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

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1-(α-Alkoxybenzyl)benzotriazoles undergo reversible ionization in solution to a benzotriazolyl anion (Bt^-) and carboxonium cations $PhCH{:}O^+R$. These cations can attack the β carbon atom of enol ethers to give cation adducts which add the Bt^- to form new α-(benzotriazol-1-yl)alkyl ethers in which the carbon chains are extended by an α-ethoxybenzyl group. Reactions of these adducts with Grignard reagents produce the corresponding 1,3-diethers in high yield. Reduction of the adducts with lithium aluminum hydride gives the corresponding diethers via substitution of the benzotriazolyl moiety with a hydrogen atom or 1-(3-alkoxyalkyl)benzotriazoles via substitution of the α-alkoxy group, depending on the reaction conditions and the nature of the adduct.

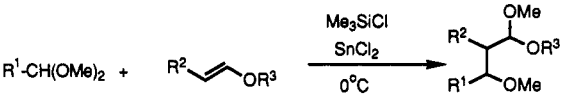
Introduction

Lewis acid catalyzed additions of acetals to vinyl ethers to give 3-alkoxy acetals were discovered by Müller-Cunradi and Pieroh in 1939.[2] Oxocarbenium ions are suggested as intermediates in such additions.[3,4] Important applications in organic synthesis include additions of unsaturated acetals to ethyl vinyl ethers as key steps for the construction of the polyene system in the Isler carotene synthesis.[5,6] A bromine atom at the β-carbon of methyl vinyl ether does not inhibit the reaction and allows the synthesis of 2-bromo-3-methoxy acetals.[7] Catalytic amounts of trimethylsilyl chloride and tin(II) chloride induce the reaction of vinyl ethers (and styrene) with acetals to afford the corresponding adducts in good yields under mild conditions (Scheme I).[8]

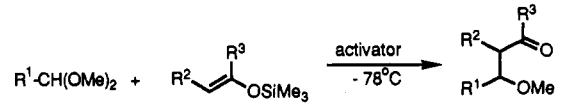
Recently, the more reactive silyl vinyl ethers were used instead of alkyl vinyl ethers; reaction then occurs at −78 °C in the presence of an activator (tin(II) chloride + trimethylsilyl chloride, trityl perchloride or trimethylsilyl triflate) and gives the corresponding β-alkoxycarbonyl compounds in high yields (Scheme II).[9-12] The influence of silyloxy groups on unsaturated systems is so strong that 2,5-bis((trimethylsilyl)oxy)furan reacts readily with acetals, giving the corresponding 3,4-bis(α-alkoxyalkyl)-2,5-furandiones.[13] However, in these reactions the acetal protection of the carbonyl group is lost in the products, which may be undesirable. Also, not all (silyloxy)alkenes are readily available.

We have previously reported that 1-(α-alkoxyalkyl)-benzotriazoles behave analogously to acetals: because the benzotriazolyl substituent is a better leaving group than alkoxy, they are frequently effective in reactions where the corresponding acetals or ketals failed.[14-16] In this paper we report the addition of 1-(α-alkoxybenzyl)benzotriazoles to vinyl ethers.

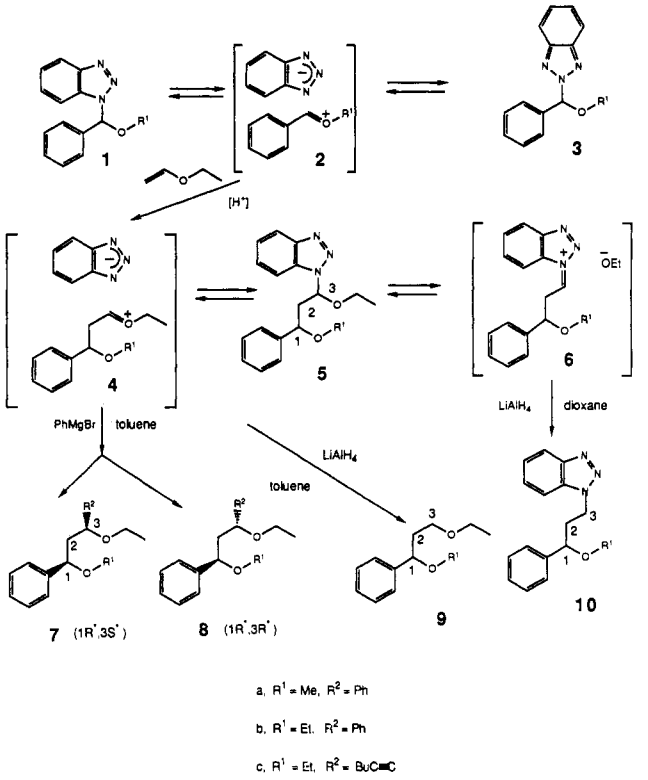
Scheme I



Scheme II



Scheme III



a, R^1 = Me, R^2 = Ph

b, R^1 = Et, R^2 = Ph

c, R^1 = Et, R^2 = BuC≡C

Results and Discussion

Additions to Ethyl Vinyl Ether. 1-(α-Alkoxybenzyl)benzotriazoles (**1a–b**) were readily obtained by

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0022-3263/92/1957-4925$03.00/0

reaction of benzaldehyde acetals with benzotriazole. Compound **1a** was previously prepared in 91% yield by condensation of benzaldehyde with benzotriazole and methanol.[17] In solution, compounds **1a–b** equilibrate rapidly with their benzotriazol-2-yl isomers (**3**); for example, in deuteriochloroform at 22 °C we found the ratio of **1b**:**3b** to be 12:1. We believe that this equilibrium occurs via an intermediate ion pair **2** (Scheme III) by analogy to the extensively studied N-1 to N-2 isomerization of *N*-(α-aminoalkyl)benzotriazoles.[18–21] The easy ionization to **2** depends on the phenyl group in **1**, and consequently aryl aldehyde derivatives **1** are much more sensitive to moisture then the analogous derivatives of aliphatic aldehydes;[17] exposed to air, compounds **1** decompose spontaneously to benzaldehyde, benzotriazole, and the corresponding alcohol. Despite the high purity indicated by NMR, **1b** failed to give correct CHN microanalyses probably because of easy hydrolysis; it was characterized by HRMS.

In the presence of catalytic amounts of *p*-toluenesulfonic acid, α-benzotriazolylbenzyl ethers **1a** and **1b** spontaneously add to ethyl vinyl ether to give mixtures of diastereomeric adducts **5a,b** plus (in small quantities) isomers containing benzotriazole residues substituted at N-2 (analogous to **3**). This method is described in the Experimental Section as a procedure for the preparation of **5a**. In the absence of an acid catalyst, **1** has to be heated with ethyl vinyl ether in a sealed vial, but now the adducts **5** are obtained in higher purity (see procedure given for **5b**). Diastereomers **5a,b**, not separatable by column chromatography, are clearly distinguished in the mixture by NMR spectroscopy, e.g., by two N–CH–O double doublets in the ^{1}H NMR spectrum at δ 6.23 and 6.40 for **5b**, which integrate for a diastereomeric ratio of 5:4. The ^{13}C NMR spectra of the product mixtures allowed full assignment of the resonances of the predominant diastereomers of **5a** and **5b**.

The intermediate carboxonium cations **4** are less stable than the starting cations **2** in which the positive charge is conjugated with the phenyl ring. Hence, cations **4** rapidly add benzotriazolyl anion to produce adducts **5** which show less tendency to ionize than **2**. This stops the reaction and further addition of **4** to ethyl vinyl ether does not occur.

By applying a previously developed procedure,[14] adducts **5** were treated with phenylmagnesium bromide. The reaction proceeded rapidly in boiling toluene (**5a**), whereas use of THF as solvent (**5b**) required refluxing for 16 h. Under both sets of conditions, ionization to **4** evidently occurs, and the subsequent reaction gave mixtures of diastereomers **7** and **8** in an approximate ratio of 1:1, easily separated by column chromatography. The individual diastereomers were fully characterized and their structures elucidated based on the different patterns exhibited by the C-2 methylene protons in ^{1}H NMR–one triplet of two protons at δ 1.96 ($J_{1,2}$ = 7.5 Hz) for the *R**,*S** diastereomer (**7a**) and two double triplets at δ 1.85 ($J_{1,2}$ = 6.6 Hz) and 2.46 ($J_{1,2}$ = 7.8 Hz) for the *R**,*R** form (**8a**), in agreement with the literature data for similar diastereomers.[22]

Reaction of **5b** with 1-hexyn-1-ylmagnesium bromide gave in good yield a mixture of two diastereomers (**7c**, **8c**) in a ratio of 3:1, not separable by column chromatography. The assignments of the C-1, C-2, and C-3 resonances in the ^{13}C NMR spectra were made for both diastereomers in the mixture. The predominant diastereomer appeared to have the C-1 and C-3 resonances shifted to a lower field and the C-2 resonance shifted to a higher field than the corresponding resonances of the minor isomer. This feature seems to be characteristic for diastereomers of all 1,3-diethers: as in both cases where the individual diastereomers were separated, we observed downfield shifts of about 0.9 ppm for the C-1 and C-3 resonances and upfield shifts of about 1.5 ppm of the C-2 resonances for *R**,*R** (**8a** and **8b**) vs *R**,*S** (**7a** and **7b**) diastereomers. This allowed assignment of structure **8c** to the predominant diastereomer obtained from the reaction of **5b** with 1-hexyn-1-ylmagnesium bromide.

A simple homolog of ethers **7a**, **7b**, **8a**, and **8b**, 1,3-dimethoxy-1,3-diphenylpropane was previously prepared by the addition of benzaldehyde dimethyl acetal to styrene[23] or by the reaction of 1,2-diphenylcyclopropane with NBS in methanol.[24] Similar methods should be applicable to the preparation of **7b** or **8b**. However, the preparation of the previously unknown unsymmetrical diethers **7a**, **8a**, **7c**, and **8c** by existing methods would be much more difficult, requiring a complex multistep procedure.

Benzotriazolyl groups suitably activated by heteroatoms are normally easily replaced by hydrogen by reduction with sodium borohydride or lithium aluminum hydride.[25] Although attempts to reduce adducts **5** with sodium borohydride to the corresponding 1-phenyl-1,3-dialkoxypropanes failed, lithium aluminum hydride gave the expected 1,3-diethers **9** when the reduction was carried out in refluxing toluene; it was ineffective in refluxing THF. Surprisingly, $LiAlH_4$ reduction in dioxane as the solvent replaced the α-ethoxy instead of the benzotriazole group by hydrogen to give **10** (some **10** was also isolated from the reduction in toluene). It is evident that adduct **5** can ionize in two different ways. In the expected mode, on which is based the previously elucidated diverse chemistry of 1-(α-alkoxyalkyl)benzotriazoles,[14–16] the benzotriazolyl anion behaves as a leaving group, giving alkoxycarbenium cation **4** (Scheme III). However, the assistance of the C-3 alkoxy group apparently enables the alternative ionization to the iminium cation **6** which is essential in the observed reduction of **5** to **10** in dioxane solution.

Diether **9b** was previously prepared in 35% yield by boron trifluoride catalyzed addition of dimethoxymethane to styrene.[26] However, **9a** was previously unknown, and no simple route to unsymmetrical ethers of this type by existing methodology is evident.

Addition to β-Methoxystyrene. Addition of **1a** and **1b** to β-methoxystyrene smoothly produced adduct **11** as a mixture of four stereoisomers (three asymmetric carbon atoms) with one isomer strongly predominant. Trituration of the product mixture with hexane gave in both cases this stereoisomer (**12a** and **12b**) in a pure crystalline form in 43 and 66% yield, respectively (Scheme IV); the stereochemistry of adduct **12a** was assigned by X-ray crystallography as (1*R**,2*S**,3*R**). The crystallographic structure of **12a** revealed a feature which seems to be characteristic for all 1,3-diethers: the conformation of the molecule with the (C-1)–O and (C-3)–H bonds oriented parallel is energetically favorable. This is in agreement with the reported

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Scheme IV

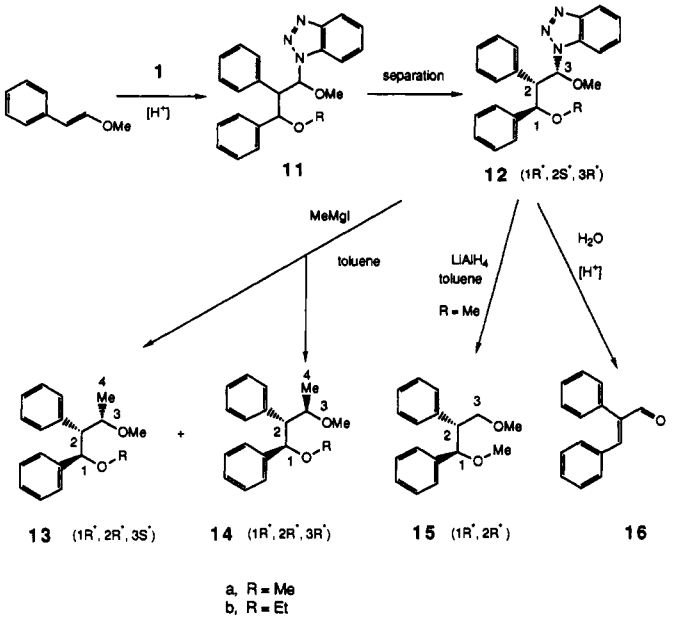
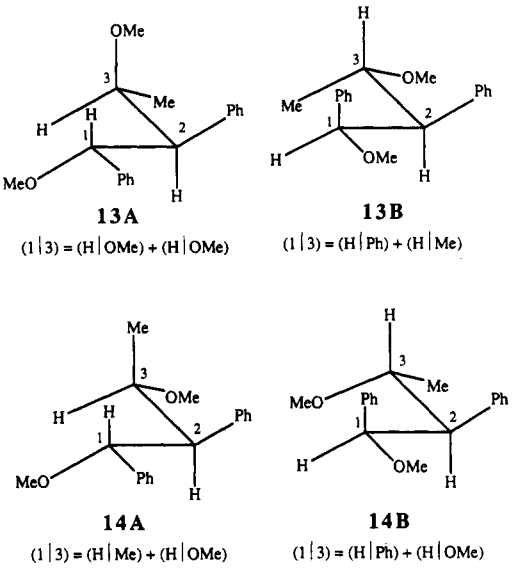
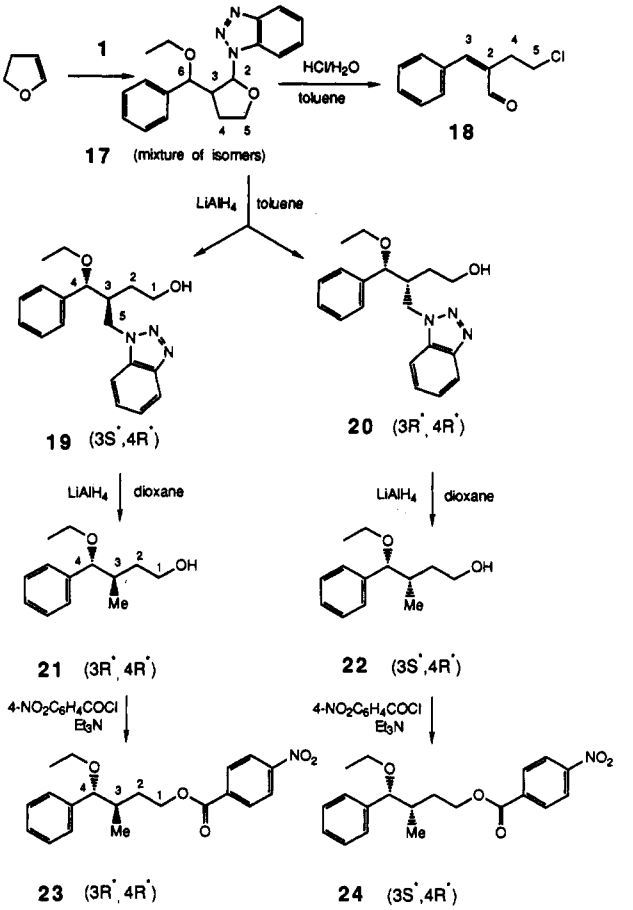


Chart I



Scheme V



data on quantum mechanical calculations of 1,3-substituent parallel interaction energies.[22] The similar ^1H and ^{13}C NMR pattern for adduct **12b** allowed its assignment to the same configuration as **12a**.

Treatment of **12** with methylmagnesium iodide in toluene gave a 1:1 mixture of two diastereomeric 1,3-diethers **13** and **14**; the structures are consistent with transformation proceeding via a planar carboxonium ion which results in the loss of chirality at C-3, but not at C-1 or C-2. Analysis of molecular models revealed, of the possible conformers of **13a**, two (**13A** and **13B**) minimize the repulsive interactions[27] and should have the lowest energy. In other conformers, gauche interactions[27] or cyclohexane axial–axial type interactions between the large substituents cause a significant energy increase. Because the two 1|3 (hydrogen|methoxy) interactions[27] in conformer **13A** are relatively weak in comparison with the (hydrogen|methyl)[28] and (hydrogen|phenyl)[29] repulsion of conformer **13B**, the predominant conformation of the molecule should be 13A. The measured vicinal proton–proton coupling constants of isomers **13** ($J_{1,2}$ = 10.3 Hz, $J_{2,3}$ = 3.1 Hz, for **13a**) accord with conformation **13A**. The two distinguished forms of diastereomers **14** are **14A** and **14B**. In both of them, there is a weak (hydrogen|methoxy) and a stronger (hydrogen|methyl) (**14A**) or (hydrogen|phenyl) (**14B**) 1|3 interaction. There is no significant energy difference between **14A** and **14B**, and they probably exist in an approximately equimolar equilibrium. This equilibrium will be rapid on the NMR time scale, and this is reflected by the similar vicinal coupling constants ($J_{1,2}$ = 6.2 Hz, $J_{2,3}$ = 7.9 Hz, for **14a**).

Reduction of adduct **12a** with lithium aluminum hydride in toluene produced 1,3-diether **15** in which the stereochemistry at C-1 and C-2 remains as in the starting material (**12a**). Hydrolysis of the adduct **12** with 37% hydrochloric acid in refluxing toluene gave (*E*)-α-phenylcinnamaldehyde, **16**.

Addition to 2,3-Dihydrofuran. Addition of **1** to 2,3-dihydrofuran produced the adduct **17** as a mixture of the four isomers, characterized by their ^1H NMR N–CH–O signals at δ 6.27, 6.40, 6.65, and 6.70 in a ratio of 25:7:54:14 (Scheme V). Hydrolysis of the mixture with hydrochloric acid gave an 89% yield of the single isomer, (*Z*)-α-(2-chloroethyl)cinnamaldehyde (**18**). The configuration of the substituents in **18** was elucidated by measurements of the nuclear Overhauser effect (NOE) in analogy to the recent work on substituted 1,3-dienes.[30] Irradiation of the H-4 protons enhanced the H-3 signal, fixing their location on the same side of the double bond. Irradiation of the

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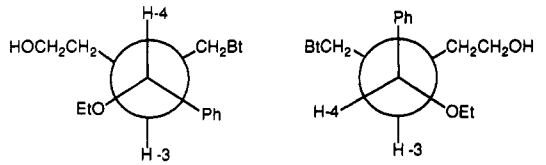
Chart II



19 20

aldehyde proton enhanced only the aromatic (ortho proton) signals.

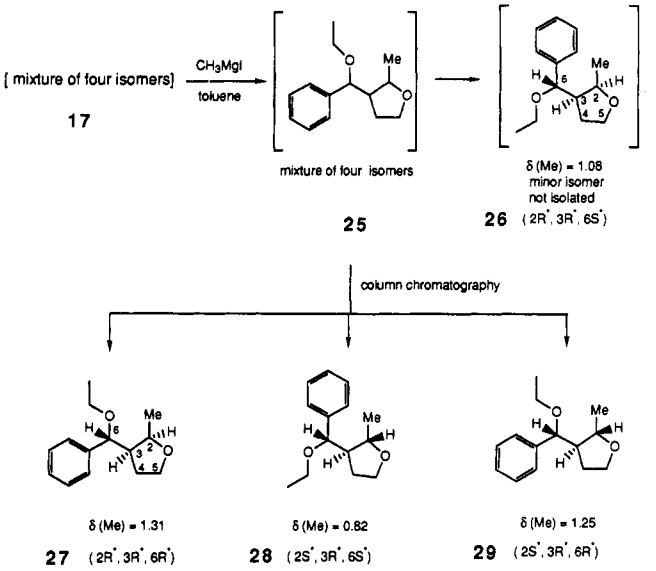
Reduction of the adduct mixture (**17**) with lithium aluminum hydride in refluxing toluene gave the C–O ring cleavage products **19** and **20** which were isolated by column chromatography in yields of 16 and 40%, respectively. The ^1H and ^{13}C NMR spectra allowed assignment of the stereochemistry of diastereomers **19** and **20**. The coupling constants $J_{3,4}$ of 4.8 Hz in **19** and of 6.3 Hz in **20** suggest the dihedral angles between these protons are approximately 40° (or 125°) and 30° (or 135°), respectively. Assuming intramolecular hydrogen bonding between the hydroxy group and the ethoxy oxygen atom (a seven-membered ring) in the molecules of **19** and **20**, one should expect the (H-3)–(C-3)–(C-4)–(H-4) dihedral angles to be 120–180° and 0–60° for the molecules of **19** and **20**, respectively. The hydrogen bonding tends to bring the oxygen atoms together, reducing the vicinal angle between the hydrogens H-3 and H-4 of **19** which reduces the strain caused by the Ph|CH_2Bt repulsion. On the other hand, repulsion between the phenyl and CH_2Bt groups is resisting such deformation of **20** and thus the energy minimum of both interactions corresponds to an angle of 30°.

An unexpected result was obtained from reduction of adduct **17** with lithium aluminum hydride in dioxane. Not only was the tetrahydrofuran ring cleaved, but the benzotriazolyl moiety was replaced by a hydrogen atom to give methyl groups in the diastereomeric ethoxy alcohols **21** and **22**. Careful examination of the NMR spectra of the crude products obtained from reduction of **17** in toluene revealed that alcohols **21** and **22** were also formed as contaminants of alcohols **19** and **20**. To our knowledge, this is the first example of reductive removal of a nonactivated benzotriazol-1-yl group. Attempted separation of diastereomeric mixture of alcohols **21** and **22** by column chromatography failed. The individual diastereomers of alcohols **21** and **22** were obtained by reduction of isomerically pure benzotriazolyl intermediates **19** and **20**, respectively. Complete retention of the configuration was observed. Anchimeric assistance by the ethoxy and/or hydroxy groups in this process is likely. Alcohols **21** and **22** were characterized as their 4-nitrobenzoates **23** and **24**, respectively.

The isomeric mixture **17** was treated with methylmagnesium iodide to give a mixture of four isomeric diethers **25** in a total yield of 70%. They were recognized in their ^1H NMR spectrum by the methyl doublets at δ 0.82, 1.08, 1.25, and 1.31 with the integral ratio of 32:2:18:48 and in the ^{13}C NMR by the C-2 signals at δ 76.8, 75.4, 76.3, and 79.4, respectively. The three more abundant isomers **27–29** were separated by column chromatography. Applying proton–carbon correlation (HETCOR) and selective irradiation of the individual proton resonances enabled assignment of all the proton and carbon resonances in the NMR spectra of diastereomers **27–29**.

Most of the proton resonances of **27–29** revealed simple patterns or were sufficiently simplified by selective decoupling to reveal their coupling constants. Nevertheless, stereochemical assignments were not straightforward. Unlike six-membered rings, vicinal proton coupling constants for five-membered rings reveal little stereochemical information because of the conformational mobility.[31] In addition, literature data on the NMR of individual stereoisomers of tetrahydrofuran derivatives are sparse and do not allow a full comparative study. The nuclear Overhauser effect (NOE) is reported to be useful for assignments of cis or trans configuration of the substituents on the C-2 and C-3 of the tetrahydrofuran ring.[32] Applying this technique, the methyl group doublets of **27**, **28**, and **29** (at δ 1.31, 0.82, and 1.25, respectively) were selectively irradiated. In the case of isomer **27**, irradiation gave a NOE effect on the H-6 resonance that must indicate a cis relationship. In the case of isomer **28**, irradiation of the methyl doublet caused NOE enhancement of the H-3 signal, evidence that the tetrahydrofuran ring substituents have the trans configuration. Irradiation of the methyl group signal of isomer **29** did not produce a clear picture because of overlap of the methyl and H-4 resonances.

Scheme VI



Inspection of molecular models of compounds **26–29** revealed that the bulky substituent at C-3 would tend to assume a conformation with the hydrogen atom H-6 pointed toward the tetrahydrofuran ring due to the repulsive interaction with the methyl group or the hydrogen atom H-2 and the cis hydrogen atom H-4. Because the phenyl group could not be located in the plane with the H-2 and H-4 atoms or with the methyl group, a strong diamagnetic shielding effect should be expected for the neighboring protons in the ^1H NMR.

From the above considerations, the structural assignments of the isomers obtained could be made. Thus, the upfield shift of the H-4 resonances of the cis isomer **27** (δ 1.31 and 1.62) in comparison with *cis*-2,3-dimethyltetrahydrofuran (δ 1.82–2.35)[33] can be easily attributed to structure given in Scheme VI. The upfield shift of the methyl group (δ 0.82) resonance of the trans isomer **28** in comparison with δ 1.00 for *trans*-2,3-dimethyltetrahydrofuran[33] also corresponds well with the structure given (Scheme VI). The upfield shift of the H-4 resonances of the third isolated isomer (**29**, δ 1.32 and 1.48) are explained by the structure assigned. Additional support for structural assignments of the isolated isomers **27–29** was ob-

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tained from comparison of their ^1H and ^{13}C NMR spectra with the data of the similar products bearing morpholine groups instead of the ethoxy, in which series the structural assignments were more conclusive, being based in part on X-ray crystallographic data.[34] The minor (not isolated) isomer **26** was necessarily assigned the fourth possible structure, as presented in Scheme VI.

Conclusion

Addition of 1-(α-alkoxybenzyl)benzotriazoles to enol ethers allows the extention of the molecular carbon skeleton by a benzyl moiety. Substitution of the benzotriazolyl group in the adduct by an alkyl or aryl residue from a Grignard reagent further extends the carbon skeleton and produces 1,3-diether in good yield. Enhancement of differences in physicochemical properties of the adducts by a polar and bulky benzotriazolyl group allows for separation of complex stereoisomeric mixtures. The presented methodology provides a more efficient synthesis of unsymmetrical 1,3-diethers than existing routes and should be capable of considerable generalization.

Experimental Section

General. Melting points were determined on a capillary melting point apparatus and are uncorrected. NMR spectra were taken for solutions in $CDCl_3$ with tetramethylsilane as internal standard for ^1H (300 MHz) and ^{13}C (75 MHz). Solvents for the Grignard reactions (ether, THF, toluene, benzene, dioxane) were dried by reflux with sodium benzophenone under nitrogen and distilled immediately before use. Dry methylene chloride was obtained by storage over molecular sieves. Column chromatography was conducted with silica gel grade 60–200 mesh.

1-(α-Ethoxybenzyl)benzotriazole (1b). A solution of benzotriazole (23.83 g, 200 mmol), benzaldehyde diethyl acetal (36.05 g, 200 mmol) and $4\text{-}MeC_6H_4SO_3H\cdot H_2O$ (95 mg, 0.5 mmol) in dry CH_2Cl_2 (100 mL) was stirred at room temperature overnight, during which the reactants slowly dissolved. Evaporation of the solvent gave an oily product (50.54 g) as a mixture of the benzotriazol-1-yl and benzotriazol-2-yl isomers that slowly crystallized at room temperature to give large prisms. The crude product was used directly for further reactions (NMR purity >95%, the product is sensitive to moisture). An analytical sample of **1b** was prepared by washing the crystals with ether–hexane (1:1) and drying under vacuum at 25 °C: mp 49–50 °C; ^1H NMR δ 1.24 (t, 3 H, Me, J = 7.0 Hz), 3.48 (m, 1 H), 3.75 (m, 1 H), 7.21 (s, 1 H, CH), 7.32 (m, 6 H), 7.44 (m, 2 H), and 8.06 (m, 1 H); ^{13}C NMR δ 14.5 (Me), 65.0 (CH_2), 89.6 (CH), 111.7 (Bt), 119.8 (Bt), 124.2, (Bt), 125.9 (Ph, 2 C), 127.4 (Bt), 128.5 (Ph, 2 C), 129.0 (Ph), 131.1 (Bt), 136.3 (Ph), and 146.9 (Bt); HRMS calcd for $C_{15}H_{15}N_3O$ 253.1215 (M^+), found 253.1212.

3-(Benzotriazol-1-yl)-3-ethoxy-1-methoxy-1-phenylpropane (5a). Ethyl vinyl ether (10.5 mL, 110 mmol) was added dropwise to a solution of **1a** (23.9 g, 100 mmol) and $4\text{-}MeC_6H_4SO_3\cdot H_2O$ (100 mg, 0.5 mmol) in ether (100 mL) stirred at room temperature in a flask equipped with a reflux condenser (exothermic reaction). After 2 h, the reaction mixture was poured into ice-cold water (200 mL). The organic layer was separated, washed with 10% Na_2CO_3 followed by water, and dried over Na_2CO_3. Evaporation of the solvent gave a crude oily product **5a** as a mixture of two diastereomers (ratio 1:1) of purity about 90% (by NMR). An analytical sample of **5a** (a mixture of two diastereomers in a ratio of 56:44) was obtained by column chromatography (toluene). The predominant stereoisomer (in the analytical sample) was characterized by the following: ^{13}C NMR δ 14.7, 43.4 (C-2), 56.6 (Me), 64.6 (Et), 79.5 (C-1), 87.7 (C-3), 110.9 (Bt), 120.1 (Bt), 124.1 (Bt), 126.5 (2 C, Ph), 127.6 (Bt), 128.0 (Ph), 128.6 (2 C, Ph), 131.7 (Bt), 140.9 (Ph), and 146.7 (Bt). Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.79; N, 13.49. Found: C, 69.52; H, 6.79; N, 13.46.

3-(Benzotriazol-1-yl)-1,3-diethoxy-1-phenylpropane (5b). A mixture of ethyl vinyl ether (11.5 mL, 120 mmol) and **1b** (25.33 g, 100 mmol) was stirred in a sealed vial at 120 °C (oil bath) for 40 h. After cooling, the crude reaction mixture was dissolved in toluene, and the solvent and excess vinyl ether were evaporated under reduced pressure to give a mixture of isomers of **5b** (30.59 g, 94%) of purity >90% (by NMR) as an oil. An analytical sample of **5b** (column chromatography, toluene/ethyl acetate, 5:1) was a mixture of two diastereomers in a ratio of 5:4. For the predominant diastereomer: ^{13}C NMR δ 14.6 (CH_3), 15.2 (CH_3), 42.9 (C-2), 64.2 (Et), 64.6 (Et), 77.5 (C-1), 87.8 (C-3), 110.9 (Bt), 120.0 (Bt), 124.3 (Bt), 126.3 (2 C, Ph), 127.5 (Bt), 127.9 (Ph), 128.5 (2 C, Ph), 131.6 (Bt), 141.7 (Ph), and 146.5 (Bt). Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.41; H, 7.00; N, 12.87.

(1*R,3*S**)- and (1*R**,3*R**)-3-Ethoxy-1-methoxy-1,3-diphenylpropanes (7a and 8a).** A solution of **5a** (14.7 g, 45 mmol) in toluene (100 mL) in a flask equipped with a thermometer, a distillation condenser, and a dropping funnel was heated to 110 °C. An ethereal solution of the Grignard reagent prepared from bromobenzene (10.0 mL, 100 mmol) and Mg (2.67 g, 110 mmol) activated by I_2 (0.50 g, 2 mmol) was added dropwise at such a rate that the ether distilled off and the temperature was kept above 100 °C. After the addition was complete, the mixture was stirred at reflux for an additional 1 h. After cooling to room temperature, the product mixture was poured into ice–water (200 mL), acidified with acetic acid to pH 5, and extracted with ether (200 mL). The ethereal solution was washed with water, 10% Na_2CO_3, and water again. Drying over $MgSO_4$, evaporation of the solvent, and distillation of the residue (132 °C (0.3 mm)) gave a mixture of **7a** and **8a** as a light brown oil (9.83 g, 80%, ratio of **7a**:**8a** = 1:1, by NMR). A sample of the crude product (2.00 g) subjected to column chromatography (hexane) gave **7a**, as a second fraction (the first fraction was biphenyl): oil, 0.62 g; ^1H NMR δ 1.19 (t, J = 7.0 Hz, 3 H), 1.96 (t, J = 7.5 Hz, 2 H, H-2), 3.26 (s, 3 H), 3.43 (m, 2 H), 4.44 (t, J = 7.5 Hz, 1 H, H-1), 4.55 (t, J = 7.5 Hz, 1 H, H-3), and 7.30 (m, 10 H); ^{13}C NMR δ 15.3 (Et), 47.7 (C-2), 56.8 (Me), 64.3 (Et), 77.9 (C-1), 80.1 (C-3), 126.5 (2 C), 126.6 (2 C), 127.3, 127.4, 128.3 (4 C), 142.4, and 143.2. Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.06; H, 8.17. Isomer **8a** was obtained as the third fraction (0.79 g): ^1H NMR δ 1.15 (t, J = 7.0 Hz, 3 H, Et), 1.85 (dt, J = 13.6 and 6.6 Hz, 1 H, H-2), 2.44 (dt, J = 13.6 and 7.8 Hz, 1 H, H-2), 3.14 (s, 3 H, Me), 3.20 (q, J = 7.0 Hz, 1 H, Et), 3.28 (q, J = 7.0 Hz, 1 H, Et), 4.07 (dd, J = 7.0 and 7.4 Hz, 1 H, H-1), 4.14 (dd, J = 6.7 and 7.6 Hz, 1 H, H-3), and 7.27 (m, 10 H, Ph); ^{13}C NMR δ 15.3 (Et), 46.2 (C-2), 56.1 (Me), 63.7 (Et), 78.9 (C-1), 80.8 (C-3), 126.6, 126.8, 127.4, 127.5, 127.7, 127.8, 128.2 (2 C), 128.3 (2 C), 141.6, and 142.3. Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.97; H, 8.16.

(1*R,3*S**)- and (1*R**,3*R**)-1,3-Diethoxy-1,3-diphenylpropanes (7b and 8b).** An ether solution of the Grignard reagent prepared from bromobenzene (20.1 mL, 200 mmol) and Mg (4.86 g, 200 mmol) activated by I_2 (1.25 g, 5 mmol) was added to a stirred solution of **5** (16.25 g, 50 mmol) in dry THF (100 mL). An additional portion of THF (100 mL) was added, and the ether was distilled off. When the distillation temperature reached 60 °C, the distillation condenser was replaced by a reflux condenser and reflux was continued for 16 h. Workup as above gave a product mixture which was subjected to column chromatography (hexane) to give as the first fraction isomer **7b** (5.62 g, 40%): ^1H NMR δ 1.19 (t, J = 7.1 Hz, 6 H, Et), 1.94 (dd, J = 7.6 and 6.0 Hz, 2 H, H-2), 3.33–3.50 (m, 4 H, Et), 4.59 (dd, J = 7.6 and 6.0 Hz, 2 H, H-1 and H-3), and 7.15–7.40 (10 H, 2 Ph); ^{13}C NMR δ 15.3 (2 C, Et), 47.8 (C-2), 64.2 (2 C, Et), 77.9 (2 C, C-1, C-3), 126.4 (4 C), 127.2 (2 C), 128.2 (4 C), and 143.2 (2 C). Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.33; H, 8.50. The second fraction was isomer **8b** (7.26 g, 51%): ^1H NMR δ 1.16 (t, J = 7.1 Hz, 6 H, 2 Et), 1.85 (dt, J = 13.7 and 6.8 Hz, 1 H, H-2), 2.44 (dt, J = 13.7 and 7.8 Hz, 1 H, H-2), 3.23 (q, J = 7.1 Hz, 2 H, Et), 3.28 (q, J = 7.1 Hz, 2 H, Et), 4.16 (dd, J = 7.8 and 6.8 Hz, 2 H, H-1 and H-3), and 7.30 (m, 10 H, 2 Ph); ^{13}C NMR δ 15.4 (2 C, Et), 46.5 (C-2), 63.9 (2 C, Et), 79.1 (2 C, C-1, C-3), 126.8 (4 C), 127.5 (2 C), 128.3 (4 C), and 142.4 (2 C). Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.30; H, 8.53.

1,3-Diethoxy-1,3-diphenyl-4-nonyne (7c and 8c). A mixture of the Grignard reagent prepared from 1-hexyne (11.4 mL, 100 mmol), bromoethane (7.5 mL, 100 mmol), magnesium turnings (2.67 g, 110 mmol), and iodine (0.50 g) in dry ether (50 mL) was

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added to a stirred refluxing toluene solution of **5b** (10.5 g, 32 mmol). The reaction mixture was heated at reflux for 30 min and worked up as above to give 10.9 g of crude oily product (80%, NMR). An analytical sample (a mixture of two diastereomers in the ratio of 3:1) was obtained by column chromatography (hexane). The predominant diastereomer was characterized by the following: ^{1}H NMR δ 4.04 (tt, J = 2.0 and 7.1 Hz, H-3), 4.49 (dd, J = 5.6 and 8.5 Hz, H-1); ^{13}C NMR δ 13.5, 15.2, 15.3, 18.4, 21.9, 30.8, 44.5 (C-2), 63.9 (Et), 64.1 (Et), 67.2 (C-3), 78.8 (C-1), 79.1, 86.2, 126.6 (2 C), 127.4, 128.3 (2 C), and 142.3. Some NMR signals of the minor diastereomer: ^{1}H NMR δ 4.23 (tt, J = 2.0 and 6.6 Hz, H-3), 4.48 (dd, overlap with the main isomer resonance, H-1); ^{13}C NMR δ 45.3 (C-2), 65.9 (C-3), 77.6 (C-1), 85.6, 142.8. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.19; H, 9.77.

3-Ethoxy-1-methoxy-1-phenylpropane (9a). $LiAlH_4$ (1.52 g, 40 mmol) was added to a stirred solution of **5a** (9.3 g, 30 mmol) in dry toluene (100 mL) and the reaction mixture was stirred and refluxed under nitrogen for 6 h. After the mixture was cooled to room temperature, MeOH (10 mL) was added dropwise to decompose the excess $LiAlH_4$. The mixture was poured into ice-cold 40% KOH (150 mL) and extracted with ether (3 × 100 mL). The combined extracts were dried (Na_2CO_3) and evaporated. Column chromatography (toluene) of the residue gave pure **9a** as the first fraction: colorless oil (1.75 g, 30%); ^{1}H NMR δ 1.20 (t, J = 7.0 Hz, 3 H), 1.87 (m, 1 H, H-2), 2.07 (m, 1 H, H-2), 3.21 (s, 3 H), 3.44 (m, 4 H, Et and H-3), 4.29 (dd, J = 6.0 and 7.8 Hz, 1 H, H-1), and 7.30 (m, 5 H); ^{13}C NMR δ 15.2, 38.2 (C-2), 56.6, 66.1, 66.9 (C-3), 80.8 (C-1), 126.7 (2 C), 127.5, 128.4 (2 C), and 142.0. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.25; H, 9.36.

1,3-Diethoxy-1-phenylpropane (9b). Adduct **5b** (16.25 g, 50 mmol) was reduced in a manner analogous to **5a**. Fractional vacuum distillation of the crude product gave **9b** (4.52 g, 43%) as a colorless liquid: bp 87–89 °C (1.1 mmHg) [lit.[26] bp 167–168 °C (17 mm)]; ^{1}H NMR δ 1.16 (t, J = 7.0 Hz, 3 H), 1.20 (t, J = 7.0 Hz, 3 H), 1.87 (m, 1 H), 2.05 (m, 1 H), 3.45 (m, 6 H), 4.41 (dd, J = 5.7 and 8.1 Hz, 1 H, H-1), and 7.31 (m, 5 H); ^{13}C NMR δ 15.16, 15.24, 38.4, 64.0, 66.0, 66.9, 78.7 (Ph-CH-O), 126.5 (2 C), 127.3, 128.2 (2 C), and 142.8. Column chromatography (toluene) of the distillation residue gave **10b** (2.18 g, 15%): ^{1}H NMR δ 1.17 (t, J = 7.0 Hz, 3 H, Et), 2.38 (m, 2 H, H-2), 3.20 (dq, J = 9.1 and 6.9 Hz, 1 H, Et), 3.35 (dt, J = 8.8 and 7.4 Hz, 1 H, Et), 4.12 (dd, J = 5.7 and 7.4 Hz, 1 H, H-1), 4.68 (dt, J = 14.1 and 6.1 Hz, 1 H), 4.87 (dt, J = 13.9 and 7.5 Hz, 1 H), 7.30 (m, 6 H), 7.50 (m, 2 H), and 8.05 (ddd, 1 H, J = 0.9, 1.1, and 8.1 Hz); ^{13}C NMR δ 15.0 (Et), 37.9, 44.4, 63.9 (C-3), 78.2 (C-1), 109.2 (Bt), 119.6 (Bt), 123.5 (Bt), 126.1 (2 C, Ph), 126.9 (Bt), 127.5 (Ph), 128.2 (2 C, Ph), 132.9 (Bt), 141.4 (Ph), and 145.6 (Bt). Anal. Calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.42; H, 6.89; N, 14.70.

1-(3-Ethoxy-3-phenylpropyl)benzotriazole (10b). Reduction of **5b** (12.80 g, 40 mmol) with $LiAlH_4$ (1.52 g, 40 mmol) in refluxing dioxane (100 mL) for 16 h gave **10b** (8.30 g, 74%) as an oil of purity >90% (NMR), identical with the side product obtained above from the toluene reduction.

(1*R,2*S**,3*R**)-3-(Benzotriazol-1-yl)-1,2-diphenyl-1,3-dimethoxypropane (12a).** A mixture of **1a** (4.78 g, 20 mmol), and β-methoxystyrene (2.68 g, 20 mmol) with a catalytic amount of 4-$MeC_6H_4SO_3H{\cdot}H_2O$ was heated in an oil bath at 60 °C for 20 min and then kept for 1 week at room temperature. Trituration of the obtained glassy product with n-hexane, cooling overnight in a freezer, separation by filtration, and drying in a vacuum oven gave **12a** as a crystalline product (3.21 g, 43%). Recrystallization from toluene gave an analytical sample: mp 134–135 °C;^{1}H NMR δ 3.22 (s, 3 H), 3.39 (s, 3 H), 3.59 (dd, J = 9.6 and 4.4 Hz, 1 H, H-2), 4.73 (d, J = 9.8 Hz, 1 H, H-1), 6.79 (d, J = 8.5 Hz, 1 H, Bt), 6.87 (d, J = 4.4 Hz, 1 H, H-3), 6.88–7.25 (m, 12 H, Bt and Ph), and 7.91 (d, J = 8.3 Hz, 1 H, Bt); ^{13}C NMR δ 56.7 (Me), 57.7 (Me), 58.4 (C-2), 83.6 (C-1), 93.3 (C-3), 111.7 (Bt), 119.1 (Bt), 123.6 (Bt), 126.7 (Ph), 127.2 (Bt), 127.6 (3 C, Ph and Bt), 127.8 (2 C, Ph), 127.9 (2 C, Ph), 130.2 (2 C, Ph), 132.3 (Bt), 135.4 (Ph), 139.0 (Ph), and 145.8 (Bt). Anal. Calcd for $C_{23}H_{23}N_3O_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 73.86; H, 6.12; N, 11.14.

(1*R,2*S**,3*R**)-3-(Benzotriazol-1-yl)-1,2-diphenyl-1-ethoxy-3-methoxypropane (12b).** A similar procedure to the above gave **12b** in 66% yield as white crystals (5.16 g, 66%): mp 125–128 °C; ^{1}H NMR δ 1.16 (t, J = 7.0 Hz, 3 H, Et), 3.33 (m, 2 H, Et), 3.39 (s, 3 H, Me), 3.58 (dd, J = 9.8 and 4.4 Hz, 1 H, H-2), 4.86 (d, J = 9.8 Hz, 1 H, H-1), 6.80 (d, J = 8.5 Hz, 1 H, Bt), 6.88 (m, 2 H, Ph), 6.91 (d, J = 4.4 Hz, H-3), 6.95 (m, 2 H, Ph), 7.08 (m, 8 H, Ph and Bt), and 7.92 (d, J = 8.3 Hz, 1 H, Bt); ^{13}C NMR δ 15.2 (Et), 57.7 (Me), 58.5 (C-2), 64.2 (Et), 81.7 (C-1), 93.5 (C-3), 111.7 (Bt), 119.1 (Bt), 123.5 (Bt), 126.6 (Bt), 127.2 (Ph), 127.4 (Ph), 127.5 (2 C, Ph), 127.76 (2 C, Ph), 127.82 (2 C, Ph), 130.3 (2 C, Ph), 132.4 (Bt), 135.6 (Ph), 139.8 (Ph), and 146.0 (Bt). Anal. Calcd for $C_{24}H_{25}N_3O_2$: C, 74.39; H, 6.50; N, 10.84. Found: C, 74.23; H, 6.56; N, 10.96.

(1*R,2*R**,3*S**)- and (1*R**,2*R**,3*R**)-1,2-Diphenyl-1,3-dimethoxybutanes (13a and 14a).** Following the procedure given above, **12a** (1.12 g, 3 mmol) in dry toluene (20 mL) was treated with CH_3MgI (15 mmol) to afford a mixture of isomers **13a** and **14a** (0.98 g) as an oily product of purity above 90% and a molar ratio of 3:4 (NMR). Column chromatography of the crude product (toluene) gave as the first fraction pure isomer **13a** (0.32 g, 39%): an oil; ^{1}H NMR δ 0.93 (d, J = 6.4 Hz, 3 H, H-4), 2.78 (dd, J = 3.2 and 10.4 Hz, 1 H), 3.25 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 4.20 (dq, J = 3.1 and 6.4 Hz, 1 H, H-3), 4.57 (d, J = 10.3 Hz, 1 H, H-1), and 7.03 (m, 10 H); ^{13}C NMR δ 17.1 (C-1), 56.5 (OMe), 57.3 (OMe), 59.3 (C-2), 75.3 (C-3), 84.2 (C-1), 126.1, 127.0, 127.4 (2 C), 127.58 (2 C), 127.63 (2 C), 130.5 (2 C), 138.1, and 140.9. Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.78; H, 8.23. The second fraction appeared to be a mixture of two isomers in a ratio of 1:1 (0.25 g) and the third fraction was isomer **14a** (0.38 g, 47%): oil; ^{1}H NMR δ 1.01 (d, J = 6.1 Hz, 3 H, H-4), 3.22 (s, 3 H, OMe), 3.29 (dd, J = 6.2 and 7.9 Hz, 1 H, H-2), 3.40 (s, 3 H, OMe), 3.66 (dq, J = 7.9 and 6.2 Hz, 1 H, H-3), 4.76 (d, J = 6.2 Hz, 1 H, H-1), 6.82 (m, 2 H, Ph), 7.03 (m, 2 H, Ph), 7.12 (m, 3 H, Ph), and 7.19 (m, 3 H, Ph); ^{13}C NMR δ 16.4 (C-4), 55.7 (Me), 56.7 (Me), 57.0 (C-2), 76.4 (C-3), 83.5 (C-1), 126.3, 127.2, 127.3 (2 C), 127.5 (2 C), 128.0 (2 C), 130.2 (2 C), 138.2, and 139.4. Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.75; H, 8.21.

(1*R,2*R**,3*S**)- and (1*R**,2*R**,3*R**)-1,2-Diphenyl-1-ethoxy-3-methoxybutanes (13b and 14b).** The same procedure as above, starting from **11b** (3.87 g, 10 mmol) in dry toluene (50 mL) and CH_3MgI (30 mmol), gave after a 3-h reflux an oily product (2.96 g, 94%) of purity >90% (a mixture of isomers **13b** and **14b** in a molar ratio of 1:1). Column chromatography of 2.10 g of the crude product (toluene) gave as the first fraction pure isomer **13b** (0.72 g, 25%) as an oil: ^{1}H NMR δ 0.93 (d, J = 6.5 Hz, 3 H, Me), 1.21 (d, J = 7.0 Hz, 3 H, Et), 2.77 (dd, J = 10.4 and 3.0 Hz, 1 H, H-2), 3.38 (m, 2 H, Et), 3.46 (s, 3 H, OMe), 4.24 (dq, J = 6.5 and 3.1 Hz, 1 H, H-3), 4.69 (d, J = 10.5 Hz, 1 H, H-1), and 7.06 (m, 10 H, 2 Ph); ^{13}C NMR δ 15.3 (Et), 17.0 (C-4), 57.3 (OMe), 59.32 (C-2), 64.1 (OEt), 75.3 (C-3), 82.3 (C-1), 126.1, 126.8, 127.4 (2 C), 127.5 (2 C), 127.6 (2 C), 130.5 (2 C), 138.1, and 141.7. Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.17; H, 8.54. The second fraction was isomer **14b** (0.74 g, 26%): oil; ^{1}H NMR δ 1.05 (d, J = 6.2 Hz, 3 H, Me), 1.14 (t, J = 7.0 Hz, 3 H, Et), 3.35 (m, 3 H, Et and H-2), 3.37 (s, 3 H, OMe), 3.73 (dq, J = 7.4 and 6.2 Hz, 1 H, H-3), 4.83 (d, J = 6.5 Hz, 1 H, H-1), 6.87 (m, 2 H, Ph), and 7.00–7.20 (m, 8 H, Ph); ^{13}C NMR δ 15.3 (Et), 16.3 (C-4), 55.7 (Me), 56.8 (C-2), 64.0 (Et), 76.5 (C-3), 81.5 (C-1), 126.2, 127.0, 127.2 (2 C), 127.4 (2 C), 127.7 (2 C), 130.2 (2 C), 138.4, and 140.4. Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.03; H, 8.40.

(1*R,2*R**)-1,3-Dimethoxy-1,2-diphenylpropane (15).** By applying a procedure similar to the preparation of **9a**, adduct **11** was reduced with $LiAlH_4$ in toluene to give **15** (61% yield after column chromatography with toluene as an eluent) as a colorless oil: ^{1}H NMR δ 3.19 (s, 3 H, Me), 3.23 (m, 1 H, H-2), 3.28 (s, 3 H, Me), 3.79 (dd, J = 5.1 and 9.3 Hz, 1 H, H-3), 3.83 (dd, J = 7.5 and 9.5 Hz, 1 H, H-3), 4.38 (d, J = 7.6 Hz, 1 H, H-1), 7.02 (m, 4 H, Ph), and 7.15 (m, 6 H, Ph); ^{13}C NMR δ 52.7 (C-2), 56.9 (Me), 58.9 (Me), 73.2 (C-3), 85.2 (C-1), 126.4, 127.3, 127.4, (2 C), 127.77 (2 C), 127.81 (2 C), 128.9 (2 C), 139.7, and 140.0. Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.73; H, 7.90.

(*E*)-α-Phenylcinnamaldehyde (16). A solution of **12a** (0.37 g, 1 mmol) in a mixture of toluene (10 mL), and 37% HCl (0.5 mL) was stirred under reflux for 30 min. The reaction mixture was poured into ice–water and neutralized with 10% Na_2CO_3. The organic layer was separated, washed with 10% Na_2CO_3 and water, and dried ($MgSO_4$). Evaporation of the solvent gave an oil (0.23

g) that soon crystallized. The crystals were washed with ether and dried to afford pure **16** (0.19 g, 88%): mp 94–95 °C (lit.[35] mp 96–97 °C); ^{1}H NMR δ 7.20 (m, 8 H), 7.39 (m, 3 H), and 9.77 (s, 1 H); ^{13}C NMR δ 128.3, 128.5 (2 C), 128.9 (2 C), 129.3 (2 C), 130.2, 130.7 (2 C), 133.3, 134.0, 141.8, 150.1, and 193.9.

2-(Benzotriazol-1-yl)-3-(α-ethoxybenzyl)tetrahydrofuran (17). A mixture of **1** (25.33 g, 100 mmol) and 2,3-dihydrofuran (7.6 mL, 100 mmol) was heated in a sealed vial at 120 °C for 40 h to give an oily mixture of four stereoisomers of **17**. The ^{1}H NMR of this mixture exhibited the H-2 doublets at δ 6.27 (J = 4.6 Hz), 6.40 (J = 4.3 Hz), 6.65 (J = 2.5 Hz), and 6.70 (J = 6.0 Hz) in a ratio of 25:7:54:14. Column chromatography (toluene/ethyl acetate, 5:1) of crude **17** gave an analytical sample (as a mixture of 4 stereoisomers). The predominant isomer was fully characterized by ^{13}C NMR: δ 14.9 (Et), 27.8 (C-4), 51.1 (C-3), 64.0 (Et), 69.0 (C-5), 82.9 (C-6), 89.6 (C-2), 109.9 (Bt), 119.5 (Bt), 123.8 (Bt), 126.6 (Ph), 127.1 (Bt), 127.2 (2 C, Ph), 128.3 (2 C, Ph), 132.7 (Bt), 139.6 (Ph), and 145.8 (Bt); HRMS calcd for $C_{19}H_{22}N_3O_2$ (M^+ + 1) 324.1712, found 324.1712.

(*Z*)-α-(2-Chloroethyl)cinnamaldehyde (18). Similarly to preparation of **16**, a mixture of isomers **17** was hydrolyzed with 37% HCl (3.5 h) to give compound **18** in 80% yield. An analytical sample was purified by column chromatography (toluene) to give **18** as an oil: ^{1}H NMR δ 3.01 (t, J = 7.5 Hz, 2 H, CH_2), 3.66 (t, J = 7.2 Hz, 2 H, CH_2Cl), 7.35–7.55 (m, 6 H), and 9.53 (s, 1 H, CH=O); ^{13}C NMR δ 28.1 (C-4), 41.5 (C-5), 128.7 (2 C, Ph), 129.3 (2 C, Ph), 129.8 (Ph), 133.9 (Ph), 138.1 (C-2), 152.1 (C-3), and 194.6 (C=O). Anal. Calcd for $C_{11}H_{11}ClO$: C, 67.87; H, 5.70. Found: C, 67.52; H, 5.71.

(3*S,4*R**)-3-((Benzotriazol-1-yl)methyl)-4-ethoxy-4-phenylbutanol (19) and (3*R**,4*R**)-3-((Benzotriazol-1-yl)-methyl)-4-ethoxy-4-phenylbutanol (20).** A suspension of $LiAlH_4$ (0.57 g, 15 mmol) in a solution of **17** (3.23 g, 10 mmol) in toluene (50 mL) was stirred and refluxed under nitrogen for 5 h. Workup (as for **9a**) and column chromatography of the residue ($CHCl_3$) gave a nonidentified mixture (0.81 g) as the first fraction and **19** (0.54 g,16%) as the second fraction: colorless oil; ^{1}H NMR δ 1.22 (t, J = 7.0 Hz, 3 H, Et), 1.71 (m, 2 H, H-2), 2.64 (m, 1 H, H-3), 3.23 (dq, J = 9.1 Hz and 7.0 Hz, 1 H, Et), 3.40 (dq, J = 9.1 and 7.0 Hz, 1 H, Et), 3.55 (m, 1 H, H-1), 3.59 (m, 1 H, H-1), 4.15 (d, J = 4.8 Hz, 1 H, H-4), 4.59 (dd, J = 6.7 and 13.9 Hz, 1 H, H-5), 4.74 (dd, J = 8.0 and 14.0 Hz, 1 H, H-5), 7.30 (m, 8 H), and 8.03 (d, J = 8.1 Hz, 1 H, Bt); ^{13}C NMR δ 15.2 (Et), 30.0 (C-2), 43.5 (C-3), 49.1 (C-5), 60.5 (C-1), 64.9 (Et), 80.1 (C-4), 109.5 (Bt), 119.9 (Bt), 124.0 (Bt), 126.8 (2 C, Ph), 127.3 (Bt), 127.7 (Ph), 128.5 (2 C, Ph), 133.3 (Bt), 139.9 (Ph), and 145.8 (Bt). Acetate: HRMS calcd for $C_{21}H_{25}N_3O_3$ (M^+) 367.1895, found 367.1884. The third fraction gave diastereomer **20** (1.32 g, 40%) as a colorless oil: ^{1}H NMR δ 1.17 (t, J = 7.1 Hz, 3 H, Et), 1.50 (dddd, $J_{2,3}$ = 6.8 Hz, $J_{3,3}$ = 14.4 Hz, 1 H, H-2), 1.61 (dddd, $J_{2,3}$ = 6.1 Hz, $J_{3,3}$ = 14.3 Hz, 1 H, H-2), 2.60 (m, 1 H, H-3), 2.68 (bs, 1 H, OH), 3.25 (dq, J = 9.6 and 7.1 Hz, 1 H, Et), 3.39 (dq, J = 9.6 and 7.1 Hz, 1 H, Et), 3.60 (m, 2 H, H-1), 4.27 (d, $J_{1,2}$ = 6.3 Hz, 1 H, H-4), 4.71 (dd, $J_{2,5}$ = 4.4 Hz, $J_{5,5}$ = 14.4 Hz, 1 H, H-5), 4.80 (dd, $J_{2,5}$ = 7.3 Hz, $J_{5,5}$ = 14.4 Hz, 1 H, H-5), 7.32 (m, 8 H, Ph and Bt), and 7.97 (d, J = 8.2 Hz, 1 H, Bt); ^{13}C NMR δ 15.1 (Et), 31.3 (C-2), 43.0 (C-3), 47.6 (C-5), 60.1 (C-1), 64.4 (Et), 80.6 (C-4), 109.6 (Bt), 119.6 (Bt), 123.7 (Bt), 127.00 (Ph), 127.04 (2 C, Ph), 127.7 (Bt), 128.4 (2 C, Ph), 133.2 (Bt), 139.9 (Ph), and 145.3 (Bt). Acetate: HRMS calcd for $C_{21}H_{25}N_3O_3$ (M^+) 367.1895, found: 367.1892.

(3*R*,4*R)-4-Ethoxy-3-methyl-4-phenylbutyl 4-Nitrobenzoate (23).** A solution of **19** (0.56 g, 1.7 mmol) and $LiAlH_4$ (0.19 g, 5 mmol) in dry dioxane (5 mL) was heated at reflux under nitrogen for 5 h. The excess of $LiAlH_4$ was decomposed by addition of methanol (1 mL), and the reaction mixture was poured into 10% NaOH (20 mL) and extracted with ether (3 × 20 mL). The solution was dried over Na_2SO_4 and the solvent evaporated. The residue (compound **21**) dissolved in dioxane (2 mL) was treated with 4-nitrobenzoyl chloride (0.31 g, 1.7 mmol) and triethylamine (0.24 mL, 1.7 mmol) and stirred under nitrogen at room temperature for 1 h. The reaction mixture was poured into ice–water (10 mL) and extracted with chloroform (2 × 10 mL). The chloroform solution was dried (Na_2CO_3) and evaporated and the residue subjected to column chromatography (toluene) to give **23** (0.26 g, 43%): sticky oil; ^{1}H NMR δ 0.84 (d, J = 6.8 Hz, 3 H, Me), 1.16 (t, J = 7.0 Hz, 3 H, Et), 1.64 (m, 1 H, H-2), 1.97 (m, 1 H, H-3), 2.20 (m, 1 H, H-2), 3.29 (m, 1 H, Et), 3.36 (m, 1 H, Et), 3.99 (d, J = 7.5 Hz, 1 H, H-4), 4.44 (m, 2 H, H-1), 7.28 (m, 5 H, Ph), 8.17 (d, J = 8.4 Hz, 2 H, 4-$NO_2C_6H_4$), 8.28 (d, J = 8.4 Hz, 2 H, 4-$NO_2C_6H_4$); ^{13}C NMR δ 15.3 (Et), 16.5 (Me), 31.7 (C-2), 37.1 (C-3), 64.4 (Et), 64.8 (C-1), 86.5 (C-4), 123.5 (2 C, 4-$NO_2C_6H_4$), 127.3 (2 C, Ph), 127.5 (Ph), 128.2 (2 C, Ph), 130.7 (2 C, 4-$NO_2C_6H_4$), 135.9 (4-$NO_2C_6H_4$), 141.3 (Ph), 150.5 (4-$NO_2C_6H_4$), and 164.7 (C=O). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.30; H, 6.58, C, 3.82.

(3*S,4*R**)-4-Ethoxy-3-methyl-4-phenylbutyl 4-Nitrobenzoate (24).** Via a procedure similar to the above, ester **24** was obtained in 55%: an oil; ^{1}H NMR δ 1.02 (d, J = 6.8 Hz, 3 H, Me), 1.18 (t, J = 7.0 Hz, 3 H, Et), 1.55 (m, 1 H, H-2), 1.86 (m, 1 H, H-2), 1.99 (m, 1 H, H-3), 3.30 (m, 1 H, Et), 3.40 (m, 1 H, Et), 4.10 (d, J = 5.9 Hz, 1 H, H-4), 4.38 (m, 2 H, H-1), 7.29 (m, 5 H, Ph), 8.16 (d, J = 8.6 Hz, 2 H, 4-$NO_2C_6H_4$), and 8.27 (d, J = 8.6 Hz, 2 H, 4-$NO_2C_6H_4$); ^{13}C NMR δ 15.26 (Me), 15.30 (Et), 31.8 (C-2), 36.9 (C-3), 64.4 (C-1), 64.5 (Et), 85.5 (C-4), 123.5 (2 C, 4-$NO_2C_6H_4$), 127.2 (2 C, Ph), 127.4 (Ph), 128.2 (2 C, Ph), 130.6 (2 C, 4-$NO_2C_6H_4$), 135.8 (4-$NO_2C_6H_4$), 141.1 (Ph), 150.5 (4-$NO_2C_6H_4$), and 164.6 (C=O). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.59; H, 6.53; N, 3.89.

3-(α-Ethoxybenzyl)-2-methyltetrahydrofurans (25). Reaction of **17** (3.23 g, 10 mmol) with CH_3MgI (30 mmol) in toluene (50 mL) in a manner similar to preparation of **7a** afforded an oily product **25** (1.75 g, 70%) as a mixture of four isomers in approximate ratio of 32:2:18:48 (by integration of the methyl group doublets at δ 0.83, 1.08, 1.25, and 1.31). The first fraction from column chromatography (toluene/ethyl acetate, 4:1) gave isomer **27** (0.82 g, 37%): oil; ^{1}H NMR δ 1.13 (t, J = 7.0 Hz, 3 H, Et), 1.31 (d, J = 6.1 Hz, 3 H, Me), 1.50 (ddt, $J_{4,5}$ = 7.1 Hz, $J_{3,4}$ = $J_{4,5'}$ = 7.6 Hz, $J_{4,4'}$ = 12.7 Hz, 1 H, H-4), 1.62 (dddd, $J_{3,4'}$ = 8.6 Hz, $J_{4,4'}$ = 12.7 Hz, $J_{4'5}$ = 5.8 Hz, $J_{4'5'}$ = 7.1 Hz, 1 H, H-4'), 2.06 (dddd, $J_{3,6}$ = 9.0 Hz, $J_{2,3}$ = 6.1 Hz, $J_{3,4}$ = 7.6 Hz, $J_{3,4'}$ = 8.6 Hz, 1 H, H-3), 3.22 (dq, J = 10.0 and 7.0 Hz, 1 H, Et), 3.31 (dq, J = 10.0 and 7.0 Hz, 1 H, Et), 3.74 (m, 2 H, H-5), 3.98 (dq, J = 6.6 and 6.1 Hz, 1 H, H-2), 4.04 (d, J = 9.0 Hz, 1 H, H-6), and 7.30 (m, 5 H); ^{13}C NMR δ 15.1 (Et), 21.4 (Me), 30.1 (C-4), 52.5 (C-3), 64.0 (Et), 66.4 (C-5), 79.4 (C-2), 84.7 (C-6), 127.1 (2 C), 127.6, 128.2 (2 C), and 141.6. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.41; H, 91.17.

The second fraction gave isomer **28** (0.55 g, 25%) as a colorless oil: ^{1}H NMR δ 0.82 (d, J = 6.1 Hz, 3 H, Me), 1.15 (t, J = 7.0 Hz, 3 H, Et), 2.05 (m, 3 H, H-3 and H-4), 3.27 (dq, J = 9.6 and 7.0 Hz, 1 H, Et), 3.38 (dq, J = 9.4 and 7.0 Hz, 1 H, Et), 3.65 (dq, $J_{1,2}$ = 6.1 Hz, $J_{2,3}$ = 6.4 Hz, 1 H, H-2), 3.78 (m, 1 H, H-5), 3.84 (m, 1 H, H-5), 4.06 (d, J = 7.1 Hz, 1 H, H-6), and 7.31 (m, 5 H, Ph); ^{13}C NMR δ 15.2 (Et), 20.2 (Me), 30.0 (C-4), 53.4 (C-3), 64.1 (Et), 66.8 (C-5), 76.8 (C-2), 83.2 (C-6), 127.1 (2 C), 127.7, 128.4 (2 C), and 141.4. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.20; H, 9.10.

The third fraction gave stereoisomer **29** (0.27 g, 12%) as a colorless oil; ^{1}H NMR δ 1.13 (t, J = 7.1 Hz, 3 H, Et), 1.25 (d, J = 6.4 Hz, 3 H, Me), 1.32 (m, 1 H, H-4), 1.48 (m, 1 H, H-4'), 2.55 (dddd, $J_{2,3}$ = 7.1 Hz, $J_{3,6}$ = 10.5 Hz, $J_{3,4}$ = 6.9 Hz, $J_{3,4'}$ = 10.7 Hz, 1 H, H-3), 3.21 (dq, J = 9.0 and 7.1 Hz, 1 H, Et), 3.28 (dq, J = 9.0 and 7.1 Hz, 1 H, Et), 3.59 (ddd, J = 6.9, 8.4, and 9.3 Hz, 1 H, H-5), 3.87 (dt, J = 2.7 and 8.3 Hz, 1 H, H-5'), 4.05 (d, $J_{3,6}$ = 10.5 Hz, 1 H, H-6), 4.37 (dq, $J_{2,3}$ = 7.1 Hz, $J_{1,2}$ = 6.4 Hz, 1 H, H-2), and 7.33 (m, 5 H, Ph); ^{13}C NMR δ 15.2 (Et), 16.2 (Me), 28.5 (C-4), 49.0 (C-3), 63.7 (Et), 66.4 (C-5), 76.3 (C-2), 82.5 (C-6), 127.1 (2 C), 127.7, 128.3 (2 C), and 144.8. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.41; H, 9.18.

Supplementary Material Available: The ORTEP structure (Figure 1) and X-ray data (Tables I–VI) for **12** (6 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.

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