Tetrahydro-1,5-benzoxazepines and Tetrahydro-1*H*-1,5-benzodiazepines by a Tandem Reduction-Reductive Amination Reaction

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A tandem reduction-reductive amination reaction has been applied to the synthesis of (±)-4-alkyl-2,3,4,5-tetrahydro-1,5-benzoxazepines and (±)-4-alkyl-1-benzoyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines. The nitro aldehydes and ketones required for 1,5-benzoxazepine ring closures were prepared by nucleophilic aromatic substitution of the alkoxides from several 3-buten-1-ol derivatives with 2-fluoro-1-nitrobenzene followed by ozonolysis. Precursors for the 1,5-benzodiazepines were prepared by similar addition of *N*-(3-butenyl)benzamide anions to 2-fluoro-1-nitrobenzene followed by ozonolysis. Catalytic hydrogenation of the nitro carbonyl compounds using 5% palladium-on-carbon in methanol then gave the target heterocycles by a tandem reduction-reductive amination sequence. The 1,5-benzoxazepines were isolated in high yield following chromatographic purification; the 1,5-benzodiazepines were isolated as solids directly from the hydrogenation mixture and possessed differentiated functionality on the two nitrogen atoms.

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Introduction.

We recently reported a new synthesis of tetrahydrobenzoxazines and tetrahydroquinoxalines from 1-(2-nitrophenoxy)-2-alkanone and *N*-(2-nitrophenyl)-*N*-(2-oxoalkyl)-acetamide derivatives using the tandem reduction-reductive amination reaction [2]. We have also demonstrated that this reductive cyclization can be successfully used to prepare seven-membered heterocycles [3]. The current project sought to extend this tandem reaction sequence to the synthesis of (±)-4-alkyl-2,3,4,5-tetrahydro-1,5-benzoxazepines and (±)-4-alkyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepines.

Tetrahydro-1,5-benzoxazepines and tetrahydro-1*H*-1,5-benzodiazepines are desirable targets for synthesis due to their potential as pharmaceutical agents. Many structures incorporating these ring systems are known to have significant biological activity. For example, benzoxazepines have been investigated as central nervous system depressants [4], as orexin receptor antagonists for the treatment of obesity and sleep disorders [5], and as angiotensin converting enzyme inhibitors for the treatment of cardiovascular disease [6]. Benzodiazepines have proven effective as arginine vasopressin antagonists for the treatment of hypertension [7] and have also shown activity as anxiolytics [8,9], analgesics [10,11], antiaggressives [10], anticonvulsants [10,11], antidepressants [12], antimicrobials [13] and antiinflammatories [14].

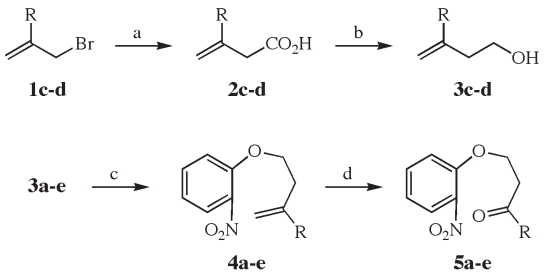
Earlier work by others has described the synthesis of these ring systems [15,16], but substitution patterns were limited and yields were generally low. The use of a tandem reduction-reductive amination strategy should permit greater structural diversity as well as higher yields. As expected, modification of our previous benzoxazine synthesis, using homoallylic alcohols in place of allylic alcohols, provided precursors to the benzoxazepines. Direct extension of our quinoxaline work to the synthesis of benzodiazepines, however, was not successful. Thus, new methodology was developed to substitute *N*-(3-butenyl)-benzamide derivatives onto nitroaromatic systems. We report here a simple and efficient approach to the synthesis of tetrahydro-1,5-benzoxazepines and tetrahydro-1*H*-1,5-benzodiazepines from homoallylic alcohols and amines and define the parameters for success in the reaction.

Results and Discussion.

The syntheses of our cyclization substrates are summarized in Schemes 1 and 2. Nucleophilic aromatic substitution of anions derived from 3-buten-1-ol [17] or *N*-(3-butenyl)benzamide derivatives [18] with 2-fluoro-1-nitrobenzene provided an efficient route to nitro alkenes **4a-e** and **9a-b**. Homoallylic alcohols **3a-b** were commercially available. Alcohols **3c-d** were prepared from previously reported allylic halides **1c-d** [19] by conversion to the corresponding Grignard reagents using Rieke magnesium [20], carboxylation, and reduction with lithium aluminum hydride. The use of Rieke magnesium was required to minimize coupling which occurred during attempts to prepare the Grignard reagents under standard conditions. Preparation of the alcohols *via* the carboxylic acids was found to be superior to direct synthesis by reaction with formaldehyde gas and offered a convenient scheme for purification. Finally, alcohol **3e** was prepared by the literature method [21]. Deprotonation of the alcohols using sodium hydride in dimethylformamide followed by reaction with 2-fluoro-1-nitrobenzene then gave nitro alkenes **4a-e**. *N*-Benzoyl homoallylic amine derivative **8a** was prepared from commercial allyl cyanide by reduction with 1:1 lithium aluminum hydride:aluminum chloride in ether [22] followed by benzoylation under Schotten-Baumann conditions [23]; **8b-c** were prepared by conversion of allylic bromides **1b-c** to cyanides **6b-c** [24] followed by a similar reduction and amidation. Deprotonation of the benzamide derivatives and reaction with 2-fluoro-1-nitrobenzene were then carried out to introduce the entire pre-fabricated *N*-(3-

butenyl)-*N*-benzoyl side chain to the nitroaromatic ring [25]. This reaction was successful for **8a** and **8b**, but failed for **8c**, which is more sterically demanding. Despite this limitation, the current synthesis represents a new approach to 1˚ and 2˚ benzamide derivatives [18]. Finally, ozonolysis of **4a-e** and **9a-b** gave clean conversion to the nitro carbonyl compounds **5a-e** and **10a-b** [26]. Overall, from the homoallylic alcohols and amines, the benzoxazepine precursors were obtained in 75-95% yields while the benzodiazepine precursors were produced in 52-58% yields.

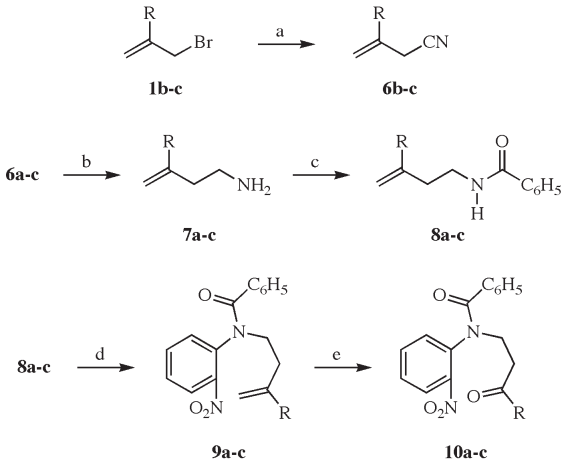
Scheme 1 [a]



a R = H **b** R = CH_3 **c** R = *n*-C_4H_9 **d** R = *t*-C_4H_9 **e** R = C_6H_5

[a] Key: (a) (i) Rieke Mg, tetrahydrofuran, (ii) CO_2; (b) $LiAlH_4$, ether; (c) (i) NaH, dimethylformamide, (ii) 2-fluoro-1-nitrobenzene, 50˚; (d) (i) O_3, CH_3OH, −78˚, (ii) $(CH_3)_2S$, *p*-$CH_3C_6H_4SO_3H$, −78˚ → 20˚, (iii) 3% aq $HClO_4$:THF (1:1), 20˚.

Scheme 2 [a]

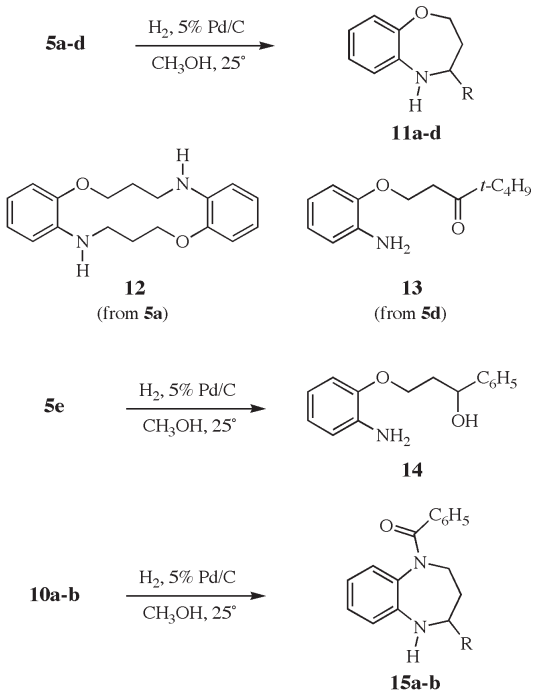


a R = H **b** R = CH_3 **c** R = *n*-C_4H_9

[a] Key: (a) CuCN, 125-150˚; (b) $LiAlH_4$, $AlCl_3$, ether; (c) C_6H_5COCl, C_6H_6, 10% NaOH; (d) (i) NaH, dimethylformamide, (ii) 2-fluoro-1-nitrobenzene, 50˚; (e) (i) O_3, CH_3OH, −78˚, (ii) $(CH_3)_2S$, *p*-$CH_3C_6H_4SO_3H$, −78˚ → 20˚, (iii) 3% aq $HClO_4$:THF (1:1), 20˚.

The results of our cyclization studies are summarized in Scheme 3. Hydrogenation of **5a-c** and **10a-b**, initiated the tandem reduction-reductive amination sequence to give the tetrahydro-1,5-benzoxazepines **11a-c** and tetrahydro-1*H*-1,5-benzodiazepines **15a-b**, respectively, in 70-88% yields. The reaction proceeded best using 4 atmospheres of hydrogen and 20 weight percent of 5% palladium-on-carbon (relative to substrate) in anhydrous methanol at 25-35˚.

Scheme 3



a R = H **b** R = CH_3 **c** R = *n*-C_4H_9 **d** R = *t*-C_4H_9 **e** R = C_6H_5

Notably among these reactions, cyclization of the parent 1,5-benzoxazepine (*e.g.* **5a**) was found to be concentration dependent. When the substrate concentration was 3.85 x 10^{-2} *M*, 72% of **11a** was formed along with 3.5% of dimer **12**. When the concentration of the substrate was reduced by a factor of three to 1.28 x 10^{-2} *M*, the yield of **11a** increased to 82% and dimer formation was negligible (<1%). Dimerization did not occur to an appreciable extent in any of the ketone cyclizations, presumably due to increased steric hindrance around the carbonyl. Cyclization of aldehyde **10a** was carried out under dilute conditions (1.32 x 10^{-2} *M*) and did not give a measurable amount of dimeric product.

The *tert*-butyl and phenyl substrates were investigated only for the 1,5-benzoxazepine series, but gave disappointing results in each case. Hydrogenation of **5d** (R = *t*-C_4H_9) gave heterocycle **11d** in only 37% yield. The major product, isolated in 49% yield, was amino ketone **13** resulting from reduction without subsequent cyclization. Apparently, the bulky *tert*-butyl group impedes approach of the aniline nitrogen to the side chain carbonyl largely

suppressing the final ring closure. Attempts to cyclize **5e** ($R = C_6H_5$) gave none of the desired heterocyclic product, but instead, gave an 84% yield of amino alcohol **14** derived from nitro and carbonyl reduction. It is well known that phenyl ketones are highly susceptible to reduction under hydrogenation conditions [27]. In this case, cyclization of the larger seven-membered ring was sufficiently slow [28] to allow for reduction of the phenyl ketone before cyclization could occur. By comparison, closure of the homologous phenyl-substituted benzoxazine [2] proceeded in 76% yield without significant carbonyl reduction.

In conclusion, an efficient synthetic route has been developed for the preparation of substituted tetrahydro-1,5-benzoxazepine and tetrahydro-1*H*-1,5-benzodiazepine derivatives. The tetrahydro-1,5-benzoxazepines were prepared from homoallylic alcohols in three steps with a 66% average overall yield; the tetrahydro-1*H*-1,5-benzodiazepines were prepared from homoallylic amines in four steps with a 42% average overall yield. By comparison to the analogous six-membered ring closures [2], the larger rings are less readily formed, giving incomplete closure in substrates that have sterically hindered side chain carbonyls and competitive carbonyl reduction from substrates requiring cyclization on an aromatic ketone. On balance, however, this approach offers a new entry to uniquely substituted derivatives of the target heterocycles.

EXPERIMENTAL

All reactions (except hydrogenations) were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech no. 21521) with ultraviolet detection. Preparative separations were performed by one of the following methods: (1) flash column chromatography [29] on silica gel (grade 62, 60-200 mesh) containing ultraviolet-active phosphor (Sorbent Technologies, UV-5) packed into quartz columns or (2) preparative thin layer chromatography on 20-cm x 20-cm silica gel GF plates (Analtech no. 02015). Band elution for both methods was monitored using a hand-held ultraviolet lamp. Melting points were uncorrected. Infrared spectra were run as thin films on sodium chloride disks and referenced to polystyrene. ^1H and ^{13}C Nuclear magnetic resonance spectra were measured in deuteriochloroform at 300 MHz and 75 MHz, respectively, using tetramethylsilane as an internal standard; coupling constants (J) are given in Hz. Unless otherwise noted, mass spectra (electron impact/direct probe) were obtained at 70 electron volts.

Caution: The following operations were carried out in a glove bag under dry nitrogen to minimize the potential for fires: (1) cutting and weighing potassium metal used to prepare Rieke magnesium, (2) weighing lithium aluminum hydride, and (3) addition of 5% palladium-on-carbon to methanol solutions prior to hydrogenation.

Representative Procedure for the Preparation of 3-Butenoic Acids: 3-Butyl-3-butenoic Acid (**2c**).

This compound was prepared on a 20-mmole scale by carboxylation of the Grignard reagent from **1c** generated using activated Rieke magnesium [20]. A 250-mL, three-necked, round-bottomed flask equipped with magnetic stirring and a reflux condenser was charged with 100 mL of anhydrous tetrahydrofuran, 3.80 g (40.0 mmoles) of anhydrous magnesium chloride, 3.32 g (20.0 mmoles) of anhydrous potassium iodide and 2.72 g (70.0 mmoles) of freshly cut potassium metal. The mixture was heated at reflux with vigorous stirring for 3 hours to give the activated magnesium as a viscous black suspension. The suspension was cooled to 0° and 3.54 g (20.0 mmoles) of **1c** was added dropwise with vigorous stirring. Stirring was continued for 45 minutes at 0° and the Grignard reagent was transferred by cannula under nitrogen pressure to a large excess of solid carbon dioxide in a 500-mL three-necked round-bottomed flask. The reaction was stirred for 3 hours, quenched with saturated ammonium chloride, acidified to pH 2 with 1 *M* hydrochloric acid and extracted with ether (three times). The acidic product was extracted into 0.2 *M* sodium hydroxide then reacidified with 1 *M* hydrochloric acid, and ether extracted (three times). The combined ether extracts were washed with saturated sodium chloride, dried (magnesium sulfate) and concentrated under vacuum to afford 1.99 g (70%) of **2c** as a colorless oil. The product was spectroscopically pure and used without further purification; ir: 3686-2287, 1710, 1646, 899 cm^{-1}; ^1H nmr: δ 11.0 (br s, 1H), 4.96 (m, 1H), 4.93 (m, 1H), 3.08 (d, 2H, J = 0.8), 2.13 (t, 2H, J = 7.1), 1.44 (m, 2H), 1.33 (m, 2H), 0.91 (t, 3H, J = 7.4); ^{13}C nmr: δ 178.2, 142.0, 114.0, 41.7, 35.5, 29.5, 22.3, 13.9; ms: *m/z* 142 (M^+).

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.61; H, 9.86. Found: C, 67.91; H, 9.92.

3-*tert*-Butyl-3-butenoic Acid (**2d**).

This compound (2.04 g, 72%) was isolated as a colorless oil and used without further purification; ir: 3467-2382, 1710, 1636, 908 cm^{-1}; ^1H nmr: δ 11.6 (br s, 1H), 5.10 (s, 1H), 4.93 (s, 1H), 3.11 (s, 2H), 1.09 (s, 9H); ^{13}C nmr: δ 179.2, 149.8, 112.0, 38.1, 36.3, 28.8; ms: *m/z* 142 (M^+).

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.61; H, 9.86. Found: C, 67.51; H, 9.92.

Representative Preparation of 3-Buten-1-ols: 3-Butyl-3-buten-1-ol (**3c**).

A solution of 2.10 g (14.8 mmoles) of **2c** in 20 mL of anhydrous ether was added dropwise to a stirred suspension of 0.56 g (14.8 mmoles) of lithium aluminum hydride in 50 mL of dry ether. The mixture was refluxed for 30 minutes, then carefully quenched with water and 5% aqueous sodium hydroxide and ether extracted (three times). The combined ether extracts were washed with saturated sodium chloride, dried (magnesium sulfate) and concentrated under vacuum to give 1.80 g (95%) of **3c** as a colorless oil. The product was used without further purification; ir: 3338, 1643, 885 cm^{-1}; ^1H nmr: δ 4.86 (s, 1H), 4.81 (s, 1H), 3.71 (br t, 2H, J = 6.6), 2.30 (t, 2H, J = 6.3), 2.03 (t, 2H, J = 6.9), 1.50-1.24 (complex, 5H), 0.91 (t, 3H, J = 7.2); ^{13}C nmr: δ 146.2, 108.5, 60.3, 39.1, 35.4, 29.9, 22.4, 13.9; ms: *m/z* 128 (M^+).

Anal. Calcd. for $C_8H_{16}O$: C, 75.00; H, 12.50. Found: C, 74.94; H, 12.55.

3-*tert*-Butyl-3-buten-1-ol (**3d**).

This compound (1.61 g, 96%) was isolated as a colorless oil and used without further purification; ir: 3339, 1633, 892 cm^{-1}; ^1H nmr:

δ 4.98 (s, 1H), 4.74 (s, 1H), 3.77 (br t, 2H, J = 6.0), 2.35 (t, 2H, J = 6.7), 1.59 (br s, 1H), 1.08 (s, 9H); ^{13}C nmr: δ 154.1, 107.8, 61.9, 36.3, 31.0, 29.3 (3); ms: *m/z* 128 (M^+).

Anal. Calcd. for $C_8H_{16}O$: C, 75.00; H, 12.50. Found: C, 75.08; H, 12.54.

Representative Procedure for the Preparation of 3-Butenyl 2-Nitroaromatic Ethers: 2-(3-Butenyloxy)-1-nitrobenzene (**4a**).

This compound was prepared on a 5.00-mmole scale by nucleophilic aromatic substitution of the alkoxide derived from 3-butyl-3-buten-1-ol with 2-fluoro-1-nitrobenzene according to the procedure of Bunce and Easton [17]. The product (0.82 g, 85%) was purified on a 40 cm x 2.5 cm silica gel column eluted with 5% ether in hexanes to give 0.82 g (85%) of **4a** as a light yellow oil. The spectral data matched those reported previously [17].

2-(3-Methyl-3-butenyloxy)-1-nitrobenzene (**4b**).

This compound (0.87 g, 84%) was isolated as a light yellow oil; ir: 1650, 1525, 1351 cm^{-1}; ^{1}H nmr: δ 7.81 (dd, 1H, J = 8.1, 1.6), 7.51 (ddd, 1H, J = 8.4, 7.5, 1.3), 7.08 (d, 1H, J = 8.4), 7.00 (t, 1H, J = 8.1), 4.86 (s, 1H), 4.81 (s, 1H), 4.21 (t, 2H, J = 6.8), 2.56 (t, 2H, J = 6.8), 1.81 (s, 3H); ^{13}C nmr: δ 152.2, 141.5, 140.0, 133.9, 125.5, 120.2, 114.5, 112.6, 68.4, 36.8, 22.8; ms: *m/z* 207 (M^+).

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.77; H, 6.28; N, 6.76. Found: C, 63.89; H, 6.34; N, 6.67.

2-(3-Butyl-3-butenyloxy)-1-nitrobenzene (**4c**).

This compound (1.09 g, 88%) was isolated as a light yellow oil; ir: 1645, 1358, 1351 cm^{-1}; ^{1}H nmr: δ 7.81 (dd, 1H, J = 8.1, 1.8), 7.50 (ddd, 1H, J = 8.5, 7.5, 1.8), 7.08 (dd, 1H, J = 8.5, 1.0), 7.01 (ddd, 1H, J = 8.1, 7.5, 1.2), 4.86 (s, 1H), 4.83 (s, 1H), 4.20 (t, 2H, J = 6.9), 2.56 (t, 2H, J = 6.9), 2.09 (t, 2H, J = 7.1), 1.49-1.26 (complex, 4H), 0.91 (t, 3H, J = 7.1); ^{13}C nmr: δ 152.2, 145.6, 140.2, 133.9, 125.5, 120.2, 114.3, 111.3, 68.6, 36.1, 35.1, 29.8, 22.4, 13.9; ms: *m/z* 249 (M^+).

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.47; H, 7.63; N, 5.62. Found: C, 67.63; H, 7.71; N, 5.47.

2-(3-*tert*-Butyl-3-butenyloxy)-1-nitrobenzene (**4d**).

This compound (1.07 g, 86%) was isolated as a light yellow oil; ir: 1638, 1526, 1354 cm^{-1}; ^{1}H nmr: δ 7.81 (dd, 1H, J = 8.1, 1.8), 7.51 (ddd, 1H, J = 8.5, 7.5, 1.8), 7.09 (dd, 1H, J = 8.5, 1.0), 7.01 (ddd, 1H, J = 8.1, 7.5, 1.2), 4.99 (s, 1H), 4.78 (s, 1H), 4.21(t, 2H, J = 7.5), 2.61 (t, 2H, J = 7.5), 1.09 (s, 9H); ^{13}C nmr: δ 153.4, 152.2, 140.2, 134.0, 125.5, 120.2, 114.5, 108.3, 69.7, 36.2, 30.4, 28.9; ms (30 electron volts): *m/z* 249 (M^+).

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.47; H, 7.63; N, 5.62. Found: C, 67.52; H, 7.65; N, 5.57.

2-(3-Phenyl-3-butenyloxy)-1-nitrobenzene (**4e**).

This compound (1.21 g, 90%) was isolated as a light yellow oil; ir: 1672, 1525, 1351 cm^{-1}; ^{1}H nmr: δ 7.79 (dd, 1H, J = 8.5, 1.6), 7.48-7.42 (complex, 3H), 7.37-7.25 (complex, 3H), 7.01-6.96 (complex, 2H), 5.42 (s, 1H), 5.22 (s, 1H), 4.17 (t, 2H, J = 7.1), 3.06 (t, 2H, J = 7.1); ^{13}C nmr: δ 152.1, 146.0, 143.7, 140.2, 133.9, 128.5, 127.7, 126.1, 125.5, 120.3, 115.2, 114.6, 68.3, 34.9; ms: *m/z* 269 (M^+).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.38; H, 5.58; N, 5.20. Found: C, 71.25; H, 5.53; N, 5.26.

Representative Procedure for the Preparation of Butenenitriles: 3-Methyl-3-butenenitrile (**6b**).

This compound (4.80 g, 80%) was prepared from 10.0 g (74 mmoles) of 3-bromo-2-methyl-1-propene by the general procedure outlined for the preparation of allyl cyanide [24]. The temperature required for the substitution reaction was 125˚. The final product was a colorless oil collected at 60-70˚ (25 mm Hg). The product was spectroscopically pure and used without further purification; ir: 2253, 1651, 908 cm^{-1}; ^{1}H nmr: δ 5.10 (m, 1H), 5.01 (m, 1H), 3.06 (m, 2H), 1.84 (m, 3H); ^{13}C nmr: δ 134.3, 117.2, 115.0, 25.8, 21.9; ms: *m/z* 81 (M^+).

3-Butyl-3-butenenitrile (**6c**).

This compound (5.70 g, 82%) was prepared from 10.0 g (56.5 mmoles) of 3-bromo-2-butyl-1-propene. The temperature required for the substitution reaction was 150˚. The final product was a colorless oil collected at 94-98˚ (30 mm Hg). The product was used without further purification; ir: 2246, 1653, 902 cm^{-1}; ^{1}H nmr: δ 5.14 (s, 1H), 5.01 (s, 1H), 3.07 (s, 2H), 2.12 (t, 2H, J = 7.1), 1.40 (m, 4H), 0.92 (t, 3H, J = 7.1); ^{13}C nmr: δ 138.4, 113.8, 112.7, 35.2, 29.3, 24.5, 22.12, 13.8; ms: *m/z* 123 (M^+).

Anal. Calcd. for $C_8H_{13}N$: C, 78.04, H, 10.57; N, 11.38. Found: C, 77.97; H, 10.53; N, 11.44.

Representative Procedure for Nitrile Reduction: 3-Butenylamine (**7a**).

This compound (2.02 g, 48%) was prepared by reduction of 5.78 g (71 mmoles) of **6a** according to the procedure of Jacobson and Williard [22]. The product was isolated as a colorless oil, bp 75-77˚ (literature [30] bp 75-77˚); ir: 3372, 3301, 1640, 991, 908 cm^{-1}; ^{1}H nmr: δ 5.78 (ddt, 1H, J = 17.2, 10.3, 6.9), 5.10 (dm, 1H, J = 17.2), 5.07 (dm, 1H, J = 10.3), 2.76 (t, 2H, J = 6.6), 2.20 (apparent q, 2H, J = 6.6), 1.13 (br s, 2H); ^{13}C nmr: δ 136.2, 116.6, 41.2, 38.1.

3-Methyl-3-butenylamine (**7b**).

This compound (3.36 g, 64%) was isolated as a colorless oil, bp 93-95˚; ir: 3365, 3290, 1647, 885 cm^{-1}; ^{1}H nmr: δ 4.84 (m, 1H), 4.76 (m, 1H), 2.84 (t, 2H, J = 6.6), 2.20 (t, 2H, J = 6.6), 1.76 (m, 3H), 1.15 (br s, 2H); ^{13}C nmr: δ 143.2, 111.7, 41.9, 39.7, 22.1.

3-Butyl-3-butenylamine (**7c**).

This compound (4.75 g, 52%) was isolated as a colorless oil, bp 44-46˚ (7 mm Hg); ir: 3372, 1640, 906 cm^{-1}; ^{1}H nmr: δ 4.80 (m, 1H), 4.75 (m, 1H), 2.80 (t, 2H, J = 6.5), 2.16 (t, 2H, J = 6.5), 2.01 (t, 2H, J = 7.1), 1.41 (m, 4H), 1.11 (br s, 2H), 0.91 (t, 3H, J = 7.1); ^{13}C nmr: δ 147.3, 110.4, 40.2, 40.0, 35.5, 29.9, 22.4, 13.9; ms: *m/z* 127 (M^+).

Anal. Calcd. for $C_8H_{17}N$: C, 75.59; H, 13.38; N, 11.02. Found: C, 75.62; H, 13.41; N, 11.00.

Representative Benzoylation Procedure: *N*-(3-Butenyl)benzamide (**8a**).

This compound was prepared on a 34-mmole scale by Schotten-Baumann benzoylation of 3-butenylamine in benzene using the procedure of Dewar and co-workers [23]. The product (5.59 g, 94%) was isolated as a viscous colorless oil by flash column chromatography on silica gel eluted with 25% ether in hexanes. The spectral data matched those reported previously [31].

N-(3-Methyl-3-butenyl)benzamide (**8b**).

This compound (6.17 g, 96%) was isolated as a colorless viscous oil following flash column chromatography on silica gel

eluted with 25% ether in hexanes; ir: 3310, 1639, 1542, 889 cm^{-1}; ^1H nmr: δ 7.74 (dd, 2H, J = 8.1, 1.3), 7.55-7.39 (complex, 3H), 6.19 (br s, 1H), 4.88 (m, 1H), 4.82 (m, 1H), 3.58 (apparent q, 2H, J = 6.8), 2.34 (t, 2H, J = 6.7), 1.79 (s, 3H); ^{13}C nmr: δ 167.3, 142.7, 134.7, 131.3, 128.5, 126.8, 112.6, 37.3, 37.2, 21.9; ms: *m/z* 189 (M^+).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.19; H, 7.94; N, 7.41. Found: C, 76.04; H, 7.99; N, 7.35.

N-(3-Butyl-3-butenyl)benzamide (**8c**).

This compound (7.46 g, 95%) was isolated as a colorless viscous oil following flash column chromatography on silica gel eluted with 25% ether in hexanes; ir: 3310, 1640, 1545, 890 cm^{-1}; ^1H nmr: δ 7.74 (m, 2H), 7.51-7.38 (complex, 3H), 6.25 (br s, 1H), 4.87 (m, 1H), 4.84 (m, 1H), 3.58 (td, 2H, J = 6.8, 5.5), 2.34 (t, 2H, J = 6.8), 2.06 (t, 2H, J = 7.1), 1.39 (m, 4H), 0.91 (t, 3H, J = 7.1); ^{13}C nmr: δ 167.3, 146.8, 134.7, 131.3, 128.5, 126.8, 111.2, 37.5, 35.6, 35.2, 29.8, 22.4, 13.9; ms: *m/z* 231 (M^+).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.92; H, 9.09; N, 6.06. Found: C, 77.76; H, 9.02; N, 6.04.

Representative Procedure for Nucleophilic Aromatic Substitution of Benzamides to 2-Fluoro-1-nitrobenzene: *N*-(3-Butenyl)-*N*-(2-nitrophenyl)benzamide (**9a**).

In a 250-mL, three-necked, round-bottomed flask equipped with magnetic stirring, an addition funnel and a condenser, 0.44 g of 60% sodium hydride in mineral oil (11.0 mmoles) was washed with hexanes (three times) and suspended in 15 mL of dimethylformamide. Stirring was started and a solution of 1.75 g (10.0 mmoles) of **8a** in 15 mL of dimethylformamide was added dropwise at room temperature. The mixture was stirred for 2 hours at room temperature at which time a solution of 0.71 g (5.0 mmoles) of 2-fluoro-1-nitrobenzene in 2 mL of dimethylformamide was added. The reaction became warm and turned brown in color. The reaction was stirred for 1 hour at room temperature and for 24 hours at 50°, then cooled, added to saturated ammonium chloride, and extracted with ether (three times). The combined ether layers were washed with water and saturated sodium chloride, dried (magnesium sulfate) and concentrated under vacuum. The crude product was flash chromatographed on a 40 cm x 2 cm silica gel column eluted with 10-20% ether in hexanes to afford 1.72 g (58%) of **9a** as a yellow oil; ir: 1657, 1528, 1348, 994, 918 cm^{-1}; ^1H nmr (not coalesced): δ 7.83 (br s, 1H), 7.50 (br s, 1H), 7.43-7.20 (br m, 6H), 7.16 (br s, 1H), 5.79 (br s, 1H), 5.09 (br d, 1H, J = 16.1), 5.05 (br d, 1H, J = 9.6), 4.32 (br s, 1H), 3.55 (m, 1H), 2.47 (br s, 2H); ^{13}C nmr: δ 165.6, 146.0, 137.5, 134.9, 133.7, 131.8, 129.9, 128.2 (2), 127.9 (2), 125.7, 117.1, 49.1, 32.1; ms: *m/z* 296 (M^+).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.92; H, 5.41; N, 9.46. Found: C, 69.10; H, 5.49; N, 9.33.

N-(3-Methyl-3-butenyl)-*N*-(2-nitrophenyl)benzamide (**9b**).

This compound (1.61 g, 52%) was isolated as a light yellow solid, mp 65-66°; ir: 1653, 1529, 1348, 894 cm^{-1}; ^1H nmr (not coalesced): δ 7.84 (br s, 1H), 7.51 (br s, 1H), 7.45-7.23 (br m, 6H), 7.14 (br s, 1H), 4.79 (br s, 1H), 4.73 (br s, 1H), 4.38 (br s, 1H), 3.59 (m, 1H), 2.41 (br s, 2H), 1.75 and 1.73 (2 s, 3H); ^{13}C nmr: δ 168.4, 145.8, 142.6, 135.3, 133.7, 131.9, 130.0, 128.2 (2), 128.0 (2), 125.7, 112.1, 49.1, 35.4, 22.5; ms: *m/z* 310 (M^+).

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.68; H, 5.81; N, 9.03. Found: C, 69.79; H, 5.87; N, 8.96.

Attempted Synthesis of *N*-(3-Butyl-3-butenyl)-*N*-(2-nitrophenyl)benzamide (**9c**).

Attempted addition of the anion of **8c** to 2-fluoro-1-nitrobenzene on a 5-mmole scale gave 84% of recovered **8c** along with small quantities of products resulting from addition of traces of water and dimethylamine to the nitroaromatic substrate.

Representative Ozonolysis Procedure: 3-(2-Nitrophenoxy)-propanal (**5a**).

A solution of 0.80 g (4.14 mmoles) of **4a** in 125 mL of methanol was cooled to –78° and treated with ozone until thin layer chromatography indicated complete consumption of the starting material. Excess ozone was purged with a stream of dry nitrogen and the reaction was quenched at –78° by addition of 5.08 g (84.9 mmoles) of dimethyl sulfide and 200 mg of *p*-toluenesulfonic acid. The resulting solution was warmed to room temperature and stirred for 8 hours, then concentrated under reduced pressure. The crude reaction mixture was diluted with ether, washed with saturated sodium bicarbonate and sodium chloride, and dried (magnesium sulfate). Concentration under reduced pressure gave the dimethyl acetal of **5a** containing 5-10% of the aldehyde. This mixture was dissolved in 25 mL of tetrahydrofuran, cooled to 0°, and 25 mL of 3% aqueous perchloric acid was added dropwise with stirring [25]. The solution was stirred at 0° for 1 hour and at room temperature for 4 hours, then extracted with dichloromethane (three times). The combined organic extracts were washed with saturated sodium bicarbonate and sodium chloride, dried (magnesium sulfate) and concentrated under vacuum to yield 0.76 g (94%) of **5a**. The compound was spectroscopically pure and used without further purification; ir: 2840, 2730, 1723, 1528, 1354 cm^{-1}; ^1H nmr: δ 9.89 (t, 1H, J = 1.1), 7.83 (dd, 1H, J = 8.1, 1.8), 7.55 (ddd, 1H, J = 8.4, 7.4, 1.8), 7.13 (dd, 1H, J = 8.4, 1.0), 7.06 (ddd, 1H, J = 8.1, 7.4, 1.2), 4.44 (t, 2H, J = 6.2), 3.02 (td, 2H, J = 6.2, 1.1); ^{13}C nmr: δ 199.2, 151.8, 140.1, 134.1, 125.6, 120.9, 114.8, 63.4, 42.8; ms: *m/z* 195 (M^+).

Anal. Calcd. for $C_9H_9NO_4$: C, 55.38; H, 4.62; N, 7.18. Found: C, 55.51; H, 4.72; N, 7.05.

4-(2-Nitrophenoxy)-2-butanone (**5b**).

This compound (0.77 g, 95%) was isolated by flash column chromatography on silica gel using 5-10% ether in hexanes. The product was a light yellow oil that solidified on cooling to 0°, mp 35-36°; ir: 1717, 1523, 1353 cm^{-1}; ^1H nmr: δ 7.82 (dd, 1H, J = 8.1, 1.8), 7.53 (tm, 1H, J = 8.4), 7.12 (dd, 1H, J = 8.4, 1.0), 7.03 (ddd, 1H, J = 8.1, 7.4, 1.2), 4.37 (t, 2H, J = 6.2), 2.98 (t, 2H, J = 6.2), 2.27 (s, 3H); ^{13}C nmr: δ 206.0, 152.0, 139.8, 134.1, 125.5, 120.6, 114.7, 64.8, 42.3, 30.8; ms: *m/z* 209 (M^+).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.42; H, 5.26; N, 6.70. Found: C, 57.55; H, 5.31; N, 6.59.

1-(2-Nitrophenoxy)-3-heptanone (**5c**).

This compound (0.75 g, 93%) was isolated as a light yellow oil by flash column chromatography on silica gel eluted with 5-10% ether in hexanes; ir: 1714, 1527, 1351 cm^{-1}; ^1H nmr: δ 7.81 (dd, 1H, J = 8.1, 1.8), 7.52 (ddd, 1H, J = 8.5, 7.5, 1.8), 7.12 (dd, 1H, J = 8.5, 1.2), 7.03 (ddd, 1H, J = 8.1, 7.5, 1.2), 4.37 (t, 2H, J = 6.2), 2.95 (t, 2H, J = 6.2), 2.53 (t, 2H, J = 7.5), 1.60 (quintet, 2H, J = 7.4), 1.33 (sextet, 2H, J = 7.4), 0.92 (t, 3H, J = 7.4); ^{13}C nmr: δ 208.5, 152.0, 140.0, 134.1, 125.5, 120.5, 114.7, 64.9, 43.5, 41.4, 25.6, 22.2, 13.8; ms: *m/z* 251 (M^+).

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.15; H, 6.77; N, 5.58. Found: C, 62.07; H, 6.75; N, 5.59.

4,4-Dimethyl-1-(2-nitrophenoxy)-3-pentanone (**5d**).

This compound (0.73 g, 91%), was isolated as a light yellow oil by flash column chromatography on silica gel eluted with 5-10% ether in hexanes; ir: 1710, 1527, 1354 cm^{-1}; ^1H nmr: δ 7.81 (dd, 1H, J = 8.2, 1.8), 7.52 (ddd, 1H, J = 8.4, 7.4, 1.8), 7.13 (dd, 1H, J = 8.4, 1.2), 7.02 (ddd, 1H, J = 8.2, 7.5, 1.2), 4.39 (t, 2H, J = 6.2), 3.03 (t, 2H, J = 6.2), 1.19 (s, 9H); ^{13}C nmr: δ 213.0, 152.2, 140.0, 134.1, 125.5, 120.4, 114.6, 65.0, 44.3, 35.8, 26.0 (3); ms (30 electron volts): *m/z* 251 (M^+).

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.15; H, 6.77; N, 5.58. Found: C, 62.28; H, 6.83; N, 5.52.

3-(2-Nitrophenoxy)-1-phenyl-1-propanone (**5e**).

This compound (0.76 g, 94%) was isolated as a light yellow solid by flash column chromatography on silica gel eluted with 5-10% ether in hexanes, mp 103-105°; ir: 1684, 1525, 1352 cm^{-1}; ^1H nmr: δ 8.00 (dd, 2H, J = 7.1, 1.2), 7.81 (dd, 1H, J = 8.1, 1.8), 7.62-7.45 (complex, 4H), 7.20 (dd, 1H, J = 8.4, 1.0), 7.04 (ddd, 1H, J = 8.1, 7.5, 1.2), 4.57 (t, 2H, J = 6.6), 3.55 (t, 2 H, J = 6.6); ^{13}C nmr: δ 197.2, 152.1, 139.9, 136.4, 134.1, 133.5, 128.7, 128.1, 125.5, 120.6, 114.8, 65.1, 42.2; ms: *m/z* 271 (M^+).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.80; N, 5.17. Found: C, 66.59; H, 4.87; N, 5.05.

N-(2-Nitrophenyl)-*N*-(3-oxopropyl)benzamide (**10a**).

This compound (0.66 g, 82%) was isolated as a light yellow oil by flash column chromatography on silica gel eluted with 25% ether in hexanes; ir: 2840, 2731, 1719, 1654, 1628, 1348 cm^{-1}; ^1H nmr (not coalesced): δ 9.81 (s, 1H), 7.82 (d, 1H, J = 7.2), 7.59 (t, 1H, J = 7.5), 7.39 (apparent t, 2H, J = 8.0), 7.30-7.07 (complex, 4H), 4.36 (m, 1H), 4.07 (quintet, 1H, J = 6.6), 3.03 (br s, 3H); ^{13}C nmr: δ 200.4, 170.6, 146.2, 142.6, 134.4, 134.2, 131.2, 130.3, 128.4, 128.2, 128.0, 125.7, 45.0, 42.1; ms: *m/z* 298 (M^+).

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.70; N, 9.40. Found: C, 64.61; H, 4.82; N, 9.27.

N-(2-Nitrophenyl)-*N*-(3-oxobutyl)benzamide (**10b**).

This compound (0.68 g, 84%) was isolated as a light yellow solid by column chromatography on silica gel eluted with 25% ether in hexanes, mp 62-64°; ir: 1711, 1654, 1528, 1348 cm^{-1}; ^1H nmr (not coalesced): δ 7.78 (d, 1H, J = 7.2), 7.60 (t, 1H, J= 7.2), 7.44 (dd, 1H, J = 8.0, 1.3), 7.34 (t, 1H, J = 7.5), 7.31-7.05 (complex, 5H), 4.20 (m, 1H), 4.12 (m, 1H), 3.05 (br s, 2H), 2.16 (br s, 3H); ^{13}C nmr: δ 208.0, 170.3, 145.7, 138.1, 134.5, 134.1, 131.0, 130.2, 128.3, 128.1, 127.9, 125.7, 46.5, 41.3, 30.0; ms: *m/z* 312 (M^+).

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.12; N, 8.97. Found: C, 65.47; H, 5.18; N, 8.93.

Representative Procedure for Reductive Ring Closure: 2,3,4,5-Tetrahydro-1,5-benzoxazepine (**11a**).

To a solution of 750 mg (3.85 mmoles) of **5a** in 300 mL of methanol (substrate concentration = 1.28 x 10^{-2} *M*) was added 150 mg of 5% palladium-on-carbon and the mixture was shaken in a stainless steel vessel under 4 atmospheres of hydrogen for 3 hours at 25°. The crude reaction mixture was concentrated, diluted with ether, and vacuum filtered through a pad of Celite 545® topped with a layer of magnesium sulfate to remove the catalyst. Concentration of the filtrate produced a light yellow oil that was purified by preparative thin layer chromatography eluted with 10% ether in hexanes to give 470 mg (82%) of **11a** as a light yellow oil that solidified on standing at 0°, mp 35-37°; ir: 3358 cm^{-1}; ^1H nmr: δ 6.96 (dd, 1H, J = 7.8, 1.6), 6.87 (td, 1H, J = 7.4, 1.6), 6.79 (td, 1H, J = 7.5, 1.8), 6.72(dd, 1H, J = 7.5, 1.8), 4.08 (t, 2H, J = 5.4), 3.77 (br s, 1H), 3.24 (t, 2H, J = 5.6), 2.00 (m, 2H); ^{13}C nmr: δ 150.2, 142.0, 123.4, 121.9, 120.9, 119.6, 71.5, 46.0, 31.9; ms: *m/z* 149 (M^+).

Anal. Calcd. for $C_9H_{11}NO$: C, 72.48; H, 7.38; N, 9.40. Found: C, 72.63; H, 7.46; N, 9.32.

When the reductive ring closure was run under more concentrated conditions (substrate concentration = 3.85 x 10^{-2} *M*), the yield of heterocycle **11a** was reduced to 72% and dimer **12** was produced in 3.5% yield, mp 254-256°; ir: 3426 cm^{-1}; ^1H nmr: δ 6.88 (td, 2H, J = 7.7, 1.3), 6.72 (dd, 2H, J = 8.0, 1.3), 6.65 (td, 2H, J = 7.7, 1.5), 6.58 (dd, 2H, J = 8.0, 1.5), 5.13 (br s, 2H), 4.21 (t, 4H, J = 5.0), 3.35 (q, 4H, J = 5.0), 2.29 (quintet, 4H, J = 5.1); ^{13}C nmr: δ 145.9, 138.0, 121.3, 116.3, 109.4, 108.7, 69.5, 44.5, 27.9; ms: *m/z* 298 (M^+).

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.48; H, 7.38; N, 9.40. Found: C, 72.54, H, 7.39; N, 9.33.

(±)-4-Methyl-2,3,4,5-tetrahydro-1,5-benzoxazepine (**11b**).

This compound (473 mg, 87%) was isolated by preparative thin layer chromatography eluted with 10% ether in hexanes. The resulting oil crystallized at 0° to a yellow solid that darkened on exposure to air, mp 60-62°; ir: 3351 cm^{-1}; ^1H nmr: δ 6.93 (dd, 1H, J = 7.5, 1.6), 6.85 (td, 1H, J = 7.4, 1.6), 6.76 (td, 1H, J = 7.5, 1.8), 6.71 (dd, 1H, J = 7.5, 1.8), 4.38 (ddd, 1H, J = 12.1, 6.2, 3.8), 3.79 (ddd, 1H, J = 11.9, 8.2, 3.5), 3.32 (m, 1H), 3.32 (br s, 1H), 1.96 (ddt, 1H, J = 13.8, 6.3, 3.4), 1.78 (m, 1H), 1.29 (d, 3H, J = 6.5); ^{13}C nmr: δ 150.3, 140.8, 123.3, 121.7, 120.9, 119.8, 70.6, 51.6, 39.4, 22.9; ms: *m/z* 163 (M^+).

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.62; H, 7.98; N, 8.59. Found: C, 73.68; H, 8.02; N, 8.56.

(±)-4-Butyl-2,3,4,5-tetrahydro-1,5-benzoxazepine (**11c**).

This compound (370 mg, 90%) was isolated by preparative thin layer chromatography eluted with 10% ether in hexanes. The resulting oil crystallized at 0° to a yellow solid that darkened on exposure to air, mp 28-30°; ir: 3365 cm^{-1}; ^1H nmr: δ 6.92 (dd, 1H, J = 7.7, 1.6), 6.85 (td, 1H, J = 7.4, 1.6), 6.76 (td, 1H, J = 7.5, 1.8), 6.70 (dd, 1H, J = 7.5, 1.8), 4.39 (ddd, 1H, J = 12.1, 7.1, 3.8), 3.85 (ddd, 1H, J = 12.1, 7.4, 3.8), 3.41 (br s, 1H), 3.19 (ddt, 1H, J = 13.2, 6.5, 3.2), 2.02 (dquintet, 1H, J = 13.8, 3.7), 1.74 (dddd, 1H, J = 13.8, 10.2, 7.4, 3.8), 1.57 (m, 2H), 1.47-1.28 (complex, 4H), 0.93 (t, 3H, J = 6.9); ^{13}C nmr: δ 150.1, 140.7, 123.1, 121.4, 120.8, 119.7, 70.3, 55.8, 37.4, 36.3, 28.4, 22.7, 14.0; ms: *m/z* 205 (M^+).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.10; H, 9.27; N, 6.83. Found: C, 76.02; H, 9.23; N, 6.85.

(±)-4-*tert*-Butyl-2,3,4,5-tetrahydro-1,5-benzoxazepine (**11d**).

When the above procedure was run on 300 mg (1.20 mmoles) of **5d**, 240 mg of a mixture of **11d** and **13** was isolated. Purification by preparative thin layer chromatography eluted with 10% ether in hexanes afforded two bands. Band 1 (fastest moving) contained 90 mg (37%) of **11d** that solidified at 0° to a light yellow solid that darkened on exposure to air, mp 37-38°; ir: 3399 cm^{-1}; ^1H nmr: δ 6.87 (dd, 1H, J = 7.7, 1.6), 6.83 (td, 1 H, J = 7.5, 1.6), 6.73 (td, 1H, J = 7.5, 1.8), 6.66 (dd, 1H, J = 7.5,

1.8), 4.46 (ddd, 1H, J = 12.1, 8.2, 4.0), 3.96 (ddd, 1H, J = 11.9, 5.6, 4.6), 3.38 (br s, 1H), 3.07 (dd, 1H, J = 11.2, 3.5), 2.06 (dddd, 1H, J = 13.5, 8.2, 4.7, 3.5), 1.77 (dddd, 1H, J = 13.5, 11.2, 5.7, 4.1), 1.02 (s, 9H); ^{13}C nmr: δ 149.7, 140.8, 122.8, 120.8, 120.4, 119.0, 70.3, 64.6, 33.8, 31.8, 26.4 (3); ms (30 electron volts): *m/z* 205 (M^+).

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.10; H, 9.27; N, 6.83. Found: C, 76.17, H, 9.29; N, 6.80.

1-(2-Aminophenoxy)-4,4-dimethyl-3-pentanone (**13**).

This compound (130 mg, 49%) was isolated as a light yellow oil from band 2 (above). This oil solidified at 0° to a light yellow solid that darkened on exposure to air, mp 37-38°; ir: 3468, 3372, 1704 cm^{-1}; ^{1}H nmr: δ 6.81 (m, 2H), 6.70 (m, 2H), 4.26 (t, 2H, J = 6.3), 3.75 (br s, 2H), 2.99 (t, 2H, J = 6.3), 1.18 (s, 9H); ^{13}C nmr: δ 213.5, 146.2, 136.6, 121.6, 118.4, 115.2, 112.6, 63.9, 44.3, 36.2, 26.1 (3); ms (30 electron volts): *m/z* 221 (M^+).

Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.59; H, 8.60; N, 6.33. Found: C, 70.78, H, 8.69; N, 6.19.

(±)-3-(2-Aminophenoxy)-1-phenyl-1-propanol (**14**).

When the reductive cyclization was carried out on 400 mg (1.47 mmoles) of **5e**, 300 mg (84%) of **14** was isolated as a light brown oil that crystallized to a tan solid at 0°. Trituration of the solid with 1% ether in petroleum ether gave **14** as a light tan solid, mp 55-56°; ir: 3360 cm^{-1}; ^{1}H nmr: δ 7.40-7.20 (complex, 5H), 6.82-6.65 (complex, 4H), 4.97 (dd, 1H, J = 7.8, 5.1), 4.16 (ddd, 1H, J = 9.6, 7.1, 5.3), 4.04 (m, 1H), 3.30 (br s, 3H), 2.21(m, 2H); ^{13}C nmr: δ 146.4, 144.2, 136.2, 128.5, 127.6, 125.8, 121.4, 118.6, 115.2, 111.9, 71.9, 65.5, 38.5; ms: *m/z* 243 (M^+).

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.07; H, 7.00; N, 5.76. Found: C, 74.22; H, 7.07; N, 5.65.

1-Benzoyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**15a**).

This compound (625 mg, 82%) was isolated as a white solid that was triturated with 2% ether in petroleum ether, mp 137-138°; ir: 3338, 1632 cm^{-1}; ^{1}H nmr (not coalesced): δ 7.26 (d, 2H, J = 6.8), 7.23-7.07 (complex, 3H), 6.93 (td, 1H, J = 8.0, 1.5), 6.76 (dd, 1H, J = 8.0, 1.2), 6.54 (d, 1H, J = 6.8), 6.50 (t, 1H, J = 7.2), 5.10 and 5.06 (2 br s, 1H), 3.96 (br s, 1H), 3.58 (br s, 1H), 3.01 (t, 1H, J = 10.3), 2.89 (t, 1H, J = 10.3), 2.10 (br s, 1H), 1.97 (br s, 1H); ^{13}C nmr: δ 169.7, 145.7, 136.5, 134.0, 129.7, 129.3, 127.9, 127.7, 127.5, 120.5, 119.5, 46.1 (2), 29.5; ms: *m/z* 252 (M^+).

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.35; N, 11.11. Found: C, 76.23; H, 6.38; N, 11.06.

(±)-1-Benzoyl-4-methyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**15b**).

This compound (450 mg, 88%) was isolated as a white solid that was triturated with 2% ether in petroleum ether, mp 124-125°; ir: 3325, 1632 cm^{-1}; ^{1}H nmr (not coalesced): δ 7.37 (br s, 1H), 7.30-7.03 (complex, 3H), 6.96 (d, 1H, J = 7.2), 6.83 (d, 1H, J = 7.5), 6.59 (br s, 2H), 5.13 and 5.19 (2 br s, 0.67H), 4.82 (br s, 0.33H), 4.03 (br s, 0.33H), 3.55 (br s, 0.67H), 3.40 (br s, 0.33H), 3.08 (br s, 0.67H), 2.71 (br s, 0.67H), 2.27 (br s, 0.33H), 1.84 (br s, 2H), 1.37 (d, 3H, J = 6.0), 1.27 (br s, 1H); ^{13}C nmr: δ 169.5, 145.4, 136.5, 136.0, 129.5, 129.3, 128.4, 127.7, 127.5, 120.8, 118.2, 53.1, 45.4, 37.6, 23.8; ms: *m/z* 266 (M^+).

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.69; H, 6.77; N, 10.52. Found: C, 76.74; H, 6.79; N, 10.47.

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REFERENCES AND NOTES

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[1] Undergraduate research participant, 2003-2004

[2] R. A. Bunce, D. M. Herron and L. Y. Hale, *J. Heterocyclic Chem*., **40**, 1031 (2003).

[3] R. A. Bunce, L. B. Johnson and E. M. Holt, *J. Heterocyclic Chem*., **41**, 563 (2004).

[4] J. Sam, German Patent DE 2314392 (**1973**).

[5] H. Aissaoui, M. Clozel, T. Weller, R. Koberstein, T. Sifferien and W. Fischli, International Patent WO 0251838 (2002).

[6] K. Itoh, M. Kori, Y. Inada, K. Nishikawa, Y. Kawamatsu and H. Sugihara, *Chem. Pharm. Bull*., **34**, 3747 (1986).

[7a] D. M. Ashworth, G. R. W. Pitt, P. Hudson, C. M. Yea, R. J. Franklin and G. Semple, International Patent WO 2002000626 (**2002**); [b] A. Matsuhisa, H. Koshio, K. Sakamoto, N. Taniguchi, T. Yatsu and A. Tanaka, *Chem. Pharm. Bull*., **46**, 1566 (1998).

[8] A. Ursini, A. M. Capelli, R. A. E. Carr, P. Cassara, M. Corsi, O. Curcuroto, G. Curotto, M. Dal Cin, S. Davalli, D. Donati, A. Feriani, H. Finch, G. Finizia, G. Gaviraghi, M. Marien, G. Pentassuglia, S. Polinelli, E. Ratti, A. Reggiani, G. Tarzia, G. Tedesco, M. E. Tranquillini, D. G. Trist and F. T. M. Van Amsterdam, *J. Med. Chem*., **43**, 3596 (2000).

[9] O. E. Fancher, G. Nichols and D. A. Stauffer, U.S. Patent 3021325 (1962).

[10] W. Nawrocka, H. Liszkiewicz, A. Nawojski, M. Wilimowski, L. Kedzierska-Gozdzik, J. Barczynska, W. Wojewodzki, E. Duis, A. Szelag and M. Rutkowska, *Pol. J. Pharmacol. Pharm*., **43**, 495 (1991).

[11] A. Nawojski, W. Nawrocka, H. Liszkiewicz, M. Wilimowski, J. Barczynska, L. Kedzierska, W. Wojewodzki, M. Rutkowska, E. Duis and A. Szelag, *Pol. J. Pharmacol. Pharm*., **40**, 471 (1988).

[12] E. J. Glamkowski, J. M. Fortunato and H. M. Geyer III, *J. Med. Chem*., **23**, 1380 (1980).

[13] D. N. Nagar, M. Tushar and V. H. Shah, *Oriental J. Chem*., **18**, 543 (2002); *Chem. Abstr.*, **140**, 128390 (2004).

[14] B. Puodziunaite, R. Janciene, Z. Talaikite, A. Zaks, Y. M. Rabotnikov and E. A. Usachev, *Khim.-Farm. Zh*., **19** 1195 (1985); *Chem. Abstr*., **105**, 133861 (1986).

[15] For earlier syntheses of 1,5-benzoxazepines see: [a] J. von Braun and O. Braunsdorf, *Ber. Dtsch. Chem. Ges.*, **54B**, 685 (1921); [b] G. S. Sidhu, G. Thyagarajan and U. T. Bhalerao, *Indian J. Chem*., *2*, 211 (1964); [c] K. Nagarajan, J. David, Y. S. Kulkarni, S. B. Hendi, S. J. Shenoy and P. Upadhyaya, *Eur. J. Med. Chem*., **21**, 21 (1986); [d] H. M. Nour El-Din and H. D. A. Shawki, *Bulletin of the Faculty of Pharmacy (Cairo University)*, **9**, 253 (1970); *Chem. Abstr*., **77**, 48422 (1972); [e] P. Sebok, A. Levai and T. Timar, *Heterocyclic Commun.*, **4**, 547 (1998).

[16] For earlier syntheses of 1,5-benzodiazepines, see: [a] G. B. Bachman and L. V. Heisey, *J. Am. Chem. Soc*., **71**, 1984 (1949); [b] S. H. Dandegaonker and G. B. Desai, *Indian J. Chem*., **1**, 298 (1963); [c] M. Hasan, F. Malik, M. C. Garcia Alvarez and Z.

Maqbool, *J. Chem. Soc. Pakistan*, **12**, 210 (1990); *Chem Abstr.*, **114**, 185446 (1991); [d] L. Zhelyazkiv and A. Bizhev, *God. Vissh, Khim.-Tekhnol. Inst. Sofia*, **20**, 251 (1972); *Chem Abstr*., **83**, 179016 (1975); [e] V. D. Orlov, N. N. Kolos, S. M. Desenko and V. F. Lavrushin, *Khim. Geterotsikl. Soedin*., **6**, 830 (1982); *Chem Abstr*., **97**, 162947 (1982); [f] R. Contreras, H. R. Morales and A. Bulbarela, *Heterocycles*, **24**, 135 (1986); [g] D. Misiti, F. Gatta, R. Landi-Vittory, *J. Heterocyclic Chem*., **8**, 231 (1971).

[17] R. A. Bunce and K. M. Easton, *Org. Prep. Proced. Int*., **36**, 76 (2004).

[18] R. A. Bunce, C. L. Smith and C. L. Knight, *Org. Prep. Proced. Int*., in press.

[19] R. A. Bunce, D. M. Herron, L. B. Johnson and S. V. Kotturi, *J. Org. Chem*., **66**, 2822 (2001).

[20] R. D. Rieke and S. E. Bales, *J. Am. Chem. Soc.*, **96**, 1775 (1974).

[21] E. G. E. Hawkins and R. D. Thompson, *J. Chem. Soc*., 370 (1961).

[22] M. A. Jacobson and P. G. Williard, *J. Org. Chem*., **67**, 3915 (2002).

[23] K. M. Davies, M. J. S. Dewar and P. Rona, *J. Am. Chem. Soc*., **89**, 6294 (1967).

[24] B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell, Vogel's Textbook of Practical Organic Chemistry, 5th Ed., Longman/Wiley: New York, NY, 1989, p. 714.

[25] The alternative approach of adding the amine to the 2-fluoro-1-nitrobenzene works for the substitution reaction but the resulting *N*-(3-butenyl)aniline does not readily acylate.

[26] Aldehyde substrates **5a** and **10a** were stored as their dimethyl acetals and converted to the aldehydes immediately before cyclization. The acetal hydrolysis procedure is from T. Hudlicky, B. C. Ranu, S. M. Narqvi and A. Srnak, *J. Org. Chem*., **50**, 123 (1985).

[27a] F. C. Lightstone and T. C. Bruice, *Bioorg. Chem*., **26**, 193 (1998); [b] See also G. Illuminati and L. Mandolini, *Acct. Chem. Res*., **14**, 95 (1981); [c] F. A. Carey and R. J. Sundberg, Advanced Organic Chemistry, Part A, 4th Ed.; Kluwer Academic/Plenum Press: New York, NY, 2000; pp 166-171; [d] E. L. Eliel, S. H. Wilen, L. N. Mander, Stereochemistry of Organic Compounds; J. Wiley and Sons: New York, NY, 1994; pp 678-682.

[28a] P. N. Rylander, Catalytic Hydrogenation in Organic Syntheses; Academic Press: New York, NY, 1979, pp 100-102; [b] M. Hudlicky, Reductions in Organic Chemistry, 2nd Ed.; American Chemical Society: Washington, DC, 1996; pp 155-156; [c] Reduction of phenyl ketones has been observed under 1 atmosphere of hydrogen in ethanol at 20˚ using 5% palladium-on-carbon, see S. R. Angle and J. D. Rainier, *J. Org. Chem*., **57**, 6883 (1992).

[29] W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem*., **43**, 2923 (1978).

[30] J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc*., **73**, 2509 (1951).

[31] A. R. Katritzky, A. V. Ignatchenko and H. Lang, *J. Org. Chem*., **60**, 4002 (1995).