(±)-eudesma-4(14),7(11)-dien-8-one,[11] and (±)-vetiselinene.[10]

Experimental Section

Melting points were determined on a Büchi 550 melting point apparatus and are uncorrected. Infrared spectra of carbon tetrachloride solutions were recorded on a Perkin-Elmer 257 spectrophotometer and ^{1}H NMR spectra of deuteriochloroform solutions (internal standard Me_4Si) on a Varian EM-390 spectrometer. ^{13}C NMR spectra of deuteriochloroform solutions were taken on a Nicolet NT-200, wide-bore, broad-band spectrometer, operating with an Oxford magnet at 50.31 MHz in the Fourier transform mode. The carbon shifts are in ppm downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. GC analyses were performed on a Hewlett-Packard 5880A chromatograph with 30-m (0.2-mm diameter) SP-2340 fused silica capillary columns, an "on column" injection system, and hydrogen as the carrier gas. Absorption chromatography was carried out on Merck silica (0.040–0.063 mm, 230–400-mesh ASTM). The Diels–Alder adducts were crystallized from pentane.

4-Acetoxy-2-methyl-2-cyclohexenone (2). A mixture of 4.00 g (36 mmol) of 2-methyl-2-cyclohexenone, 8.30 g (47 mmol) of *N*-bromosuccinimide, and 300 mg (0.83 mmol) of dibenzoyl peroxide in 46 mL of dry carbon tetrachloride was refluxed for 7 h and then cooled to room temperature. The resultant precipitate was filtered and discarded and the filtrate concentrated to a 20-mL volume. A mixture of 9.2 g (93 mmol) of potassium acetate and 1.0 g (2.2 mmol) of methyltrioctylammonium chloride in 5 mL of water was added and stirred at 25 °C for 14 h. Ether (70 mL) and 35 mL of water were added and the aqueous layer was extracted with ether. The combined organic layer and extract were dried (Na_2SO_4) and evaporated. Chromatography on 100 g of silica gel and elution with 4:1 pentane–ether yielded 3.48 g (57%) of colorless, liquid keto ester **2**: IR C=O 1745 (s), 1685 (s), C—O 1230 (s) cm^{-1}; ^{1}H NMR δ 1.75 (s, 3, 2-Me), 2.05 (s, 3, acetyl Me), 5.40 (br s, 1, H-4), 6.50 (br s, 1, H-3); ^{13}C NMR δ 15.0 (Me), 20.3 (ester Me), 28.5 (C-5), 34.3 (C-6), 67.6 (C-4), 136.9 (C-2), 141.8 (C-3), 169.6 (ester C=O), 197.3 (C=O).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.33; H, 7.17.

4β-Acetoxy-8aβ-methyl-3,4α,4aβ,5,8,8a-hexahydro-1(2*H*)-naphthalenone (3a) and 4α-Acetoxy-8aβ-methyl-3,4β,4aβ,5,8,8a-hexahydro-1(2*H*)-naphthalenone (3b). Keto ester **2** (840 mg, 5 mmol) was added to a suspension of 600 mg (4.5 mmol) of anhydrous aluminum trichloride in 25 mL of dry toluene under nitrogen and the mixture stirred at room temperature for 80 min. A 3 M toluene solution of 1,3-butadiene (**1**) (15 mL) was added and the mixture degassed (2 min at −78 °C/14 Torr and the flask then closed) and kept at 40 °C for 7 h. It was cooled, poured into ice water, and extracted with ether. The extract was washed with 10% sodium bicarbonate solution, dried, and evaporated. Chromatography of the residue (a 1.3:1 **3a–3b** mixture by GC analysis) on 30 g of 20% silver nitrate impregnated silica gel and gradient elution with 200:1 to 50:1 pentane–ether mixtures gave 150 mg (13.5%) of colorless, crystalline keto ester **3a**, 100 mg (9%) of colorless, crystalline keto ester **3b**, and 416 mg (37.5%) of a colorless, solid **3a–3b** mixture.

Octalone **3a**: mp 63–64 °C; IR C=CH 3025 (w), C=O 1745 (s), 1718 (s), C=C 1660 (w), C—O 1240 (s) cm^{-1}; ^{1}H NMR δ 1.13 (s, 3, Me), 2.02 (s, 3, acetyl Me), 4.8–5.0 (m, 1, H-4), 5.60 (br s, 2, H-6, H-7); ^{13}C NMR δ 20.1 (Me), 21.1 (ester Me), 22.4 (C-5), 30.2 (C-3), 31.5 (C-8), 34.6 (C-2), 43.5 (C-4a), 46.4 (C-8a), 69.7 (C-4), 123.0 (C-6 or C-7), 123.4 (C-7 or C-6), 170.4 (ester C=O), 212.3 (C=O).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.98; H, 8.20.

Octalone **3b**: mp 40–42 °C; IR C=CH 3025 (w), C=O 1745 (s), 1715 (s), C=C 1660 (w), C—O 1240 (s) cm^{-1}; ^{1}H NMR δ 1.23 (s, 3, Me), 2.00 (s, 3, acetyl Me), 5.3–5.5 (m, 1, H-4), 5.55 (br s, 2, H-6, H-7); ^{13}C NMR δ 21.2 (ester Me), 23.6 (C-5), 23.7 (Me), 28.2 (C-3), 33.1 (C-8), 33.6 (C-2), 42.6 (C-4a), 47.1 (C-8a), 70.5 (C-4), 123.5 (C-6 or C-7), 124.3 (C-7 or C-6), 170.4 (ester C=O), 212.6 (C=O).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.01; H, 8.15.

4aβ-Methyl-3,4,4a,5,8,8aβ-hexahydro-1(2*H*)-naphthalenone (5a). A solution of 267 mg (1.2 mmol) of a 1.3:1 **3a–3b** keto ester mixture and 242 mg (1.3 mmol) of (*p*-tolylsulfonyl)hydrazine in 1 mL of 95% ethanol was heated at 75 °C for 20 min and then cooled and evaporated under reduced pressure. Chromatography of the residue on 7 g of silica gel and elution with 1:1 pentane–ether yielded 350 mg of tosylhydrazones **4a**. A solution of the latter in 1 mL of dry chloroform at 0 °C was treated with 0.16 mL (1.43 mmol) of catecholborane (slow injection by a syringe through a septum) and the mixture kept at 0 °C under nitrogen for 2 h. Upon the addition of 380 mg (2.8 mmol) of sodium acetate trihydrate, the mixture was refluxed for 1 h. It was cooled and filtered and the solid washed with chloroform. The combined filtrate and washings were evaporated and the residue chromatographed on 6 g of silica gel. Elution with 20:1 pentane–ether gave 140 mg of esters **4b**. A mixture of the latter and 150 mg (1.1 mmol) of potassium carbonate in 1 mL of water and 3 mL of methanol was refluxed for 2 h. The cooled mixture was concentrated under reduced pressure and extracted with ether. The extract was washed with 10% hydrochloric acid and with brine, dried, and evaporated. A solution of 1.4 mmol of Jones reagent (prepared from a solution of 7 g of chromium trioxide in 50 mL of water and 6 mL of concentrated sulfuric acid) was added slowly to a stirring solution of the residue in 10 mL of acetone at 0 °C and the stirring continued for 0.5 h. After the usual workup the crude product was chromatographed on 15 g of silica gel and eluted with 100:1 pentane–ether, affording 70 mg (36% overall yield) of colorless, liquid ketone **5a**: IR C=CH 3038 (m), C=O 1715 (s), C=C 1660 (w) cm^{-1}; ^{1}H NMR δ 1.11 (s, 3, Me), 5.58 (br s, 2, H-6, H-7); ^{13}C NMR δ 22.0 (C-8), 22.7 (C-3), 28.2 (Me), 32.6 (C-5), 37.3 (C-4), 37.5 (C-4a), 40.2 (C-2), 53.4 (C-8a), 123.9 (C-6 or C-7), 124.0 (C-7 or C-6), 214.4 (C=O).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.53; H, 9.80.

4aβ-Methyl-3,4,4a,5,8,8aα-hexahydro-1(2*H*)-naphthalenone (6). A dry, ethanolic, 0.1 M sodium ethoxide solution (7 mL) containing 110 mg (0.67 mmol) of ketone **5a** was stirred at room temperature for 0.5 h. The usual workup furnished 110 mg of a 4:1 **6–5a** mixture (by GC analysis), whose chromatography on 4 g of silica gel and elution with 50:1 pentane–ether gave 60 mg of colorless, liquid ketone **6**: IR C=CH 3025 (m), C=O 1715 (s), C=C 1658 (w) cm^{-1}; ^{1}H NMR δ 0.79 (s, 3, Me), 5.61 (br s, 2, H-6, H-7); ^{13}C NMR δ 18.2 (Me), 21.8 (C-8), 22.8 (C-3), 37.9 (C-4a), 40.1 (C-4), 41.4 (C-5), 41.7 (C-2), 52.9 (C-8a), 124.5 (C-6), 125.5 (C-7), 211.9 (C=O). (2,4-Dinitrophenyl)hydrazone: mp 139–140 °C (EtOH).

Anal. Calcd for $C_{17}H_{20}O_4N_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 59.60; H, 5.65; N, 15.98.

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Registry No. **1**, 106-99-0; **2**, 118631-94-0; **3a**, 118631-95-1; **3b**, 118631-96-2; **4a** (isomer 1), 118656-37-4; **4a** (isomer 2), 118631-98-4; **4b** (isomer 1), 118631-99-5; **4b** (isomer 2), 118681-75-7; **5a**, 118631-97-3; **6**, 118656-38-5; 2-methyl-2-cyclohexenone, 1121-18-2.

An Efficient Method for Preparation of 3,5-Diamino-6-chloropyrazin-2-yl Alkyl Ketones Using a Novel Acetylene Hydration Method[1]

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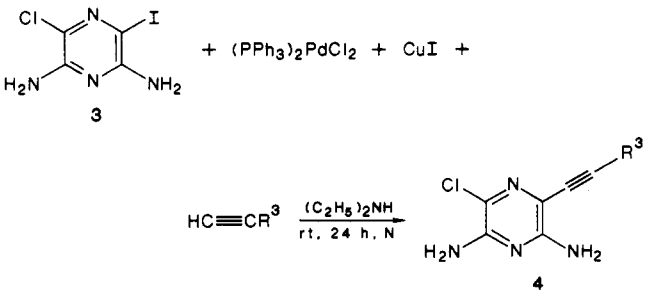
In connection with a program directed toward the preparation of new therapeutic agents, we required a

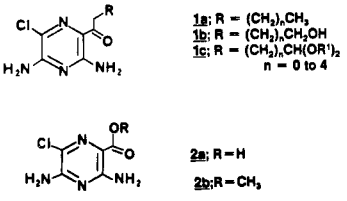
Table I. Pyrazinylalkynes Prepared via Coupling Reaction



4	R^3	yield,[a] %
a	$(CH_2)_4CH_3$	63
b	$(CH_2)_3CH_2OH$	62
c	$(CH_2)_3CH(OCH_2)_2$	58
d	$(CH_2)_3CH(OC_2H_5)_2$	56

[a] Yields are of recrystallized, analytically pure, and fully characterized compounds.

synthesis of 3,5-diamino-6-chloropyrazin-2-yl ketones 1.[2] Routes utilizing acid **2a** and several derivatives as the immediate precursors of 1 were explored to no avail.[3] The problems encountered during the attempted carboxyl to keto conversion led us to consider inserting the carbonyl group into 1 in masked form. The efficiency of the palladium-catalyzed coupling of aromatic iodides with monosubstituted acetylenes[4,5] combined with the number of means available for hydration of acetylenes to ketones[6] encouraged pursuit of the method that is the subject of this paper.

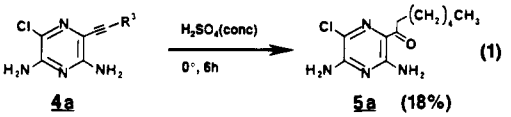


A practicable preparation of 3-chloro-5-iodo-2,6-pyrazinediamine (**3**) was required so that the proposed sequence of acetylene coupling followed by hydration could be investigated as a route to 1. Replacement of the carboxylic acid of **2a** by iodine was accomplished by heating the acid in DMF at 80 °C with 3.3 equiv of iodine.[7,8]

Electrophilic iodinations accompanied by decarboxylation are known to occur in π-excessive furan[9a] and pyrrole[9b] systems but are not known for the nominally π-deficient pyrazine system. The failure of **2a** to decarboxylate when heated in DMF alone (i.e. in the absence of iodine) permits several conclusions about the mechanism of the replacement reaction to be drawn. The observation argues against a dipolar ion similar to the one involved in the Hammick reaction.[10a] Most likely, iodide **3** is formed via an addition–elimination sequence[9c] ($+I_2$, $-HI$, $-CO_2$) rather than decarboxylation being the initial step.[10b]

The conditions described by Sonogashira,[4] bis(triphenylphosphine)palladium dichloride and copper(I) iodide as catalysts in dry diethylamine as solvent under an inert atmosphere, effected the couplings of iodide **3** with the monosubstituted acetylenes indicated in Table I. Gram quantities of pyrazinylalkynes **4** thus were made available.

The most commonly used acetylene hydration methods involve aqueous acid in the presence of catalytic mercury salts.[6] Attempts to catalyze the hydration of acetylene **4a** with mercuric ions led to extremely poor recoveries of identifiable materials. Pyrazinyl ketones **5a** and **5b** were obtained in low yields by hydration of **4a** (eq 1) and **4b** with concentrated sulfuric acid.



Our initial plans were to oxidize the ω-hydroxyl group of ketone **5b** to an aldehyde and then protect it so that acetals of type **1c**, also, would become available. Contrary to our expectations, the hydroxyl group of **5b** could not be readily oxidized.[11] The desired oxidation state of the terminal carbon of the side chain could be introduced earlier (Table I last two entries).

Introduction of the acetal functionality into **4c** and **4d**,[12] however, gave substrate alkynes that were not compatible with the forcing hydration conditions that had been used with pyrazinyl alkynes **4a** and **4b**. Ultimately, the problem was resolved by the serendipitous discovery of a new and comparatively milder acetylene hydration method.

In parallel, attempts were being made to optimize the purification of alkyne **4a**. We speculated that isolation might be facilitated by precipitating any residual transition metals from the coupling reaction mixture as the sulfides.[13]

(1) Presented in part at Tenth International Congress of Heterocyclic Chemistry, Waterloo, Ontario, August 11–16, 1985.

(2) For the preparation of pyrazinyl ketones see: Barlin, G. B. *The Pyrazines in the Chemistry of Heterocyclic Compounds*; Weisberger, A., Taylor, E. C., Eds.; John Wiley: New York, 1982; pp 294–300.

(3) (a) Attempted additions of organometallics to carbonyl compounds **2b** and the corresponding aldehyde (prepared in our laboratory by ester reduction with lithium aluminum hydride in THF and oxidation with manganese oxide) under a variety of conditions were uniformly unsuccessful. Protection of the 3,5-diamino functionality as the bis(*N,N*-dimethylformamidines) (Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675) or as bis(tetramethyldisilyl)azacyclopentanes did not alter the outcome of these reactions (Djuric, S.; Venit, J.; Magnus, P.; *Tetrahedron Lett.* **1981**, *22*, 1787). (b) 3,5-diamino-6-chlor-β-oxopyrazinepropanoic acid (Brooks, D. W.; Lu, L.D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72) and 1-(3,5-diamino-6-chloropyrazinyl)-2-(phenylsulfonyl)ethanone (Pavlickova, L.; Koutek, B.; Velek, J.; Soucek, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 1216) prepared from **2a** and **2b**, respectively, could not be further elaborated in our hands.

(4) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(5) For applications of ref 4 to less functionalized heteroaromatics see: (a) Edo, K.; Yamanaka, H.; Sakamoto, T. *Heterocycles* **1978**, *9*, 271. (b) Abe, Y.; Ohsawa, A.; Arai, H.; Igeta, H. *Ibid.* **1978**, *9*, 1397. (c) At the time our work was initiated, there had been no examples of a palladium-catalyzed cross-coupling with a pyrazine. Examples with alkyl- and arylpyrazines have subsequently been reported: Akita, Y.; Ohta, A. *Ibid.* **1982**, *19*, 329. (d) Ohta, A.; Inone, A.; Watanabe, T. *Ibid.* **1984**, *10*, 2317. (e) Ohta, A.; Akita, Y.; Inone, M. *Ibid.* **1983**, *20*, 154. (f) Konno, S.; Fujimura, S.; Yamanaka, H. *Ibid.* **1984**, *22*, 2245. (g) Sakamoto, T.; Nishimura, S.; Kondo, Y.; Yamanaka, H. *Synthesis* **1988**, 485.

(6) Hudrlik, P. F.; Hudrlik, A. M. In *The Chemistry of Functional Groups, The Chemistry of the C-C Triple Bond*; Patai, S. Ed, John Wiley: New York, 1978; pp 240–243 and references cited therein.

(7) For other methods of preparing halogenopyrazines, see (2) pp. 95-114.

(8) The Hunsdiecker reaction and variants thereof failed to transform **2a** into **3**: Meyers, A. I.; Fleming, M. P. *J. Org. Chem.* **1979**, *44*, 3405 and references cited therein.

(9) (a) Pizey, J. S. In *Synthetic Reagents*; Pizey, J. S., Ed.; Ellis Horwood: Chichester, 1977; Vol. 3, Chapter 3. (b) Newkome, G. R.; Paudler, W. M. *Contemporary Heterocyclic Chemistry Syntheses, Reactions and Applications*; Wiley: New York, 1982; p 98. (c) Reference 10b, chapter 7.

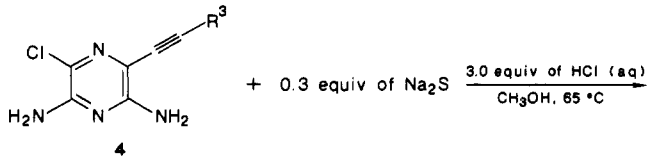
(10) (a) Paquette, L. A. *Principles of Modern Heterocyclic Chemistry*; Benjamin: Reading, 1968; pp 253–254. (b) For examples of pyrazine decarboxylations see ref 2, pp 253–258.

(11) (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647 and methods and references cited therein. (b) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.

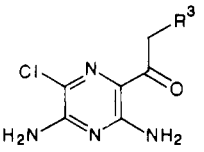
(12) Commercially available 6-hexynol was oxidized according to ref 11; crude aldehyde was then protected as the acetal and used in the coupling reaction without further purification.

(13) For the use of hydrogen sulfide as a means of removing metals see: Bergstrom, D. E.; Ogawa, M. K. *J. Am. Chem. Soc.* **1978**, *100*, 8106.

Table II. Pyrazinyl Alkyl Ketones



4



5

5	R^3	reaction time, h	yield,[a] %
a	$(CH_2)_4CH_3$	0.5	89
b	$(CH_2)_3CH_2OH$	0.5	67
c	$(CH_2)_3CH(OCH_2)_2$	0.08	40[b]
d	$(CH_2)_3CH(OC_2H_5)_2$	0.08	34[b]

[a] Yields are of recrystallized, analytically pure, and fully characterized compounds. [b] Isolated as dimethyl acetal.

Exposure of the crude organic extracts of a reaction mixture of **4a** to aqueous sodium sulfide and aqueous hydrochloric acid in methanol unexpectedly yielded ketone **5a**! Furthermore, the yield of **5a** produced in this fashion far exceeded that of the previous best method and spurred us to investigate the mechanism of this hydration.

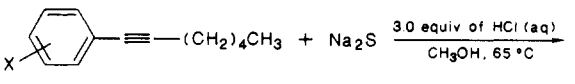
TLC analysis of a control reaction run with **4a** indicated that hydrogen sulfide alone, in aqueous methanol, produced at least two intermediates (presumed to be enethiol, the thione and/or the 1,1-dithiol;[14] no attempts were made to isolate these intermediates). Addition of hydrogen chloride to this mixture produced ketone **5a**. Hydrogen chloride alone in aqueous methanol had no effect on alkyne **4a**; these observations raise several intriguing points. First, they are not consistent with the widely accepted A_{SE2} mechanism of alkyne hydration where protonation of the alkyne is thought to be the rate-determining step.[15]

Secondly, the putative addition of hydrogen sulfide across the triple bond in a useful manner contrasts sharply with previous attempts to synthesize thiocarbonyl compounds by such a reaction. Hydrogen sulfide when used as a sole acid had been reported to result in polymerization of the primarily formed enethiols;[16] such was not the case in the presence of a stronger acid.

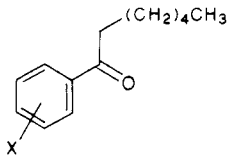
Compounds **4a–d** were converted regioselectively to the corresponding ketones in synthetically useful amounts by the H_2S–HCl mediated process (Table II). Shorter reaction times permitted survival of the acetal group, although transacetalization had taken place, **5c** and **5d**. Only one of the two possible ketone regioisomers was observed in each instance.

The results in Table III indicate that this hydration method can be extended to phenylalkynes provided that the phenyl ring is activated by an electron-donating group in the ortho or para position. Furthermore, this process offers chemoselectivity not available by established procedures.

Table III. Aryl Alkyl Ketone Preparation



6



7

6	X	equiv	time, h	yield of 7,[c] %
a	o-NH_2	1.2	8.0	63[a]
b	m-NH_2	1.2	8.0	*b*
c	p-NH_2	0.3	0.75	71
d	o-OCH_3	1.2	60.0	95[a]
e	m-OCH_3	1.2	60.0	*b*
f	p-OCH_3	1.2	60.0	92[a]
g	H	0.3	0.5	*b*
h	o-CO_2CH_3	1.2	18.0	*b*
i	m-CO_2H	1.2	18.0	*b,d*

[a] When run with catalytic amount of Na_2S and shorter reaction time, incomplete conversion observed. [b] Greater than 75% of starting material recovered. [c] Yield of isolated, purified, and fully characterized compound. [d] Starting material recovered as 1:1 mixture of acid and corresponding methyl ester.

The versatility of the palladium–copper-catalyzed aryl iodide to alkyne reaction has been extended, and a new method of arylalkyne hydration has been developed. The requirement for an electron-donating substituent in the aryl ring imparts additional chemoselectivity to this hydration reaction and adds to the utility of alkynes in organic synthesis.

Experimental Section

General Methods. All reactions were run under a positive pressure of dry nitrogen. Reactions requiring anhydrous conditions were performed in oven-dried glassware, which was cooled under a stream of nitrogen. Solvents were distilled before use: dimethylforamide (DMF) and diethylamine from calcium hydride; tetrahydrofuran (THF) from sodium benzophenone ketyl. The term in vacuo refers to solvent removal via a Büchi rotoevaporator at water aspirator pressure, followed by further evacuation of the flask at 0.5 mmHg for several hours. Analytical thin-layer chromatography (TLC) was performed on Analtech uniplates: silica gel GHLF of 250 μm. Solvent systems were as follows: (A) 2:1 $PhCH_3$ to EtOAc; (B) $CHCl_3$; (C) 2:1 EtOAc to hexane; (D) 12:1 CH_2Cl_2 to CH_3OH; (E) 9:1 CH_2Cl_2 to CH_3OH. Flash chromatography was performed on silica gel from E. Merck (Kieselgel 60, 230–400 mesh). Melting points were obtained on a Thomas-Hoover apparatus with open capillary tubes and are uncorrected.

Proton nuclear magnetic resonance (^1H NMR) spectra were determined on a Bruker WM-250 (250 MHz) or an IBM NR-80 (80 MHz) instrument. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; br, broad. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were determined on a Bruker WM-250 (62.9 MHz). Chemical shifts are reported in δ units, ppm relative to tetramethylsilane. Carbon multiplicity was determined by DEPT pulse sequence (Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.* **1982**, *48*, 323). Mass spectra (MS) were obtained on a Finnegan 4635B instrument by direct exposure probe with current programming at 100 mamp per second. Electron impact (EI) data were obtained at 70 eV; chemical ionization (CI) data were obtained with methane at estimated source pressure greater than one torr with source temperature at 190 °C. Microanalyses were performed by ICI Americas Corporate Research Analytical Services.

(14) Paquer, D.; Vialle, J. *Bull. Soc. Chim. Fr.* **1969**, 3595.
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3-Chloro-5-iodo-2,6-pyrazinediamine (3). Pyrazinecarboxylic acid **2a**,[17] 9.45 g (50.0 mmol), was suspended in 250 mL of dry DMF under a nitrogen atmosphere and heated to 80 °C until a homogeneous solution was obtained. To the above solution was added 27.92 g (110.0 mmol) of iodine in 125 mL of DMF over the course of 0.5 h. At the end of the addition, the solution was kept at 80 °C for an additional 0.5 h before being cooled to room temperature. The reaction mixture was poured into 500 mL of stirred water; to the stirred solution was then added 1.0 L of saturated aqueous sodium thiosulfate. The aqueous solution was extracted with five 350-mL portions of ethyl acetate. The combined ethyl acetate washes were extracted: two times with 350-mL of $Na_2S_2O_3$ (saturated), two times with 350 mL of $NaHCO_3$ (saturated), and two times with 350 mL of water. The solution was dried with magnesium sulfate, and the solvent was removed under reduced pressure with a 35 °C water bath. The crude solid, 11.42 g, was dissolved in 70 mL of hot toluene, treated with decolorizing charcoal, and filtered hot, and the volume was reduced to 45 mL. Upon standing overnight at 5 °C, 8.75 g (65%) of yellow needles were obtained: mp 130 °C; TLC R_f 0.22 (A); ^{1}H NMR ($CDCl_3$) δ 4.69 (s); ^{13}C NMR (DMSO-d_6) δ 153.7, 150.1, 116.6, 78.8; MS (EI) 272 (M^+ + 2, 33), 270 (base). Anal. Calcd for $C_4H_4ClIN_4$: C, 17.76; H, 1.49; Cl, 13.10; N, 20.71. Found: C, 18.04; H, 1.54; Cl, 13.05; N, 20.80.

Preparation of 3-Chloro-5-(1-heptynyl)-2,6-pyrazinediamine (4a). Typical Procedure for Synthesis of Pyrazinylalkynes. In 150 mL of dry diethylamine[18] was dissolved 5.4 g (20.0 mmol) of iodide **3** under an inert atmosphere. To the stirred solution was added 0.35 g (0.5 mmol) of bis(triphenylphosphine)palladium dichloride,[19] followed by 3.13 mL (24.0 mmol) of 1-heptyne.[12] Copper(I) iodide, 0.047 g (0.25 mmol), was then added, and stirring was continued under nitrogen until all iodide **3** had been consumed as determined by TLC (~18 h). Solvent was removed under vacuum, and the crude product mixture dissolved in 500 mL of $CHCl_3$ and extracted with three 100-mL portions of H_2O. The chloroform extracts were then filtered through 300 mL of neutral alumina and reduced in volume. Flash chromatography yielded 3.61 g (76%) of material. It was then dissolved in 100 mL of hot toluene and filtered, and the volume was reduced to 30 mL. Upon standing at 5 °C, 2.99 g (63%) of product was obtained: mp 106–107 °C; TLC R_f 0.58 (B); ^{1}H NMR ($CDCl_3$) δ 4.8 (br, 4 H, NH_2), 2.46 (t, J = 10.5 Hz, 2 H), 1.62 (quintet, J = 10.5 Hz, 2 H), 1.33 (m, 4 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.6, 148.6, 119.7, 112.0, 95.7, 75.2, 30.9, 28.1, 21.9, 19.4, 13.7; MS (CI) 239 (M^+ + 1, base). Anal. Calcd for $C_{11}H_{15}N_4Cl$: C, 55.34; H, 6.33; N, 23.45; Cl, 14.85. Found: C, 55.54; H, 6.35; N, 23.21; Cl, 14.90.

6-(3,5-Diamino-6-chloropyrazinyl)-6-hexynol (4b): mp 89–90 °C (from toluene); TLC R_f 0.2 (C); ^{1}H NMR ($CDCl_3$) δ 4.6 (br, 4 H, NH_2), 3.7 (s, 1 H, OH), 2.5 (t, J = 10.0 Hz, 2 H), 1.7 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 154.9, 149.7, 117.1, 109.0, 94.3, 76.2, 60.3, 31.8, 24.8, 18.9; MS (CI), 241 (M^+ + 1, base). Anal. Calcd for $C_{10}H_{13}N_4OCl$: C, 49.90; H, 5.44; N, 23.27; Cl, 14.72. Found: C, 50.19; H, 5.50; N, 22.90; Cl, 14.78.

3-Chloro-5-(6,6-diethoxy-1-hexynyl)-2,6-pyrazinediamine (4d): yellow oil; TLC R_f 0.8 (D); ^{1}H NMR (DMSO-d_6) δ 6.48 (s, NH_2, 2 H), 6.07 (s, NH_2, 2 H), 4.51 (t, J = 7 Hz, 1 H), 3.54 (m, 2 H), 3.43 (m, 2 H), 2.45 (t, J = 7 Hz, 2 H), 1.60 (m, 4 H), 1.10 (t, J = 7 Hz, 6 H). Anal. Calcd for $C_{14}H_{21}ClN_4O_2$: C, 53.76; H, 6.77; N, 17.91. Found: C, 53.59; H, 6.78; N, 17.77.

Preparation of 1-(3,5-Diamino-6-chloropyrazinyl)-1-heptanone (5a). Typical Alkyne Hydration Procedure. To **4a** (0.5 g, 2.10 mmol) dissolved in 50 mL of methanol was added 3.3 mL of 0.1 M sodium sulfide (0.33 mmol) and 2.0 mL of 10% hydrochloric acid (2.4 mmol); the mixture was heated to reflux temperature for 0.5 h. The cooled reaction suspension was filtered through Celite with methanol as eluent (2 × 80 mL). The solvent was removed in vacuo, and the oil was flash chromatographed on silica with $CHCl_3$; recrystallization from toluene yielded 0.48 g (89%) of product: mp 119–120 °C; TLC R_f 0.20 (B); ^{1}H NMR (DMSO-d_6) δ 8.38–7.12 (band, NH_2, 4 H), 2.82 (t, J = 7 Hz, 2 H), 1.54 (m, 2 H), 1.26 (m, 6 H), 0.89 (t, J = 8 Hz, 3 H); MS (EI) m/e 256 (M^+, 20), 186 (base). Anal. Calcd for $C_{11}H_{17}N_4OCl$: C, 51.46; H, 6.67; N, 21.82. Found: C, 51.63; H, 6.47; N, 21.81.

1-(3,5-Diamino-6-chloropyrazinyl)-6-hydroxy-1-hexanone (5b): mp 137–139 °C; TLC R_f 0.57 (E); ^{1}H NMR (DMSO-d_6) δ 8.24 (s, NH, 1 H), 7.73–6.92 (s, NH, 3 H), 3.76 (s, OH, 1 H), 3.37 (t, J = 7 Hz, 2 H), 2.85 (t, J = 7 Hz, 2 H), 1.53 (m, 2 H), 1.40 (m, 2 H), 1.30 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 198.6, 155.0, 153.4, 118.6, 118.4, 60.6, 36.3, 32.4, 25.4, 24.4; MS (CI) 259 (M^+ + 1, base). Anal. Calcd for $C_{10}H_{15}ClN_4O_2$: C, 46.43; H, 5.84; N, 21.66. Found: C, 46.03; H, 5.89; N, 21.36.

1-(3,5-Diamino-6-chloropyrazinyl)-6,6-dimethoxy-1-hexanone (5d): oil; TLC R_f 0.5 (D); ^{1}H NMR (DMSO-d_6) δ 8.19 (s, NH, 1 H), 7.33 (m, NH, 3 H), 4.30 (t, J = 8 Hz, 1 H), 3.22 (s, OCH_3, 6 H), 2.82 (t, J = 7.5 Hz, 2 H), 1.53 (m, 4 H), 1.28 (m, 2 H). Anal. Calcd for $C_{12}H_{19}ClN_4O_3$: C, 47.60; H, 6.33; N, 18.50. Found: C, 47.43; H, 6.11; N, 18.18.

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Registry No. **2a**, 4878-36-8; **3**, 118476-03-2; **4a**, 118476-04-3; **4b**, 118476-05-4; **4c**, 118476-06-5; **4d**, 118476-07-6; **5a**, 118476-08-7; **5b**, 118476-09-8; **5c**, 118476-10-1; **5d**, 118476-11-2; **6a**, 118476-12-3; **6b**, 118476-14-5; **6c**, 118476-13-4; **6d**, 113195-44-1; **6e**, 118476-15-6; **6f**, 64146-61-8; **6g**, 14374-45-9; **6h**, 118476-16-7; **6i**, 118476-17-8; **7a**, 69561-06-4; **7c**, 53033-83-3; **7d**, 118476-18-9; **7f**, 69287-13-4; **7i** (methyl ester), 118476-19-0; $HC{\equiv}C(CH_2)_4CH_3$, 628-71-7; $HC{\equiv}C(CH_2)_3CH_2OH$, 928-90-5; $HC{\equiv}C(CH_2)_3CH(OCH_2)_2$, 98558-32-8; $HC{\equiv}C(CH_2)_3CH(OC_2H_5)_2$, 1720-35-0.

Supplementary Material Available: Tables containing NMR and analytical data for compounds **6** and **7** (3 pages). Ordering information is given on any current masthead page.

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(18) In some instances a 1:1 mixture of triethylamine to methylene chloride was used as solvent. This combination appears to lengthen the time course of the reaction over that with diethylamine.

(19) Greater amounts of this reagent simply accelerated the reaction. The indicated ratio of catalysts allowed the reactions to be complete within 24 h.

Synthesis of (1-Aryl-1-alkylethyl)alkoxyamines

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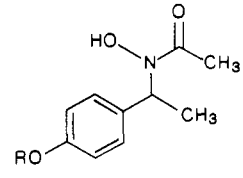
N-Hydroxy-*N*-(1-arylethyl)acetamides (**1**) have recently been shown to be potent orally active inhibitors of leukotriene biosynthesis.[1] As part of our investigations concerning the structure–activity relationships of these compounds,[1b] we examined analogs of structure **2**, which possess a second alkyl substituent in the benzylic position resulting in a tertiary carbon adjacent to nitrogen.



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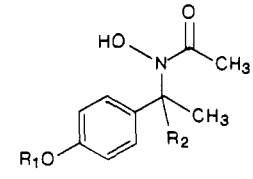

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