Additions of 1-(α-Aminoalkyl)benzotriazoles to Enol Ethers. New Routes to 1,3-Amino-Ethers

Alan R. Katritzky,*[1a] Stanislaw Rachwal,[1a] Bogumila Rachwal,[1a] and Peter J. Steel[1b]

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-2046, and Chemistry Department, University of Canterbury, New Zealand

Received April 8, 1992

1-(α-Aminoalkyl)benzotriazoles add readily to enol ethers to give the corresponding 1-benzotriazolyl-3-aminoalkyl ethers in high yields. Subsequent replacement of the benzotriazole moiety by an alkyl or aryl group (with a Grignard reagent) or by a hydrogen atom (with lithium aluminum hydride) affords 1,3-amino-ethers in good yields. Anchimeric assistance by the amino groups in the substitutions of the benzotriazolyl moiety facilitates the reactions. Full stereochemistry is assigned to the stereoisomeric products on the basis of NMR techniques and X-ray difraction.

The general concept of the reactions discussed in the preceding paper[2] involved trapping a carbocation produced in the ionic dissociation of an *N*-(α-alkoxyalkyl)benzotriazole by an electron-rich olefin with the formation of a new benzotriazole adduct nonionizable under the reaction conditions. This concept can be extended to 1-(α-aminoalkyl)benzotriazoles **1**; these compounds exist in solution in equilibrium with ion pairs **2** which are the intermediates for the isomeric interconversion of benzotriazol-1-yl (**1**) and -2-yl (**3**) derivatives[3] (Scheme I). Reactions of **1** in which the benzotriazolyl group is substituted by a nucleophile, proceeding through intermediates of type **2**, have found numerous synthetic applications.[4] In this paper we describe our synthetic results from the additions of α-(benzotriazol-1-yl)alkylamines to α,β-unsaturated ethers leading to the formation of 1,3-amino-ethers.

A three-carbon unit linking an amino nitrogen atom and an ether oxygen atom is important for the biological activity of many compounds. Three such compounds are bencyclane, a spasmolytic,[5-9] benzydamine, an analgesic/antiinflammatory agent,[10-15] and butoprozine which has antianginal and antiarrhythmic properties (Chart I).[16-18] In recent years, in searches for potential drugs, hundreds of compounds containing such amino-ether linkages have been synthesized. The main synthetic route has been the etherification of a hydroxy group with 3-chloro-*N*,*N*-dialkylpropanamines.[19-25] Other synthetic methods have

Scheme I

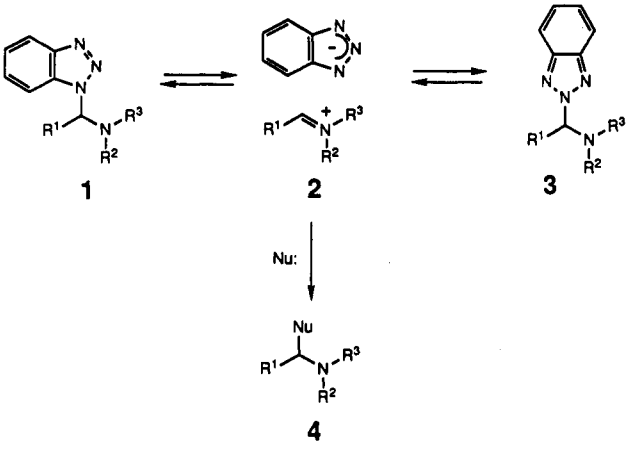
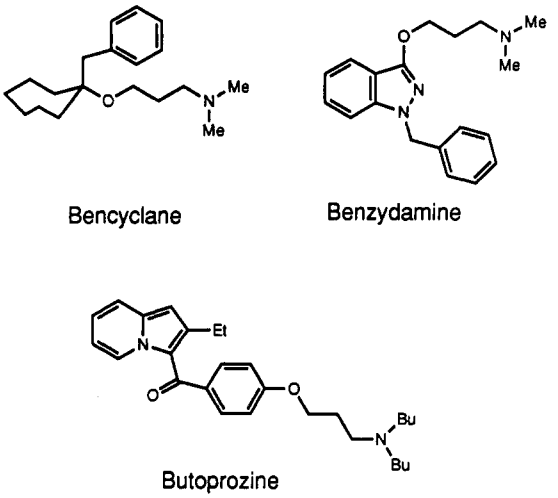


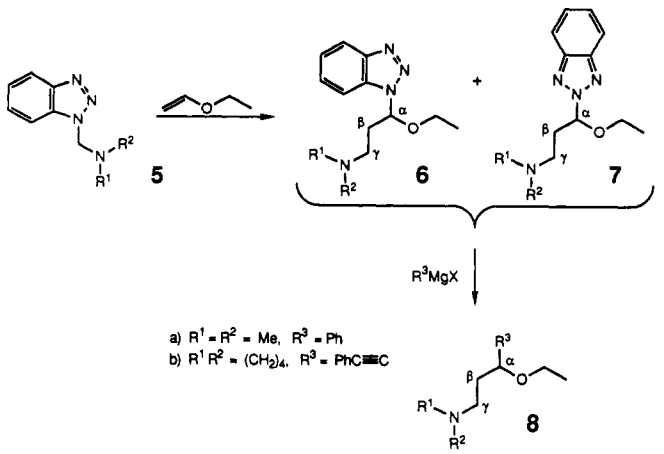
Chart I



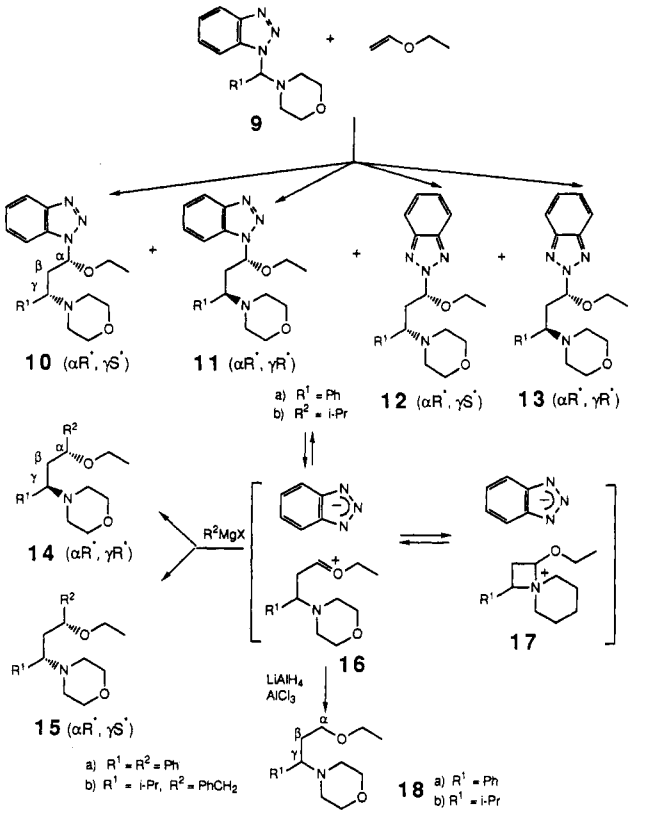
(1) (a) University of Florida. (b) University of Canterbury.
(2) Katritzky, A. R.; Rachwal, S.; Rachwal, B.; Steel, P. *J. Org. Chem.* preceding paper in this issue.
(3) Lindsay Smith, J. R.; Sadd, J. S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1181.
(4) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683.
(5) Marzo, A.; Treffner, E.; Rapelli, S.; Quadro, G. *Spectrosc.: Int. J.* **1984**, *3*, 345; *Chem. Abstr.* **1985**, *102*, 197407s.
(6) Mohri, Z.; Yasuda, T.; Kawahara, K.; Shono, F.; Yoshitake, A. *J. Pharmacobio-Dyn.* **1985**, *8*, 227; *Chem. Abstr.* **1985**, *102*, 214517x.
(7) Eckard, R.; Weyhenmeyer, R. *Arzneim.-Forsch./Drug Res.* **1985**, *35*, 1587.
(8) Nakajima, T.; Sunagawa, M.; Hirohashi, T. *Chem. Pharm. Bull.* **1984**, *32*, 401.
(9) Gielsdorf, W.; Settlage, J. A.; Jaeger, H., *Arzneim.-Forsch./Drug Res.* **1984**, *34*, 290.
(10) Baiocchi, L. Belg. Pat. 893,706, 1982; *Chem. Abstr.* **1983**, *98*, 72089g.
(11) Masui, M. Jpn. Pat. 02,188,521, 1990; *Chem. Abstr.* **1991**, *114*, 12009v.
(12) Sokolowska, B.; Kotlicki, S.; Szluker, J. Pol. Pat. 142,492, 1988; *Chem. Abstr.* **1989**, *110*, 173223t.
(13) Taylor, T.; Chasseaud, L. F.; Catanese, B. *Proc.—Eur. Congr. Biopharm. Pharmacokinet., 3rd* **1987**, *2*, 645; *Chem. Abstr.* **1989**, *110*, 160294s.
(14) Catanese, B.; Picollo, R.; Corradino, C. *Boll. Chim. Farm.* **1986**, *125*, 228; *Chem. Abstr.* **1987**, *106*, 78435x.
(15) Catanese, B.; Valeri, P.; Lagana, A.; Curini, L. *Biopharm. Drug. Dispos.* **1989**, *10*, 225.
(16) Rosseels, G.; Peiren, M.; Cornil, R.; Inion, H.; Prost, M.; Descamps, M.; Bauthier, J.; Tornay, C.; Collette, J. F.; Colot, M.; Claviere, M.; *Eur. J. Med. Chem.-Chim. Ther.* **1983**, *18*, 339.
(17) Gubin, J.; Rosseels, G.; Peiren, M.; Prost, M.; Descamps, M.; Richard, J.; Bauthier, J.; Charlier, R. *Eur. J. Med. Chem.-Chim. Ther.* **1977**, *12*, 345.
(18) Gubin, J.; Rosseels, G. Ger. Pat. 2,707,048, 1977; *Chem. Abstr.* **1978**, *88*, 6719e.
(19) Tomino, I.; Ishiguro, M.; Kitahara, T.; Yokoyama, K.; Kihara, N.; Kamiya, J.; Yoshihara, K.; Ishii, M.; Mizuchi, A. PCT Int. Appl. Wo. 89 05,289, 1989; *Chem. Abstr.* **1990**, *112*, 55583d.
(20) Protiva, M.; Dervena, I.; Metys, J.; Valchar, M. *Czech. Pat.* 263,982, 1989; *Chem. Abstr.* **1990**, *113*, 40481r.
(21) Gubin, J.; Descamps, M.; Chatelain, P.; Nisato, D. Eur. Pat. 235,111, 1987; *Chem. Abstr.* **1988**, *109*, 6405b.
(22) Danree, B.; Houziaux, P.; Lacolle, J. Y. Eur. Pat. 237,411, 1987; *Chem. Abstr.* **1988**, *109*, 55002b.
(23) Budai, Z.; Magdanyi, L.; Lay-Konya, A.; Mezei, T.; Grasser, K.; Petocz., L.; Kosoczky, I. Belg. Pat. 886,579, 1981; *Chem. Abstr.* **1982**, *96*, 20297n.

0022-3263/92/1957-4932$03.00/0 © 1992 American Chemical Society

Scheme II



Scheme III



involved alkylation of a hydroxy intermediate with a 1,3-dihalopropane followed by treatment of the 3-halopropyl ether with an amine,[26-32] and platinum-catalyzed addition of 3-(dialkylamino)propanol to a double bond[33] or its reaction with a reactive halide.[34] In all these routes, the O–C–C–C–N array was formed by closing a C–O or a C–N bond. Routes in which a C–C bond was formed last have been much less investigaetd, but it is such routes that are applicable to the preparation of 1,3-amino–ethers bearing substituents on the connecting chain of three carbon atoms.

1,3-Amino–ethers bearing alkyl or aryl substituents on the internal carbon atoms may possess even more potent biological activity, but they have been scarcely investigated due to the complex methods required for their preparation. Thus, the psychotropically active 3-(*m*-anisyloxy)-1-phenylpropylamine was prepared by reaction of *m*-methoxyphenol with 1,2-dibromoethane, treatment of the resulting ether with diethyl phenylmalonate, hydrolysis, and decarboxylation to 4-(*m*-anisyloxy)-2-phenylbutyric acid, convertion of the acid to the azide, Curtius rearrangement, and finally decomposition of the resulting isocyanate in hydrochloric acid.[35] Our new synthetic method presented below should enable such compounds to become easily accessible.

Results and Discussion

Addition to Ethyl Vinyl Ether. A mixture of 1-((*N*,*N*-dimethylamino)methyl)benzotriazole[36] (**5a**) and ethyl vinyl ether reacts on heating at 130 °C with a catalytic amount of an acid to give quantitatively a mixture of the benzotriazol-1-yl (**6**) and -2-yl (**7**) adducts (Scheme II). The integrals of the characteristic N–CH–O signals in the ^1H NMR spectra of the mixture at δ 6.25 (**6a**) and 6.06 (**7a**) allowed a determination of the **6a**:**7a** isomer ratio as 3:1. Under similar conditions, 1-((pyrrolidin-1-yl)-methyl)benzotriazole[37] (**5b**) adds to ethyl vinyl ether producing a mixture of **6b** and **7b** isomers (3:2). The isomeric mixtures of the adducts **6** and **7** were separated by column chromatography, allowing full characterization of the four compounds by NMR spectroscopy.

The above results allow some deductions regarding the reaction mechanism. Because ionization of these (aminomethyl)benzotriazoles (**5a,b**) to iminium cations of type **2** (Scheme I) occurs rapidly at room temperature,[3,37,38] it cannot be considered as the rate-limiting step. Evidently, a high activation barrier for the carbon–carbon bond formation during the addition to the vinyl group requires the heating and acid catalysis.

Substitution of the benzotriazolyl groups in the adducts **6** and **7** by alkyl groups from Grignard reagents occurred readily under the conditions applied for the analogous reactions of α-(benzotriazol-1-yl)alkyl ethers.[39,40] This thus provides a new versatile method for preparation of γ-aminoalkyl ethers, with apparently little limitation on the substituents on the nitrogen atom (R^1,R^2) and the additional substituent (R^3 from the Grignard reagent) in the α-position.

Problem of Stereoisomerism. The picture is more complex when, instead of a simple 1-(aminomethyl)-

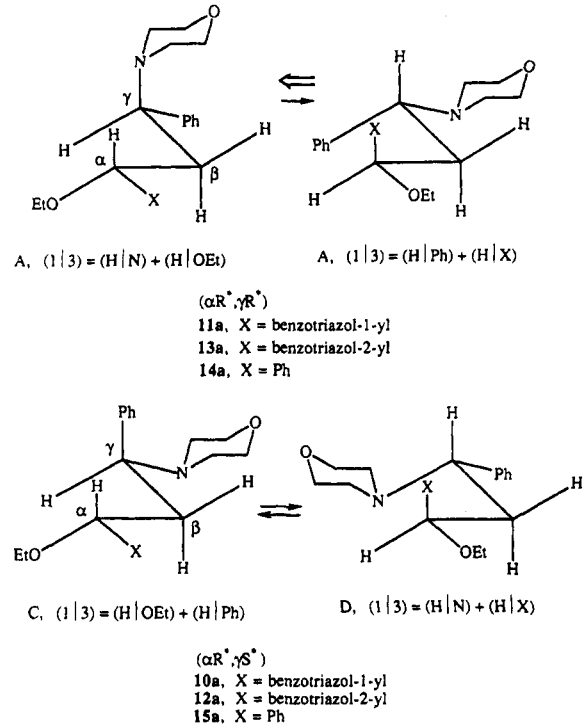
(24) Cervena, I.; Holubek, J.; Svatek, E.; Ryska, M. *Collect. Czech. Chem. Commun.* **1989**, *54*, 1955.
(25) Alhaider, A. A.; Atef Abdelkader, M.; Lien, E. J. *J. Med. Chem.* **1985**, *28*, 1394.
(26) Gubin, J.; Chatelain, P.; Inion, H.; Lucchetti, J.; Mahaux, J. M.; Vallat, J. N. Eur. Pat. 302,792, 1989; *Chem. Abstr.* **1989**, *111*, 97204r.
(27) Press, J. B. Eur. Pat. 261,912, 1988; *Chem. Abstr.* **1988**, *109*, 54775u.
(28) Narita, S.; Goto, T.; Kobayashi, A.; Kojo, K.; Oguchi, S.; Yamada, S. Jpn. Pat. 63,264,466, 1988; *Chem. Abstr.* **1989**, *111*, 7381u.
(29) Press, J. B.; Sanfilippo, P.; Urbanski, M. U.S. Pat. 4,791,200, 1988; *Chem. Abstr.* **1989**, *110*, 154293z.
(30) Pierson, M. E.; Lyon, R. A.; Titeler, M.; Kowalski, P.; Glennon, R. A. *J. Med. Chem.* **1989**, *32*, 859.
(31) Sanfilippo, P. J.; Urbanski, M.; Press, J. B.; Dubinsky, B.; Moore, J. B. *J. Med. Chem.* **1988**, *31*, 2221.
(32) Adembri, G.; Anselmi, C.; Camparini, A.; Rossetti, M. G.; Scotton, M. *J. Heterocycl. Chem.* **1988**, *25*, 1019.
(33) Mulliez, E.; Soulie, J.; Chottard, J. C.; Sanchez, C.; Guilhem, J. *J. Chem. Res. (S)* **1982**, 38.
(34) Bourzat, J. D.; Cotrel, C.; Roussel, G.; Capet, M.; Labaudiniere, R.; Pitchen, P. Fr. Pat. 2,607,506, 1988; *Chem. Abstr.* **1989**, *110*, 75313c.
(35) Lavagnino, E. R.; McShane, L. J.; Molloy, B. B. U.S. Pat. 4,207,343, 1980; *Chem. Abstr.* **1980**, *93*, 204261r.
(36) Burckhalter, J. H.; Stephens, V. C.; Hall, L. A. R. *J. Am. Chem. Soc.* **1952**, *74*, 3868.
(37) Katritzky, A. R.; Yannakopoulou, K.; Kuzmierkiewicz, W.; Aurrecoechea, J. M.; Palenik, G. J.; Koziol, A. E.; Szczesniak, M.; Skarjune, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2673.
(38) Katritzky, A. R.; Yannakopoulou, K. *Heterocycles* **1989**, *28*, 1121.
(39) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Org. Chem.* **1989**, *54*, 6022.
(40) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1717.

benzotriazole **5**, 1-(α-aminoalkyl)benzotriazoles **9** (Scheme III) derived from aldehydes higher than formaldehyde are used in the addition. α-(Benzotriazol-1-yl)-α-(morpholin-4-yl)*toluene*[41] (**9a**) underwent ready addition to ethyl vinyl ether in the presence of catalytic amounts of an acid producing a mixture of four isomers **10a–13a**. The isomers were recognized in the ^{1}H NMR spectra of the mixture by characteristic resonances of the methine Bt–CH–O protons at δ 5.56 (dd, J = 4.3 and 8.7 Hz), 5.87 (dd, J = 5.6 and 7.8 Hz), 5.97 (dd, J = 6.2 and 6.6 Hz), and 6.18 (t, J = 6.7 Hz) with the integral ratio of 1:1:1:1. In the ^{13}C NMR spectra, the resonances of the methine Bt–CH–O carbon atoms were observed at δ 88.1, 88.2, 92.9, and 93.0. Separation of the mixture by column chromatography and application of selective proton–proton decoupling and 2D proton–carbon correlation techniques allowed full assignment of the ^{1}H and ^{13}C NMR spectra of each one of the four isomers.

Conformational analysis of molecular models of the adducts revealed that if all conformers with energetically unfavorable (1|3) parallel interactions between bulky substituents are excluded,[2,42–44] only conformations A or B remain for the molecules of the $\alpha R^*,\gamma R^*$ diastereomers. Of these two, conformation A with the (H|morpholine) and (H|OEt) interactions should be of significantly lower energy than conformation B with the strong (H|Ph) and (H|Bt) repulsive interactions.[2,43–48] Because the $\alpha R^*,\gamma R^*$ molecule exists most of the time in conformation A, the H-1 and H-3 interactions with the two H-2 protons will be quite different (gauche vs anti), leading to two different coupling constants $J_{\alpha,\beta}$ and two coupling constants $J_{\beta,\gamma}$. By contrast, two conformations of the $\alpha R^*,\gamma S^*$ isomers, C and D, possess comparable (α|γ) interactions and hence similar energy and should exist in approximately equal abundance. Hence the $\alpha R^*,\gamma S^*$ should show equal coupling constants of H-1 and H-3 with the two methylene protons. These considerations lead to the conclusion that the adducts exhibiting the Bt–CH–O ^{1}H NMR resonances at δ 5.56 and 5.87 possess $\alpha R^*,\gamma R^*$ configuration, whereas the adducts with the resonances at δ 5.97 and 6.18 are of the $\alpha R^*,\gamma S^*$ configuration.

Addition of **9b** to ethyl vinyl ether gave a mixture of **10–13b** in the ratio of 50:25:13:12 with the Bt–CH–O resonances in the ^{1}H NMR spectrum at δ 6.34 (J = 5.2 and 8.1 Hz), 6.25 (J = 6.1 and 12.3 Hz), 6.19 (J = 3.8 and 8.7 Hz), and 6.17 (J = 4.9 and 8.2 Hz), respectively. Similarly to the above considerations, replacement of the bulky phenyl by a bulky isopropyl group[49,50] gives two conformers of the R^*,S^* diastereomers with comparable steric interactions and therefore similar coupling constants of H-γ with the both of the H-β and one strongly favored conformer of the R^*,R^* diasteromers leading to the two quite different H-γ/H-β coupling constants. This idealized picture is only partially realized in the real molecule as (α|γ) repulsive interactions of the phenyl and isopropyl groups are not exactly the same. However, these conditions still allow us to assign the R^*,R^* configuration to the distereomers with the larger difference in the coupling constants, i.e. that exhibiting the H-α resonances at δ 6.25 (Bt-1) and 6.17 (Bt-2), and configuration R^*,S^* to the diastereomers with smaller differences in the coupling constants, i.e., that giving the H-α signals at δ 6.34 (Bt-1) and 6.17 (Bt-2). The most abundant Bt-1 diasteromer (**10b**, δ 6.34) was separated by column chromatography in an 85% isomerically pure form and was fully characterized by ^{1}H and ^{13}C NMR.

Chart II

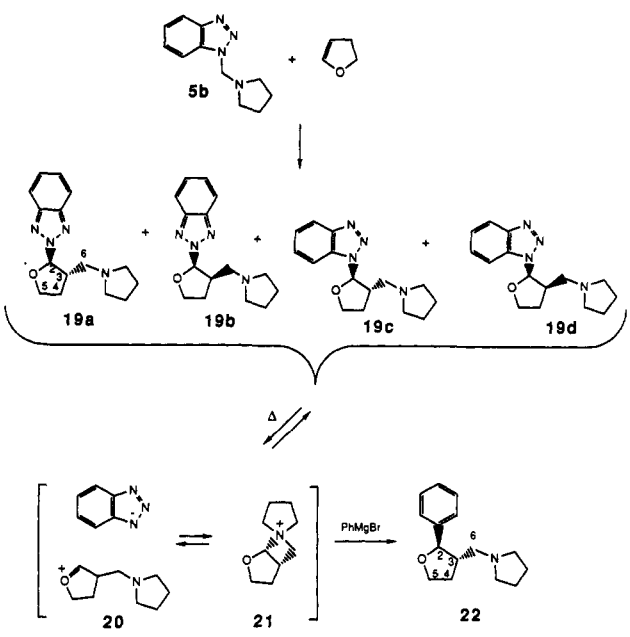


The crude product mixture of **10a–13a** was converted in high yield into a mixture of two diastereomers of 1,3-diphenyl-1-ethoxy-3-(morpholin-4-yl)propane (**14a** and **15a**) by treatment with phenylmagnesium bromide. The R^*,R^* (**14a**) and R^*,S^* (**15a**) stereoisomers were separated by column chromatography, and their NMR spectra were fully assigned. Assuming one preferred conformer of the R^*,R^* diasteromers and two equivalent forms of the R^*,S^* diasteromer, in agreement with the above considerations, we could anticipate that the methylene protons of the R^*,R^* stereoisomers would resonate at quite different fields, whereas their resonances for the R^*,S^* isomer would be close together. This allowed assignment of the configuration R^*,R^* (**14a**) to the predominant isomer obtained, in which the H-β resonances were observed as two ddd patterns at δ 1.85 and 2.37. The R^*,S^* isomer (**15a**) gave these resonances as a two-proton multiplet at δ 2.20. This structural assignment was confirmed by the occurrence of the Bt–CH–O signal as a double doublet with the two very different coupling constants with the CH_2 group in **14a** (J = 3.8 and 9.8 Hz) and with the two similar coupling constants in **15a** (J = 6.8 and 7.0 Hz). In a similar manner, reaction of **10b–13b** with benzylmagnesium chloride gave a mixture of diastereomeric aminoethers **14b** and **15b** which were separated by column chromatography, and their ^{1}H and ^{13}C NMR were fully assigned.

Adducts **10–13** were readily reduced with a lithium aluminum hydride–aluminum chloride mixture to 1,3-amino–ethers **18**. It is intriguing that the alkoxy group was not cleaved as in the similar reduction of 1-(1,3-dialkoxyalkyl)benzotriazoles.[2] This is perhaps explained by the

(41) Katritzky, A. R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc. Perkin Trans. 1* **1989**, 225.
(42) Spiessens, L. I.; Becu, C.; Hosten, N.; Anteunis-De Ketelaere, F.; Anteunis, M. J. O.; Tavernier, D. *Bull. Soc. Chim. Belg.* **1982**, *91*, 845.
(43) Kleinpeter, K.; Meusinger, R.; Duschek, Ch.; Borsdorf, R. *Magn. Reson. Chem.* **1987**, *25*, 990.
(44) Wertz, D. H.; Allinger, N. L *Tetrahedron* **1974**, *30*, 1579.
(45) Booth, H.; Everett, J. R. *J. Chem. Soc., Chem. Commun.* **1976**, 278.
(46) Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959.
(47) Schneider, H. J.; Agrawal, P. K. *Tetrahedron* **1984**, *40*, 1025.
(48) Schneider, H. J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866.
(49) Booth, H.; Everett, J. R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 255.
(50) Osawa, E.; Collins, J. B.; Schleyer, P. V. R. *Tetrahedron* **1977**, *33*, 2667.

Scheme IV



intermediacy of form **17** in the reduction. Such assistance by the oxygen atom in the corresponding diethers would be much weaker making their reduction more difficult.

Addition of 5b to 2,3-Dihydrofuran. Additions of 1-(α-aminoalkyl)benzotriazoles to α,β-unsaturated ethers extend beyond simple vinyl ethers. We proved this by investigation of the reactions with 2,3-dihydrofuran. However, even the addition of a simple 1-(pyrrolidin-1-ylmethyl)benzotriazole (**5b**) provided a mixture of four isomeric adducts (**19a–19d**) (Scheme IV). Again, the adducts could be easily recognized in the ^{1}H NMR spectrum by the Bt–CH–O doublets at δ 6.48 (J = 2.3 Hz), 6.50 (J = 2.6 Hz), 6.54 (J = 6.3 Hz), and 6.58 (J = 6.8 Hz) in the ratio of 53:19:24:4, respectively. The three most abundant isomers were separated in pure forms by column chromatography. By applying selective proton–proton decoupling and 2D proton–carbon correlation (HETCOR) techniques, their ^{1}H and ^{13}C NMR spectra were fully assigned.

The first striking differences between the isomers of **19** are the coupling constants of H-2 with H-3 ($J_{2,3}$). An extensive literature search to correlate the NMR spectra with the configuration of 2,3-disubstituted tetrahydrofurans revealed that few compounds of this type had been investigated. One such group is that of 2-substituted 3-chlorotetrahydrofurans, compounds easily obtainable by reaction of 2,3-dichlorotetrahydrofuran with nucleophiles.[51] Due to the anomeric effect, tetrahydrofuran rings bearing an electronegative substituent on an atom adjacent to the oxygen adopt a conformation in which this substituent is aligned axially.[52] In all the compounds of this type bearing strongly electronegative substituents on C-α (hydroxy, alkoxy, acetoxy, phenylthio, azido, chloro) investigated, $J_{2,3}$ = 4 Hz for the cis isomer and 1 Hz or less for the trans isomer.[51,53,54] Compounds of this type with a substituent of medium electronegativity (benzoyl, cyano, acyl) on C-2 show $J_{2,3}$ values for the trans isomer in the range of 2.0–2.5 Hz.[52] If the benzotriazolyl substituent is considered to be of medium electronegativity on this scale, these literature data suggest a trans configuration for our adducts with the coupling constants of 2.3 and 2.6 Hz and a cis configuration for the isomers and coupling constants of 6.3 and 6.8 Hz.

Evidence that this assignment is correct comes from inspection of molecular models of isomers **19a–d** and comparison of the expected implications on their NMR with the experimental spectra. Thus, a downfield shift of the H-3 resonance predicted from the molecular models for the trans isomers due to strong diamagnetic deshielding by the benzotriazolyl substituents was also observed in the spectra (δ 3.63 for the trans vs δ 3.00 for the cis isomer). The second deduction from the molecular models was that the H-6 resonance of the cis isomer should be observed at a higher field due to the location of these protons in a shielding zone of the benzotriazolyl moiety. Indeed, the resonances of the aminomethyl (H-6) protons of the cis isomer (**19d**) were found at much higher fields (δ 2.05 and 2.23) than the corresponding resonances of the trans isomer (**19c**, δ 2.52–2.63 and 2.86). A similar shielding effect by aryl substituents at C-2 on the cis methyl groups at C-3 was reported for several 2-aryl-3-methyltetrahydrofurans.[55]

Surprisingly, the reaction of the mixture of four isomers **19a–c** with phenylmagnesium bromide gave only one diastereomer of the expected amino–ether **22**. The ^{1}H NMR spectrum of the product exhibited two H-6 proton resonances as a multiplet in a region characteristic for the NCH_2 group (δ 2.54). This indicates the trans configuration of the substituents because, in the cis isomer, a strong shielding effect by the phenyl group would occur.[55] This phenomenon, as well as the relatively mild conditions required for the reaction (70 °C), suggest strong anchimeric assistance by the nitrogen atom in the intermediate. Ionization of a molecule of any isomer (**19a–d**) leads to the same intermediate **21**, which evidently possesses the ammonium structure instead of the energetically unfavorable oxonium structure (**20**), and this in turn prevents formation of isomeric products in the following nucleophilic attack by the Grignard reagent. Inspection of molecular models revealed that apart from the strain in the four-membered ring, no other interactions between the substituents should contribute significantly to the molecular energy of **21**. An attack of the phenylmagnesium reagent from the opposite side to the azetidine ring causes inversion of the C-2 configuration and formation of the trans isomer (**22**).

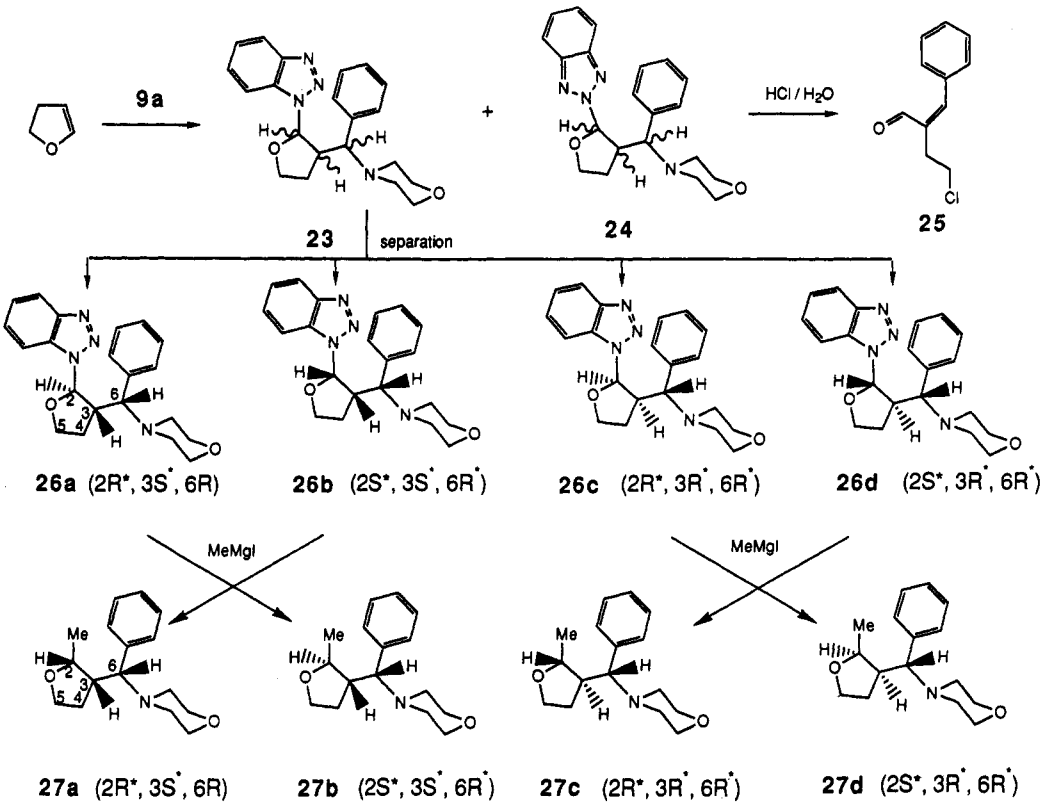
Addition of **9a** to 2,3-dihydrofuran (Scheme V) gave a complex mixture of eight isomeric adducts (stereoisomers plus Bt-1 and Bt-2 isomers) easily recognizable by the Bt–CH–O proton signals in the ^{1}H NMR spectrum in the range of δ 5.8–6.8. The four strongest doublets originating from the four Bt-1 derivatives at δ 5.89, 6.02, 6.65, and 6.71 showed integral ratios of 32:20:16:32, respectively. Careful column chromatography allowed the separation of pure or at least enriched samples of each of the four Bt-1 isomers. Analysis of the NMR spectra (including 2D-HETCOR and selective decoupling techniques) allowed total assignments of the ^{1}H and ^{13}C resonances for all four isomers.

The crude product mixture (**23** and **24**) was hydrolyzed by refluxing with 36% hydrochloric acid to give only one isomer of α-(2-chloroethyl)cinnamaldehyde (**25**). This experiment proved the complex product mixture which could not directly be characterized by NMR essentially consists of isomers of the same compound.

The ^{1}H NMR spectrum of the first Bt-1 isomer obtained from column chromatography (**26a**) exhibited the H-2

(51) Stone, T. E.; Doyle Daves, G. *J. Org. Chem.* **1977**, *42*, 2151.
(52) Crombie, L.; Wyvill, R. D. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1971.
(53) Zezula, V.; Kratochvil, M. *Collect. Czech. Chem. Commun.* **1970**, *35*, 1745.
(54) Decor, J. P.; Descotes, G. *Bull. Soc. Chim. Fr.* **1970**, 2370.
(55) Dana, G.; Touboul, E.; Convert, O.; Pascal, Y. L. *Tetrahedron* **1988**, *44*, 429.

Scheme V



resonance as a doublet at δ 6.71 (J = 3.7 Hz). The second isomer (in the order of elution from the column) showed a doublet at δ 6.65 (J = 6.1 Hz). The third isomer (**26c**) had a doublet at δ 6.02 (J = 6.4 Hz) and the fourth (**26d**) a doublet at δ 5.89 (J = 2.4 Hz). From the anomeric effects of the benzotriazolyl substituents,[52] the trans configuration was assigned to the isomers with the smaller coupling constants of their H-2 resonances (**26a** and **26d**). The X-ray crystallographic data of compounds **26a** and **26c** confirmed these assignments and more importantly, also showed the configuration of the C-6 atoms. Parallel short distance location of the benzotriazolyl and phenyl rings in a molecule of **26c** results in unusual upfield shifts of the benzotriazolyl H-7 (δ 6.41) and phenyl ortho (δ 6.52) proton resonances due to the strong shielding effects the rings impose on each other.

Treatment of pure **26a** with methylmagnesium iodide in refluxing toluene afforded a mixture of amino–ethers **27a** and **27b** in a ratio of 2:1. The same mixture of **27a** and **27b** was obtained from a mixture of **26a** and **26b**. Because the configuration of the C-3 and C-6 atoms could not change during the reaction, compounds **26a** and **26b** must differ only at C-2. Additionally, the reactions of pure isomers **26c** and **26d** with methylmagnesium iodide both gave the same result, a mixture of amino–ethers **27c** and **27d** in a ratio 2:1, indicating the same stereochemistry of atoms C-3 and C-6 in both products. Hence, as molecular structures of **26a** and **26c** were known from their X-ray crystallographic data, full stereochemical assignments for all isomers **26** were deduced.

Because, as noted above, the configuration of the substituents at atoms C-3 and C-6 cannot change during the Grignard reaction, full assignments of structures **27a–d** could be obtained by elucidating the configurations of their C-2 atoms. DNOE ^{1}H NMR studies were very helpful in this case; the technique has previously been used for structural assignment of 2,3,5-trisubstituted tetrahydrofurans.[56] Thus, irradiation of the methyl group signal of **27c** gave 7% nuclear Overhauser enhancement of the H-3 resonance, indicating the trans configuration of the substituents on the tetrahydrofuran ring. Irradiation of the methyl group of isomer **27d** gave a 15% enhancement of the H-6 doublet, indicating the cis configuration of the substituents at the tetrahydrofuran ring. Irradiation of the H-3 signal of **27d** gave a 12% enhancement of the H-2 resonance and 9% enhancement of the phenyl ortho proton signals, giving further support for the assignment. No such strong evidence for structural assignment could be produced for isomer pair **27a** and **27b** because **27b** was not available in a pure form. However, irradiation of the methyl group signal of **27a** gave 9% NOE enhancement of the H-6 doublet suggesting the cis configuration of the substituents at the tetrahydrofuran ring and hence the trans configuration for isomer **27b**.

The question remains as to why the Grignard reactions depicted in Scheme V are not stereoselective as are reactions of Scheme IV. Inspection of molecular models revealed that an intermediate azetidine structure derived from **26** would require a dramatic increase in the strain compared to **21** because of the phenyl substituent. Therefore, the transition state of the reactions of compounds **26** must resemble more the oxonium ion **20** than the ammonium ion **21**. The rather severe reaction conditions required (refluxing toluene) for **26** reflect this difference. Cations of type **20** can be attacked from both sides, giving mixtures of diastereomeric products.

Conclusion

A novel and efficient synthesis of 1,3-amino–ethers by the addition of 1-(α-aminoalkyl)benzotriazoles to enol ethers followed by reduction of the adducts with lithium aluminum hydride or their reaction with Grignard reagents has been described. Achimeric assistance of the alkoxy

(56) Hauser, F. M.; Ellenberger, S. R.; Rhee, R. P. *J. Org. Chem.* **1987**, *52*, 5041.

group facilitates the reactions of the adducts and, to some degree, determines the stereochemistry of the obtained products. Separation of complex diastereomeric mixtures of the adducts to dihydrofuran and their exhaustive stereochemical study on the basis of the X-ray data and NMR spectra has produced a model for structural assignments of 2,3-disubstituted tetrahydrofurans which should be useful in further studies of compounds of this type.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. Mass spectra were obtained by EI (70 eV). Solvents for the Grignard reactions (ether, toluene, benzene) were dried by reflux under nitrogen with sodium benzophenone and distilled immediately before use. Column chromatography was conducted with silica gel grade 60–200 mesh.

1-(Benzotriazol-1-yl)-1-ethoxy-3-(*N*,*N*-dimethylamino)propane (6a) and 1-(Benzotriazol-2-yl)-1-ethoxy-3-(*N*,*N*-dimethylamino)propane (7a). A mixture of **5a** (8.80 g, 50 mmol), ethyl vinyl ether (5.04 g, 70 mmol), and 4-$MeC_6H_4SO_3H{\cdot}H_2O$ (0.05 g) was heated in a sealed vial at 130 °C for 3 h. The reaction mixture was dissolved in toluene, and the toluene solution was washed with 10% NaOH followed by water and dried over $MgSO_4$. Evaporation of the solvent and excess ethyl vinyl ether afforded a mixture of **6a** and **7a** in the ratio of 3:1. Column chromatography (toluene/ethyl acetate, 9:1) gave pure **7a** and amino-ether **6a**. Fraction 1, **7a**: colorless oil, 2.48 g (20%); ^1H NMR δ 1.17 (t, J = 7.1 Hz, 3 H, Et), 2.21 (s, 6 H, 2 Me), 2.27 (m, 2 H, H-γ), 2.47 (m, 2 H, H-β), 3.39 (dq, J = 9.5 and 7.0 Hz, 1 H, Et), 3.60 (dq, J = 9.6 and 7.1 Hz, 1 H, Et), 6.06 (t, J = 6.4 Hz, 1 H, H-α), 7.40 (m, 2 H, Bt), and 7.91 (m, 2 H, Bt); ^{13}C NMR δ 14.6 (Et), 33.4 (C-β), 45.3 (2 C, 2 Me), 54.5 (C-γ), 65.2 (Et), 93.3 (C-α), 118.5 (2 C), 126.6 (2 C), 144.1 (2 C). Anal. Calcd for $C_{13}H_{20}N_4O$: C, 62.88; H, 8.12; N, 22.56. Found: C, 62.91; H, 8.11; N, 22.50. Fraction 2 was amino-ether **6a** (colorless oil, 8.69 g (70%): ^1H NMR δ 1.14 (t, J = 7.0 Hz, 3 H, Et)), 2.19 (s, 6 H, 2 Me), 2.28 (m, 3 H, 2 H-γ and 1 H-β), 2.48 (m, 1 H, H-β), 3.30 (dq, J = 9.5 and 7.0 Hz, 1 H, Et), 3.54 (dq, J = 9.4 and 7.0 Hz, 1 H, Et), 6.25 (dd, J = 6.0 and 6.3 Hz, 1 H, H-α), 7.40 (ddd, J = 8.1, 7.0, and 1.1 Hz, 1 H, Bt), 7.49 (ddd, J = 8.3, 7.0, and 1.2 Hz, 1 H, Bt), 7.80 (ddd, J = 8.3, 1.1, and 1.0 Hz, 1 H, Bt), and 8.08 (ddd, J = 8.3, 1.1, and 1.0 Hz, 1 H, Bt); ^{13}C NMR δ 14.7 (Et), 33.0 (C-β), 45.4 (2 C, 2 Me), 54.7 (C-γ), 64.5 (Et), 88.7 (C-α), 111.1, 120.0, 124.1, 127.4, 131.5, and 146.7. Anal. Calcd for $C_{13}H_{20}N_4O$: C, 62.88; H, 8.12; N, 22.56. Found: C, 62.98; H, 8.13; N, 22.47.

1-(Benzotriazol-1-yl)-1-ethoxy-3-(pyrrolidin-1-yl)propane (6b) and 1-(Benzotriazol-2-yl)-1-ethoxy-3-(pyrrolidin-1-yl)-propane (7b). By the above procedure a mixture of **6b** and **7b** (isomer ratio 3:2) was obtained in 92% yield. Fraction 1 from column chromatography (toluene/ethyl acetate, 9:1) was pure **7b**, as a colorless oil: ^1H NMR δ 1.16 (t, J = 7.1 Hz, 3 H, Et), 1.73 (m, 4 H), 2.50 (m, 8 H, H-β, H-γ and pyrrolidine), 3.39 (dq, J = 9.4 and 7.1 Hz, 1 H, Et), 3.60 (dq, J = 9.4 and 7.0 Hz, 1 H, Et), 6.09 (m, 1 H, H-α), 7.39 (m, 2 H, Bt), and 7.91 (m, 2 H, Bt); ^{13}C NMR δ 14.5 (Et), 23.4 (2 C), 34.6 (C-β), 51.0 (C-γ), 53.9 (2 C), 65.1 (Et), 93.4 (C-α), 118.5 (2 C), 126.5 (2 C), and 144.0 (2 C). Anal. Calcd for $C_{15}H_{22}N_4O$: C, 65.67; H, 8.08; N, 20.42. Found: C, 65.67; H, 7.92; N, 20.43.

Fraction 2 was amino-ether **6b**, colorless oil: ^1H NMR δ 1.14 (t, J = 7.0 Hz, 3 H, Et), 1.74 (m, 4 H), 2.46 (m, 8 H, H-β, H-γ, and pyrrolidine), 3.53 (dq, J = 9.4 and 7.1 Hz, 1 H, Et), 3.54 (dq, J = 9.4 and 7.0 Hz, 1 H, Et), 6.22 (dd, J = 5.9 and 6.5 Hz, H-α), 7.39 (dd, J = 8.3 and 6.9 Hz, 1 H, Bt), 7.48 (ddd, J = 8.1, 7.0, and 1.2 Hz, 1 H, Bt), 7.80 (d, J = 8.3 Hz, 1 H, Bt), and 8.08 (d, J = 8.0 Hz, 1 H, Bt); ^{13}C NMR δ 14.6 (Et), 23.3 (2 C), 34.1 (C-β), 51.3 (C-γ), 54.0 (2 C), 64.4 (Et), 88.9 (C-α), 111.1, 119.9, 124.0, 127.3, 131.3, and 146.6. Anal. Calcd for $C_{15}H_{22}N_4O$: C, 65.67; H, 8.08; N, 20.42. Found: C, 65.50; H, 7.83; N, 20.39.

1-Ethoxy-3-(dimethylamino)-1-phenylpropane (8a). Phenylmagnesium bromide (40 mmol) in ether (20 mL) was added portionwise to a boiling solution of **6a** (2.50 g, 10 mmol) in toluene (50 mL) and allowed distillation of the ether to keep the internal temperature at 100 °C. After the addition was complete, stirring at reflux was continued for 20 min. The reaction mixture was poured into water and extracted with ether (2 × 50 mL). The organic layer was separated, washed with 10% Na_2CO_3 and then water, and dried over Na_2CO_3. Evaporation of the solvent gave a crude product which on column chromatography gave **8a** as an oil, 1.76 g (85%): ^1H NMR δ 1.16 (t, J = 7.1 Hz, 3 H, Et), 1.78 (m, 1 H, H-β), 1.98 (m, 1 H, H-β), 2.20 (s, 6 H, 2 Me), 2.28 (m, 2 H, H-γ), 3.33 (m, 2 H, Et), 4.30 (dd, J = 5.9 and 7.8 Hz, 1 H, H-α), and 7.31 (m, 5 H, Ph); ^{13}C NMR δ 15.3 (Et), 36.4 (C-β), 45.5 (2 C, 2 Me), 56.2 (C-γ), 64.1 (Et), 80.2 (C-α), 126.5 (2 C), 127.3, 128.3 (2 C), and 143.0. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.22; N, 6.76. Found: C, 75.01; H, 10.20; N, 6.52.

3-Ethoxy-5-(pyrrolidin-1-yl)-1-phenyl-1-pentyne (8b). In a manner similar to the above, reaction of **6b** (3.56 g, 13 mmol) with phenylmagnesium bromide (50 mmol) gave **8b**. Distillation of the crude product gave analytically pure **8b** (2.18 g, 65%) as a colorless oil: bp 107–109 °C (0.2 mmHg); ^1H NMR δ 1.25 (t, J = 7.1 Hz, 3 H, Et), 1.78 (m, 4 H), 2.03 (m, 2 H, H-β), 2.53 (m, 4 H), 2.70 (m, 2 H, H-γ), 3.50 (dq, J = 9.2 and 7.1 Hz, 1 H, Et), 3.86 (dq, J = 9.1 and 7.1 Hz, 1 H, Et), 4.37 (t, J = 6.6 Hz, 1 H, H-γ), 7.29 (m, 3 H, Ph), and 7.42 (m, 2 H, Ph); ^{13}C NMR δ 15.2 (Et), 23.5 (2 C), 35.3 (C-β), 52.3 (C-γ), 54.2 (2 C), 64.3 (Et), 68.3 (C-α), 85.5 (C≡C), 88.5 (C≡C), 122.9, 128.2 (3 C), and 131.7 (2 C); HRMS calcd for $C_{17}H_{23}NO$ (M^+) 257.1780, found 257.1782.

α-(Benzotriazol-1-yl)-α-(morpholin-4-yl)toluene (9a). A mixture of benzotriazole (23.83 g, 200 mmol), benzaldehyde (21.23 g, 200 mmol), and morpholine (17.42 g, 200 mmol) was refluxed for 2 h under a Dean–Stark trap. After evaporation of the solvent, the crude oily product was triturated with ethyl ether and set aside overnight to give a white precipitate. The crystals were filtered off, recrystallized from ethanol, and dried in a vacuum oven to give pure **9a** as a mixture of Bt-1 and Bt-2 isomers in a 3:1 molar ratio (54.82 g, 93%): white prisms, mp 112–113 °C (lit.[41] mp 104–105 °C); ^1H NMR (isomer Bt-1) δ 2.62 (t, 4 H, J = 4.8 Hz), 3.75 (m, 4 H), 6.69 (s, 1 H, CH-Bt), 7.35 (m, 4 H), 7.43 (m, 4 H), and 8.08 (m, 1 H, Bt); ^{13}C NMR (isomer Bt-1) δ 50.1 (2 C), 66.8 (2 C), 83.0 (CH-N), 111.5 (Bt), 120.1 (Bt), 124.0 (Bt), 127.3 (Bt), 127.6 (2 C, Ph), 128.8 (2 C, Ph), 128.9 (Ph), 133.0 (Ph), 135.0 (Bt), and 146.2 (Bt). Anal. Calcd for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.45; H, 6.21; N, 19.08.

A Mixture of 1-(Benzotriazol-1-yl)-1-(morpholin-4-yl)-2-methylpropane (9b) with the 1-(Benzotriazol-2-yl) Isomer (1:1). A solution of benzotriazole (11.91 g, 100 mmol), morpholine (8.8 mL, 100 mmol), and isobutyraldehyde (9.1 mL, 100 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 30 min with 20.0 g of $MgSO_4$. Filtration off, evaporation of the solvent, and recrystallization of the residue from ethanol gave crystalline **9b** as a mixture of Bt-1 and Bt-2 isomers in a ratio of 1:1 (23.4 g, 93%): mp 98–100 °C. Anal. Calcd for $C_{14}H_{20}N_4O$: C, 64.59; H, 7.74; N, 21.52. Found: C, 64.25; H, 7.94; N, 21.14.

Adducts of 9a to Ethyl Vinyl Ether (10a–13a). A mixture of **9a** (5.89 g, 20 mmol), ethyl vinyl ether (2.17 g, 30 mmol), and a catalytic amount of 4-$MeC_6H_4SO_3H{\cdot}H_2O$ (40 mg) was heated in a sealed vial at 120 °C for 6 h. The crude product was dissolved in toluene, and an excess of the vinyl ether was removed with the toluene using a rotary vacuum evaporator. The NMR spectra of the crude product showed it was a mixture of isomers (**10a–13a**) in total yield >90%. A sample of the crude product (4.52 g) was subjected to column chromatography (toluene/ethyl acetate, 6:1) to give **12a**, **13a**, **10a**, and **11a**. Fraction 1, isomer **12a** (0.95 g, 21%): ^1H NMR δ 1.13 (t, 3 H, J = 7.0 Hz, Et), 2.37 (m, 4 H), 2.61 (dt, J = 14.2 and 6.7 Hz, 1 H, H-β), 3.03 (ddd, J = 14.4, 8.4, and 6.3 Hz, H-β), 3.38 (dq, J = 10.0 and 7.0 Hz, 1 H, Et), 3.47 (dd, J = 6.7 and 8.2 Hz, 1 H, H-γ), 3.53 (dq, J = 10.0 and 7.0 Hz, 1 H, Et), 3.57 (m, 4 H), 5.97 (dd, J = 6.2 and 6.6 Hz, H-α), 7.16 (m, 2 H, Ph), 7.31 (m, 3 H, Ph), 7.41 (m, 2 H, Bt-2), and 7.92 (m, 2 H, Bt-2): ^{13}C NMR δ 14.5 (Et), 37.2 (C-β), 50.0 (2 C), 65.1 (Et), 65.4 (C-γ), 67.0 (2 C), 92.9 (C-α), 118.4 (2 C, Bt), 126.6 (2 C, Bt), 127.6 (Ph), 128.1 (2 C, Ph), 128.5 (2 C, Ph), 137.4 (Ph), and 144.1 (2 C, Bt); HRMS calcd for $C_{21}H_{27}N_4O_2$ (M + 1) 367.2134, found 376.2133. Fraction 2 was isomer **13a** (0.68 g, 15%): oil; ^1H NMR δ 1.12 (t, J = 7.0 Hz, 3 H, Et), 2.38 (m, 1 H, H-β), 2.46 (m, 4 H), 3.17 (m, 1 H, H-β), 3.29 (m, 2 H, Et), 3.43 (m, 1 H, H-γ), 3.58 (m, 2 H), 3.68 (m, 2 H), 5.56 (dd, J = 4.3 and 8.7 Hz, 1 H, H-α), 7.32 (m, 5 H, Ph), 7.38 (m, 2 H, Bt), and 7.85 (m, 2 H, Bt); ^{13}C NMR δ 14.6 (Et), 38.2 (C-β), 51.1 (2 C), 65.3 (Et), 66.2 (C-γ), 67.0 (2 C), 93.0 (C-α), 118.5 (2 C, Bt), 126.7 (2 C, Bt), 128.2 (Ph), 128.5 (2 C, Ph), 128.6 (2 C, Ph), 138.5 (Ph), and 144.1 (Bt); HRMS calcd

for $C_{21}H_{27}N_4O_2$ (M + 1) 367.2134, found 367.2141. Fraction 3 appeared to be **10a** (0.90 g, 20%): oil; ^1H NMR δ 1.12 (t, J = 7.0 Hz, 3 H, Et), 2.26 (m, 2 H), 2.35 (m, 2 H), 2.56 (ddd, J = 6.3, 6.7, and 14.2 Hz, H-β), 2.86 (ddd, J = 6.6, 8.7, and 14.4 Hz, 1 H, H-β), 3.29 (m, 1 H, Et), 3.45 (m, 1 H, Et), 3.50 (m, 1 H, H-γ), 3.52 (m, 4 H), 6.18 (t, J = 6.7 Hz, 1 H, H-α), 7.12 (dd, J = 1.2 and 7.3 Hz, 2 H, Ph), 7.30 (m, 5 H), 7.70 (dd, J = 0.9 and 8.2 Hz, 1 H, Bt), and 8.10 (dd, J = 1.0 and 8.4 Hz, 1 H, Bt); ^{13}C NMR δ 14.5 (Et), 36.4 (C-β), 49.7 (2 C), 64.4 (Et), 65.3 (C-γ), 66.9 (2 C), 88.1 (C-α), 110.9 (Bt), 119.9 (Bt), 124.0 (Bt), 127.2 (Bt), 127.6 (Ph), 128.1 (2 C, Ph), 128.5 (2 C, Ph), 131.6 (Bt), 136.8 (Ph), and 146.6 (Bt); HRMS calcd for $C_{21}H_{27}N_4O_2$ (M^+ + 1) 367.2134, found 367.2135. Fraction 4 gave **11a** (0.45 g, 10%): ^1H NMR δ 1.09 (t, 3 H, J = 7.0 Hz, Et), 2.37 (m, 5 H, H-β and morpholine), 3.02 (dt, J = 13.8 and 7.0 Hz, 1 H, H-β), 3.18 (dq, J = 9.3 and 7.1 Hz, 1 H, Et), 3.31 (dq, J = 9.3 and 7.1 Hz, 1 H, Et), 3.49 (dd, J = 7.1 and 8.5 Hz, 1 H, H-γ), 3.67 (t, J = 4.7 Hz, 4 H), 5.87 (dd, J = 5.6 and 7.8 Hz, 1 H, H-α), 7.10–7.50 (m, 7 H), 7.73 (d, 1 H, J = 8.2 Hz), and 8.05 (d, J = 8.3 Hz, 1 H); ^{13}C NMR δ 14.5 (Et), 37.2 (C-β), 50.3 (2 C), 64.3 (Et), 65.7 (C-γ), 67.9 (2 C), 88.2 (C-α), 110.8 (Bt), 119.8 (Bt), 123.9 (Bt), 127.2 (Bt), 127.6 (Ph), 128.1 (2 C, Ph), 128,3 (2 C, Ph), 131.3 (Bt), 137.2 (Ph), and 146.3 (Bt); HRMS calcd for $C_{21}H_{27}N_4O_2$ (M + 1) 367.2134, found 367.2136.

Adducts of 9b with Ethyl Vinyl Ether (10b–13b). A mixture of **9b** (13.02 g, 50 mmol), vinyl ether (5.40 g, 75 mmol) and 4-$MeC_6H_4SO_3H{\cdot}H_2O$ (40 mg) was heated at 110–120 °C (oil bath) for 48 h to give a mixture of the Bt-1 isomers (**10b** and **11b**) and Bt-2 isomers (**12b** and **13b**) in the molar ratio of 50:25:13:12, respectively. Column chromatography (toluene/AcOEt, 5:1) allowed the separation of the predominant isomer (**10b**) as a viscosous oil: ^1H NMR δ 0.71 (d, J = 6.6 Hz, 3 H, i-Pr), 0.81 (d, J = 6.4 Hz, 3 H, i-Pr), 1.14 (t, J = 7.1 Hz, 3 H, Et), 1.84 (m, 2 H, i-Pr and H-γ), 2.32 (m, 2 H, H-β), 2.50 (m, 2 H), 2.75 (m, 2 H), 3.26 (dq, J = 9.3 and 7.1 Hz, 1 H, Et), 3.55 (dq, J = 9.5 and 6.9 Hz, 1 H, Et), 3.72 (m, 4 H), 6.34 (dd, J = 5.2 and 8.1 Hz, 1 H, H-α), 7.39 (m, 1 H, Bt), 7.49 (m, 1 H, Bt), 7.79 (d, J = 8.3 Hz, 1 H, Bt), and 8.09 (d, J = 8.4 Hz, 1 H, Bt); ^{13}C NMR δ 14.8 (Et), 19.7 (i-Pr), 21.8 (i-Pr), 28.4 (i-Pr), 32.7 (C-β), 49.5 (2 C), 64.6 (Et), 66.0 (C-γ), 67.6 (2 C), 89.4 (C-α), 110.9, 120.1, 124.2, 127.5, 131.6, and 146.6; HRMS calcd for $C_{18}H_{29}N_4O_2$ (M^+ + 1) 333.2291, found 333.2291.

1-Ethoxy-1,3-diphenyl-3-(morpholin-4-yl)propanes (14a and 15a). Phenylmagnesium bromide prepared from Mg (0.29 g, 12 mmol), I_2 (0.10 g, 0.4 mmol), and PhBr (1.1 ml, 10 mmol) in ether (10 mL) was added portionwise to a stirred and boiling toluene solution of **10a–13a** (1.30 g, 3.6 mmol) with simultaneous distillation of the ether. The procedure and workup similar to those for **8a** gave a mixture of two diastereomers. Column chromatography (toluene/ethyl acetate, 5:1 at the beginning, then slowly changed to 2:1) gave the diastereomer *R*,R** (**14a**) as a first fraction (0.46 g, 39%): ^1H NMR δ 1.12 (t, 3 H, J = 7.0 Hz, Et), 1.85 (ddd, J = 3.8, 10.0 and 13.7 Hz, 1 H, H-β), 2.37 (ddd, overlapped with morpholine resonances, 1 H, H-β), 2.39 (m, 4 H), 3.00 (dq, J = 9.2 and 7.0 Hz, 1 H, Et), 3.23 (dq, J = 9.1 and 7.0 Hz, 1 H, Et), 3.57 (dd, 1 H, J = 4.4 and 10.0 Hz, H-γ), 3.63 (t, J = 4.5 Hz, 4 H), 3.82 (dd, J = 3.8 and 9.8 Hz, 1 H, H-α), and 7.31 (m, 10 H, 2 Ph); ^{13}C NMR δ 15.3 (Et), 41.8 (C-β), 50.9 (2 C), 64.0 (Et), 66.9 (C-γ), 67.23 (2 C), 79.01 (C-α), 126.2 (2 C), 127.2 (2 C), 128.1 (2 C), 128.2 (2 C), 128.8 (2 C), 139.7, and 143.1. Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.40. Found: C, 77.63; H, 8.40; N, 4.36. As the second fraction, isomer *R*,S** (**15a**), was obtained (0.34 g, 29%): ^1H NMR δ 1.10 (t, J = 7.0 Hz, 3 H, Et), 2.20 (m, 2 H, H-β), 2.33 (m, 4 H, morpholine), 3.24 (m, 2 H, Et), 3.39 (t, J = 7.6 Hz, 1 H, H-γ), 3.62 (t, J = 4.3 Hz, 4 H), 4.22 (dd, J = 6.8 and 7.0 Hz, 1 H, H-α), and 7.10–7.40 (m, 10 H, 2 Ph); ^{13}C NMR δ 15.3 (Et), 40.1 (C-β), 50.1 (2 C), 63.9 (Et), 65.9 (C-γ), 67.3 (2 C), 79.1 (C-α), 126.8 (2 C), 127.2, 127.5, 127.9 (2 C), 128.3 (2 C), 128.9 (2 C), 138.4, and 142.7. *p*-Toluenesulfonate: prisms (THF–ether, 1:1), mp 141–142 °C. Anal. Calcd for $C_{28}H_{35}NO_5S$: C, 67.58; H, 7.09; N, 2.81. Found: C, 67.37; H, 7.07; N, 2.69.

1-Phenyl-2-ethoxy-4-(morpholin-4-yl)-5-methylhexanes (14b and 15b). Via the above procedure, a mixture of **14b** and **15b** was obtained in overall yield 90% from **10b–13b** and benzylmagnesium choride. Column chromatography of the product (toluene) gave pure diastereomer **14b** as fraction 1: ^1H NMR δ 0.82 (d, J = 6.9 Hz, 3 H, Me), 0.90 (d, J = 6.8 Hz, 3 H, Me), 1.14 (t, J = 7.1 Hz, 3 H, Et), 1.35 (ddd, J = 3.1, 9.2, and 14.5 Hz, 1 H, H-β), 1.45 (ddd, J = 2.7, 10.1, and 14.5 Hz, 1 H, H-β), 1.80 (m, 1 H, i-Pr), 2.44 (m, 4 H), 2.55 (m, 1 H, H-γ), 2.62 (dd, J = 7.4 and 13.2 Hz, 1 H, $PhCH_2$), 2.94 (dd, J = 5.8 and 13.3 Hz, 1 H, $PhCH_2$), 3.42 (m, 1 H, Et), 3.54 (m, 4 H), 3.65 (m, 1 H, Et), 3.70 (m, 1 H, H-α), and 7.11–7.29 (m, 5 H); ^{13}C NMR δ 15.5 (Et), 19.8 (i-Pr), 21.9 (i-Pr), 28.6 (i-Pr), 32.4 (C-β), 41.3 ($PhCH_2$), 49.6 (2 C), 64.9 (Et), 65.9 (C-3), 67.7 (2 C), 78.5 (C-α), 125.9, 128.1 (2 C), 129.3 (2 C), and 139.2; HRMS calcd for $C_{19}H_{31}NO_2$ (M^+) 305.2355, found 305.2361. Fraction 2 gave **15b**: ^1H NMR δ 0.78 (d, J = 6.7 Hz, 3 H, i-Pr), 0.85 (d, J = 6.8 Hz, 3 H, i-Pr), 1.10 (t, J = 7.1 Hz, 3 H, Et), 1.36 (dt, J = 14.4 and 6.8 Hz, 1 H, H-β), 1.72 (dt, J = 14.4 and 6.8 Hz, 1 H, H-β), 1.76 (octet, J = 6.7 Hz, 1 H, i-Pr), 2.15 (q, J = 6.6 Hz, 1 H, H-γ), 2.52 (m, 4 H), 2.73 (dd, J = 5.6 and 13.6 Hz, 1 H, $PhCH_2$), 2.80 (dd, J = 6.3 and 13.2 Hz, 1 H, $PhCH_2$), 3.41 (q, J = 7.0, 1 H, Et), 3.42 (q, J = 7.1 Hz, 1 H, Et), 3.57 (m, 1 H, H-α), 3.64 (t, J = 4.5 Hz, 4 H), and 7.10–7.40 (m, 5 H); ^{13}C NMR δ 15.5 (Et), 19.7 (i-Pr), 21.2 (i-Pr), 29.4 (i-Pr), 31.8 (C-β), 40.8 ($PhCH_2$), 49.7 (2 C), 64.9 (Et), 66.6 (C-γ), 67.6 (2 C), 79.7 (C-α), 126.0, 128.1 (2 C), 129.4 (2 C), and 138.9; HRMS calcd for $C_{19}H_{31}NO_2$ (M^+) 305.2355, found 305.2351.

1-Ethoxy-3-(morpholin-4-yl)-3-phenylpropane (18a). A solution of the isomeric mixture of the adducts **10a–13a** (3.65 g, 10 mmol), $LiAlH_4$ (0.95 g, 25 mmol), and $AlCl_3$ (3.32 g, 25 mmol) in THF (30 mL) was stirred and refluxed under nitrogen for 18 h. The mixture was poured into ice-cold 10% NaOH (100 mL) and extracted with ether (3 × 50 mL). The combined extracts were dried over Na_2CO_3, the solvent was evaporated, and the residue was chromatographed (toluene/ethyl acetate, 5:1) to give **18a** (2.35 g, 94%): an oil; ^1H NMR δ 1.14 (t, J = 7.0 Hz, 3 H, Et), 1.88 (m, 1 H, H-β), 2.27 (m, 1 H, H-β), 2.40 (m, 4 H), 3.15 (m, 1 H, H-γ), 3.34 (m, 4 H, Et and H-α), 3.65 (dd, J = 4.6 and 4.8 Hz, 4 H), and 7.26 (m, 5 H, Ph); ^{13}C NMR δ 15.2 (Et), 32.6 (C-β), 51.0 (2 C), 66.1 (Et), 67.2 (2 C), 67.3 (C-γ), 67.8 (C-α), 127.2, 128.1 (2 C), 128.5 (2 C), and 140.1; HRMS calcd for $C_{15}H_{24}NO_2$ (M^+ + 1) 250.1807, found 250.1807.

1-Ethoxy-3-(morpholin-4-yl)-4-methylpentane (18b). A mixture of isomers **10b–13b** (6.64 g, 20 mmol) was treated with $LiAlH_4$ (0.76 g, 20 mmol) and $AlCl_3$ (2.66, 20 mmol) in THF (50 mL) in a manner analogous to the above. The workup and purification afforded **18b** (3.55 g, 87%): an oil; ^1H NMR δ 0.89 (d, J = 6.6 Hz, 3 H, Me), 0.93 (d, J = 6.7 Hz, 3 H, Me), 1.20 (t, J = 7.0 Hz, 3 H, Et), 1.62 (m, 1 H, i-Pr), 1.77 (m, 2 H, H-β), 2.15 (m, 1 H, H-γ), 2.57 (m, 4 H), 3.48 (m, 4 H, Et and H-α), and 3.64 (t, J = 4.5 Hz, 4 H); ^{13}C NMR δ 15.3 (Et), 19.9 (i-Pr), 21.3 (i-Pr), 27.6 (C-β), 29.6 (i-Pr), 49.8 (2 C), 66.1 (Et), 67.1 (C-γ), 67.7 (2 C), and 69.8 (C-α). Picrate: mp 93 °C. Anal. Calcd for $C_{18}H_{28}N_4O_9$: C, 48.64; H, 6.35; N, 12.61. Found: C, 48.88; H, 6.35; N, 12.58.

Addition of 5b to 2,3-Dihydrofuran. A mixture of 2,3-dihydrofuran (0.85 g, 12 mmol), **5b** (2.42 g, 12 mmol), and 4-$MeC_6H_4SO_3H{\cdot}H_2O$ (0.01 g) was heated in a sealed tube at 130 °C for 16 h. The NMR showed a mixture of isomeric adducts: *trans*-Bt-2 (δ 6.48, 53%), *trans*-Bt-1 (δ 6.50, 19%), *cis*-Bt-1 (δ 6.54, 24%), and *cis*-Bt-2 (δ 6.58, 3%). Column chromatography (toluene) gave (1) **19a**: yellowish oil; ^1H NMR δ 1.73 (m, 4 H), 1.93 (m, 1 H, H-4), 2.49–2.66 (6 H, 4 H of pyrrolidine, 1 H-4 and 1 H-6), 2.76 (dd, J = 9.3 and 11.9 Hz, 1 H, H-6), 3.26 (m, 1 H, H-3), 4.21 (m, 1 H, H-5) 4.34 (m, 1 H, H-5), 6.48 (d, J = 2.3 Hz, 1 H, H-2), 7.37 (m, 2 H), and 7.88 (m, 2 H); ^{13}C NMR δ 23.4 (2 C), 29.3 (C-4), 45.1 (C-3), 54.0 (2 C), 58.4 (C-6), 69.7 (C-5), 97.3 (C-2), 118.4 (2 C), 126.4 (2 C), and 144.0 (2 C); HRMS calcd for $C_{15}H_{20}N_4O$ (M^+) 272.1637, found 272.1634. (2) Isomer **19c** was obtained as a colorless oil: ^1H NMR δ 1.72 (m, 4 H), 1.91 (m, 1 H, H-4), 2.52–2.63 (m, 6 H, 1 H-4, 1 H-6, 4 H pyrrolidine), 2.86 (dd, J = 10.1 and 11.8 Hz, 1 H, H-6), 3.63 (m, 1 H, H-3), 4.03 (m, 1 H, H-5), 4.15 (m, 1 H, H-5), 6.50 (d, J = 2.6 Hz, 1 H, H-2), 7.36 (ddd, J = 1.0, 6.8, and 7.9 Hz, 1 H), 7.48 (ddd, J = 1.0, 6.8, and 8.2 Hz, 1 H), 7.74 (d, J = 8.3 Hz, 1 H), and 8.05 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 23.4 (2 C), 29.4 (C-4), 43.3 (C-3), 54.0 (2 C), 58.7 (C-6), 68.6 (C-5), 90.7 (C-2), 110.4, 119.6, 123.9, 127.2, 132.8, and 146.1. Anal. Calcd for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.40; N, 20.57. Found: C, 66.08; H, 7.42; N, 20.14. (3) **19d**: colorless oil; ^1H NMR δ 1.61 (m, 4 H), 2.00 (m, 2 H, H-4), 2.05 (dd, J = 8.8 and 12.3 Hz, 1 H, H-6), 2.23 (dd, J = 6.2 and 12.4 Hz, 1 H, H-6), 2.40 (m, 4 H), 3.00 (m, 1 H, H-3) 4.17 (m, 1 H, H-5), 4.57 (m, 1 H, H-5), 6.54 (d, J = 6.3 Hz, 1 H, H-2), 7.35 (ddd, J = 1.1, 6.9, and 8.3 Hz, 1

H), 7.45 (ddd, J = 1.1, 6.9, and 8.0 Hz, 1 H), 7.58 (dt, J = 8.4 and 0.9 Hz, 1 H), and 8.04 (dt, J = 8.3 and 1.0 Hz, 1 H); ^{13}C NMR δ 23.4 (2 C), 28.4 (C-4), 44.6 (C-3), 54.0 (2 C), 54.4 (C-6), 69.9 (C-5), 88.5 (C-2), 110.2, 119.5, 123.6, 126.9, 133.3, and 145.1. Anal. Calcd for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.40; N, 20.57. Found: C, 66.12; H, 7.43; N, 20.59.

***trans*-2-Phenyl-3-[(pyrrolidin-1-yl)methyl]tetrahydrofuran (22).** A mixture of isomers **19a–d** (1.10 g, 4 mmol) was treated with phenylmagnesium bromide (8 mmol) in toluene at 70 °C for 3 h. Workup as above gave the crude product which appeared to contain only one isomer. Column chromatography (ethyl acetate) gave compound **22**: colorless oil (0.69 g, 75%); ^{1}H NMR δ 1.70 (m, 4 H), 1.80 (m, 1 H, H-4), 2.22 (m, 1 H, H-4), 2.30 (m, 1 H, H-3), 2.45 (m, 4 H), 2.54 (m, 2 H, H-6), 3.96 (m, 1 H, H-5), 4.09 (m, 1 H, H-5), 4.55 (d, J = 6.3 Hz, 1 H, H-2), and 7.30 (m, 5 H); ^{13}C NMR δ 23.4 (2 C), 31.7 (C-4), 47.4 (C-3), 54.3 (2 C), 59.1 (C-6), 68.0 (C-5), 84.9 (C-2), 126.0 (2 C), 127.1, 128.1 (2 C), and 143.1; HRMS calcd for $C_{15}H_{21}NO$ (M^+) 231.1623, found 231.1620.

Addition of 9a to 2,3-Dihydrofuran. A mixture of 2,3-dihydrofuran (0.70 g, 10 mmol), **9a** (2.94 g, 10 mmol), and 4-$MeC_6H_4SO_3H{\cdot}H_2O$ (0.02g) was heated in a sealed vial at 130 °C for 13 h. Column chromatography (toluene/ethyl acetate, 9:1) of the reaction mixture gave (1) a mixture of Bt-2 isomers. Fraction 2 appeared to be pure adduct **26a** which crystallized from ethanol as colorless needles: mp 132 °C; ^{1}H NMR δ 1.61 (m, 1 H, H-4), 2.25 (m, 5 H, H-4′ + morpholine), 3.04 (m, 2 H), 3.33 (m, 2 H), 3.58 (d, J = 12.2 Hz, 1 H, H-6), 4.12 (m, 2 H, H-5), 4.31 (m, 1 H, H-3), 6.71 (d, J = 3.7 Hz, 1 H, H-2), 7.10–7.50 (m, 6 H), 7.57 (m, 1 H, Bt), 7.78 (d, J = 8.4 Hz, 1 H, Bt), and 8.09 (d, J = 8.3 Hz, 1 H, Bt); ^{13}C NMR δ 30.5 (C-4), 44.6 (C-3), 49.3 (2 C), 66.8 (2 C), 69.1 (C-5), 72.8 (C-6), 90.9 (C-1), 110.2 (Bt), 119.9 (Bt), 124.2 (Bt), 127.5 (Ph or Bt), 127.8 (Ph or Bt), 128.1 (2 C, Ph), 129.1 (2 C, Ph), 133.1 (Bt), 134.1 (Ph), and 146.0 (Bt). Anal. Calcd for $C_{21}H_{24}N_4O_2$: C, 69.21; H, 6.64; N, 15.37. Found: C, 69.14; H, 6.69; N, 15.40. Fraction 3 appeared to be **26b**: colorless prisms (ethanol); mp 194 °C; ^{1}H NMR δ 1.48 (m, 2 H), 1.96 (m, 1 H, H-4), 2.33 (m, 2 H), 2.44 (m, 1 H, H-4), 3.10 (m, 2 H), 3.13 (d, J = 11.7 Hz, 1 H, H-6), 3.27 (m, 2 H), 3.60 (m, 1 H, H-3), 4.17 (m, 1 H, H-5), 4.52 (m, 1 H, H-5), 6.65 (d, J = 6.1 Hz, 1 H, H-2), 7.04 (d, J = 6.4 Hz, 2 H, Ph), 7.29 (m, 3 H, Ph), 7.38 (dd, J = 8.2 and 7.1, 1 H, Bt), 7.54 (dd, J = 8.3 and 7.3 Hz, 1 H, Bt), 7.71 (d, J = 8.4 Hz, 1 H, Bt), and 8.09 (d, J = 8.3 Hz, 1 H, Bt); ^{13}C NMR δ 28.0 (C-4), 45.1 (C-3), 49.0 (2 C), 66.6 (2 C), 69.0 (C-6), 70.0 (C-5), 87.3 (C-2), 110.3 (Bt), 119.7 (Bt), 123.8 (Bt), 127.1 (Bt), 127.7 (Ph), 128.0 (2 C, Ph), 129.0 (2 C, Ph), 133.8 (2 C, Bt and Ph), and 144.7 (Bt). Anal. Calcd for $C_{21}H_{24}N_4O_2$: C, 69.21; H, 6.64; N, 15.37. Found: C, 69.12; H, 6.68; N, 15.35. Fraction 4, **26c**: colorless prisms (ethanol); mp 215–216 °C; ^{1}H NMR δ 2.21 (m, 2 H), 2.38 (m, 2 H), 2.54 (m, 1 H, H-4), 2.90 (m, 1 H, H-4′), 3.14 (d, J = 11.6 Hz, 1 H, H-6), 3.62 (m, 5 H, H-3 and morpholine), 4.22 (m, 1 H, H-5), 4.59 (ddd, J = 2.8, 9.0, and 10.9 Hz, 1 H, H-5′), 6.02 (d, J = 6.4 Hz, 1 H, H-2), 6.41 (d, J = 8.4 Hz, 1 H, Bt), 6.52 (d, J = 7.1 Hz, 2 H, Ph), 6.95 (t, J = 7.8 Hz, 2 H, Ph), 7.05 (m, 2 H, Bt + Ph), 7.18 (m, 1 H, Bt), and 7.93 (d, J = 8.4 Hz, 1 H, Bt); ^{13}C NMR δ 29.3 (C-4), 45.7 (C-3), 49.2 (2 C), 67.1 (2 C), 69.0 (C-6), 70.2 (C-5), 86.7 (C-2), 108.4 ((Bt), 119.1 (Bt), 123.4 (Bt), 126.9 (Bt), 127.5 (Ph), 127.7 (2 C, Ph), 128.1 (2 C, Ph), 133.3 (Bt), 134.5 (Ph), and 144.3 (Bt). Anal. Calcd for $C_{21}H_{24}N_4O_2$: C, 69.21; H, 6.64; N, 15.37. Found: C, 69.26; H, 6.80; N, 15.36. As fraction 5, **26d** was collected: colorless needles (ethanol); mp 114–115 °C; ^{1}H NMR δ 2.30 (m 2 H, H-4), 2.51 (m, 4 H), 3.55 (d J = 11.5 Hz, 1 H, H-6), 3.66 (m, 4 H), 4.10 (m, 2 H, H-5), 4.23 (m, 1 H, H-3), 5.89 (d, J = 2.4 Hz, 1 H, H-2), 7.06 (m, 2 H), 7.14–7.22 (m, 4 H), 7.30 (m, 2 H), and 8.00 (m, 1 H, Bt); ^{13}C NMR δ 29.0 (C-4), 45.2 (C-3), 49.6 (2 C), 67.2 (2 C), 69.3 (C-5), 71.9 (C-6), 90.4 (C-1), 109.9 (Bt), 119.6 (Bt), 123.9 (Bt), 127.3 (Bt or Ph), 127.8 (Bt or Ph), 128.2 (2 C, Ph), 129.0 (2 C, Ph), 132.7 (Bt), 135.0 (Ph), and 146.0 (Bt). Anal. Calcd for $C_{21}H_{24}N_4O_2$: C, 69.21; H, 6.64; N, 15.37. Found: C, 69.29; H, 6.71; N, 15.44.

(*Z*)-α-(2-Chloroethyl)cinnamaldehyde (25). A mixture of the isomers **23** and **24** (3.65 g, 10 mmol), toluene (10 mL), and 36% HCl (2 mL) was stirred and heated at reflux for 90 min. The mixture was poured into water (20 mL), alkalized with 10% Na_2CO_3, and extracted with ether (2 × 20 mL). The combined extracts were dried over $MgSO_4$, and the solvent was evaporated to give pure α-(2-chloroethyl)cinnamaldehyde (**27**) (1.42 g, 81%) as a yellow oil.[2]

Reaction of 26a with Methylmagnesium Iodide. Adduct **26a** (0.30 g, 0.8 mmol) was treated with methylmagnesium iodide (3 mmol) in toluene at reflux for 2 h and worked up. Column chromatography (toluene/ethyl acetate, 9:1) gave (1) **27a** (0.12 g, 57%) as colorless oil: ^{1}H NMR δ 1.32 (m, 1 H, H-4), 1.41 (d, J = 6.1 Hz, 1 H, Me), 1.81 (m, 1 H, H-4), 2.24 (m, 2 H), 2.42 (m, 1 H, H-3), 2.45 (m, 2 H), 3.34 (d, J = 11.2 Hz, 1 H, H-6), 3.58 (m, 4 H), 3.68 (m, 1 H, H-5), 3.80 (m, 1 H, H-5), 3.98 (dq, J = 6.4 and 6.1 Hz, 1 H, H-2), 7.10 (d, J = 6.8 Hz, 2 H, Ph), and 7.31 (m, 3 H, Ph); ^{13}C NMR δ 21.5 (Me), 31.3 (C-4), 45.4 (C-3), 49.8 (2 C), 66.3 (C-5), 67.1 (2 C), 73.3 (C-6), 80.0 (C-2), 127.3, 127.8 (2 C), 129.1 (2 C), and 135.8. Picrate, yellow prisms (from methanol), mp 208 °C. Anal. Calcd for $C_{22}H_{26}N_4O_9$: C, 53.88; H, 5.34; N, 11.42. Found: C, 54.08; H, 5.40; N, 11.40. Fraction 2 was a mixture enriched in isomer **27b** (to 60%), as a colorless oil (0.07 g, 33%): ^{1}H NMR δ 1.24 (d, J = 6.6 Hz, 3 H, Me), 1.45 (m, 1 H, H-4), 1.52 (m, 1 H, H-4), 2.26 (m, 2 H), 2.49 (m, 2 H), 3.00 (m, 1 H, H-3), 3.38 (d, J = 12.3 Hz, 1 H, H-6), 3.64 (m, 4 H), 3.71 (m, 1 H, H-5), 3.90 (m, 1 H, H-5), 4.38 (dq, J = 7.1 and 6.5 Hz, 1 H, H-2), 7.13 (d, J = 7.9 Hz, 2 H), and 7.34 (m, 3 H); ^{13}C NMR δ 15.9 (Me), 29.3 (C-4), 42.7 (C-3), 49.7 (2 C), 66.5 (C-5), 67.7 (2 C), 70.2 (C-6), 76.6 (C-2), 127.8, 128.3 (2 C), 129.2 (2 C), and 136.1.

Reaction of 26d with Methylmagnesium Iodide. Adduct **26d** (0.72 g, 2.0 mmol) was treated with methylmagnesium iodide (6.0 mmol) in toluene (10 mL) at reflux for 3 h. Workup as above gave a mixture of **27c** and **27d** (0.42 g, 81%) in a ratio of 2:1. Column chromatography (toluene/ethyl acetate, 9:1) afforded (1) compound **27c**: colorless oil (0.24 g, 45%); ^{1}H NMR δ 0.86 (d, J = 6.1 Hz, 3 H, Me), 2.13 (m, 1 H, H-4), 2.27 (m, 1 H, H-4), 2.32 (m, 2 H), 2.42 (m, 2 H), 2.45 (m, 1 H, H-3), 3.31 (d, J = 10.9 Hz, 1 H, H-6), 3.52 (dq, J = 5.2 and 6.1 Hz, 1 H, H-2), 3.66 (m, 4 H), 3.78 (m, 1 H, H-5), 3.88 (m, 1 H, H-5), 7.10 (d, J = 6.8 Hz, 2 H), and 7.31 (m, 3 H); ^{13}C NMR δ 20.8 (Me), 30.1 (C-4), 46.2 (C-3), 49.2 (2 C), 66.0 (C-5), 66.9 (2 C), 72.1 (C-6), 78.3 (C-2), 127.1, 127.5 (2 C), 129.0 (2 C), and 135.8. Picrate, yellow prisms (methanol), mp 191–193 °C. Anal. Calcd for $C_{22}H_{26}N_4O_9$: C, 53.88; H, 5.34; N, 11.42. Found: C, 53.76; H, 5.30; N, 11.36. Fraction 2 was isomer **27d** (0.12 g, 22%): colorless oil; ^{1}H NMR δ 0.80 (d, J = 6.5 Hz, 3 H, Me), 2.00 (m, 1 H, H-4), 2.20 (m, 1 H, H-4), 2.25 (m, 2 H), 2.44 (2 H), 3.02 (m, 1 H, H-3), 3.35 (d, J = 11.9 Hz, 1 H, H-6), 3.65 (m, 4 H), 3.81 (m, 1 H, H-5), 3.87 (dq, J = 6.9 and 6.5 Hz, 1 H, H-2), 4.02 (dt, J = 3.0 and 8.7 Hz, 1 H, H-5), 7.12 (d, J = 6.8 Hz, 2 H), 7.32 (m, 3 H); ^{13}C NMR δ 16.0 (Me), 29.4 (C-4), 42.5 (C-3), 49.1 (2 C), 66.4 (C-5), 67.3 (2 C), 69.3 (C-6), 75.1 (C-2), 127.3, 127.8 (2 C), 128.9 (2 C), and 135.2. Picrate, yellow prisms (methanol), mp 185–187 °C. Anal. Calcd for $C_{22}H_{26}N_4O_9$: C, 53.88; H, 5.34; N, 11.42. Found: C, 53.77; H, 5.27; N, 11.71.

Supplementary Material Available: The ORTEP structures (Figures 1 and 2) and X-ray data (Tables I–XI) for **26a** and **26c** (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.