Lewis Acid-Catalyzed Additions of (Benzotriazol-1-yl)diethoxymethane to Enol Ethers and Enamides. New Syntheses of β-Alkoxyalkanal and β-Aminoalkanal Acetals

Alan R. Katritzky,* Sergei A. Belyakov, Bogumila Rachwal, and Jean-Luc Moutou

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200

Received July 1, 1996[⊗]

Addition of (benzotriazol-1-yl)diethoxymethane **11** to various acyclic and cyclic enol ethers and enamides produces the corresponding adducts, which were reacted with either $NaAlH_4$ or Grignard reagents to afford acyclic acetal-ethers (**18a**−**f**), cyclic α-(substituted)-β-acetals (**19a**−**c**), amino-acetals (**24a,b**), and 1,3-amino-ethers (**25**), all known but previously difficult-to-access classes of compounds.

Introduction

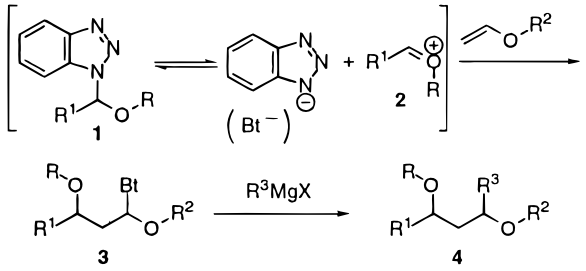
Recent reports from our laboratory have described the additions of 1-(α-alkoxybenzyl)benzotriazoles to enol ethers which opened a new route to 1,3-diethers (Scheme 1),[1] of 1-(α-aminoalkyl)benzotriazoles to enol ethers leading to 1,3-amino-ethers,[2] and of 1-(α-aminoalkyl)benzotriazoles to *N*-vinyl amides to give unsymmetrically substituted 1,3-diamines (Scheme 2).[3,4] The benzotriazole-containing starting materials **1** and **5** (Schemes 1, 2) can be considered as protected oxonium (**2**) or immonium (**6**) cations because of the easy heterolysis of the C−Bt bond under mild acidic catalysis (*p*-toluenesulfonic acid) and consequently react with enol ethers and enamides to form the corresponding benzotriazolyl-substituted addition products (*c.f.* **3**, **7**, **9**). Replacement of the benzotriazole moiety in **3**, **7**, **9** then gives the final 1,3-diethers, 1,3-amino-ethers, or 1,3-diamines (*c.f.* **4**, **8**, **10**).

We have now investigated similar Lewis acid-catalyzed additions of (benzotriazol-1-yl)diethoxymethane to enol ethers and enamides and have shown that the benzotriazole-substituted acetals thus obtained undergo further transformations (Grignard reaction, reduction, followed by another Grignard reaction, *etc.*) to provide direct and efficient routes to a wide range of β-alkoxy- and β-aminoalkanal acetals, and 1,3-amino-ethers.

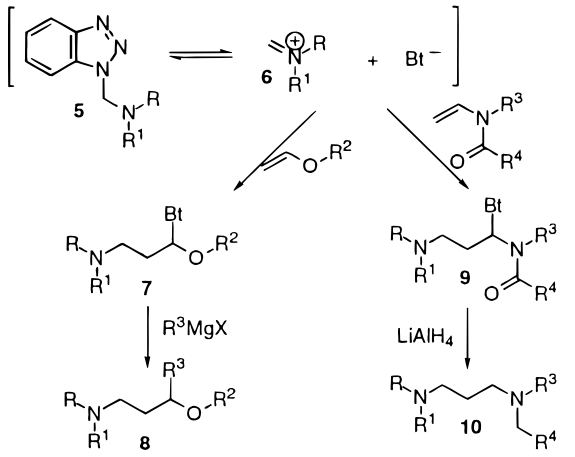
(Benzotriazol-1-yl)diethoxymethane **11** (Scheme 3) was readily prepared in good yield as a stable (shelf life more than 8 months), colorless, viscous liquid by the reaction of benzotriazole with ethyl orthoformate. The crude product **11** usually contains *ca.* 5−10% of 1-ethylbenzotriazole as a byproduct, which can be removed by distillation; however, this byproduct does not affect the further reactions of **11**, and we therefore used crude **11** in subsequent transformations.

Reactions with Enol Ethers. Acetal **11** reacted with enol ethers **12a**−**c** under catalysis by boron trifluoride, *p*-toluenesulfonic acid, or zinc bromide to give the addition compounds **13a**−**c**. These acid catalysts all work well for each vinyl substrate. Data in the Experimental Section simply underline the equality of the catalytic effect of such Lewis acids in our reactions. The mechanism of the reaction clearly involves the ionization of **11** followed by stepwise addition of the ion pair thus formed to the double bond of enol ether (Scheme 3). The crude products contained small amounts (5−9%) of ethers **14a**−**c**, as shown by NMR spectra.[23] The formation of the byproduct ethers **14** is explained by the addition to the double bond of vinyl ether of free benzotriazole which generated by reaction of ethanol with **11**, the ethanol being formed by elimination from **13a**−**c** (compare with formation of vinyl ethers from diacetals[5,6]). Compounds **13a**−**c** were separated by column chromatography and were characterized by NMR spectroscopy. However, the presence of small amounts of **14a**−**c** does not affect the

Scheme 1



Scheme 2



[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1997.

(1) Katritzky, A. R.; Rachwal, S.; Rachwal, B.; Steel, P. J. *J. Org. Chem.* **1992**, *57*, 4925.

(2) Katritzky, A. R.; Rachwal, S.; Rachwal, B.; Steel, P. J. *J. Org. Chem.* **1992**, *57*, 4932.

(3) Katritzky, A. R.; Rachwal, B.; Rachwal, S. *J. Org. Chem.* **1993**, *58*, 812.

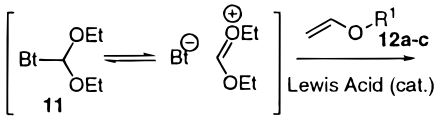
(4) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *J. Org. Chem.* **1994**, *59*, 5206.

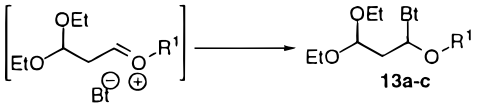
(5) Povarov, L. S. *Russ. Chem. Rev. (Engl. Transl.)* **1965**, *34*, 639.

(6) Mikhailov, B. M.; Povarov, L. S. *J. Gen. Chem. USSR (Engl. Transl.)* **1959**, *29*, 2048.

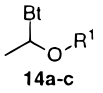
S0022-3263(96)01233-9 CCC: $14.00

Scheme 3

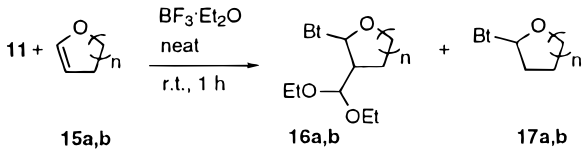




12,13,14		Yield, % (NMR)	
	R^1	13	14
a	Et	85	9
b	*i*-Bu	88	9
c	*n*-dodecyl	87	5

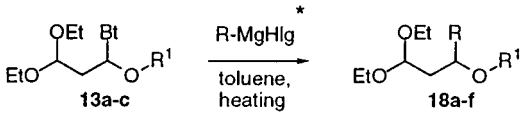


Scheme 4



15,16,17		Yield, % (NMR)	
	n	16	17
a	1	84	16
b	2	82	12

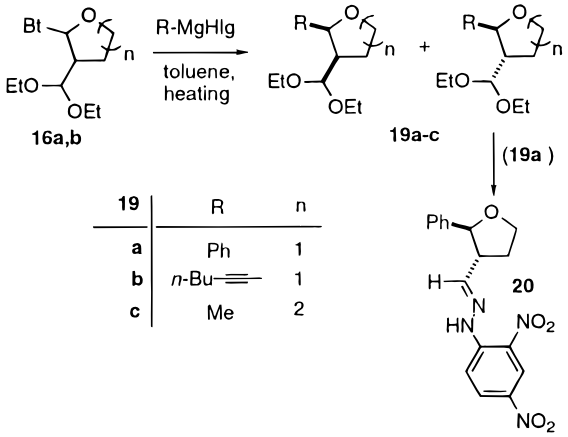
Scheme 5



18	R^1	R
a	Et	Ph
b	Et	Ph–≡
c	*i*-Bu	Me
d	*i*-Bu	Ph–≡
e	*n*-dodecyl	Ph
f	*n*-dodecyl	Me

* Hlg = I for R = Me, otherwise Hlg = Br

Scheme 6



19	R	n
a	Ph	1
b	*n*-Bu–≡	1
c	Me	2

course of further chemical transformations of **13a**−**c**, and we therefore normally used the crude products **13a**−**c** for subsequent transformations.

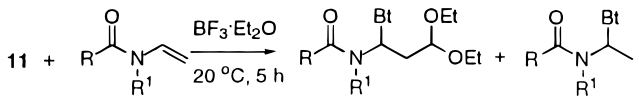
Acetal **11** reacts similarly with cyclic enol ethers **15a,b** to give 2-(benzotriazolyl)-3-(diethoxymethyl)tetrahydrofuran (**16a**) and 2-(benzotriazolyl)-3-(diethoxymethyl)-tetrahydropyran (**16b**) in high yields (Scheme 4). The crude products **16a,b** also contained compounds **17a,b**. We separated one pure stereoisomer of acetal **16b**, namely *erythro*-2-(benzotriazol-1-yl)-3-(diethoxymethyl)-tetrahydropyran, to assist with the complete assignment of the NMR signals, since the spectrum of a crude reaction mixture was complex. On the basis of HETCOR results, we assigned doublets at 4.42 and 6.36 ppm in the ^{1}H NMR spectrum of the isolated isomer to the protons at C(2) and at C(3′) positions of the pyran−acetal system. Irradiation of the former proton during NOEDIF experiment caused a *ca.* 10% resonance enhancement of the C(3′) proton signal, which allowed assignment of the isolated isomer as *erythro*. The coupling constant of the proton adjacent to the C(3′) atom (acetal proton) is characteristic (*ca.* 8.0 Hz), which was useful for the assignment of the related compound, **19c** (see below). However, for further preparative work, we used the crude product mixtures (**16a**/**17a** and **16b**/**17b**) without separation at this stage.

Transformations of the β-(Diethoxymethyl)-α-benzotriazolylalkyl Ethers 13 and 16. The acetals **13a**−**e** underwent Grignard reactions with various alkyl-, aryl-, and alkynylmagnesium halides in refluxing toluene with selective replacement of the benzotriazolyl group to give the corresponding substituted acyclic acetal-ethers **18a**−**f** (Scheme 5) and cyclic acetal-ethers **19a**−**c** (Scheme 6). These reactions of the acyclic compounds **13a**−**c** gave crude reaction products containing 70−85% of the desired acetal-ethers **18a**−**f**, according to the NMR data. Pure acetal-ethers **18a**−**f** were isolated either by column chromatography (**18a**,**b**,**d**−**f**) or by Kugelrohr distillation (**18c**). NMR spectra of the compounds **18a**−**f** do not contain signals for a benzotriazolyl substituent, but instead have the appropriate sets of the signals for the corresponding R-substituents. No transformations of the geminal diethoxy functionality with the Grignard reagents were detected in any of these reactions: in the ^{1}H and ^{13}C NMR spectra of all the acetal-ethers **18a**−**f** the signals for both geminal ethoxy substituents are essentially unchanged from those in **13a**−**c**.

Formation of the five-membered cyclic acetal-ethers **19a,b** occurred stereoselectively to give only the *threo*-isomers, *i.e.*, the introduction of the bulky phenyl substituent proceeds in the less sterically hindered way. The six-membered cyclic acetal-ether **19c** was obtained as a 1:2 mixture of *erythro*- and *threo*-isomers, which were separated by column chromatography. Assignment of the ^{1}H NMR signals for both *erythro*- and *threo*-**19c** is hindered by overlapping of the C(3) proton signals with the signals for the one of CH_2 groups. Nevertheless, based on the results for compound **16b**, the *erythro*-configuration was assigned to the specimen of **19c** with a ^{1}H NMR doublet located in the same position and with the same coupling constant as **16b**. Total yields of the cyclic acetal-ethers were above 80% (based on the NMR of reaction mixtures) for all the compounds **19a**−**c**.

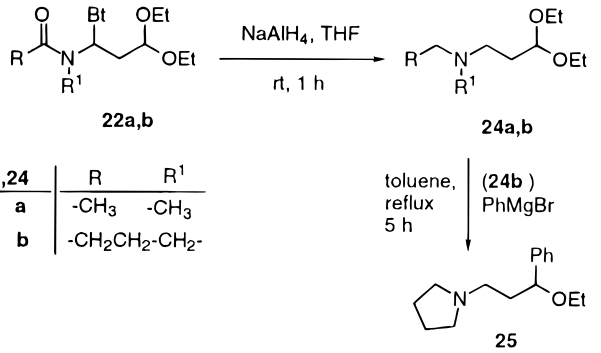
Diethyl acetals **18**, **19** are unstable compounds and readily decompose during column chromatography. Therefore, isolated yields given for these compounds in the Experimental Section are substantially lower than those estimated from the NMR. However, as shown on the examples of the amino-acetals **24a,b**, larger than preparative amounts of such acetals might be successfully purified by distillation.

Scheme 7



21,22,23	R	R^1	Yield, % (NMR) 22	23
a	$-CH_3$	$-CH_3$	90	5
b	$-CH_2CH_2-CH_2-$		70	12

Scheme 8



22,24	R	R^1
a	$-CH_3$	$-CH_3$
b	$-CH_2CH_2-CH_2-$	

We prepared *threo*-2-phenyl-1,2,3,4-tetrahydrofuran-3-carboxaldehyde 2,4-dinitrophenylhydrazone (**20**) in 72% yield by reacting the cyclic acetal-ether **19a** with 2,4-dinitrophenylhydrazine in refluxing acetic acid.

Reactions with Enamides. Addition of boron trifluoride etherate to a neat mixture of acetal **11** and enamides **21a** or **21b** at 20 °C (Scheme 7) produces in high yield the amido-acetals **22a** and **22b**, respectively, each admixed with the corresponding amide **23a,b** (*ca.* 5−12%), similar to the reactions involving enol ethers. Yields were based on NMR of the crude mixtures. We isolated and characterized the individual amido-acetal **22b** as a solid; however, as in the case of ether-acetals **13a**−**c**, we used **22a** with its minor impurities of **23a** for the further reactions, because reduction of the contaminant **23a** gives a volatile product easily removable by distillation or column chromatography. Compound **22a** was characterized by the ^{13}C NMR data (see Experimental Section).

Reductions of amido-acetals **22a,b** with $NaAlH_4$ in THF at 20 °C afforded the corresponding β-amino aldehyde ethyl acetals **24a,b** in good yields (82% and 92%, respectively) as a result of reduction of amido group and simultaneous substitution of benzotriazole moiety by a hydrogen atom (Scheme 8). These reactions are vigorous and require external cooling, especially at the beginning. Both **24a** and **24b** can be purified by column chromatography; however, distillation provides much better yields and comparable purity. Both the ^1H and the ^{13}C NMR spectra of β-amino aldehyde ethyl acetals **24a,b** contain characteristic sets of signals: in the proton NMR there is a triplet at *ca.* 4.5−4.6 ppm assigned to the proton of the acetal group, and no signals in the aromatic region of the spectra, thus indicating a complete displacement of the benzotriazolyl moiety by hydrogen. In the carbon NMR there are no signals at low field responsible for the carbon atom of amido group, but instead an extra secondary carbon signal appears at high field (*ca.* 40−60 ppm), corresponding to the carbon atom from the reduced amido group.

Grignard reaction of the acetal **24b** with PhMgBr in refluxing toluene after 5 h afforded the corresponding substituted amino-ether **25** in 60% yield. In the ^1H NMR spectrum of **25** a new multiplet at *ca.* 7.27 ppm appeared, and the integration of the signals of ethoxy group was decreased, matching a calculation for three and two protons, respectively, thus confirming the successful displacement of one of the acetal ethoxy groups. Displacement of one of the oxygens (ethoxy group) by carbon (phenyl ring) resulted in the upfield shift of the signal of ethereal α-carbon atom (from 101.6 to 80.4 ppm) in the ^{13}C NMR spectrum of the amino-ether **25**. Manipulations with the type of substituents in the starting vinyl amides **21** and in Grignard reagents thus open the possibility to vary substantially the structure of the amino-ethers **25**.

Comparison with Previous Work. Mayr and coworkers[7] synthesized variously substituted propanal dimethyl acetals and investigated systematically the reactions of acetals and ortho esters with vinyl methyl ether, concluding the following order of reactivity: formaldehyde acetals < aliphatic acetals < ortho esters < aromatic acetals = unsaturated aliphatic acetals. The addition of ortho esters to enol ethers has significant synthetic value since the final 1,1,3,3-tetraalkoxypropanes are malonaldehyde equivalents and are widely used in the heterocyclic chemistry. They are commercially available products but are usually manufactured by other methods (see *e.g.* lit.[8]). By contrast, the addition of either acetals or ortho esters to enamides has not been previously studied.

An advantage of our new methodology is that the acetals **13** are inactive toward competitive addition to enol ethers: in all the cases we used acetal and vinyl ether in equimolar ratio and did not observe the formation of any secondary addition products, while previously described reactions of stoichiometric amounts of acetals and enol ethers led to the formation of oligomers.[5,9] This difference in the reactivity patterns in acetals and **11** becomes crucial as far as their reactions with cyclic enol ethers are concerned. Substituted tetrahydrofurans and tetrahydropyrans are the structural subunits in naturally occurring polyether antibiotics, pheromones, *etc.*[10,11] Additions of acetals to dihydrofurans and dihydropyrans were previously found to yield the corresponding 2-alkoxy-3-(α-alkoxy)alkyltetrahydrofurans or -pyrans;[5,12,13] however, these reactions are often complicated by the formation of secondary condensation products.

2-Substituted tetrahydrofuran(pyran)-3-carboxaldehydes were previously difficult to access: the most frequently used method for their preparation is a three-step procedure based on (i) the preparations of either 2-(disubstituted)-4,7-dihydro-1,3-dioxepines or 2-(disubstituted)-5,6-dihydro-1,3-dioxocins, (ii) ruthenium hydride-catalyzed isomerization of these cyclic compounds (migration of double bond), and (iii) 1,3-alkyl migration ring construction catalyzed by Lewis acids to give, after hydrolysis of the intermediate acetal, the corresponding aldehydes in *ca.* 20−30% overall yields.[10,11,14,15]

(7) von der Brüggen, U.; Lammers, R.; Mayr, H. *J. Org. Chem.* **1988**, *53*, 2920.
(8) Eckhardt, H.; Halbritter, K.; Rohr, W. Ger. Offen. DE 3,145,709; *Chem. Abstr.* **1983**, *99*, 53734.
(9) Hoaglin, R. I.; Hirsh, D. H. *J. Am. Chem. Soc.* **1949**, *71*, 3468.
(10) Frauenrath, H.; Philipps, T. *Tetrahedron* **1986**, *42*, 1135.
(11) Frauenrath, H.; Sawicki, M. *Tetrahedron Lett.* **1990**, *31*, 649.
(12) Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1950**, 1155.
(13) Brannock, K. C. *J. Org. Chem.* **1959**, *24*, 1382.
(14) Suzuki, H.; Yashima, H.; Hirose, T.; Takahashi, M.; Moro-oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1980**, *21*, 4927.

β-Amino aldehydes are considered to be an important building blocks in the biosynthesis and total synthesis of various alkaloids, *i.e.*, antitumor alkaloids Manzamine A1 and Manzamine D2[16] and all *Elaecarpus* alkaloids.[17] Most β-amino aldehydes are unstable and spontaneously polymerize.[16] Some examples of the Michael addition of acrolein or related compounds to secondary amines which resulted in the preparation of substituted β-amino aldehydes are described in the literature,[16] but the stability of these compounds was low and they had to be used immediately after their preparation in solution. More stable acetals of β-amino aldehydes were recently prepared by the reaction of *N*-alkenyl-*N*,*N*-dialkylamines with methanol catalyzed by $CuCl_2/LiPdCl_4$ in moderate to good yields.[18] We believe that the presently reported preparation of β-amino-acetals holds great promise as precursors of β-amino aldehydes and 1,3-amino-ethers because of the easy manipulation and readily available starting materials.

In summary, we found that the addition of (benzotriazol-1-yl)diethoxymethane **11** to various acyclic and cyclic enol ethers and enamides produces the corresponding 1:1 adducts with no further additions observed. These adducts can be easily modified by the reactions with either $NaAlH_4$ or with Grignard reagents, thus yielding several classes of compounds which were previously known but accessible only with difficulty: acyclic acetal-ethers **18a**−**f**, cyclic α-(substituted)-β-acetals **19a**−**c**, amino-acetals **24**, and the corresponding 1,3-amino-ethers of type **25**.

Experimental Section

General. See refs 19, 20. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra at 75 MHz in $CDCl_3$. All the compounds containing the benzotriazole moiety which are described in the present paper consist of the mixture of benzotriazol-1-yl (Bt^1) and benzotriazol-2-yl (Bt^2) isomers in different ratios. Both isomers readily undergo the transformations described here, and therefore their isolation was not performed. Experimental Section contains NMR data of the mixtures of Bt^1 and Bt^2 isomers, without their complete assignments.

(Benzotriazol-1-yl)diethoxymethane (11). A mixture of benzotriazole (5.96 g, 50 mmol) and triethyl orthoformate (7.41 g, 50 mmol) was heated together with perfluorocarbon fluid (3M Co. performance fluid, FC-84;[21,22]) (30 mL) in a round-bottom flask fitted with a reversed Dean−Stark trap. After 20 h of reflux (during this time ethanol was collected in the trap), the mixture was allowed to cool and ethyl acetate (40 mL) was added. The ethyl acetate layer was separated, the solvent was evaporated *in vacuo*, and the residue was subjected to fractional distillation, collecting the fraction with bp 95−97 °C/0.15−0.20 Torr. Colorless, viscous liquid; yield 86%; ^{1}H NMR δ 1.25 (t, *J* = 7.1 Hz, 6H), 3.54 (dq, *J* = 9.4 and 7.1 Hz, 2H), 3.80 (dq, *J* = 9.4 and 7.1 Hz, 2H), 6.79 (s, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.50 (t, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 14.6, 63.1, 105.9, 112.2, 119.6, 124.4, 127.7, 130.8, 146.4. Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83. Found: C, 59.36; H, 6.54.

General Procedure for the Preparation of 1-(Benzotriazolyl)-1-alkoxy-3,3-diethoxypropanes (13a−c), 2-(Benzotriazolyl)-3-(diethoxymethyl)tetrahydrofuran (16a), and 2-(Benzotriazolyl)-3-(diethoxymethyl)tetrahydropyran (16b). A mixture of acetal **11** (6.75 mmol), alkyl vinyl ether **12a**−**c** or cycloalkyl vinyl ether **15a,b** (6.75 mmol), and the corresponding Lewis acid catalyst (see below) was stirred at rt for a time specified (see below). The residue was diluted with diethyl ether, and the organic layer was successively washed with NaOH (1 M solution in water) and then with brine, separated, and dried over anhyd $MgSO_4$. Evaporation of the solvent *in vacuo* gave acetal **13** or **16** together with small amounts of the ether **14** or **17**. NMR assignments below are given only for compounds **13** or **16**.

1-(Benzotriazolyl)-1,3,3-triethoxypropane (13a): catalyst: *p*-TsOH (0.01 g), reaction time: 1 h; oil; yield 85% (based on the NMR); ^{1}H NMR δ 1.11−1.21 (m, 9 H), 2.43 (ddd, *J* = 14.0, 6.4 and 6.4 Hz, 1H), 2.63 (ddd, *J* =13.9, 7.4 and 5.2 Hz, 1H), 3.24−3.35 (m, 1H), 3.40−3.69 (m, 5H), 4.51 (dd, *J* = 6.6 and 5.2 Hz, 1H), 6.21 (dd, *J* = 7.4 and 6.1 Hz, 1H), 7.40 (t, *J* = 8.2 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 14.3, 14.9, 38.6, 61.2, 61.5, 64.1, 87.0, 98.9, 110.6, 119.7, 123.8, 127.1, 131.2, 146.3.

1-(Benzotriazolyl)-1-(isobutyloxy)-3,3-diethoxypropane (13b): catalyst: $BF_3{\cdot}Et_2O$ (0.03 mL), reaction time: 20 h; oil; yield 88% (based on the NMR); ^{1}H NMR δ 0.80 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H), 1.16 (t, *J* = 7.0 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.81 (sextet, *J* = 6.7 Hz, 1H), 2.37−2.46 (m, 1H), 2.65 (ddd, *J* = 14.0, 7.7 and 5.0 Hz, 1H), 2.97 (dd, *J* = 8.9 and 6.7 Hz, 1H), 3.25 (dd, *J* = 9.0 and 6.4 Hz, 1H), 3.40−3.54 (m, 2H), 3.56−3.70 (m, 2H), 4.55 (dd, *J* = 6.7 and 5.1 Hz, 1H), 6.19 (dd, *J* = 7.6 Hz and 5.9 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.49 (t, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR δ 15.0, 15.1, 18.9, 27.9 (2 C), 38.7, 61.4, 61.5, 75.4, 87.6, 99.0, 110.8, 119.8, 123.9, 127.2, 131.3, 146.4.

1-(Benzotriazolyl)-1-(dodecyloxy)-3,3-diethoxypropane (13c): catalyst: *p*-TsOH (0.01 g), reaction time: 2 h; oil; yield 87% (based on the NMR); ^{1}H NMR δ 0.80 (t, *J* = 6.5 Hz, 3H), 1.08−1.17 (m, 24H), 1.36−1.47 (m, 2H), 2.35 (dt, *J* = 14.0 and 6.3 Hz, 1H), 2.56 (ddd, *J* = 12.7, 7.6 and 5.2 Hz, 1H), 3.09−3.18 (m, 1H), 3.33−3.45 (m, 3H), 3.50−3.61 (m, 2H), 4.55 (dd, *J* = 6.6 and 5.1 Hz, 1H), 6.12 (dd, *J* = 7.5 and 6.2 Hz, 1H), 7.31 (t, *J* = 7.1 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 14.0, 15.1, 15.2, 22.6, 25.8, 29.1, 29.2 (2 C), 29.4 (2 C), 29.5 (2 C), 31.8, 38.9, 61.5, 61.7, 69.0, 87.6, 99.2, 110.9, 120.0, 124.1, 127.3, 131.5, 146.7.

2-(Benzotriazolyl)-3-(diethoxymethyl)tetrahydrofuran (16a): catalyst: $BF_3{\cdot}Et_2O$ (0.03 mL), reaction time: 1 h; oil; yield 84% (based on the NMR); ^{1}H NMR δ 1.12 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 2.07−2.20 (m, 1H), 2.42−2.55 (m, 1H), 3.48−3.70 (m, 4H), 3.70−3.82 (m, 1H), 4.02−4.22 (m, 2H), 4.62 (d, *J* = 7.4 Hz, 1H), 6.43 (d, *J* = 3.1 Hz, 1H), 7.35−7.40 (m, 1H), 7.47−7.52 (m, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 14.7, 14.8, 26.9, 47.3, 61.2, 61.9, 68.8, 88.6, 102.3, 109.8, 119.4, 123.7, 127.1, 132.4, 145.8.

***erythro*-2-(Benzotriazol-1-yl)-3-(diethoxymethyl)tetrahydropyran (16b):** catalyst: $BF_3{\cdot}Et_2O$ (0.03 mL), reaction time: 24 h; oil; yield 82% (based on the NMR); ^{1}H NMR δ 0.64 (t, *J* = 7.0 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.80−1.90 (m, 3H), 2.00−2.10 (m, 1H), 2.62−2.76 (m, 3H), 3.42−3.70 (m, 5H), 4.42 (d, *J* = 8.0 Hz, 1H), 6.36 (d, *J* = 4.2 Hz, 1H), 7.40 (t, *J* = 8.2 Hz, 1H), 7.52 (t, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 14.6, 15.5, 20.9, 24.7, 42.9, 61.8, 63.1 (2C), 81.0, 103.5, 110.3, 119.7, 124.2, 127.5, 133.9, 145.1.

General Procedure for the Preparation of 1-(Substituted)-1-alkoxy-3,3-diethoxypropanes (18a−f), 2-(Substituted)-3-(diethoxymethyl)tetrahydrofurans (19a,b), and 2-Methyl-3-(diethoxymethyl)tetrahydropyran (19c). To a refluxing solution of the corresponding diethyl acetal **13a**−**c** or **16a,b** (10 mmol) in toluene (50 mL) was added a solution of the corresponding Grignard reagent RMgHlg,

(15) Frauenrath, H.; Philipps, T. *Liebigs Ann. Chem.* **1985**, 1951.
(16) Chesney, A.; Marko, I. E. *Synth. Commun.* **1990**, *20*, 3167.
(17) Chen, C.-K.; Hortmann, A. G.; Marzabadi, M. R. *J. Am. Chem. Soc.* **1988**, *110*, 4829.
(18) Lai, J.-y.; Shi, X.-x.; Dai, L.-x. *J. Org. Chem.* **1992**, *57*, 3485.
(19) Katritzky, A. R.; Rachwal, B.; Rachwal, S.; Abboud, K. A. *J. Org. Chem.* **1996**, *61*, 3117.
(20) Katritzky, A. R.; Xie, L. *J. Org. Chem.* **1995**, *60*, 3707.
(21) Zhu, D.-W. *Synthesis* **1993**, 953.
(22) Katritzky, A. R.; Toader, D.; Jiang, J. *Org. Prep. Proced. Int.* **1995**, *27*, 179.

prepared immediately prior to use from the appropriate alkyl, aryl, or arylalkynylhalide (20 mmol) and magnesium turnings (5.34 g, 22 mmol), in ether (50 mL) dropwise at such rate that the ether distilled off and the temperature of the reaction mixture was kept above 100 °C. After the addition was completed, the mixture was refluxed for an additional time (see below). The course of reaction was monitored by TLC and/or NMR spectroscopy. After cooling to rt, the reaction mixture was poured into ice−water mixture (200 mL), acidified by the addition of acetic acid (5% solution in water), and extracted with ether (50 mL). The ethereal solution was washed with water, 5% Na_2CO_3, and again with water and dried over anhyd $MgSO_4$. Evaporation of the solvent *in vacuo* gave crude acetal **18** or **19** which was purified by column chromatography (eluent, hexane:ether 4:1 for **18a,b,d,f, 19a,b**, or 8:1 for **18e** and **19c**) or distilled (**18c**). Scale-up syntheses products can be easily purified by distillation.

1-Phenyl-1,3,3-triethoxypropane (18a): reaction time: 0.5 h; oil; yield 70% (based on the NMR);[23] isolated yield 52%; bp 86−88 °C/2 Torr; ^{1}H NMR δ 1.13−1.25 (m, 9H), 1.85−1.98 (m, 1H), 2.07−2.17 (m, 1H), 3.25−3.75 (m, 6H), 4.38 (dd, J = 9.0 and 5.0 Hz, 1H). 4.64−4.66 (m, 1H), 7.25−7.40 (m, 5H); ^{13}C NMR δ 15.1, 15.2, 15.3, 42.3, 61.0, 61.2, 63.8, 78.3, 100.2, 126.4 (2 C), 127.3, 128.2 (2 C), 142.4. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.36.

1-Phenyl-3,5,5-triethoxypent-1-yne (18b): reaction time: 2 h; oil; yield 85% (based on the NMR); isolated yield 33%; ^{1}H NMR δ 1.20−1.28 (m, 9H), 2.03−2.12 (m, 1H), 2.20 (ddd, J = 13.7, 8.2 and 5.5 Hz, 1H), 3.46−3.61 (m, 3H), 3.64−3.76 (m, 2H), 3.83−3.93 (m, 1H), 4.39 (dd, J = 8.0 and 6.1 Hz, 1H), 4.80 (dd, J = 6.1 and 5.8 Hz, 1H), 7.27−7.40 (m, 3H), 7.42−7.46 (m, 2H); ^{13}C NMR δ 15.2, 15.4 (2 C), 40.2, 61.5, 61.7, 64.3, 66.6, 85.5, 88.2, 100.1, 122.8, 128.2 (3 C), 131.7 (2 C). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.85; H, 8.78.

1,1-Diethoxy-3-(2-methylpropoxy)butane(18c): reaction time: 0.5 h; oil; yield 72%; bp 61−63 °C/1.0−1.2 Torr; ^{1}H NMR δ 0.90 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 1.13 (d, J = 6.2 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, H), 1.68 (ddd, J = 14.0, 7.6 and 4.3 Hz, 1H), 1.75−1.87 (m, 2H), 3.03 (dd, J = 8.9 and 7.0 Hz, 1H), 3.30 (dd, J = 9.0 and 6.3 Hz, 1H), 3.45−3.74 (m, 5 H), 4.69 (dd, J = 7.6 and 4.0 Hz, 1H); ^{13}C NMR δ 15.3, 15.4, 19.4, 19.5, 19.8, 28.8, 41.5, 61.0, 61.7, 72.1, 75.5, 100.7; HRMS calcd for $C_{12}H_{27}O_3$ 219.1960 [M^+ + 1], found 219.1953.

1-Phenyl-3-(2-methylpropoxy)-5,5-diethoxypent-1-yne (18d): reaction time: 6 h; oil; yield 85% (based on the NMR); isolated yield 37%; ^{1}H NMR δ 0.94 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.87−1.96 (m, 1H), 2.05−2.14 (m, 1H), 2.21 (ddd, J = 13.5, 8.5 and 5.2 Hz, 1H), 3.19 (dd, J = 8.5 and 6.8 Hz, 1H), 3.50−3.62 (m, 3 H), 3.66−3.78 (m, 2 H), 4.37 (dd, J = 8.2 and 5.8 Hz, 1H), 4.81 (dd, J = 6.6 and 5.2 Hz, 1H), 7.29−7.33 (m, 3H), 7.41−7.46 (m, 2H); ^{13}C NMR δ 15.3 (2 C), 19.4, 19.5, 28.5, 40.3, 61.5, 61.7, 66.9, 75.8, 85.4, 88.3, 100.1, 122.5, 128.2 (3 C), 131.7 (2 C). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.28. Found: C, 75.38; H, 9.42.

1-(Dodecyloxy)-1-phenyl-3,3-diethoxypropane(18e): reaction time: 1 h; oil; yield 70% (based on the NMR); isolated yield 29%; ^{1}H NMR δ 0.89 (t, J = 6.9 Hz, 3H), 1.15−1.40 (m, 22H), 1.50−1.62 (m, 2H), 1.89 (ddd, J = 13.9, 7.4 and 4.8 Hz, 1H), 2.11 (ddd, J = 13.7, 9.1 and 4.4 Hz, 1H), 3.18−3.25 (m, 1H), 3.27−3.37 (m, 1H), 3.45−3.75 (m, 6H), 4.35 (dd, J = 9.1 and 4.7 Hz, 1H), 4.65 (dd, J = 7.4 and 4.4 Hz, 1H), 7.20−7.50 (m, 5H); ^{13}C NMR δ 14.0, 15.3 (2 C), 22.6, 26.2, 29.3, 29.4, 29.6 (3 C), 29.8, 31.8, 42.5, 60.9, 61.0, 61.4, 68.7, 78.6, 100.3, 126.4 (2 C), 127.3, 128.2 (2 C), 142.6; HRMS calcd for $C_{25}H_{45}O_3$ 393.3369 [M^+ + 1], found 393.3347.

(23) The "NMR yield" here and elsewhere indicates the percentage yield based on the desired product contained in the crude reaction mixture. This was calculated for compounds **13a**−**c**, **16a,b**, **22a,b** as the proportion of the ^{1}H NMR signal integrals of the protons in the α-position (to the benzotriazole moiety) of the intermediate to the corresponding byproduct. For compounds **18a,b,d**−**f**, **19a**−**c** a similar calculations were used for acetal group proton signals in the desired product and unreacted starting material.

1,1-Diethoxy-3-(dodecyloxy)butane (18f): reaction time: 4 h; oil; yield 70% (based on the NMR); isolated yield 34%; ^{1}H NMR δ 0.88 (t, J =7.0 Hz, 3H), 1.13−1.26 (m, 27H), 1.48−1.60 (m, 2H), 1.67 (ddd, J = 13.9, 12.0 and 4.4 Hz, 1H), 1.82 (ddd, J = 13.9, 8.9 and 4.0 Hz, 1H), 3.28 (dt, J = 9.1 and 6.8 Hz, 1H), 3.47−3.55 (m, 4H), 3.58−3.72 (m, 2H), 4.67 (dd, J = 7.5 and 3.4 Hz, 1H); ^{13}C NMR δ 14.1, 15.4 (2 C), 19.9, 22.7, 26.3, 29.4, 29.5, 26.6 (4 C), 30.2, 31.9, 41.4, 61.0, 61.7, 68.6, 72.0, 100.8; HRMS calcd for $C_{20}H_{42}O_3$ 330.3134 [M^+], found 330.3042.

***threo*-2-Phenyl-3-(diethoxymethyl)tetrahydrofuran (19a):** reaction time: 0.5 h; oil; yield 90% (based on the NMR); ^{1}H NMR δ 1.13 (t, J = 7.0 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H), 1.91−2.16 (m, 2H), 2.49−2.58 (m, 1H), 3.42−3.58 (m, 3H), 3.60−3.75 (m, 1H), 3.91−3.98 (m, 1H), 4.04−4.12 (m, 1H), 4.51 (d, J = 7.2 Hz, 1H), 4.82 (d, J = 5.8 Hz, 1H), 7.21−7.40 (m, 5H); ^{13}C NMR δ 15.0, 15.2, 28.2, 50.7, 61.4, 62.0, 68.0, 82.2, 103.7, 126.0 (2 C), 127.0, 128.1 (2 C), 143.1. This compound was characterized as its DNP derivative **20** (see below).

***threo*-2-(1-Hexyn-1-yl)-3-(diethoxymethyl)tetrahydrofuran (19b):** reaction time: 2.5 h; oil; yield 70% (based on the NMR); isolated yield 25%; ^{1}H NMR δ 0.89−0.94 (m, 6H), 1.20−1.25 (m, 7H), 1.35−1.55 (m, 4H), 1.75−1.95 (m, 1H), 2.05−2.15 (m, 1H), 2.19−2.26 (m, 2H), 2.61 (ddd, J = 13.2, 7.9 and 5.3 Hz, 1H), 3.40−3.60 (m, 1H), 3.62−3.78 (m, 1H), 3.82−3.98 (m, 2H), 4.38 (d, J = 7.4 Hz, 1H), 4.49−4.51 (m, 1H); ^{13}C NMR δ 13.4, 15.1 (2 C), 18.3, 21.8, 27.5, 30.5, 50.0, 61.2, 61.5, 67.1, 70.1, 79.3, 85.3, 103.0. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.83; H, 10.29.

2-Methyl-3-(diethoxymethyl)tetrahydropyran (19c): reaction time: 3 h; oil; yield 70% (based on the NMR); *erythro*-isomer: yield 13% (after column chromatography, eluent: hexane:ether 8:1); ^{1}H NMR δ 1.17−1.25 (m, 9H), 1.40−1.55 (m, 1H), 1.57−1.68 (m, 3H), 1.98−2.06 (m, 1H), 3.43−3.80 (m, 6H), 3.92 (ddd, J = 13.5, 6.9 and 3.9 Hz, 1H), 4.42 (d, J = 8.7 Hz, 1 H); ^{13}C NMR δ 15.3, 15.4, 20.0, 22.3, 24.4, 41.0, 60.6, 61.2, 63.3, 71.7, 102.5; HRMS calcd for $C_{11}H_{23}O_3$ 203.1647 [M^+ + 1], found 203.1651. *Threo*-isomer: yield 26% (after column chromatography, eluent: hexane:ether 8:1); ^{1}H NMR δ 1.20−1.26 (m, 9H), 1.45−1.70 (m, 4H), 1.90−1.95 (m, 1H), 3.35−3.55 (m, 4H), 3.60−3.80 (m, 2H), 3.87−3.98 (m, 1H), 4.37 (d, J = 3.0 Hz, 1H); ^{13}C NMR δ NMR 15.1, 15.2, 19.9, 22.4, 25.8, 46.0, 63.3, 63.4, 67.6, 74.7, 103.8; HRMS calcd for $C_{11}H_{22}O_3$ 202.1569 [M^+], found 202.1610.

2-Phenyl-1,2,3,4-tetrahydrofuran-3-carboxaldehyde 2,4-Dinitrophenylhydrazone (20). Acetal **19a** (0.50 g, 2 mmol) was dissolved in glacial acetic acid (15 mL), 2,4-dinitrophenylhydrazine (0.59 g, 3 mmol) was added, and the mixture was refluxed for 2 h. After cooling, the reaction mixture was dissolved in water, neutralized with 5% Na_2CO_3, and extracted with $CHCl_3$ (2 × 20 mL). The combined organic extracts were washed with water, dried over anhyd $MgSO_4$, and the solvent was evaporated *in vacuo* to give yellow solid which was recrystallized from EtOH to give dark yellow plates; yield 72%; mp 142−143 °C; ^{1}H NMR δ 2.20−2.50 (m, 2H), 3.10−3.21 (m, 1H), 4.09−4.17 (m, 1H), 4.20−4.28 (m, 1H), 4.92 (d, J = 7.5 Hz, 1H), 7.20−7.50 (m, 5H), 7.60 (d, J = 5.8 Hz, 1H), 7.85 (d, J = 9.5 Hz, 1H), 8.27 (dd, J = 9.5 and 2.5 Hz, 1H), 9.07 (d, J = 2.6 Hz, 1H), 11.08 (br s, 1H); ^{13}C NMR δ 31.0, 50.7, 68.1, 83.5, 116.5, 123.3, 125.9 (2 C), 127.9, 128.6 (2 C), 129.1, 129.9, 138.1, 140.6, 144.4, 150.6. Anal. Calcd for $C_{17}H_{15}N_4O_5$: C, 15.77; H, 57.46; N, 4.25. Found: C, 15.70; H, 57.13; N, 4.52.

General Procedure for the Preparation of *N*-Methyl-*N*-[1-(benzotriazolyl)-3,3-diethoxypropyl]acetamide(22a) and 1-[1-(Benzotriazolyl)-3,3-diethoxypropyl]pyrrolidin-2-one (22b). A mixture of acetal **11** (1.00 g, 4.5 mmol), 1-vinyl-2-pyrrolidinone or *N*-methyl-*N*-vinylacetamide (4.5 mmol), and $BF_3{\cdot}Et_2O$ (0.03 mL) was stirred at 20 °C for 5 h. The reaction mixture was diluted with ether (50 mL) and subsequently washed with 1 M NaOH, brine, and water. Organic phase was separated and dried over anhyd $MgSO_4$. Solvent was evaporated *in vacuo* to give colorless oil.

***N*-Methyl-*N*-[1-(benzotriazolyl)-3,3-diethoxypropyl]acetamide (22a):** oil; yield 90% (based on the NMR); ^{13}C NMR δ 15.0, 16.6, 21.9, 30.0, 34.9, 61.2, 62.3, 99.5, 110.6, 119.4, 124.2, 127.7, 132.7, 145.5, 171.1.

1-[1-(Benzotriazolyl)-3,3-diethoxypropyl]pyrrolidin-2-one (22b): oil isolated after synthesis solidified upon trituration with hexanes. White microcrystals; mp 79−81 °C; yield 70%; ^{1}H NMR δ 1.11 (t, J = 7.0 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H), 1.78−1.95 (m, 1H), 1.95−2.11 (m, 1H), 2.28 (ddd, J = 17.2, 9.6 and 6.4 Hz, 1H), 2.44 (ddd, J = 17.2, 9.6 and 7.0 Hz, 1H), 2.68 (ddd, J = 14.0, 6.9 and 6.9 Hz, 1H), 3.07 (ddd, J = 14.0, 8.2 and 4.9 Hz, 1H), 3.20−3.37 (m, 2H), 3.45−3.71 (m, 4H), 4.38 (dd, J = 6.6 and 4.9 Hz, 1H), 7.00 (dd, J = 8.1 and 6.9 Hz, 1H), 7.35−7.43 (m, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.83−7.89 (m, 1H), 8.02−8.07 (m, 1H); ^{13}C NMR δ 15.0, 15.1, 17.6, 30.6, 34.9, 42.3, 60.2, 61.4, 62.4, 99.3, 110.4, 119.3, 124.2, 127.7, 132.6, 145.4, 174.9. Anal. Calcd for $C_{17}H_{24}N_4O_3$: C, 61.43; H, 7.28; N, 16.86. Found: C, 61.64; H, 7.22; N, 17.48.

General Procedure for the Preparation of the Amino-Acetals (24a,b). To a stirred under nitrogen solution of the corresponding acetal **22a,b** (10 mmol) in dry THF (100 mL) was added $NaAlH_4$ (1.08 g, 20 mmol) in one portion. (CAUTION! A strong evolution of heat is observed; use external cooling). The reaction mixture was stirred at rt for 1 h, and 20% NaOH was then added portionwise. A mixture was stirred for 20 min and extracted with ether (3 × 50 mL). The combined extracts were washed twice with 5% NaOH and then with water and dried over anhyd $MgSO_4$. The solvent was evaporated *in vacuo* to yellow-orange oil. The crude product was subjected to flash column chromatography (ethyl acetate) and then to distillation.

***N*-[1-(3,3-Diethoxypropyl)]-*N*-ethylmethylamine (24a):** oil; yield 82%; bp 42−45 °C/4 Torr; ^{1}H NMR δ 1.09 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 6H), 1.80−1.87 (m, 2H), 2.26 (s, 3H), 2.44−2.51 (m, 4H), 3.47−3.57 (m, 2H), 3.62−3.72 (m, 2H), 4.58 (t, J = 5.5 Hz, 1H); ^{13}C NMR δ 12.0, 15.0, 31.2, 41.3, 51.1, 52.3, 60.7, 101.4; HRMS calcd for $C_{10}H_{24}NO_2$ 190.1807 [M^++ 1], found 190.1809.

***N*-[1-(3,3-Diethoxypropyl)]pyrrolidine (24b):** oil; yield 92%; bp 65−68 °C/1 Torr; ^{1}H NMR δ 1.21 (t, J =7.1 Hz, 6H), 1.76−1.82 (m, 4H), 1.83−1.90 (m, 2H), 2.45−2.55 (m, 6H), 3.46−3.56 (m, 2H), 3.61−3.71 (m, 2H), 4.59 (t, J = 5.6 Hz, 1H); ^{13}C NMR δ 15.3, 23.4, 33.1, 51.8, 54.2, 60.9, 101.6; HRMS calcd for $C_{11}H_{24}NO_2$ 202.1807 [M^+ + 1], found 202.1812.

Reaction of Acetal 24b with Phenylmagnesium Bromide. To a stirred solution of the acetal **24b** (0.61 g, 3 mmol) in toluene (50 mL) was added a solution of phenylmagnesium bromide (9 mmol) in ether (6 mL) dropwise at reflux under nitrogen. The course of the reaction was monitored by NMR. After 5 h the reaction mixture was cooled to rt and poured into water (200 mL), extracted with ether (2 × 50 mL), and successively washed with brine and water. Organic phase was separated and dried over anhyd $MgSO_4$. The solvent was evaporated *in vacuo* to give the oily residue. Column chromatography (ethyl acetate/MeOH, 9:1) afforded *N*-[1-(3-ethoxy-3-phenylpropyl)]pyrrolidine (**25**); oil; yield 60%; ^{1}H NMR δ 1.17 (t, J = 7.0 Hz, 3H), 1.73−1.90 (m, 5H), 1.99−2.11 (m, 1H), 2.39−2.56 (m, 6H), 3.26−3.43 (m, 2H), 4.31 (dd, J = 7.4 and 6.0 Hz, 1H), 7.23−7.36 (m, 5H); ^{13}C NMR δ 15.2, 23.4, 37.6, 52.8, 54.1, 63.9, 80.4, 126.4 (2 C), 127.2, 128.2 (2 C), 142.9; HRMS calcd for $C_{15}H_{24}NO$ 234.1858 [M^+ + 1], found 234.1857.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **18c**, **18e**, **18f**, **19c**, **24a**, **24b**, **25** (14 pages). This material is contained in 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.

JO9612335