87762-26-3; **13b**, 87762-27-4; **14**, 87781-73-5; **15a**, 87762-35-4; **15b**, 87762-36-5; **15c**, 87762-37-6; **15d**, 87762-38-7; **15e**, 87762-39-8; **15f**, 87762-40-1; **19**, 87762-30-9; **20**, 87762-29-6; **21**, 87762-51-4; **22**, 87762-52-5; **24**, 87762-28-5; ethyl 6-[(ethylamino)carbonyl]-1,4-dihydro-4-oxo-3-pyridinecarboxylate, 87762-48-9; ethyl 6-(aminocarbonyl)-1,4-dihydro-4-oxo-3-pyridinecarboxylate, 87762-49-0; ethyl 6-(morpholinocarbonyl)-1,4-dihydro-4-oxo-3-pyridinecarboxylate, 87762-50-3; benzophenone, 119-61-9.

Isoquinoline-*N*-Boranes as Precursors to Substituted Tetrahydroisoquinolines[1]

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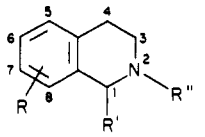
A new approach to the syntheses of 1,2-disubstituted 1,2,3,4-tetrahydroisoquinolines from isoquinoline-*N*-boranes is described. The method is a "one-pot" operation in which substituents are introduced consecutively as electrophiles and nucleophiles with accompanying reduction of the heterocyclic ring. This procedure differs from the classical ones in that both requisite rings are present in the starting material and thus avoids the inefficient cyclizations of phenethylamine derivatives when unactivated substrates would be required. The synthetic utility of this process is demonstrated with several examples including the alkaloids carnegine and hydrohydrastinine.

Since the early 1900s, construction of the 1,2,3,4-tetrahydroisoquinoline ring system **1** has been a popular area

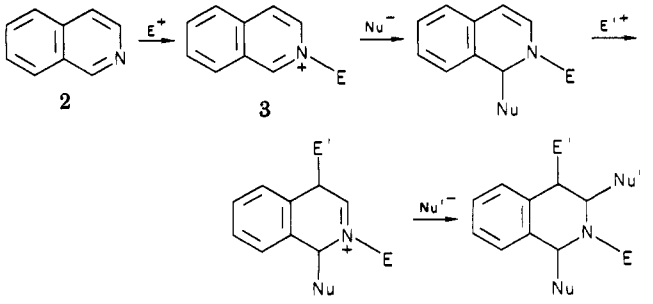


1

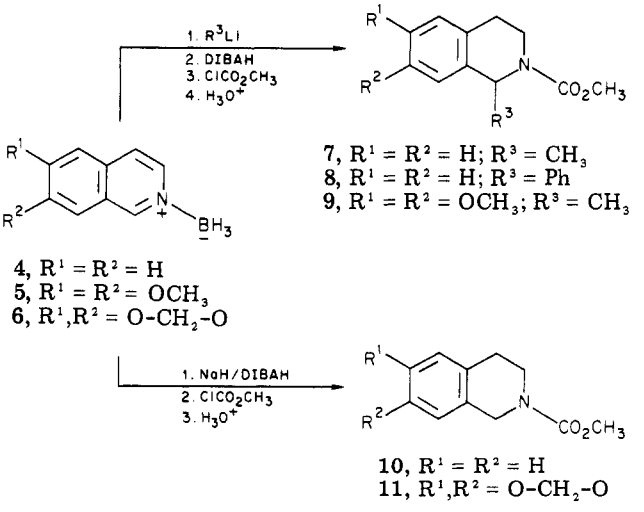
of research in natural products chemistry. Preparative routes to **1** are diverse and include such familiar methods as Pictet-Spengler,[2] Bischler-Napieralski,[3] and other cyclization reactions[4,5] as well as various hydride reductions[6-8] of isoquinolines and isoquinolinium salts. None of these is without limitation, but the most serious is the failure of certain β-phenethylamine derivatives to cyclize efficiently in the absence of electron-donating aromatic substituents para to the site of ring closure. In order to circumvent this problem, we have formulated an alternative approach to the synthesis of **1** based partly on an investigation by Francis et al.[9] and supported by some recent work these laboratories.[10]

Scheme I depicts a general synthetic strategy which would allow a variety of substituted 1,2,3,4-tetrahydroisoquinolines to be synthesized from isoquinoline. The investigation described below demonstrates the validity of this approach to 1,2-disubstituted examples including the alkaloids carnegine and hydrohydrastinine.

Scheme I



Scheme II



7, $R^1 = R^2 = H$; $R^3 = CH_3$
8, $R^1 = R^2 = H$; $R^3 = Ph$
9, $R^1 = R^2 = OCH_3$; $R^3 = CH_3$

4, $R^1 = R^2 = H$
5, $R^1 = R^2 = OCH_3$
6, $R^1, R^2 = O\text{-}CH_2\text{-}O$

10, $R^1 = R^2 = H$
11, $R^1, R^2 = O\text{-}CH_2\text{-}O$

Results and Discussion

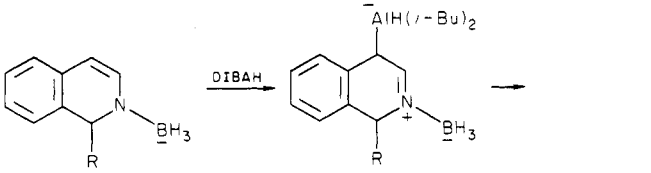
The general reaction pathway previously outlined in Scheme I has now been used to synthesize tetrahydroisoquinolines **7**-**11** in 60-70% yields from the corresponding isoquinolines (Scheme II). Amine-boranes **4**-**6**, which correlate with **3** in Scheme I, are air-stable crystalline solids and can be isolated if desired. In practice, **4** was generated quantitatively by addition of 1.0 equiv of BH_3·THF to a tetrahydrofuran solution of freshly distilled **2** at -78 °C

(1) A preliminary account of this study was presented at the 37th Southwest Regional Meeting of the American Chemical Society, San Antonio, TX, Dec 9-11, 1981.
(2) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74.
(3) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151.
(4) For an extensive discussion of tetrahydroisoquinoline synthesis, see: Kametani, T. In "The Total Synthesis of Natural Products"; Vol. 3, ApSimon, J., Ed.; Wiley: New York, 1977; Vol. 3, pp 1-272 and references cited therein.
(5) Falck, J. R.; Manna, S.; Mioskowski, C. *J. Org. Chem.* **1981**, *46*, 3742.
(6) Gribble, G. W.; Heald, P. W. *Synthesis* **1975**, 650.
(7) Kikugawa, Y.; Kuramoto, M.; Saito, I.; Yamada, S. *Chem. Pharm. Bull.* **1973**, *21*, 1914, 1927. Dyke, S. F. *Adv. Heterocycl. Chem.* **1972**, *14*, 280, 295. Lyle, R. E.; Anderson, P. S. *Ibid.* **1966**, *6*, 68. Rao, K. V.; Jackman, D. *J. Heterocycl. Chem.* **1973**, *10*, 213.
(8) Neumann, W. P. *Justus Liebigs Ann. Chem.* **1958**, *618*, 90; *Angew. Chem.* **1958**, *70*, 401.
(9) Francis, R. F.; Crews, C. D.; Scott, B. S. *J. Org. Chem.* **1978**, *43*, 3227.
(10) Minter, D. E.; Stotter, P. L. *J. Org. Chem.* **1981**, *46*, 3965.

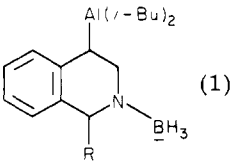
0022-3263/84/1949-0130$01.50/0

and used directly. However, **5** and **6** were usually isolated and recrystallized since these compounds are easier to purify than the free bases.

Alkyl and aryl substituents were introduced by reactions of **4** (or **5**) with appropriate lithium reagents[11] at −78 °C. The intermediate produced by nucleophilic attack at C-1 is enaminoborohydride **12**. In principle, **12** could react with a number of electrophiles; but in this study, DIBAH was used to effect the desired transformation of **12** to **14** presumably by formation of **13** (eq 1) and subsequent intra-



12 13

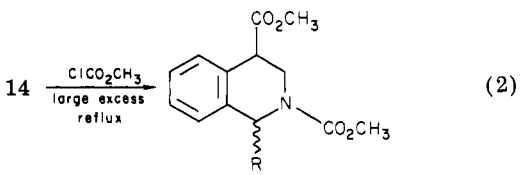


14 (1)

molecular hydride migration from aluminum to C-3. Thus, DIBAH served to supply both the electrophile and the nucleophile for the last two steps of the reaction sequence generalized in Scheme I.

Intermediate **14** is an aminoborohydride which reacts readily with acyl halides to produce the corresponding amides. This methodology has been described in previous work from these laboratories.[10] The benzylic C–Al bond at C-4 of **14** is also labile but less reactive with acylating agents than the aminoborohydride functionality. As indicated in Scheme II, aqueous acid conveniently hydrolyzes the C–Al bond without destroying the urethane.

It should be noted that selective acylation of nitrogen was accomplished most efficiently by using 5–6 molar equiv of the acyl halide at room temperature. When a larger excess was used at elevated temperatures, **15** became the major product (eq 2). Although yields have not been

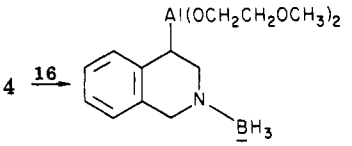


(2)

15

optimized, conversions as high as 75% of **15** have been achieved. This procedure represents an indirect but potentially important method for introducing C-4 substituents.

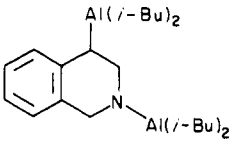
Syntheses of **10** and **11** required nucleophilic hydride attack at C-1. We had anticipated that a reducing agent such as sodium bis(2-methoxyethoxy)aluminum dihydride (**16**) would supply both nucleophiles and the electrophile necessary to convert isoquinoline-*N*-borane (**4**) to **17** (eq 3) according to Scheme I. However, attempts to prepare **10** by this approach led to mixtures containing substantial amounts of **15** (R = H) regardless of the quantity of methyl chloroformate used. Apparently, the C4–Al bond is more



(3)

17

reactive in **17** (with alkoxide ligands on aluminum) than in **14**, a trialkylaluminum; but the mechanistic basis for this observation is not immediately obvious. A similar problem arose when **18**, generated from **2** and 2 equiv of



18

DIBAH, was acylated. In this case, the rates of acylation at nitrogen and C-4 were nearly equal. Consequently, only **14** (R = H), produced from reaction of the isoquinoline-*N*-borane with a mixture of NaH and DIBAH, has the correct combination of funtionalities to allow selective acylation of nitrogen. The actual reducing agent is probably sodium diisobutyldihydroaluminate generated in situ.

The use of methyl chloroformate as acylating agent provided a methyl group equivalent on nitrogen. Reductions of **9** and **11** with $LiAlH_4$ gave carnegine and hydrohydrastinine, respectively, in high yields.

All of the reactions in Scheme II were carried out as "one-pot" operations. However, **8** was not readily separated from aromatic impurities contained in commercial phenyllithium. The most efficient synthesis of **8** involved hydrolysis of **14** (R = Ph) and isolation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**19**). Impurities were removed by extraction of an aqueous acidic solution of crude **19**; subsequent acylation of recovered **19** gave **8** quantitatively.

The results of these reactions indicate that 1,2-disubstituted tetrahydroisoquinolines can be prepared conveniently from isoquinolines by a method which circumvents the use of cyclization reactions at a late stage in the synthesis. The procedure takes advantage of the high susceptibility of isoquinoline-*N*-boranes to nucleophilic attack at C-1 and the high regioselectivity of the reactions of enaminoborohydrides with alkylaluminums. Although isoquinolines themselves react slowly with strong nucleophiles at C-1, the use of the corresponding *N*-borane is essential to the success of the sequence. Attempts to carry out the reactions of Scheme II with the free bases led to intractable mixtures which appear to arise form sundry disproportionation and coupling reactions. Expansion of this work to include 1,2,4-trisubstituted products is in progress and will be reported in due course.

Experimental Section

General Methods. Methyllithium, phenyllithium, DIBAH (diisobutylaluminum hydride), BH_3·THF complex, and Redal [sodium bis(2-methoxyethoxy)aluminum dihydride (**16**), 70% in benzene] were purchased from Aldrich Chemical Co. and standardized before use. Modification of a procedure by Birch et al.[12] for synthesizing isoquinolines gave 6,7-dimethoxyisoquinoline in 62% overall yield from 3,4-dimethoxybenzaldehyde and 6,7-(methylenedioxy)isoquinoline in 78% overall yield from 3,4-(methylenedioxy)benzaldehyde. All reactions were carried out by using degassed solvents under a nitrogen atmosphere.

(11) The corresponding Grignard reagent gives a copious precipitate when added to the amine–borane and is not suitable for introducing the carbon substituent. Apparently, **12** is insoluble in THF even at room temperature when the counterion is a magnesium species.

(12) Birch, A. J.; Jackson, A. H.; Shannon, P. V. R.; Varma, P. S. P. *Tetrahedron Lett.* **1972**, 4789.

Anhydrous tetrahydrofuran (THF) was purified by distillation from sodium benzophenone ketyl. ^1H NMR spectra were recorded with a Varian EM390 spectrometer using $CDCl_3$ solutions with Me_4Si as an internal standard. ^{13}C NMR spectra were recorded with a JEOL FX-60 spectrometer using $CDCl_3$ solutions with Me_4Si as an internal standard. IR spectra were recorded with a Beckman IR 4250 by using a thin film of the neat liquid between NaCl plates or KBr pellets for solid samples. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Combustion analyses were obtained from Galbraith Laboratories, Inc., Knoxville, TN.

Methyl 1-Methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (7) from Isoquinoline (2). To 0.47 g (3.64 mmol) of isoquinoline (2) in 25 mL of dry THF at −78 °C under a nitrogen atmosphere was added 3.7 mL of 1.0 M BH_3·THF complex in THF (3.7 mmol). After 30 min at −78 °C, 3.0 mL of 1.25 M CH_3Li in ether (3.75 mmol) was added in one portion. The resulting yellow-brown solution was stirred at −78 °C for 30 min after which 3.8 mL of 1.0 M DIBAH in hexane (3.8 mmol) was introduced dropwise via syringe into the flask. The dry ice bath was removed, and the reaction mixture was allowed to warm slowly to room temperature. During this time, the yellow-brown color faded to pale yellow. After 5 h at room temperature, the reaction mixture was cooled to 0 °C, and 2.1 g (22.0 mmol, 6 equiv) of methyl chloroformate was added dropwise. The ice bath was removed, and the acylation reaction was allowed to proceed at room temperature. After 19 h at room temperature, the reaction mixture was cooled again to 0 °C, and a solution of 2.0 mL of concentrated HCl in 25 mL of water was added slowly. After 1 h at 0 °C (rapid stirring), the mixture was poured into a separatory funnel containing 40 mL water. The product was extracted from the acidic solution with CH_2Cl_2 (1 × 40 mL and 2 × 20 mL). The extracts were combined, dried over Na_2SO_4, and concentrated by rotary evaporation. Short-path distillation [bp 115–117 °C (0.3 mm)] of the residual oil gave 0.48 g (64%) of pure **7**: ^1H NMR δ 1.37 (3 H, d, J = 6.6 Hz, CH_3), 2.33–3.40 and 3.88–4.27 (4 H, m, H3, H4), 3.67 (3 H, s, OCH_3), 5.15 (1 H, q, J = 6.6 Hz, H1), 7.02 (4 H, br s, H5-8). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 70.12; H, 7.15.

1-Phenyl-1,2,3,4-tetrahydroisoquinoline (19) from Isoquinoline (2). To 1.16 g (9.0 mmol) of isoquinoline (2) in 60 mL of dry THF at −78 °C under nitrogen atmosphere was added 9.0 mL of 1.0 M BH_3·THF complex in THF (9.0 mmol). After 30 min at −78 °C, 4.8 mL of 1.9 M PhLi in 70:30 cyclohexane/ether (9.1 mmol) was added in one portion. The resulting brown solution was allowed to stir at −78 °C for 45 min after which the dry ice bath was removed, and 10.0 mL of 1.0 M DIBAH in hexane (10.0 mmol) was added immediately. The reaction mixture was allowed to warm to room temperature, during which time the brown color changed to red-orange. After 18 h at room temperature, the reaction mixture was cooled to 0 °C and quenched by addition of 15 mL of 6 M HCl. After 45 min at 0 °C (rapid stirring), the mixture was poured into a separatory funnel containing 50 mL of water. Nonbasic impurities were extracted from the acidic solution with ether (2 × 20 mL), and the aqueous layer was then made strongly basic by addition of solid KOH at 0 °C. The product was extracted with CH_2Cl_2 (3 × 20 mL), and the extracts were combined, dried over Na_2SO_4, and concentrated by rotary evaporation. Recrystallization of the crude semisolid from cyclohexane gave pure **19**: 1.54 g (82%, two crops); mp 96.5–97.0 °C (lit.[13] mp 98–100 °C); ^1H NMR δ 1.87 (1 H, br s, NH), 2.75–3.03 (2 H, m, H4), 3.03–3.33 (2 H, m, H3), 5.04 (1 H, br s, H1), 6.60–7.18 (4 H, m, H5-8), 7.21 (5 H, s, Ph).

Methyl 1-Phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (8) from 19. A solution containing 1.25 g (6.0 mmol) of **19** in 10 mL of dry pyridine was cooled to 0 °C and stirred rapidly as 0.70 g (7.4 mmol) of methyl chloroformate was added dropwise. The reaction mixture was allowed to warm slowly to room temperature. After 18 h, the cloudy, yellow suspension was poured into 50 mL cold 3 M HCl. The product was extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, and concentrated by rotary evaporation. The residual solvents were removed in vacuo [25 °C (0.05 mm), 24 h]. The remaining pale yellow oil (1.54 g, 96%) was analytically pure **8**: ^1H NMR δ 2.51–3.38 and 3.83–4.17 (4 H, m, H3, H4), 3.70 (3 H, s, OCH_3), 6.32 (1 H, s, H1), 6.86–7.39 (9 H, m, aromatic H). Anal. (Calcd for $C_{17}H_{17}NO_2$): C, 76.38; H, 6.41. Found: C, 76.12; H, 6.53.

Attempts to prepare **8** directly from **2** by the procedure above for preparation of **7** gave mass recoveries much greater than 100%. The high-field absorptions of the NMR spectra for these mixtures were virtually identical with those for **8**, but the aromatic regions were complex and integrated approximately 50% too high.

Methyl 1,2,3,4-Tetrahydroisoquinoline-2-carboxylate (10) from Isoquinoline (2). To a suspension of 0.22 g (9.2 mmol) of oil-free NaH in 10 mL of THF was added 9.0 mL of 1.0 M DIBAH in hexane (9.0 mmol) at room temperature. After 30 min, 9.0 mmol of isoquinoline–*N*-borane (**4**) in 25 mL of THF (prepared in situ by addition of 9.0 mL of 1.0 M BH_3·THF complex in THF to 1.16 g of **2** in 16 mL of THF at −78 °C) was transferred via syringe into the reaction flask. The resulting red-brown solution was allowed to stir at room temperature for 18 h and was then cooled to 0 °C. Methyl chloroformate [5.1 g (54 mmol, 6 equiv)] was added all at once, and the ice bath was removed. After 19 h at room temperature, the reaction mixture was cooled again to 0 °C, and a solution of 5 mL of concentrated HCl in 25 mL of water was added slowly. After 1 h at 0 °C (rapid stirring), the mixture was poured into a separatory funnel containing 40 mL of water. The product was extracted from the acidic solution with CH_2Cl_2 (1 × 40 mL and 2 × 20 mL). The extracts were combined, dried over Na_2SO_4, and concentrated by rotary evaporation. Short-path distillation [bp 96–98 °C (0.1 mm)] of the residual oil gave 1.17 g (68%) of pure **10**: ^1H NMR δ 2.72 (2 H, t, J = 6 Hz, H4), 3.58 (2 H, t, J = 6 Hz, H3), 3.66 (3 H, s, OCH_3), 4.50 (2 H, s, H1), 6.83–7.20 (4 H, m, H5-8). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 68.88; H, 6.75.

6,7-Dimethoxyisoquinoline–*N*-Borane (5) from 6,7-Dimethoxyisoquinoline.[12] A magnetically stirred solution of 3.0 g (15.8 mmol) of 6,7-dimethoxyisoquinoline[12] in 100 mL of dry THF was cooled to −78 °C under N_2 atmosphere, and 16.0 mL of 1.0 M BH_3·THF complex in THF (16.0 mmol) was added slowly via syringe. The resulting solution was stirred for 20 min, after which 5 mL of water was added, and the dry ice bath was removed. The reaction mixture (at room temperature) was transferred with 100 mL of CH_2Cl_2 to a separatory funnel and shaken with 200 mL of 5% aqueous NaCl. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The extracts were combined with the original organic layer, dried over Na_2SO_4, and concentrated by rotary evaporation. Recrystallization of the crude residual solid from isopropyl alcohol gave 2.82 g (88%, 2 crops) of pure **5**: white needles; mp 158–160 °C dec; ^1H NMR δ 3.99 (3 H, s, C6 or C7-OCH_3), 4.02 (3 H, s, C6 or C7-OCH_3), 7.06 (1 H, s, H5 or H8), 7.13 (1 H, s, H5 or H8), 7.54 (1 H, d, J = 6.0 Hz, H4), 8.15 (1 H, d, J = 6.0 Hz, H3), 8.94 (1 H, br s, H1). Anal. Calcd for $C_{11}H_{14}BNO_2$: C, 65.07; H, 6.95; N, 6.90. Found: C, 65.28; H, 7.08; N, 7.00.

6,7-(Methylenedioxy)isoquinoline–*N*-Borane (6). The general procedure described above for preparation of **5** was used to convert 4.0 g (23.1 mmol) of 6,7(methylenedioxyiso)quinoline[12] to crude **6** (4.17 g, 97%). An analytical sample (mp 185–187 °C dec, sealed tube) was obtained by sublimation at 170 °C (0.05 mm): ^1H NMR δ 6.14 (2 H, s, OCH_2O), 7.08 (1 H, s, H5 or H8), 7.15 (1 H, s, H5 or H8), 7.53 (1 H, d, J = 6.0 Hz, H4), 8.18 (1 H, d, J = 6.0 Hz, H3), 8.92 (1 H, br s, H1). Anal. Calcd for $C_{10}H_{10}BNO_2$: C, 64.23; H, 5.39; N, 7.49. Found: C, 64.07; H, 5.42; N, 7.34.

Methyl 6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (9). The general procedure described above for preparation of **7** was used to convert 0.81 g (4.0 mmol) of **5** to crude **9** (0.71 g, 67%). An analytical sample was obtained by bulb to bulb distillation [pot 140 °C (0.05 mm)] with considerable loss due to thermal decomposition: ^1H NMR δ 1.42 (3 H, d, J = 6.6 Hz, CH_3), 2.57–3.55 and 3.90–4.27 (4 H, m, H3, H4), 3.68 (3 H, s, CO_2CH_3), 3.78 (6 H, s, C6 and C7-OCH_3), 5.10 (1 H, q, J = 6.6 Hz, H1), 6.52 (2H, br s, H5, H8). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22. Found: C, 63.19; H, 7.33.

6,7-Dimethoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (Carnegine) from 9. A solution of 0.78 g (2.94 mmol) of crude **9** in 20 mL of dry THF was added dropwise in 15 min to an ice-cooled solution prepared by diluting 6.0 mL of 1.0 M ethereal $LiAlH_4$ (6.0 mmol) with 15 mL of THF. The ice bath was re-

(13) Van Binst, G.; Baert, R. B. *J. Heterocycl. Chem.* **1975**, *12*, 1165.

moved, and the reaction mixture was heated at reflux for 6 h. The ice bath was then replaced, and the reaction was quenched by dropwise addition of 3 mL of H_2O. The THF solution was decanted from aluminum salts into a separatory funnel containing 75 mL of H_2O. The product was extracted with CH_2Cl_2 (3 × 30 mL). The extracts were combined, dried over Na_2SO_4, and concentrated by rotary evaporation. Bulb to bulb distillation of the residual oil gave 0.56 g (86%) of pure carnegine as a viscous yellow oil: bp 150–160 °C (0.2 mm) [lit.[14] bp 170 °C (1 mm)]; ^1H NMR δ 1.36 (3 H, d, J = 7.0 Hz, CH_3), 2.43 (3 H, s, NCH_3), 2.48–3.12 (4 H, m, H3, H4), 3.50 (1 H, q, J = 7.0 Hz, H1), 3.80 (6 H, s, C6 and C7-OCH_3), 6.50 (1 H, s, H5 or H8), 6.53 (1 H, s, H5 or H8). Spectral data were identical with those obtained from an authentic sample of natural carnegine.

6,7-(Methylenedioxy)-2-methyl-1,2,3,4-tetrahydroisoquinoline (Hydrohydrastinine) from 6. The general procedure described above for preparation of **10** was used to convert 0.38 g (2.0 mmol) of **6** to crude **11**: 0.39 g (83%); ^1H NMR δ 2.67 (2 H, t, J = 6.0 Hz, H4), 3.58 (2 H, t, J = 6.0 Hz, H3), 3.68 (3 H, s, OCH_3), 4.43 (2 H, br s, H1), 5.81 (2 H, s, OCH_2O), 6.45 (1 H, s, H5 or H8), 6.47 (1 H, s, H5 or H8).

(14) "The Merck Index", 9th ed.; Merck & Co.: Rahway, NJ, 1976.

Reduction of crude **11** by $LiAlH_4$ according to the procedure for preparation of carnegine gave a pale yellow oil which was added to a saturated solution of anhydrous HCl in ether. Recrystallization of the crude salt from EtOH gave 0.31 g (68% from **6**) of pure hydrohydrastinine hydrochloride, 270 °C dec (lit.[14] 278 °C dec).

Acknowledgment. This research was supported by grants from the Texas Christian University Research Fund (Grant 5-23649) and The Robert A. Welch Foundation (Grant P-853). D.E.M. also thanks Prof. Manfred G. Reinecke for providing an authentic sample of natural carnegine.

Registry No. **2**, 119-65-3; **5**, 87803-18-7; **6**, 87803-19-8; **7**, 87803-12-1; **8**, 87803-13-2; **9**, 87803-15-4; **10**, 87803-14-3; **11**, 87803-16-5; **11**·HCl, 87803-17-6; **19**, 3340-78-1; 6,7-dimethoxyisoquinoline, 15248-39-2; 6,7-(methylenedioxy)isoquinoline, 269-44-3; carnegine, 71783-56-7; hydrohydrastinine, 494-55-3.

Supplementary Material Available: Additional spectral data for compounds **5–10**; full experimental details for preparations of compounds **6**, **9**, and hydrohydrastinine (4 pages). Ordering information is given on any current masthead page.

General Method for the Synthesis of Selectively N-Alkylated Polyamines

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A versatile method is presented for the synthesis of linear polyamines—in particular, the naturally ubiquitous putrescine, spermidine, and spermine—regiospecifically N-alkylated or N-polyalkylated. The new approach is based on the acylation of amines with *N*-(trifluoroacetyl)amino acid chlorides, optional alkylation followed by selective saponification of the (trifluoroacetyl)amino function, analogous reacylation, and polyamide to polyamine reduction.

The naturally ubiquitous polyamines putrescine (**1**), spermidine (**2**), and spermine (**3**) play a complex set of roles

$$H_2N(CH_2)_4NH_2 \quad 1$$

$$H_2N(CH_2)_4NH(CH_2)_3NH_2 \quad 2$$

$$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2 \quad 3$$

in cell life whose detailed understanding has become the object of extensive research.[1] Much of the action of the polyamines is broadly linked with their essentially complete protonation under physiological conditions and coulombic complexation of the resultant polycations with particular conformations of nucleic acids and other polyanionic molecules.[1] The polyamines have also been found within a variety of conjugate structures.[1,2] Medical interest has been spurred by the observation of abnormal polyamine levels in several disease states, including cystic fibrosis[1a,h,3] and cancer.[1a,4]

Considerable progress has been made in delineating the biosynthesis of the polyamines.[1a,b,e,f,5] Less detail is known about their catabolism[1a,e,g,6] as well as their vital noncovalent interactions.[1a,7] Further advances in all three directions would be promoted by extended structure/activity

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