3.69–3.73 (dd, $J = 11.8$, 2.8 Hz, 1 H), 3.12–3.23 (m, $J = 9.5$, 6.7, 5.2 Hz, 1 H), 2.77–2.85 (dd, $J = 18.5$, 9.5 Hz, 1 H), 2.43–2.50 (dd, $J = 18.5$, 6.7 Hz, 1 H), 1.72 (s, 3 H), 1.06 (s, 9 H); high-resolution MS m/z calcd for $C_{20}H_{21}O_3Si$ ($M^+ - t$-Bu) 337.1260; obsd 337.1270.

Acknowledgment. Discussions with David C. Baker and P. C. Raveendranath concerning conjugate additions of organocuprates to α,β-butenolides are gratefully acknowledged, as is the assistance of Ley Hathcock and Russell Timkovich with mass spectral analyses. Grants from the National Science Foundation and the National Institutes of Health for the purchase of high-resolution NMR instrumentation and from the National Institutes of Health for the purchase of a high-resolution mass spectrometer are gratefully acknowledged.

Supplementary Material Available: ^1H NMR spectra of compounds 5–8 (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Heteroatom-Facilitated Ortho-Directed Lithiations of 2-Arylimidazoles

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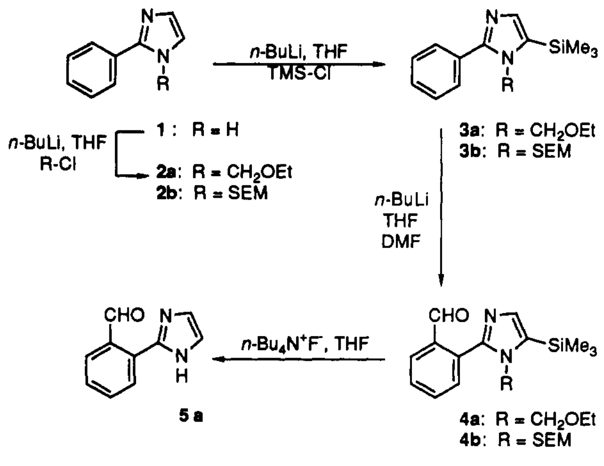
Over the last two decades, the utility of heteroatom-mediated ortho-metalation of aromatic rings has proven of high value in the synthesis of complex aromatic systems.[1] During the course of work in our laboratories on the preparation of novel fused-tricyclic imidazo[4,5-*f*]quinoline immunomodulating agents,[2] we sought to synthesize related nonfused ring systems, such as aryl- and heteroarylimidazoles, which might possess similar activity. To prepare these bicyclic analogues, we decided to investigate the use of the imidazolyl substituent as a potential heteroatom-facilitated, ortho-directing group for the metalation of aromatic compounds. Although precedence existed for the utility of a variety of heterocyclic groups in this context, including for example, oxazolidine, imidazolidine, and benzimidazole,[3] the use of imidazole had not been previously reported.

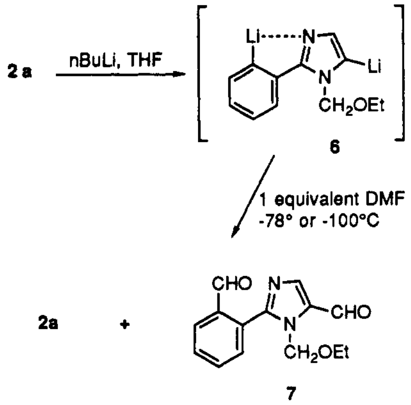
The direct metalation of commercial 2-phenylimidazole (1) using the conditions employed by Houlihan[3b] for the dilithiation of 2-phenylimidazolidine gave complex reaction mixtures. Therefore, compound 1 was reacted initially with n-butyllithium (n-BuLi) and ethoxymethyl chloride or (trimethylsilyl)ethoxymethyl (SEM) chloride in THF to give the N-protected compounds 2a and 2b in 51% and 60% yield, respectively (Scheme I).[4]

Scheme I. Metalation of 2-Arylimidazoles



SEM = $CH_2OCH_2CH_2SiMe_3$

Scheme II. Reaction of 2-Phenylimidazole Dianion



Treatment of 2a or 2b with 1 equiv of n-BuLi in THF (−78 °C) selectively formed the α-lithiated imidazole intermediate, rather than the ortho-lithiated derivative.[1b] Subsequent reaction of this lithiated intermediate with chlorotrimethylsilane (TMS-Cl) then gave the 5-(trimethylsilyl)-2-phenylimidazoles 3a and 3b (52% and 54%, respectively). Since Ganem[5] had previously demonstrated that the TMS moiety can be used as a removable blocking group for metalation sequences, the imidazoles 3a and 3b were further reacted.

Reaction of the silylated imidazoles 3a or 3b with n-BuLi (THF, −78 °C) then indeed formed the desired ortho-metalated species. Trapping of the lithiated intermediates with DMF yielded the 2-(o-formylphenyl)imidazoles 4a[6] and 4b[7] in 73% and 52% yield, respectively.

Desilylation of 4a was conveniently carried out using tetrabutylammonium fluoride. However, removal of the ethoxymethyl group from the imidazole could only be accomplished in low yield after prolonged refluxing in aqueous 6 M HCl. This result with the ethoxymethyl protecting group was consistent with previous reported findings.[8] In contrast, deblocking of both the SEM and TMS protecting groups on 4b could be simultaneously

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[1] (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 880. (b) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (c) Snieckus, V. *Heterocycles* **1980**, *14*, 1649.

[2] (a) Demuth, T. P., Jr.; Cabrera, E. J.; Skuster, J. R.; Alaimo, R. J.; Spencer, C. F.; Snyder, H. R., Jr. Organic Chemistry Abstract Number 633, International Chemical Congress of Pacific Basin Societies, 1989. (b) Alaimo, R. J.; Andersen, J. A. U.S. Patent 4,716,168, 1987.

[3] (a) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837. (b) Houlihan, W. J.; Parrino, V. A. *J. Org. Chem.* **1982**, *47*, 5177. (c) Ranade, A. C.; Gopal, J. *Chem. Ind.* (*London*) **1978**, 582.

[4] For use of SEM-protecting group with imidazoles, see: (a) Whitten, J. P.; Matthews, D. P.; McCarthy, J. R. *J. Org. Chem.* **1986**, *51*, 1891. (b) Lipshutz, B. H.; Huff, B.; Hagen, W. *Tetrahedron Lett.* **1988**, *29*, 3411. (c) Lipshutz, B. H.; Vaccaro, W.; Huff, B. *Tetrahedron Lett.* **1986**, *27*, 4095.

[5] Wood, R. D.; Ganem, B. *Tetrahedron Lett.* **1983**, *24*, 4391.

[6] Compound 4a was satisfactorily characterized as the hydrochloride salt by NMR, IR, and MS analyses. A satisfactory elemental analysis was obtained for C, H, and N, while the Cl analysis was within 0.53% of theoretical, being outside the normally accepted ±0.4% limit (see the Experimental Section).

[7] Compound 4b was characterized by NMR and then carried immediately on to the next step without further treatment.

[8] See, for example: (a) Roe, A. M. *J. Chem. Soc.* **1963**, 2195. (b) Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918.

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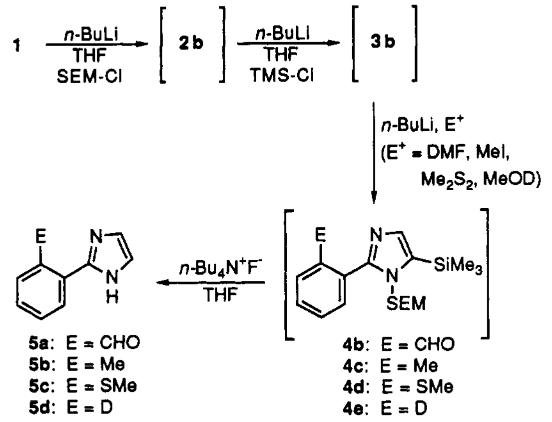
Scheme III. One-Pot Multistep Ortho-Directed Lithiation of 2-Phenylimidazole



achieved by reaction with tetrabutylammonium fluoride in refluxing THF to yield the *o*-(2-imidazolyl)benzaldehyde (**5a**).

The synthesis of **5a** demonstrated that sequential lithiation of the 2-phenylimidazole **2a** initially occurred at the α-position on the imidazole. The second lithiation occurred at the ortho position of the phenyl ring after the imidazole α-position was blocked. Treatment of compound **2a** with excess *n*-BuLi resulted in the formation of the dianion **6** (Scheme II), supporting this analysis. Quenching of **6** with excess DMF produced the corresponding dialdehyde **7**. However, attempts to selectively trap the presumed more reactive ortho anion with 1 equiv of DMF failed, even at −100 °C. Instead, the bis-formylated product **7** and unreacted **2a** predominated in the product mixtures.

The success of the multistep sequence that ultimately led to the ortho-substituted arylimidazole **5a** (Scheme I) prompted us to attempt this conversion in a more convenient one-pot execution (Scheme III). Thus, reaction of 2-phenylimidazole with 1 equiv of *n*-BuLi at −20 °C and the subsequent addition of SEM-Cl formed the intermediate SEM-protected imidazole **2b**. Recooling of the reaction mixture to −78 °C followed by treatment with a second equivalent of *n*-BuLi and quenching with TMS-Cl then formed the intermediate **3b**. In situ treatment of **3b** at −78 °C with a third equivalent of *n*-BuLi and 1 mol of an electrophilic reagent (such as DMF, methyl iodide, dimethyl disulfide or deuteriomethanol) then formed the ortho-substituted bis-protected arylimidazoles **4b–e**. The reaction was then subjected to aqueous ammonium chloride workup, dried, and concentrated. The crude residue was then immediately taken up in tetrabutylammonium fluoride/THF and refluxed for 3 h. Final workup then afforded the desired ortho-substituted arylimidazoles **5a–d** in 41%, 56%, 52%, and 38% from 2-phenylimidazole, respectively. Thus, this one-pot, multistep lithiation sequence provided a convenient method for preparing a number of ortho-substituted arylimidazoles in good overall yields.

Experimental Section

General. Proton magnetic resonance (^{1}H-NMR) spectra were obtained on 100-MHz (IBM) and 300-MHz (GE) spectrometers. Infrared (IR) spectra were obtained on a Nicolet FT-IR in KBr. Mass spectra (MS) were obtained on HP5987A spectrometer in EI, CI, or FAB ionization mode. For solid samples, adsorbed water was determined by thermogravimetric analysis (TGA) using a Perkin Elmer TGS-2.

3-(Ethoxymethyl)-2-phenylimidazole (2a). To 10.0 g of 2-phenylimidazole (1, 70 mmol) in 550 mL of anhydrous THF at −20 °C under nitrogen was added slowly 48 mL of 1.6 M *n*-BuLi in hexanes (77 mmol) with stirring. After 45 min, 7.1 mL of chloromethyl ethyl ether (7.5 g, 94 mmol) was added slowly to the cloudy solution at −20 °C. The cloudy white reaction mixture was allowed to warm to room temperature overnight, and the resultant clear solution was poured into 700 mL of saturated aqueous ammonium chloride solution. The aqueous layer was separated and washed twice with 200 mL of diethyl ether. The combined organic layers were washed with saturated aqueous sodium chloride and then dried over sodium sulfate. Filtration and drying of the solution gave 9.0 g of a clear yellow oil. Chromatography (silica gel, ethyl acetate/hexanes) yielded 8.4 g of purified **2a** (51%). The hydrochloride salt was generated by treatment of **2a** with saturated anhydrous hydrochloric acid in diethyl ether. ^{1}H NMR (DMSO-d_6): δ 7.6 (7 H, m), 5.6 (2 H, s), 3.8 (2 H, q, J = 10 Hz), 1.3 (3 H, t, J = 10 Hz). IR (KBr): ν_{max} 2800 (br), 1590, 1500, 1100 cm^{-1}. MS (EI): m/z 202 (M$^+$), 158. Anal. Calcd for $C_{12}H_{14}N_2O \cdot HCl$: C, 60.38; H, 6.33; N, 11.73; Cl, 14.85. Found: C, 60.06; H, 6.40; N, 11.74; Cl, 15.07.

3-[[2-(Trimethylsilyl)ethoxy]methyl]-2-phenylimidazole (2b) was prepared using (trimethylsilyl)ethoxymethyl chloride (SEM-Cl) according to the procedure for **2a** in 60% yield. The hydrochloride salt was generated by treatment of **2b** with saturated anhydrous hydrochloric acid in diethyl ether. ^{1}H NMR (DMSO-d_6): δ 8.0 (1 H, d, J = 2 Hz), 7.7 (6 H, m), 5.5 (2 H, s), 3.5 (2 H, t, J = 12 Hz), 0.7 (2 H, t, J = 12 Hz), 0.1 (9 H, s). IR (KBr): ν_{max} 2800 (br), 1500, 1240, 1100, 830 cm^{-1}. MS (EI): m/z 274 (M$^+$), 215, 201, 158, 73. Anal. Calcd for $C_{15}H_{22}N_2OSi \cdot HCl$: C, 57.95; H, 7.46; N, 9.01; Cl, 11.40. Found: C, 57.88; H, 7.29; N, 8.84; Cl, 11.40.

1-(Ethoxymethyl)-2-phenyl-5-(trimethylsilyl)-1*H*-imidazole (3a). To 5.0 g of **2a** (20 mmol) in 250 mL of anhydrous THF at −78 °C under nitrogen with stirring was slowly added 18.6 mL of 1.6 M *n*-BuLi in hexanes (30 mmol). After 1 h, chlorotrimethylsilane (3.6 g, 4.2 mL, 33 mmol) was added to the deep purple reaction mixture. The reaction mixture was stirred for one additional hour at −78 °C and then allowed to warm to room temperature. The clear yellow solution was poured into 250 mL of saturated aqueous ammonium chloride, and the layers were separated. The aqueous layer was washed twice with 100 mL of ethyl acetate, and the combined organic layers were washed with saturated aqueous sodium chloride solution. The organic layer was then dried over sodium sulfate, filtered, and evaporated to dryness, yielding an oily semisolid product. Silica gel chromatography (ethyl acetate/hexanes) yielded 3.5 g of **3a** (52%) as a yellow oil. Final characterization was performed on the hydrochloride salt generated by treatment of **3a** with saturated anhydrous hydrochloric acid in diethyl ether. ^{1}H NMR (DMSO-d_6): δ 7.7 (2 H, m), 7.4 (3 H, m), 7.3 (1 H, s), 5.3 (2 H, s), 3.4 (2 H, q, J = 10 Hz), 1.1 (3 H, t, J = 10 Hz), 0.5 (9 H, s). IR (KBr): ν_{max} 2900, 2800 (br), 1590, 1500, 850 cm^{-1}. MS (FAB): m/z 275 (M + H$^+$), 157. Anal. Calcd for $C_{15}H_{22}N_2OSi \cdot HCl$: C, 57.95; H, 7.46; N, 9.01; Cl, 11.40. Found: C, 57.82; H, 7.33; N, 8.86; Cl, 11.50.

2-Phenyl-5-(trimethylsilyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-imidazole (3b) was prepared according to the procedure for **3a** in 54% yield. Final characterization was performed on the hydrochloride salt generated by treatment of **3b** with saturated anhydrous hydrochloric acid in diethyl ether. ^{1}H NMR (acetone-d_6): δ 7.7 (2 H, m), 7.5 (3 H, m), 7.2 (1 H, s), 5.4 (2 H, s), 3.4 (2 H, br t), 0.9 (2 H, br t), 0.4 (9 H, s), 0.0 (9 H, s). IR (KBr): ν_{max} 2600 (br), 1260, 1090, 850 cm^{-1}. MS (EI): m/z 346 (M$^+$). Anal. Calcd for $C_{18}H_{30}N_2OSi_2 \cdot HCl$: C, 56.43; H, 8.16; N, 7.31; Cl, 9.26. Found: C, 56.10; H, 8.30; N, 7.61; Cl, 8.96.

2-[1-(Ethoxymethyl)-5-(trimethylsilyl)-1*H*-imidazol-2-yl]benzaldehyde (4a). To a solution of 2.5 g of **3a** (9 mmol) in 200 mL of anhydrous THF at −42 °C under nitrogen with stirring was slowly added 15 mL of 1.6 M *n*-BuLi in hexanes (24 mmol). After 2 h, anhydrous DMF (6 mL, 5.7 g, 77 mmol) was added to the dark orange reaction mixture, and stirring was continued for 1 h. The reaction mixture was allowed to warm to room temperature and then poured into 200 mL saturated aqueous ammonium chloride. The layers were separated, and the aqueous layer was washed twice with 100 mL of ethyl acetate. The combined organic layers were washed with 150 mL of saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and evaporated to dryness. The crude product was purified by silica gel chromatography (ethyl acetate/hexanes) yielding 2.0 g of **4a**

as a clear yellow oil (73%). Final characterization was performed on the hydrochloride salt generated by treatment of **4a** with saturated anhydrous hydrochloric acid in diethyl ether. ^{1}H NMR (DMSO-d_6): δ 10.0 (1 H, s), 7.6 (4 H, m), 7.5 (1 H, s), 5.2 (2 H, s), 3.3 (2 H, q, J = 10 Hz), 1.1 (3 H, t, J = 10 Hz), 0.5 (9 H, s). IR (KBr): ν_{max} 2900 (br), 1700, 1200, 850 cm^{-1}. MS (FAB): m/z 303 (M + H$^+$), 257, 245. Anal. Calcd for $C_{16}H_{22}N_2O_2Si{\cdot}HCl$: C, 54.67; H, 7.00; N, 7.97; Cl, 10.62. Found: C, 54.62; H, 6.84; N, 7.97; Cl, 10.09.[6]

2-[5-(Trimethylsilyl)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1*H*-imidazol-2-yl]benzaldehyde (4b) was prepared according to the procedure for **4a** in 52% yield. ^{1}H NMR (DMSO-d_6): δ 9.9 (1 H, s), 8.1 (1 H, d, J = 10 Hz), 7.7 (3 H, m), 7.3 (1 H, s), 5.2 (2 H, s), 3.2 (2 H, t, J = 9 Hz), 0.7 (2 H, t, J = 9 Hz), 0.4 (9 H, s), –0.1 (9 H, s).[7]

One-Pot Multistep Synthesis of Ortho-Substituted 2-Arylimidazoles: Preparation of 2-(2-Imidazolyl)benzaldehyde (5a) from 1. Under a nitrogen atmosphere, a 1.0-g (6.9-mmol) sample of 2-phenylimidazole (**1**) was dissolved in 35 mL of anhydrous THF and cooled to –20 °C. This solution was treated with 3.0 mL (7.6 mmol) of 2.5 M *n*-BuLi in hexanes and stirred for 1 h, after which 1.3 g (1.35 mL, 7.6 mmol) of [2-(trimethylsilyl)ethoxy]methyl chloride was added dropwise. Stirring was continued for 15 min at –20 °C. The reaction mixture was warmed to room temperature and stirred for 3.5 h. The clear yellow solution was cooled to –78 °C, treated with 3.0 mL (7.6 mmol) of 2.5 M *n*-BuLi in hexanes, and stirred for 1 h, followed by the addition of 0.8 g (0.97 mL, 7.6 mmol) of chlorotrimethylsilane. After 1 h the reaction mixture was warmed to –42 °C, treated with 3.0 mL (7.6 mmol) of 2.5 M *n*-BuLi in hexanes, and stirred for 2 h. DMF (0.6 mL, 7.6 mmol) was then added, and the reaction mixture was stirred for 1 h in the cold. After warming to room temperature, the reaction mixture was stirred overnight. The reaction mixture was poured into 35 mL of saturated aqueous ammonium chloride, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated to an oil.

Under a nitrogen atmosphere, this oil was treated with 5 equiv of a 1 M solution of tetrabutylammonium fluoride in THF and heated at reflux for 3.5 h. The reaction was then cooled and diluted with pH 7.0 phosphate buffer. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with additional buffer and saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated to an oil. Purified product was obtained by chromatography over silica gel (50% ethyl acetate/hexanes). The product was dissolved in methylene chloride and treated dropwise with saturated anhydrous hydrochloric acid in diethyl ether, resulting in precipitation of the hydrochloride salt. The salt was then collected by filtration in a yield of 41% based on 2-phenylimidazole. ^{1}H NMR (DMSO-d_6): δ 9.89 (s, 1 H), 8.06 (s, 1 H), 7.75 (m, 2 H), 7.53 (m, 2 H), 7.4 (s, 2 H). MS (FAB): m/z 173 (M + H$^+$), 145. Anal. Calcd for $C_{10}H_8N_2O{\cdot}HCl{\cdot}0.25H_2O$: C, 56.24; H, 4.51; N, 13.12. Found: C, 56.23; H, 4.91; N, 13.30. TGA (H_2O): Found: 2.7–3.0 wt %.

2-(2-Methylphenyl)-1*H*-imidazole hydrochloride (5b) was prepared from **1** using methyl iodide, according to the procedure for **5a** in 56% yield. ^{1}H NMR (DMSO-d_6): δ 7.75 (m, 2 H), 7.50 (m, 2 H), 7.43 (s, 2 H), 2.28 (3 H, s). MS (FAB): m/z 159 (M + H$^+$), 145. Anal. Calcd for $C_{10}H_{10}N_2{\cdot}HCl{\cdot}0.5H_2O$: C, 58.97; H, 5.94; N, 13.75. Found: C, 58.67; H, 6.20; N, 13.73. TGA (H_2O): 2.2 wt %.

2-[2-(Methylthio)phenyl]-1*H*-imidazole hydrochloride (5c) was prepared from **1** using dimethyl disulfide, according to the procedure for **5a** in 52% yield. ^{1}H NMR (DMSO-d_6): δ 7.77 (m, 2 H), 7.62 (m, 2 H), 7.42 (s, 2 H), 2.39 (s, 3 H). MS (FAB): m/z 146 (M + H$^+$), 145. Anal. Calcd for $C_{10}H_{10}N_2S{\cdot}HCl$: C, 52.98; H, 4.45; N, 12.36. Found: C, 52.79; H, 4.82; N, 12.09.

2-(2-Deuteriophenyl)-1*H*-imidazole hydrochloride (5d) was prepared from **1** using deuteriomethanol, according to the procedure for **5a** in 38% yield. ^{1}H NMR (DMSO-d_6): δ 7.73 (m, 2 H), 7.54 (m, 2 H), 7.39 (s, 2 H). MS (FAB): m/z 146 (M + H$^+$), 145. Anal. Calcd for $C_9H_7DN_2{\cdot}HCl{\cdot}0.25H_2O$: C, 58.07; H, 4.60; N, 14.90. Found: C, 58.05; H, 5.17; N, 14.53. TGA (H_2O): Found 1.9 wt %.

1-(Ethoxymethyl)-2-(2-formylphenyl)-1*H*-imidazole-5-carboxaldehyde (7). To a solution of 3.0 g of **2a** (15 mmol) in 300 mL of anhydrous THF at –20 °C under nitrogen with stirring was slowly added 24.1 mL of 1.6 M *n*-BuLi in hexanes (39 mmol), and the resulting dark greenish-brown mixture was stirred for 1 h. Anhydrous DMF (5.0 mL, 4.7 g, 65 mmol) was then added, and the reaction mixture was stirred at –20 °C for 2.5 h. After warming to room temperature, the reaction was poured into 350 mL of saturated aqueous ammonium chloride, the layers were separated, and the aqueous layer was washed twice with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and evaporated to dryness. Chromatography (silica gel, ethyl acetate/hexanes) then yielded 2.0 g of **7** (52%) as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 9.9 (1 H, s), 9.8 (1 H, s), 8.1 (1 H, m), 7.9 (1 H, s), 7.7 (3 H, m), 5.6 (2 H, s), 3.6 (2 H, q, J = 10 Hz), 1.2 (3 H, t, J = 10 Hz). IR (KBr): ν_{max} 2850 (br), 1720, 1690, 1150 cm^{-1}. MS (CI): m/z 259 (M$^+$), 213. Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.99; H, 5.69; N, 10.93.

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Registry No. 1, 670-96-2; **2a**, 86119-53-1; **2b**, 139975-85-2; **2b**·HCl, 139975-86-3; **3a**, 139975-87-4; **3a**·HCl, 139975-88-5; **3b**, 139975-89-6; **3b**-HCl, 139975-90-9; **4a**, 139975-91-0; **4a**·HCl, 139975-92-1; **4b**, 139975-93-2; **5a**, 139975-94-3; **5a**·HCl, 139975-97-6; **5b**, 61698-31-5; **5c**, 139975-95-4; **5d**, 139975-96-5; **7**, 140110-68-5; $ClCH_2OEt$, 3188-13-4; $ClCH_2O(CH_2)_2SiMe_3$, 76513-69-4.

Luffalactone and (4*E*,6*E*)-Dehydromanoalide from the Sponge *Luffariella variabilis*

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The Western Pacific sponge *Luffariella variabilis* is the source of manoalide (1), which is a potent antiinflammatory agent and irreversible inhibitor of phospholipase A_2.[2] The isolation and structural elucidation of manoalide (1) was reported in 1980 by de Silva and Scheuer,[3] who, in 1981, described *seco*-manoalide (2) and (*E*)- and (*Z*)-neomanoalide (3, 4).[4] In order to provide large quantities of manoalide for clinical evaluation,[5] we collected over 400 specimens of *L. variabilis* from three locations in Palau and were surprised to find considerable variation in their secondary metabolite content.[6] We have earlier reported

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[5] The clinical evaluation of manoalide for the treatment of psorriasis produced no evidence of efficacy (Garst, M. E., personal communication).

[6] Since we were involved in a large-scale collection of a previously identified sponge, the specimens were identified in the field by color and form. A random selection of the sponge specimens were extracted on site and the presence of "manoalide" was confirmed by TLC. *Luffariella variabilis* can be distinguished from closely related sponges by the orange skeletal fibers. The orange color may arise by the reaction of manoalide with lysine residues in the proteins that constitute the fibers. The sponges were not examined individually by a taxonomist. Voucher specimens from many collections of *L. variabilis* are available on request.

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