, 128.1, 128.0, 127.6, 127.3, 64.7, 63.3, 59.1, 46.6, 44.9, 37.1, 31.4, 31.2, 30.0, 22.6, 13.8; HRMS calcd for $C_{24}H_{30}N_2OS$ *m/e* 394.2079, found 394.2093.

(3aα,4β,6aα)-1,3-Dibenzylhexahydro-4-pentyl-1*H*-thieno-[3,4-*d*]imidazol-2(3*H*)-one (7). A. Continued flash chromatography (methylene chloride) afforded endo isomer **7** (16 mg, 28% yield).

B. A mixture of **9**[24,35,36] (93.5 mg, 0.436 mmol), dioxane (8 mL, distilled from Na), and sodium hydride (75.8 mg, 3.16 mmol, 725 mol %) was heated to 50 °C for 10 min. Benzyl bromide (173 mg, 0.12 mL, 101 mmol, 232 mol %) was added and the mixture was heated to 65 °C for 3 h. The white precipitate (NaBr) was filtered and the filtrate evaporated to dryness then heated to 65 °C, 0.2 mmHg, to afford **7** (172 mg, 100% yield): mp 66–67 °C; mass spectrum, *m/e* (relative intensity) 394 (10, M^+), 347 (5), 303 (12), 277 (22), 265 (12), 187 (11), 91 (100); IR ($CHCl_3$) 3020, 2950, 1690, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19–7.36 (10 H, m, Ar), 5.07, 4.71, 4.11, 3.92 (4 H, 4 d (J = 15.2), benzylic), 3.94 (1 H, ddd (J = 3.9, 5.9, 9.5), NCH), 3.80 (1 H, dd (J = 5.4, 9.5), NCH), 3.05 (1 H, ddd (J = 5.4, 6.5, 9.0), CHS), 2.72 (1 H, dd (J = 12.5, 3.9), $CH_{endo}S$), 2.62 (1 H, dd (J = 12.5, 5.9), $CH_{exo}S$), 1.60, 1.48 (2 H, 2 dd, $SCHCH_2$), 1.2 (6 H, m), 0.87 (3 H, t (J = 8), CH_3); ^{13}C NMR ($CDCl_3$) δ 161.1, 137.3, 128.6, 128.5, 127.5, 63.0, 61.6, 54.5, 48.1, 46.8, 34.8, 31.5, 28.9, 28.7, 22.4, 13.0; HRMS calcd. for $C_{24}H_{30}N_2OS$ *m/e* 394.2079, found 394.2087.

(3aα,4α,6aα)-1,3-Dibenzylhexahydro-4-(pentyloxy)-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (8). Pentyllithium (0.80 mL, 1.15 mmol, 207 mol %) was added to a solution of 1-pentanol (73 mg, 90 μL, 0.828 mmol, 150 mol %) in anhydrous ethyl ether (0.2 mL) under argon at −80 °C. After 0.3 h α-chloro thioether **2** (199.3 mg, 0.555 mmol) was added as a solution in dry THF (2 mL). After 1.5 h at −80 °C, water (2 mL) was added (reaction medium froze), and the mixture was warmed to 22 °C, extracted with methylene chloride, and heated to 50 °C at 0.6 mmHg as usual to afford crude product (236.3 mg). Chromatography on silica gel afforded **8** as a colorless oil (170 mg, 75% yield): mass spectrum, *m/e* (relative intensity) 410.2029 (1, M^+, calcd 410.2028), 277 (6), 234 (5), 187 (9), 92 (7), 91 (100); IR ($CHCl_3$) 3020, 2950, 1700, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22–7.27 (10 H, m, Ar), 4.72, 4.60, 4.30, 4.15 (4 H, 4 d (J = 15.3), benzylic), 4.70 (1 H, s, SCHO), 4.14 (1 H, ddd, NCH), 3.94 (1 H, d (J = 8.0), NCH), 3.49, 3.03 (2 H, dt (J = 6.3, 9.3), OCH_2), 2.80 (1 H, dd (J = 4.0, 13.1), $CH_{exo}S$), 2.72 (1 H, d (J = 13.1), 1.35 (2 H, m, OCH_2CH_2), 1.2 (4 H, CH_2CH_2), 0.81 (3 H, t (J = 8.0), CH_3); ^{13}C

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NMR ($CDCl_3$) δ 159.4, 137.2, 136.9, 128.4, 128.3, 127.9, 127.8, 127.5, 127.4, 127.3, 92.1, 68.5, 68.3, 60.5, 47.3, 46.1, 34.5, 28.5, 28.1, 22.2, 13.9.

Anal. Calcd for $C_{24}H_{30}N_2O_2S$, C, 70.21; H, 7.37; N, 6.82. Found: C, 69.98; H, 7.20; N, 6.98.

Reaction of 2 with (Pentyl)$_2$CuCNLi$_2$. Pentyllithium (1.91 mL, 1.5 M, 2.87 mmol, 510 mol %) containing an equivalent amount of LiBr was added dropwise over 0.5 h to CuCN (128 mg, 1.43 mmol, 254 mol %) in dry THF (5 mL) at -78 °C. The resulting light tan solution of (pentyl)$_2$CuCNLi$_2$ was allowed to warm to 0 °C for 0.5 h and recooled to -78 °C. A solution of **2** (202 mg, 0.563 mmol) in THF (6 mL) was added dropwise over 0.5 h to the solution of (pentyl)$_2$CuCNLi$_2$ at -78 °C under argon. The resulting yellowish solution was stirred an additional 11 h. The reaction was then quenched by addition of water (5 mL) and saturated ammonium chloride (3 mL). The mixture was filtered and extracted with methylene chloride as previously described. Flash chromatography (2:1 hexane/ethyl acetate) afforded *N*,*N'*-dibenzylurea[37] (81.2 mg, 37% yield), **6** (45.5 mg, 21% yield), and a mixture of **1** (35 mg, 19% yield) and **11** (35 mg, 19% yield). When this reaction was begun at -65 °C, warmed to 22 °C over 5 h, and stirred at 22 °C for 11 h, **1** (18%), **6** (2%), **11** (18%), and *N*,*N'*-dibenzylurea (60%) were formed.

***N*-Benzyl-*N*-((benzylamino)carbonyl)-2,3-dihydro-3-thiophenamine (11)** was purified by chromatography on silica gel: mp 74-82 °C; mass spectrum, *m/e* (relative intensity) 324 (26, M^+), 277 (7), 266 (8), 240 (33), 233 (35), 149 (16), 106 (46), 100 (26), 91 (100); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.4 (10 H, m, Ar), 6.37 (1 H, dd (*J* = 1.7, 5.7), HC=CH), 5.85 (1 H, m, NCH), 5.58 (1 H, dd (*J* = 3.1, 5.7), HC=CH), 5.48 (1 H, br t (*J* = 4.9), NH), 4.40 (1 H, d (*J* = 8), benzylic), 4.29 (2 H, d (*J* = 4.9), benzylic), 4.27 (1 H, d (*J* = 8), benzylic), 3.53 (1 H, dd (*J* = 10.2, 13.0), $CH_{exo}S$), 3.03 (1 H, dd (*J* = 4.3, 13.0), $CH_{endo}S$); ^{13}C NMR ($CDCl_3$) δ 157.7, 139.7, 139.0, 131.0, 128.7, 128.5, 128.2, 127.4, 127.2, 127.0, 126.7, 126.1, 121.3, 62.8, 47.2, 44.6, 35.5.

Anal. Calcd for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.81; H, 6.13; N, 8.95.

(3aα,4α,6aα)-1,3-Dibenzylhexahydro-4-hydroxy-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (12). Aqueous 1 M NaOH (1.3 mL, 1.3 mmol, 250 mol %) was added to a solution of **2** (190.3 mg, 0.530 mmol) in 1,2-dimethoxyethane (1.5 mL). After 1 h at 22 °C, the solvent was evaporated. The residue was dissolved in water and neutralized with 1 M HCl, and the solution was extracted three times with CH_2Cl_2. The organic layer was dried and the solvent was evaporated to afford the product (166.3 mg, 92% yield) as a white crystalline solid: mp 146-148 °C (lit.[3] mp 144-145); IR ($CHCl_3$) 3550, 3020, 2950, 1695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.35 (10 H, m, Ar), 5.17 (s, CH-O), 4.75, 4.68, 4.32, 4.21, (4 H, 4 d (*J* = 15.1), benzylic), 4.22 (1 H, dd (*J* = 7.9, 4.7), NCH), 4.01 (1 H, d, *J* = 8.0, NCH), 3.01 (1 H, dd (*J* = 12.7, 4.7), $CH_{exo}S$), 2.87 (1 H, d (*J* = 12.7), $CH_{endo}S$), 1.7 (1 H, br s, OH); ^{13}C NMR ($CDCl_3$) δ 159.5, 137.2, 137.0, 128.8, 128.2, 128.1, 127.5, 84.3, 69.3, 61.0, 47.4, 46.8, 35.2; mass spectrum, *m/e* (relative intensity) 340 (M^+, 15), 187 (56), 91 (100).

(3aα,6aα)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]-imidazole-2(3*H*),4-dione (13). Me_2SO (0.16 mL, 176 mg, 2.26 mmol, 353 mol %) was added over 25 min to trifluoroacetic anhydride (0.30 mL, 444 mg, 1.78 mmol, 278 mol %) in ethanol-free chloroform (washed three times with water, dried over $CaCl_2$, and distilled, 1.0 mL) at -60 °C (bath temperature). The mixture was stirred 5 min and a solution of **12** (218 mg, 0.64 mmol) in $CHCl_3$ (2.0 mL) was added over 20 min via syringe. The reaction was stirred at -60 °C for 2 h and then additional TFAA (0.30 mL) and Me_2SO (0.16 mL) were added as above. After an additional 2 h, the reaction was warmed to 0 °C, water (2 mL) was added, and the mixture was extracted three times with chloroform. The organic layers were dried and the solvent was evaporated to afford crude product (227 mg) which was purified by flash chromatography on silica gel (hexane-EtOAc, 50:50) to afford **13** (154 mg, 72% yield) as a white solid: mp 125-127 °C (lit.[3] mp 126-127 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.35 (10 H, m, Ar), 5.03, 4.68, 4.36, 4.35, (4 H, 4 d (*J* = 15.2), benzylic), 4.13 (1 H, ddd (*J* = 2.2, 5.5, 8.1), CHN), 3.80 (1 H, d (*J* = 8.1), CHN), 3.38 (1 H, dd (*J* = 5.5, 12.8), $CH_{exo}S$), 3.28 (1 H, dd, (*J* = 2.2, 12.8), $CH_{endo}S$); IR ($CHCl_3$) 1800, 1700 cm^{-1}; mass spectrum, *m/e* (relative intensity) 338 (17), 187 (33), 91 (100).

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A Selective Method for Oxygen Deprotection in Bistrimethylsilylated Terminal Alkynols

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A selective method for oxygen deprotection of bistrimethylsilylated ω-alkynols is described using sulfonic acid type exchange resins in ether solvent. The method offers the advantages of selectivity toward the silicon-oxygen bond, easier monitoring of the reaction and workup, and higher yields (>75%). Comparisons are made between standard aqueous acid procedures and a series of resins.

Synthetic studies in this laboratory recently required ω-alkynols having the terminal alkynyl carbon protected with a trimethylsilyl (Me_3Si) grouping. Since carbon selectivity is not possible in the silylation of these compounds, it is necessary to protect both positions then remove the oxygen-bound silyl moiety.[2] A method was, therefore, sought for selective Si-O cleavage in these doubly protected substrates.

It is well-known that silicon groups are readily, but indiscriminantly, cleaved from both carbon and oxygen in the presence of fluoride ion.[3] Selective removal of the Me_3Si group from oxygen in bistrimethylsilylated terminal alkynols using aqueous 1 M hydrochloric acid[2] and 30%

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