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Imino-*C*-nucleoside Synthesis: Heteroaryl Lithium Carbanion Additions to a Carbohydrate Cyclic Imine and Nitrone

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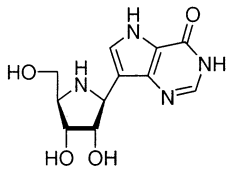
Abstract: Promotion by Lewis acid of the addition of some aryllithiums to a carbohydrate-based imine, which has allowed a more facile synthesis of some imino-*C*-nucleoside analogues, is described. Use of the corresponding nitrone does not assist in some cases, but lithiated acetonitrile adds to it efficiently to give a product from which further *C*-nucleoside analogues can be derived.

In connection with the design and synthesis of transition state analogue inhibitors of human purine nucleoside phosphorylase, as agents capable of preventing T cell proliferation, we recently reported[1] a convergent synthesis of immucillin-H **1**. This material is under clinical



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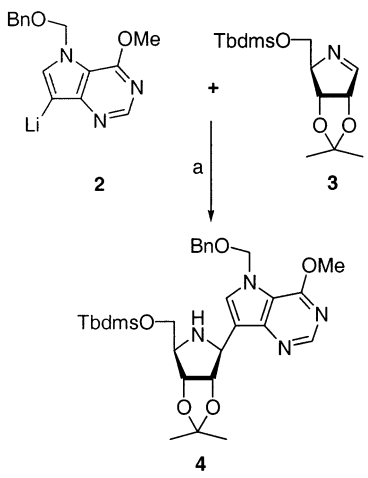
study to assess its utility for the control of T-cell proliferative disorders.[2−5] A critical step in the synthesis was the addition of the 9-lithio-9-deazapurine derivative **2** to the carbohydrate-based imine **3** that affords an excellent yield of the protected immucillin **4** (Scheme 1). However, a number of other alkyl and aryllithium derivatives, for example **5**−**9**, either failed to add to this

SCHEME 1[a]



[a] Conditions: (a) ether−anisole, −70 to 0 °C.

imine or gave disappointingly poor yields of adducts. The syntheses of other immucillin analogues that were sought, such as **10**−**12**, which are obtainable in principle from lithiated species **5**−**7**, respectively, would be greatly simplified if such additions could be carried out satisfactorily. We report here two adaptations of the reaction exemplified in Scheme 1 which have proved helpful.

The addition of organometallic reagents to imines is a well-known and synthetically useful procedure, but it is equally well-known that, especially in the case of imines having hydrogen atoms at the α-carbon positions, it can be problematical.[6] For example, while the reaction depicted in Scheme 1 affords a high yield, it proceeds only above −20 °C, and in practice the solution was allowed to warm to 0 °C.[1] However, the heterocyclic aryllithiums **5**−**7** appear not to survive these temperatures and are probably quenched by proton abstraction from solvent and/or substrate. The alkynyllithium **8** decomposes at the same temperature as it adds to the imine **3** (10 °C), limiting the yield of target **10** which is available from the adduct.[7] Furthermore, targets **11** and **12** are accessible in an alternative manner from compound **18** (illustrated in Scheme 3), obtained by addition of lithiated acetonitrile **9** to **3** at −70 °C,[8] but this reaction is capricious and difficult to scale-up because the 1:1 adduct reacts further with the imine to give the 2:1 adduct. A significant objective, therefore, became the discovery of improved means of adding lithio derivatives such as **5**−**9** to **3**.

Here we report the exploitation of two opportunities based on the facts that Lewis acids can activate imines

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(1) Evans, G. B.; Furneaux, R. H.; Hutchison, T. L.; Kezar, H. S.; Morris, P. E., Jr.; Schramm, V. L.; Tyler, P. C. *J. Org. Chem.* **2001**, *66*, 5723−5730.
(2) Miles, R. W.; Tyler, P. C.; Furneaux, R. H.; Bagdassarian, C. K.; Schramm, V. L. *Biochemistry* **1998**, *37*, 8615−8621.
(3) Kicska, G. A.; Long, L.; Hörig, H.; Fairchild, C.; Tyler, P. C.; Furneaux, R. H.; Schramm, V. L.; Kaufman, H. L. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 4593−4598.
(4) Bantia, S.; Miller, P. J.; Parker, C. D.; Ananth, S. L.; Horn, L. L.; Kilpatrick, J. M.; Morris, P. E.; Hutchison, T. L.; Montgomery, J. A.; Sandhu, J. S. *Int. Immunopharmacol.* **2001**, *1*, 1199−1210.
(5) Bantia, S.; Miller, P. J.; Parker, C. D.; Ananth, S. L.; Horn, L. L.; Babu, Y. S.; Sandhu, J. S. *Int. Immunopharmacol.* **2002**, *2*, 913−923.
(6) Volkmann, R. A. In *Comprehensive Organic Synthesis, Additions to C*−*Xπ Bonds, Part 1*; Schreiber, S. L., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, Chapter 1.12. Katritzky, A. R.; Hong, Q.; Yang, Z. *J. Org. Chem.* **1995**, *60*, 3405−3408. Yamada, H.; Kawate, T.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **1999**, *64*, 8821−8828 and references therein.
(7) Evans, G. B.; Furneaux, R. H.; Gainsford, G. J.; Hanson, J. C.; Kicska, G. A.; Sauve, A. A.; Schramm, V. L.; Tyler, P. C. *J. Med. Chem.* **2003**, *46*, 155−160.
(8) Evans, G. B.; Furneaux, R. H.; Gainsford, G. J.; Schramm, V. L.; Tyler, P. C. *Tetrahedron* **2000**, *56*, 3053−3062.

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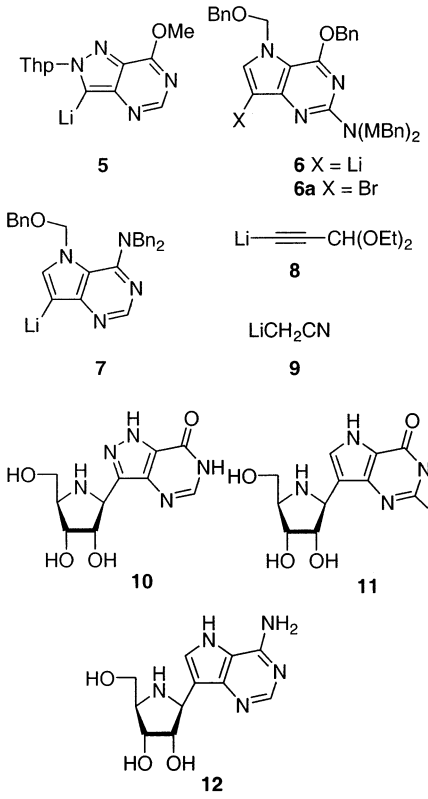
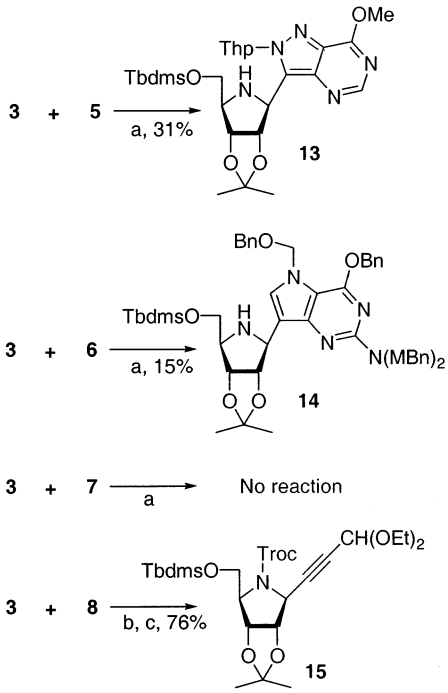
toward nucleophilic addition,[9] and nitrones are more electrophilic than the corresponding imines.[6] In the latter case, addition of organometallic reagents to nitrones gives hydroxylamines which are readily reduced to the parent amines. Consequently, the Lewis acid activation of imine **3** and the use of its nitrone analogue **17** were assessed as means of increasing the range of carbon nucleophiles that could be used in reactions such as that illustrated in Scheme 1.

Lewis Acid Activation. A number of Lewis acids were surveyed as facilitators of the reaction between **2** and **3** with the temperature maintained at −70 °C (Scheme 1). As indicated above, in the absence of Lewis acid promoters, temperatures above −20 °C are required for significant reaction to occur. When $BF_3{\cdot}OEt_2$, $TiCl_4$, $SnCl_4$, $InCl_3$, TmsOTf, $Sc(OTf)_3$, Bu_2BOTf and $ZnCl_2$ were separately added to the reaction mixture at −70 °C, only the first three promoted the formation of product **4**. The reaction involving $SnCl_4$ was clearly the most selective and efficient (TLC evidence), but the isolated yield of **4** obtained with this catalyst (~60%) was nevertheless less than that obtained from the uncatalyzed process.[1]



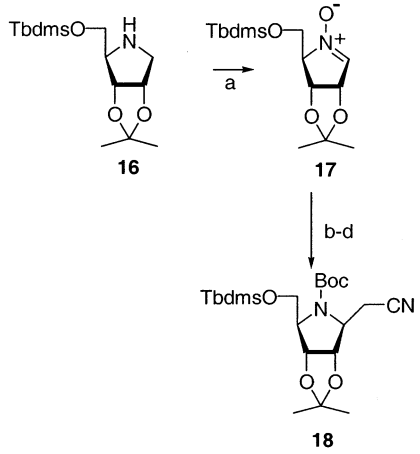
Reaction of the organolithium reagents **5, 6** and **8** with imine **3**, when promoted by $SnCl_4$ at −70 °C, gave the required adducts (Scheme 2), but compound **7** did not. The 8-aza-9-deazahypoxanthine *C*-nucleoside analogue **13** was obtained for the first time in 31% yield and the 9-deazaguanine **14** analogue in an improved 15% yield, while the alkyne adduct **15** was generated consistently in 76% yield. The yields from the corresponding unpromoted reactions are 0%, 5%, and ~50% respectively. The alkyne adduct **15** may be converted into the 8-aza-immucillin **10**.[7]

SCHEME 2[a]



[a] Reagents and conditions: (a) $SnCl_4$, ether−anisole, −70 °C; (b) $SnCl_4$, THF, −70 °C; (c) $^iPr_2NEt$, Cl_3CCH_2OCOCl.

SCHEME 3[a]



[a] Reagents and conditions: (a) SeO_2, H_2O_2, Me_2CO, −4 °C, 3−4 h; (b) **9**, THF, −70 °C, 0.5 h; (c) Zn, HOAc, 6 h, 20−30 °C; (d) $(^tBuOCO)_2O$, $CHCl_3$ 15 h.

Additions to Nitrone 17. Treatment of the iminoribitol derivative **16** with SeO_2 and H_2O_2 converted it directly into nitrone **17**, a stable crystalline solid. Exposure of this material separately to the organolithiums **8** and **9** in THF at −70 °C resulted in facile additions to afford the corresponding *N*-hydroxy adducts. In the latter case, reduction of the product with zinc in acetic acid followed by *N*-protection with $(Boc)_2O$ afforded the acetonitrile adduct **18** in up to 90% overall yield (Scheme 3). This compares extremely favorably with the unreliable approach to this product involving reaction of **3** with **9**. On the other hand, reduction of the hydroxylamine

(9) Yamaguchi, M. In *Comprehensive Organic Synthesis, Additions to C−Xπ Bonds, Part 1*; Schreiber, S. L., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, Chapter 1.11.

derived by reaction of alkyne **8** with nitrone **17** with zinc in acetic acid was capricious and was generally accompanied by significant reduction of the acetylene moiety to an alkene. Consequently this procedure was inappropriate for the synthesis of **10**.

When the aryllithium **2** was allowed to react with nitrone **17** at −70 °C the highly basic aryllithium appeared to promote degradation of the nitrone. Treatment of the crude product with zinc in acetic acid generated some **4**, but in a poor yield relative to that obtained on treatment of imine **3** with the lithiated **2**. The addition of $SnCl_4$ to the reaction did not improve matters in this case.

In conclusion, we have shown that $SnCl_4$ promotes the addition of some aryllithiums to imine **3** and allows the formation of adduct **13** for the first time. Its use led to the consistent production of **15** in an enhanced yield. Importantly, for our purposes, the use of the nitrone **17** has enabled the reproducible synthesis of adduct **18**, and thus the immucillins **11** and **12**, on a large scale. Variations in the efficiencies of the reactions attempted with compound **17**, however, show that each target compound should be made by the procedure best suited to the specific purpose.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ unless stated otherwise. "Normal processing" means the organic phase was washed with aqueous acid and/or base as appropriate, dried, and concentrated to dryness. Chromatography was conducted on silica gel.

General Procedure for the Lewis Acid Promoted Condensation of Aryllithium 2 with Imine 3. *n*-Butyllithium (0.77 mL, 1.5 M, 1.15 mmol) was added to a solution of 7-*N*-benzyloxymethyl-9-bromo-9-deaza-6-*O*-methylhypoxanthine[1] (375 mg, 1.08 mmol) in ether (6 mL) and anisole (3 mL) at −45 °C, and after 10 min, the reaction mixture was cooled to −78 °C. A solution of the imine **3**[1] (0.1 g, 0.35 mmol) in ether (2 mL) was added, followed by the Lewis acid (0.7 mmol), and the temperature was kept at −78 °C for 2 h. The reaction was quenched by the addition of Na_2CO_3 (saturated, aqueous) or NaOH and processed in the normal manner. Chromatography afforded syrupy **4**, in those cases in which product was formed, with ^{1}H and ^{13}C NMR data identical to those reported for the compound.[1]

5-O-*tert*-Butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-1-*β*-(7-methoxy-2-tetrahydropyran-2-yl-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl)-D-ribitol (13). A stirred solution of 3-bromo-7-methoxy-2-(tetrahydropyran-2-yl)-pyrazolo[4,3-*d*]pyrimidine[10] (1.0 g, 3.19 mmol) in dry THF at −78 °C was treated with *n*-butyllithium (2.2 mL, 1.5 M, 3.3 mmol) to give the lithiate **5**, and after 20 min a solution of the imine **3** (0.63 g, 2.21 mmol) in THF (1 mL) was added followed by $SnCl_4$ (0.51 mL, 4.4 mmol). The mixture was stirred at −70 °C for 2 h and then allowed to warm to 20 °C over 1 h, after which time the reaction was quenched by addition of NaOH (10 mL, 4 M). Ether (20 mL) was added, the organic phase was separated and dried, and the solvent was evaporated. Chromatography afforded the title compound **13** (0.355 g, 0.68 mmol, 31%) as a clear oil: ^{1}H NMR (the product was a ∼ 6:4 diastereomeric mixture due to the tetrahydropyranyl protecting group) δ 8.38 (s, 1 H), 5.97 (dd, J = 9.2, 2.7 Hz, 0.4 H), 5.87 (dd, J = 9.9, 2.2 Hz, 0.6 H), 5.31 (dd, J = 6.8, 4.9, Hz 0.6 H), 4.99 (t, J = 6.4 Hz, 0.4 H), 4.82−4.69 (m, 2H), 4.15 (s, 3 H), 4.01 (m, 1H), 3.92−3.52 (m, 4H), 3.33 (q, J = 4.1 Hz, 0.4 H), 3.27 (q, J = 3.9 Hz, 0.6 H), 2.59 (m, 1 H), 2.08 (m, 2 H), 1.70 (m, 2 H), 1.59, 1.56, 1.34, 1.32 (s, 3 H), 0.88, 0.84 (s, 9 H), 0.049, 0.031, 0.0 (s, 6H); ^{13}C NMR δ 162.3 (C), 151.4 (CH), 139.6, 135.5, 135.3, 131.7, 114.9, 114.4 (C), 87.6, 87.1, 86.4, 85.9, 83.1, 82.8 (CH), 68.3, 68.0 (CH_2), 66.9, 66.4 (CH), 63.0, 62.3(CH_2), 61.7, 61.5 (CH), 54.3 (CH_3), 30.0, 29.7 (CH_2), 28.0, 26.2, 25.2 (CH_3), 25.0 (CH_2), 22.8, 22.6 (CH_3), 18.6 (C), −4.9 (CH_3); HRMS m/z ($M^+ + 1$) calcd for $C_{25}H_{42}N_5O_5Si$ 520.2955, found 520.2943.

6-*O*-Benzyl-7-*N*-benzyloxymethyl-9-bromo-9-deaza-2-*N*,*N*-bis(4-methoxybenzyl)guanine (6a). Sodium hydride (0.3 g, 60%, 7.5 mmol) was added to a stirred solution of 6-*O*-benzyl-7-*N*-benzyloxymethyl-9-bromo-9-deazaguanine[1] (1.2 g, 2.73 mmol) in DMF (25 mL) followed by 4-methoxybenzyl chloride (1.1 mL, 8.1 mmol). The mixture was stirred for 16 h, toluene (100 mL) was added, and the solution was washed with water (2×) and processed in the normal manner. Chromatography of the crude material afforded the title compound (1.7 g, 2.5 mmol, 91%) as a white solid. Recrystallized from ethanol it had: mp 102−104 °C; ^{1}H NMR δ 7.31−7.16 (m, 15 H), 6.82 (d, J = 8.6 Hz, 4 H), 5.56 (s, 2 H), 5.42 (s, 2 H), 4.82 (s, 4 H), 4.39 (s, 2 H), 3.78 (s, 6 H); ^{13}C NMR δ 159.0, 158.5, 156.5, 151.5, 137.4, 137.0 (C), 131.8 (CH), 131.6 (C), 129.7, 128.9, 128.8, 128.4, 128.3, 128.0, 114.3 (CH), 110.5, 91.1(C), 77.9, 70.6, 68.0 (CH_2), 55.7 (CH_3), 49.4 (CH_2). Anal. Calcd for $C_{37}H_{35}BrN_4O_4$: C, 65.39; H, 5.19; Br, 11.76; N, 8.24. Found: C, 65.47; H, 5.17; Br, 11.55; N, 8.42.

1-*β*-(6-*O*-Benzyl-7-*N*-benzyloxymethyl-9-deaza-2-*N*,*N*-bis-(4-methoxybenzyl)guanin-9-yl)-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidine-D-ribitol (14). *n*-Butyllithium (0.33 mL, 1.5 M, 0.5 mmol) was added to a stirred solution of 6-*O*-benzyl-7-*N*-benzyloxymethyl-9-bromo-9-deaza-2-*N*,*N*-bis(4-methoxybenzyl)guanine (0.312 g, 0.46 mmol) in ether (6 mL) and anisole (3 mL) at −78 °C to give the lithiated **6**, and after 20 min, a solution of imine **3** (0.1 g, 0.35 mmol) was added followed by $SnCl_4$ (82 μL, 0.7 mmol). Stirring was maintained for 2 h, after which time NaOH (5 mL, 4 M) and ether (10 mL) were added. Normal processing and chromatography afforded the title compound **14** (0.047 g, 0.053 mmol, 15%) as a syrup: ^{1}H NMR δ 0.00 (2s, 6 H), 0.84 (s, 9 H), 1.22 (s, 3 H), 1.53 (s, 3 H), 3.21 (dd, J = 5.0, 10.1 Hz, 1 H), 3.78 (m, 2 H), 3.80 (s, 9 H), 4.26 (d, J = 4.80 Hz, 1 H), 4.40 (s, 2 H), 4.44 (m, 1 H), 4.57 (d, J = 26.3 Hz, 1 H), 5.02 (m, 2 H), 5.42 (s, 2 H), 5.60 (s, 2 H), 6.81 (s, 1 H), 6.83 (m, 4 H), 7.15−7.30 (m, 9 H); ^{13}C NMR δ 158.9, 157.6, 156.3, 152.5, 137.8, 137.3, 132.0, 130.9, 129.2, 128.8, 128.7, 128.3, 128.1, 127.9, 114.8, 114.1, 111.2, 86.4, 82.4, 77.6, 70.4, 67.5, 66.5, 63.9, 61.5, 55.6, 49.5, 27.9, 26.3, 25.6, 18.8; HRMS m/z ($M^+ + 1$) calcd for $C_{51}H_{64}N_5O_7Si$ 886.4575, found 886.4589.

5-*O*-*tert*-Butyldimethylsilyl-1,4-dideoxy-1-*β*-(3,3-diethoxyprop-1-ynyl)-1,4-imino-2,3-*O*-isopropylidene-*N*-(2,2,2-trichloroethoxycarbonyl)-D-ribitol (15). *n*-Butyllithium (109.5 mL, 1.6 M, 175 mmol) was added to a solution of propiolaldehyde diethyl acetal (27.2 mL, 189.5 mmol) in THF (400 mL) with the reaction temperature kept below −60 °C, and the solution was stirred at −70 °C for 20 min. A solution of the imine **3** (20 g, 70.2 mmol) in THF (40 mL) was added followed by stannic chloride (8.2 mL, 70.2 mmol), and the resulting solution was stirred at −70 °C for 30 min. Aqueous sodium hydroxide (150 mL, 2.5 M) and petroleum ether (400 mL) were added, and the organic phase was processed normally to give a syrup (35.4 g). A solution of this material in dichloromethane (150 mL) was treated with *N*,*N*-diisopropylethylamine (30 mL, 310 mmol) and then trichloroethyl chloroformate (9.7 mL, 70.4 mmol) with cooling to control the initial exotherm. After 1 h at 20 °C, the solution was processed normally and chromatography afforded title compound **15** as a syrup (31.5 g, 53.5 mmol, 76%) with ^{1}H and ^{13}C NMR spectra identical to those reported.[8]

5-*O*-*tert*-Butyldimethylsilyl-1,*N*-dehydro-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol *N*-Oxide (17). A stirred solution of **16**[8] (30 g, 104 mmol) and selenium dioxide (0.6 g, 5.4 mmol) in acetone (100 mL) was cooled to 0 °C, and hydrogen peroxide (30%) was added slowly, with the temperature kept below 4 °C, until the reaction was complete (TLC evidence) (3−4 h). Chloroform (250 mL) was added, the mixture was washed with water, and the organic phase was dried ($MgSO_4$) and concentrated. Chromatography of the crude product afforded crystalline nitrone **17** (18.3 g, 60.8 mmol, 58%): mp

(10) Stone, T. E.; Eustace, E. J.; Pickering, M. V.; Doyle Daves, G., Jr. *J. Org. Chem.* **1979**, *44*, 505−509.

121−124 °C (from petroleum ether); ^{1}H NMR δ 6.86 (s, 1 H), 5.11 (m, 1 H), 4.81 (d, J = 6.2 Hz, 1 H), 4.22 (dd, J = 2.0, 11.0 Hz, 1 H), 4.01 (d, J = 0.7 Hz, 1 H), 3.82 (dd, J = 2.1, 11.0 Hz, 1 H), 1.40 and 1.35 (2s, 3 H each), 0.83 (s, 9 H), 0.04 and 0.02 (2s, 3 H each); ^{13}C NMR δ 133.5 (CH), 112.0 (C), 81.1, 79.5, 77.5 (CH), 60.2 (CH_2), 27.7, 26.3, 26.1 (CH_3), 18.5 (C). Anal. Calcd for $C_{14}H_{27}NO_4Si$: C, 55.78; H, 9.03; N, 4.65. Found: C, 55.81; H, 8.88; N, 4.75.

***N*-*tert*-Butoxycarbonyl-7-*O*-*tert*-butyldimethylsilyl-2,3,6-trideoxy-3,6-imino-4,5-*O*-isopropylidene-D-*allo*-heptononitrile (18).** Acetonitrile (4.2 mL, 80.2 mmol) was added slowly to a solution of *n*-butyllithium (32.5 mL, 74.8 mmol) in THF (300 mL) with the reaction temperature kept below −65 °C to give the lithiated **9**. The resulting mixture containing a white precipitate was stirred at −70 °C for 0.5 h, and a solution of the nitrone **17** (15.0 g, 49.8 mmol) in THF (30 mL) was added. After 0.5 h at −70 °C, the reaction was quenched with water and partitioned between petroleum ether (500 mL) and water (500 mL). The organic layer was dried ($MgSO_4$) and concentrated to dryness. The residue was dissolved in acetic acid (100 mL), and zinc dust (30 g) was added with stirring. The resulting mixture was stirred for 6 h with occasional cooling to keep the reaction temperature below 30 °C, the solids and solvent were removed, and a solution of the residue in chloroform (200 mL) was washed with $NaHCO_3$ (aqueous, saturated), dried and concentrated to dryness. The residue in chloroform (100 mL) was treated with di-*tert*-butyl dicarbonate (11.5 g, 52.7 mmol) and allowed to stand overnight. The solution was concentrated and chromatography of the residue afforded title compound **18** (19.1 g, 44.8 mmol, 90%) as a colorless syrup with ^{1}H and ^{13}C NMR spectra identical to those reported for the compound.[8]

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