Stereoselective Synthesis of 3(2*H*)-Dihydrofuranones by Addition of Lithiated Methoxyallene to Chiral Aldehydes

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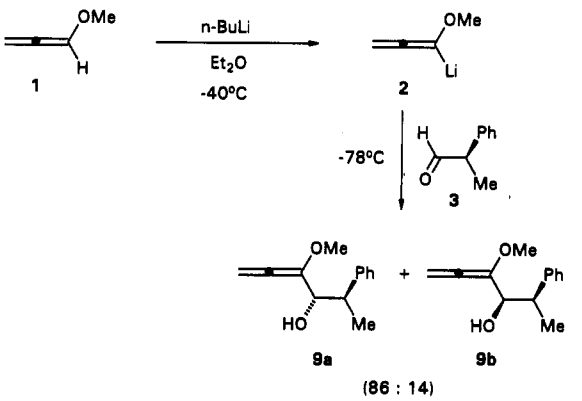
Lithiated methoxyallene **2** adds to chiral aldehydes such as 2-phenylpropanal and *N*,*N*-dibenzylated α-amino aldehydes **4–8** to give products **9–14** in good yields and with excellent *anti*-selectivity. The stereochemical outcome of these reactions can be explained by the Felkin–Anh model in a straightforward manner. The crude reaction products can either be transformed to enones by hydrolysis with acid or be converted into 2,5-dihydro-3-methoxyfuran derivatives **19–24** by treatment with potassium *tert*-butoxide in DMSO. The latter can be hydrolyzed to give 3(2*H*)-dihydrofuranones **25–29**. The diastereoselectivity of the initial addition step is transferred to the dihydrofuran derivative without a major change in the isomer ratio. Compounds derived from α-amino aldehydes **5**, **6**, and **8** are assumed to be enantiomerically pure. Sodium borohydride reductions of and Grignard additions to 3(2*H*)-dihydrofuranones **27a** and **28a** demonstrate that these chiral ketones react in a highly diastereoselective manner. In summary, this paper shows that lithiated methoxyallene **2** can serve as a very useful equivalent for α,β-unsaturated acyl anions and 1,3-dipolar synthons in asymmetric synthesis.

The conversion of α-amino acids into other classes of enantiomerically pure compounds is an important tool for synthetic chemists.[1] *N*-Protected α-amino aldehydes[2] are extremely suitable intermediates for this purpose, and many nucleophiles have been added with excellent stereocontrol[3] to provide amino alcohols and other compounds of general importance.[4] Lithiated methoxyallene[5] is a very promising nucleophile because the products of its addition to aldehydes or to ketones can be converted into a variety of interesting compound classes such as enones[6] or dihydrofuran derivatives.[7] However, additions of this organometallic species to *chiral* aldehydes have rarely been studied,[8] and there has been no systematic investigation of its utility in asymmetric synthesis. Therefore, we examined the diastereoselectivity of the reaction of lithiated methoxyallene with 2-phenylpropanal (as a test aldehyde) and several *N*,*N*-dibenzyl-protected α-amino aldehydes[3a] and explored the transformations of the products obtained.[9]

Addition Reactions. Lithiated methoxyallene (**2**) was generated according to the method of Hoff, Brandsma, and Arens:[5] treatment of methoxyallene (**1**) with *n*-butyllithium in diethyl ether at −40 °C. Racemic 2-phenylpropanal (**3**) was added to the mixture at −78 °C, and aqueous workup after 1.5 h provided a 86:14 mixture of adducts **9a**/**b**. Distillation slightly shifted the ratio of



diastereomers to 81:19 (84% yield). The *anti*:*syn* ratio of 86:14 demonstrates that lithiated methoxyallene displays reasonable diastereofacial selectivity comparable to that of other (α,β-unsaturated) acyl anion equivalents.[10] Lithi-

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(1) (a) Reetz, M. T. *Angew. Chem.* **1991**, *103*, 1559. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531. (b) Coppola, G. M.; Schuster, H. F. In *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987. (c) Martens, J. *Top. Curr. Chem.* **1984**, *125*, 165. (d) Williams, R. M. In *Synthesis of Optically Active α-Amino Acids*; Baldwin, J., Magnus, P. D., Eds., Organic Chemistry Series, Pergamon Press: Oxford, 1989; Vol. 7.

(2) For reviews on the preparation and the use of α-amino and α-alkoxy aldehydes see: (a) Fisher, C. E.; Muchowski, J. M. *Org. Prep. Proced. Int.* **1990**, *22*, 399. (b) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

(3) (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem.* **1987**, *99*, 1186. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141. (b) Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hübel, M. *Angew. Chem.* **1991**, *103*, 76. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 103.

(4) (a) Lednicer, D. A.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; Wiley: New York, 1975. (b) Nakanishi, K.; Goto, T.; Natori, S.; Nozoe, S. *Natural Products Chemistry*; Oxford University Press: Oxford, 1983; Vol. 3. (c) Kennedy, F. J.; White, A. C. *Bioactive Carbohydrates*; Ellis Horwood: Chichester, 1983.

(5) (a) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916. (b) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1985**, *50*, 5308. (c) For a recent review of the chemistry of alkoxyallenes see: Zimmer, R. *Synthesis* **1993**, 165. (d) For a detailed discussion of structure and reactivity of **2** based on *ab initio* calculations and NMR studies see: Schleyer, P. v. R.; Lambert, C.; Würthwein, E. U. *J. Org. Chem.* **1993**, *58*, 6377.

(6) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1179.

(7) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 609.

(8) (a) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179. (b) Shishido, K.; Takahashi, K.; Oshio, Y.; Fukumoto, K. *Heterocycles* **1988**, *27*, 495. (c) Gange, D.; Magnus, P. *J. Am. Chem. Soc.* **1978**, *100*, 7746. (d) For further applications of alkoxyallenes in asymmetric synthesis see: Rochet, P. R.; Vatèle, J.-M.; Goré, J. *Synlett* **1993**, 105. Arnold, T.; Orschel, B.; Reissig, H.-U. *Angew. Chem.* **1992**, *104*, 1084. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1033.

(9) For a preliminary communication see: Hormuth, S.; Reissig, H.-U. *Synlett* **1991**, 179.

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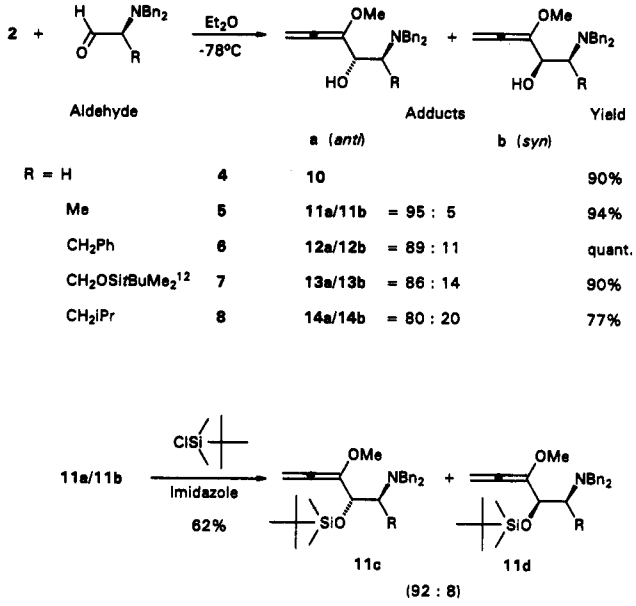
Scheme 1

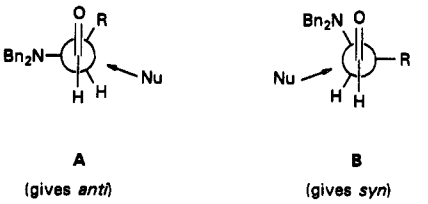


ated methoxyallene (2) also added smoothly to readily available *N,N*-dibenzyl-protected α-amino aldehydes 4–8[3a] (Scheme 1). Adducts **10**–**14** were formed in excellent crude yields, but they could not be purified by distillation or chromatography without extensive decomposition. Therefore, the diastereomer ratios were determined by NMR spectroscopy at the crude stage, and the full characterization and purification were carried out on subsequent products (*vide infra*). Alanine-derived adducts **11a/b** were also converted into the dimethyl-*tert*-butylsilylated[11] compounds, which are stable to chromatography.

The configuration of major diastereomer **11a** was deduced unambiguously by X-ray analysis of cyclization product **27a**,[13] and, hence, for all additions of **2** to aldehydes **3**–**8**, the formation of *anti*-configurated compounds can be assumed. These results are rationalized by applying the Felkin–Anh model.[14] According to Reetz, *N*-dibenzylated α-amino aldehydes are attacked by organolithium compounds without chelate formation.[1a] Thus, conformer **A**, with the dibenzylamino group in the position of the largest substituent, governs the additions of **2** and, hence, leads to *anti*-adducts (Scheme 2). The trend that larger groups R on the amino aldehydes lead to slightly decreased diastereoselectivity is also in accordance with this explanation since, as the size of R increases, conformer **B** competes with conformer **A**, which is still preferred, and the formation of a larger amount of minor diastereomer **b** is observed.

In order to reverse the diastereoselectivity of the additions of **2**, we used *N*-Boc-protected amino aldehydes[15]

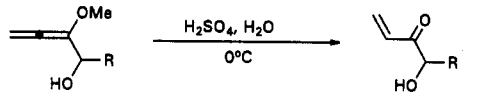
Scheme 2



as electrophiles. However, the expected products were formed in very low yields (<5%), and their configurations could not be determined. However, the reactions of **2** with *N*-Boc-*N*-benzylamino aldehydes also produced *anti*-adducts with good selectivity.[16]

Transmetalation of **2** was only successful with $CeCl_3$,[17] but the resulting species added to **5** with a selectivity very similar to that of **2**. More interestingly, when **2** was converted to a titanium compound by reaction with $ClTi(OiPr)_3$,[18] the regioselectivity of the addition to amino aldehydes such as **5** was completely reversed, and γ-adducts (1-methoxyalkyne derivatives) were produced.[19] In conclusion, no method has been found so far to add metalated methoxyallene to α-amino aldehydes with good *syn*-selectivity.

Transformation of the Primary Products to Enones and Furan Derivatives. One possible method to convert primary products of methoxyallene additions into preparatively useful intermediates is the acidic hydrolysis to α,β-unsaturated ketones.[6] Treatment of **15** (obtained from **2** and benzaldehyde[20]) with dilute sulfuric acid provided enone **16** in good yield. The diastereomers of **9** were



		(a : b)		(a : b)	Yield
R = Ph	15	–	16	–	76%
= Ph, Me	9	85 : 15	17	84 : 16	38%
= NBn2, Me	11	95 : 5	18	–	–

similarly converted into enone **17**, but its purification was rather inefficient. Amino aldehyde adduct **5** could also be hydrolyzed, but product **18** was very impure; attempts to purify the material failed. Nevertheless, even in their impure state, enones such as **17** and **18** may be interesting precursors for Michael-type additions or cycloadditions.[21]

A more general transformation of methoxyallene adducts seems to be the base-induced cyclization with potassium *tert*-butoxide in DMSO, which produces 2,5-dihydro-3-methoxyfuran derivatives.[7] This mechanistically inter-

(10) (a) Hünig, S.; Marschner, C. *Chem. Ber.* **1989**, *122*, 1329. (b) Hünig, S.; Marschner, C.; Peters, K.; v. Schnering, H.-G. *Chem. Ber.* **1989**, *122*, 2131 and refs cited therein. (c) Barett, A. G. M.; Lebolg, S. A. *J. Org. Chem.* **1990**, *55*, 5818. (d) Braun, M.; Mahler, H. *Synlett* **1990**, *587* and refs cited therein. (e) See also: Senjupta, S.; Snieckus, V. *J. Org. Chem.* **1990**, *55*, 5680 and refs cited therein. (f) For a comprehensive list of acyl anions see: *Umpolung synthons*; Hase, T. A., Ed.; Wiley: New York, 1987.

(11) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(12) Amino aldehyde **7** was employed as its racemate; consequently, compounds **13** and **23**, derived from **7**, were also racemates.

(13) Hormuth, S.; Reissig, H.-U.; Foro, S.; Lindner, H.-J. *Z. Kristallogr.* **1993**, in press.

(14) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145. (c) See also: Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1993**, *49*, 3971.

(15) (a) Nahm, S.; Weinreb, S. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Fehrentz, J.-A.; Castro, F. *Synthesis* **1983**, 676.

(16) Hormuth, S.; Reissig, H.-U.; Dorsch, D. *Liebigs Ann. Chem.* **1994**, in press.

(17) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

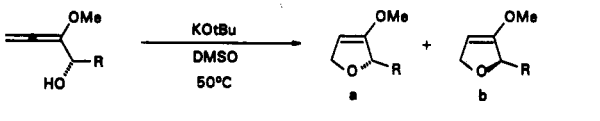
(18) Seebach, D. In *Modern Synthetic Methods 1983*; Scheffold, R., Ed.; Salle & Sauerländer: Frankfurt, 1983.

(19) Hormuth, S.; Reissig, H.-U.; Dorsch, D. *Angew. Chem.* **1993**, *105*, 1513. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1449.

(20) Zimmer, R.; Reissig, H.-U. *Liebigs Ann. Chem.* **1991**, 553.

(21) For examples see: Choy, W.; Reed, L. A., III; Masamune, S. *J. Org. Chem.* **1983**, *48*, 1139.

esting reaction[22] proceeds smoothly with crude primary adducts **9–14** to give the heterocycles **19–24** in good overall yields (based on the amount of the corresponding aldehyde). An exception is the conversion of **13** into **23**, which afforded the dihydrofuran derivative in a very poor yield of 4%, probably due to desilylation under the strongly basic reaction conditions. In all other examples, the ratio



		(a : b)		(a : b)	Yield*
R =	Ph, Me (rac.)	9	81 : 19	19	85 : 15	60%
	NBn_2, H (rac.)	10	–	20	–	41%
	NBn_2, Me	11	95 : 5	21	>99 : 1	77%
	NBn_2, Ph	12	81 : 19	22	89 : 11	62%
	NBn_2, $OSitBuMe_2$ (rac.)	13	86 : 14	23	>98 : 2	4%
	NBn_2	14	80 : 20	24	80 : 20	43%

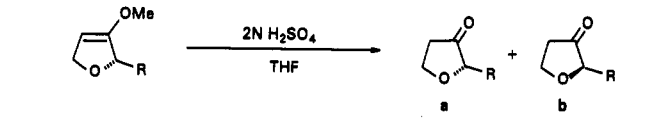
*Yields based on the amounts of 3-8.

of diastereomers was essentially unaltered during the cyclization process, but occasionally the major diastereomer was enriched during the purification procedure. For example, the alanine-derived compound **21a** was easily obtained diastereomerically pure by recrystallization. Although we have no experimental proof, we assume that the compound is also enantiomerically pure since it has frequently been shown that *N,N*-dibenzyl-protected amino aldehydes are generated and transformed without loss of enantiomeric purity.[2b,3]

The enol ether moiety of the cyclization products could be hydrolyzed by acid treatment to afford the corresponding 3(2*H*)-dihydrofuranones[7] in moderate to good yields. Again, the diastereomeric compositions of the starting materials and products were very similar. As mentioned above, the configuration of diastereomerically and enantiomerically pure **27a** was established by X-ray analysis.[13]

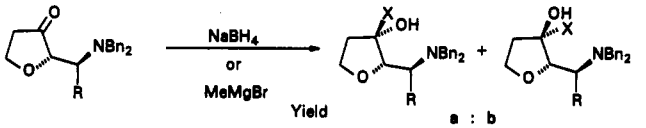
Conversion of 3(2*H*)-Dihydrofuranones to Other Products. 3(2*H*)-Dihydrofuranones such as **26–29** are interesting intermediates, e.g., they can be regarded as (protected) analogues of muscarone.[23] Their structural element also appears in other biological active natural products,[24] and their conversion to certain desoxy sugar derivatives should be easily achievable. Compounds **27a** and **28a** can serve as starting materials for highly stereoselective addition reactions as was demonstrated by their reduction with sodium borohydride and by their reactions with Grignard reagents.

The reactions of **27a** and **28a** with $NaBH_4$ provided tetrahydrofuran-3-ols **30** and **31**, respectively, with pre-



		(a : b)		(a : b)	Yield
R =	Ph, Me (rac.)	19	85 : 15	25	86 : 14	46%
	NBn_2, H (rac.)	20	–	26	–	45%
	NBn_2, Me	21a		27a		79%
	NBn_2, Ph	22	89 : 11	28	93 : 7	61%
	NBn_2	24	80 : 20	29	82 : 18	81%

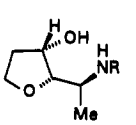
dominance of one diastereomer. By subsequent conversion of **30a** into 1,3-oxazin-2-one **36** and NMR analysis of **36** (*vide infra*), it could be proven that the hydride reagent preferentially attacks **27a** *trans* to the 3(2*H*)-furanone's bulky 2-substituents. Similarly, addition of methylmagnesium bromide afforded adducts **32a** and **33a** as major isomers. The additions of nucleophiles to 3(2*H*)-furanones seem to be sterically directed, and chelate control is apparently not important.[25]



			Yield		a : b
R = Me	27a	X = H	95%	30	92 : 8
R = CH_2Ph	28a	X = H	57%	31	95 : 5
R = Me	27a	X = Me	66%	32	92 : 8
R = CH_2Ph	28a	X = Me	84%	33	>97 : 3

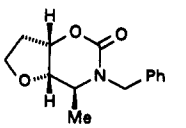
The stepwise removal of the protecting benzyl groups can be easily achieved by hydrogenolysis in the presence of palladium catalysts. The use of palladium black and formic acid as a hydrogen source[3b] allowed the isolation of secondary amine **34** after a reaction time of 18 h. With hydrogen, palladium on carbon,[3a] and an elongated reaction time (4 d), we were able to fully deprotect **39** to produce compound **35** in 80% yield. Finally, **34** was transformed into bicyclic compound **36** by treatment with diphosgene.[26] The configuration of this product was determined by an NOE experiment showing the proximity of the methyl group and the two bridgehead hydrogens.

Scheme 3



R = Bn **34**

R = H **35**



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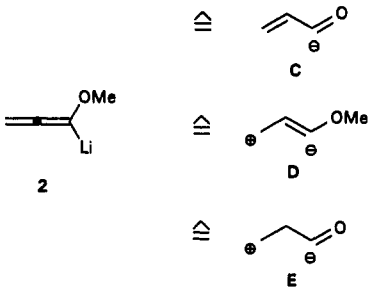
(22) For relevant experiments see: Magnus, P.; Albough-Robertson, P. J. *J. Chem. Soc., Chem. Commun.* **1984**, 804.
(23) DeAmici, M.; Dallanoce, C.; DeMicheli, C.; Grana, E.; Barbieri, A., Ladinsky, H.; Schiavi, G.; Zonta, F. *J. Med. Chem.* **1992**, *35*, 1915.
(24) Semple, J. E.; Joullié, M. M. *Heterocycles* **1980**, *14*, 1825.
(25) An intramolecular version of this reaction type preferentially yielded a *cis*-diastereomer: Armistead, D. M.; Danishefsky, S. J. *Tetrahedron Lett.* **1987**, *28*, 4959.
(26) Pridgen, L. N.; Prol, J., Jr. *J. Org. Chem.* **1989**, *54*, 3231.

Scheme 4



Conclusion

In this study, we demonstrated that the methods developed by Hoff, Brandsma, and Arens for methoxyallene (1) could be exploited for the asymmetric synthesis of a variety of interesting compound classes, in particular, with *N,N*-dibenzyl-protected α-amino aldehydes as reaction partners. The addition of lithiated methoxyallene (2) to chiral aldehydes proceeds with good to excellent diastereoselectivity, which can be interpreted by the Felkin–Anh model in a straightforward manner. Although the primary adducts could not be purified, it was possible to convert them into either enones or 2,5-dihydrofuran derivatives, which were further transformed into 3(2*H*)-furanones and tetrahydrofuran-3-ols. Thus, it was confirmed that lithiated methoxyallene (2) serves as a synthetic equivalent of an α,β-unsaturated acyl anion synthon **C** and of dipolar synthons **D** and **E** in asymmetric syntheses. Further work in our laboratory has demonstrated that the synthetic utility of 2 can even be enhanced by variations that show its equivalence to a formyl ester anion synthon and a homoenolate synthon. These results and their implications for asymmetric synthesis will be reported in due course.[16,19]

Experimental Section

General. All reactions with air- and moisture-sensitive compounds were performed under a nitrogen atmosphere in a flame-dried reaction flask, and the components were added via syringe. All solvents were dried by the standard methods. DMSO was freshly distilled from CaH_2 prior to use. For chromatography, 230–70-mesh silica gel (E. Merck No. 7734) was employed. A Büchi Kugelrohr apparatus was used for the distillation of small quantities of substances. TLC with centrifugal resolution was performed with a chromatotron (Harrison Research Model 7924 T). ^1H and ^{13}C NMR spectra were recorded at 300 MHz (75.5 MHz ^{13}C) in $CDCl_3$ with a Bruker WM 300 spectrometer, and chemical shifts are reported in ppm. The purity of crude products and the ratios of diastereomers were determined by NMR. Higher order NMR spectra were approximately interpreted as first-order spectra if possible. Missing signals of the minor isomers were either hidden or too weak. IR spectra were recorded with a Perkin-Elmer 137 or a Beckman IR 5a spectrometer. Determination of optical rotation values was performed with a Perkin-Elmer 141 polarimeter.

Addition of 2 to Aldehydes. General Procedure Analogous to That Described in Ref 5b. Methoxyallene 1 (1.03 equiv) was dissolved in dry Et_2O (2 mL/mmol) and treated at −40 °C with 1.03 equiv of *n*-BuLi (2.5 M in hexane). After 5 min, the resulting solution of 2 was cooled to −78 °C, and the aldehyde dissolved in dry Et_2O (1 mL/mmol) was added over a period of 5 min. The reaction mixture was stirred for 1.5 h at −78 °C and quenched with H_2O (2 mL/mmol). Warmup to rt was followed by extraction with Et_2O (3 × 2 mL/mmol) and drying (Na_2SO_4). The crude products were employed in subsequent reactions immediately after the determination of the purity and the ratio of diastereomers.

***rac*-(2*S*,3*R*)-, (2*S*,3*S*)-4-Methoxy-2-phenyl-4,5-hexadien-3-ol (9a,b).** Addition of 2 to racemic aldehyde 3 (6.70 g, 50.0 mmol) provided 10.1 g of crude product 9 (a:b = 86:14), which was partially purified by distillation (70 °C/0.001 Torr) to afford 8.55 g (84%) of 9 (a:b = 81:19, purity >90%).

***rac*-1-(*N,N*-Dibenzylamino)-3-methoxy-3,4-pentadien-2-ol (10).** Addition of 2 to amino aldehyde 4 (2.16 g, 9.00 mmol, and filtration of the crude product through a sintered glass plug containing a path of activity I neutral alumina provided 4.46 g (90%) of 10 (purity >80%).

(2*S*,3*S*)-, (2*S*,3*R*)-2-(*N,N*-Dibenzylamino)-4-methoxy-4,5-hexadien-3-ol (11a,b). Addition of 2 to amino aldehyde 5 (2.43 g, 9.60 mmol) yielded 2.92 g (95%) of 11 (a:b = 95:5, purity >90%). Typical analytical data of primary adducts are listed as ^1H NMR **11a**: 7.36–7.18 (m, 12 H, phenyl and impurity), 5.47 (dd, *J* = 1.2, 7.0 Hz, 1 H), 5.43 (dd, *J* = 1.2, 7.0 Hz, 1 H), 4.16 (m, 1 H), 3.73 (d, *J* = 13.5 Hz, 2 H), 3.49 (d, *J* = 13.5 Hz, 2H), 3.36 (s, 3H), 3.05 (quint, *J* = 6.9 Hz), 2.54 (d, *J* = 7.8 Hz, 1 H), 1.15 (d, *J* = 6.9 Hz, 3 H). **11b**: Assignment of signals was not possible. ^{13}C NMR **11a**: 198.1 (s), 140.1 (s), 134.9 (s), 128.9, 128.0, 126.8 (3d), 91.6 (t), 72.8 (d), 56.0, 55.9 (q, d), 54.4 (t), 9.4 (q). ^{13}C NMR **11b**: 138.8 (s), 90.7 (t), 72.6 (d), 53.5 (t). IR (film) 3600–3200 (OH), 3100–3000 (=C—H), 3000–2770 (CH), 1955 (C=C=C).

(2*S*,3*S*)-, (2*S*,3*R*)-2-(*N,N*-Dibenzylamino)-3-(*tert*-butyldimethylsiloxy)-4-methoxy-4,5-hexadiene (11c,d). To a stirred solution of 11 (1.62 g, 5.00 mmol, a:b = 95:5) in 10 mL of a 1:1 mixture of CH_2Cl_2 and dimethylformamide were added imidazole (879 mg, 12.5 mmol) and *tert*-butyldimethylsilyl chloride (904 mg, 6.00 mmol). Stirring was continued for 18 h at rt. Subsequently 15 mL of diethyl ether was added, and the mixture was washed with saturated aqueous NaCl solution (3 × 10 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo. Purification by column chromatography (activity I neutral alumina, hexane/EtOAc 2:1, containing 10 vol% triethylamine) afforded 1.36 g (62%) of product 11 (c:d = 92:8). ^1H NMR **11c**: 7.43–7.15 (m, 10 H), 5.40, 5.35 (2d, *J* = 7.5 Hz, 2 H), 4.12 (d, *J* = 8.8 Hz, 1H), 3.69 (d, *J* = 13.9 Hz, 2 H), 3.44 (d, *J* = 13.9 Hz, 2 H), 3.31 (s, 3 H), 3.13 (dq, *J* = 6.7, 8.8 Hz, 1 H), 1.12 (d, *J* = 6.7 Hz, 3 H), 0.86 (s, 9 H), 0.05–0.01 (2s, 6 H). ^1H NMR **11d**: 5.47 (m_c, 2 H), 3.37 (s, 3 H), 1.05 (d, *J* = 6.7 Hz, 3 H), 0.87 (s, 9 H), 0.14, 0.08 (2s, 6 H). ^{13}C NMR **11c**: 199.7 (s), 140.9 (s), 134.7 (s), 129.0, 127.9, 126.6 (3d), 89.9 (t), 75.6 (d), 55.7, 55.6 (q, d), 54.2 (t), 29.9 (q), 18.2 (s), 9.7 (q), −4.6, −5.1 (2q). ^{13}C NMR **11d**: 198.4 (s), 140.9 (s), 128.0, 128.1, 126.2 (3d), 91.2 (t), 74.2 (d), 56.4 (q or d), 25.7 (q), 14.1 (s), 11.7 (q), −3.0, −5.4 (2q). IR (film): 3100–3000 (=C—H), 3000–2700 (C—H), 1910 (C=C=C). Anal. Calcd for $C_{27}H_{39}NO_2Si$ (437.70): C, 74.09; H, 8.98; N, 3.20. Found: C, 73.98; H, 9.15; N, 2.71.

(2*S*,3*S*)-, (2*S*,3*R*)-2-(*N,N*-Dibenzylamino)-4-methoxy-1-phenyl-4,5-hexadien-3-ol (12a,b). Addition of 2 to aldehyde 6 (3.12 g, 9.60 mmol) afforded 3.83 g (101%) of 12 (a:b = 89:11, purity >80%).

***rac*-(2*S*,3*S*)-, (2*S*,3*R*)-1-(*tert*-Butyldimethylsiloxy)-4-methoxy-5,6-hexadien-3-ol (13a,b).**[12] Addition of 2 to aldehyde 7 (1.53 g, 4.00 mmol) yielded 1.64 g (90%) of 13 (a:b = 86:14, purity >75%).

(4*R*,5*S*)-, (4*S*,5*R*)-5-(*N,N*-Dibenzylamino)-3-methoxy-7-methyl-1,2-octadien-4-ol (14a,b). Addition of 2 to aldehyde 6 (3.12 g, 9.60 mmol) afforded 3.83 g (101%) of 14 (a:b = 89:11, purity >80%).

Preparation of Enones. General Procedure Analogous to That Described in Ref 6. The primary adduct was added dropwise at 0 °C to a cooled 5% aqueous solution of sulfuric acid. Stirring was continued at 0 °C for 1 h. After warming up to rt, the solution was saturated with NaCl and extracted with Et_2O (5 × 5 mL). The combined extracts were washed with saturated NaCl solution (2 × 5 mL) and dried over Na_2SO_4. After removal of the solvent in vacuo, the residue was purified either by Kugelrohr distillation or by column chromatography.

4-Hydroxy-4-phenyl-1-buten-3-one (16). Hydrolysis of adduct 15 (700 mg, 4.00 mmol; prepared by means of the general procedure from 2 and benzaldehyde) provided 531 mg of crude product; purification of Kugelrohr distillation (80 °C/0.01 Torr) afforded 489 mg (76%) of enone 16 as a colorless oil that turned yellow within hours. ^1H NMR: 7.44–7.15 (m, 5 H), 6.39 (m_c, 2 H), 5.70 (m_c, 1 H), 5.26 (s, 1 H), 4.56 (s, 1 H). ^{13}C NMR: 197.7

(s), 137.5 (s), 130.8 (t), 130.7 (d), 128.9, 128.7, 127.7 (3d), 78.6 (d). IR (film): 3160–3120 (OH), 3120–3000 (=C—H), 2980–2800 (C—H), 1690 (C=O), 1610 (C=C). Anal. Calcd for $C_{10}H_{10}O_2$ (162.19): C, 74.06; H, 6.21. Found: C, 73.43; H, 6.49.

***rac*-(4*S*,5*S*)-, (4*R*,5*S*)-4-Hydroxy-5-phenyl-1-hexen-3-one (17a,b).** Hydrolysis of adduct **9** (966 mg, 4.70 mmol, **a**:**b** = 85:15) provided 966 mg of crude product (**a**:**b** = 84:16). Chromatography (chromatotron, pentane/Et_2O 5:1) yielded 338 mg (38%) of enone **17** (**a**:**b** = 97:3) as a colorless oil that turned yellow upon storage. ^{1}H-NMR **17a**: 7.34–7.21 (m, 5 H), 6.49 (dd, J = 9.7, 17.5 Hz, 1 H), 6.39 (dd, J = 2.2, 17.5 Hz, 1 H), 5.84 (dd, J = 2.2, 9.7 Hz, 1 H), 4.56 (d, J = 3.4 Hz, 1 H), 3.56 (s, 1 H), 3.19 (dq, J = 3.4, 7.2 Hz), 1.17 (d, J = 7.2 Hz, 3 H). ^{1}H-NMR **17b**: 6.27 (dd, J = 1.4, 18.0 Hz, 2 H), 4.29 (d, J = 1.0 Hz, 1 H). ^{13}C NMR **17a**: 200.6 (s), 143.3 (s), 131.6 (d), 130.3 (t), 128.5, 128.0, 126.9 (3d), 79.4 (d), 42.8 (d), 14.1 (q). ^{13}C NMR **17b**: 143.6 (s), 131.7 (d), 130.0 (t), 79.7 (d), 43.1 (d), 15.4 (q). IR (film): 3660–3140 (OH), 3100–3000 (=C—H), 1690 (C=O), 1610 (C=C). Anal. Calcd for $C_{12}H_{14}O_2$ (190.24): C, 75.76; H, 7.42. Found: C, 75.14; H, 7.53.

(4*S*,5*S*)-, (4*R*,5*S*)-5-(*N*,*N*-Dibenzylamino)-4-hydroxy-1-hexen-3-one (18a,b). Hydrolysis of adduct **11** (2.97 g, crude product, **a**:**b** = 95:5) provided 1.99 g of crude product; purity >40% (**a**:**b** ratio could not be determined). Attempts to purify the crude product failed. ^{1}H-NMR **18a**: 7.41–7.18 (m, 24 H, phenyl and impurity), 6.10 (m, 2 H), 5.61 (dd, J = 2.7, 9.1 Hz, 1 H), 4.82 (d, J = 1.9 Hz, 1 H), 3.84–3.17 (m, 17 H), 1.31–0.84 (m, 13.4 H). ^{13}C NMR: 200.2 (s), 130.5 (t), 128.6, 128.3, 126.9 (3d), 54.3 (t); other signals could not be assigned. IR (film): 3600–3200 (OH), 3080–3000 (=C—H), 1700 (C=O), 1600 (C=C).

Cyclization of the Primary Adducts. General Procedure Analogous to Ref 7. To a stirred solution of potassium *tert*-butoxide (0.5 equiv in 5 mL of DMSO/mmol adduct) at 50 °C was added dropwise a solution of the crude primary adduct in 1 mL/mmol of DMSO. Stirring was continued for 1 h at the same temperature. After cooling to rt, the mixture was quenched with ice–water (2 mL/mmol) and Et_2O was added (2 mL/mmol), and the mixture was extracted with pentane/Et_2O (2:1) (3 × 3 mL/mmol). The combined organic extracts were dried with Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by distillation, column chromatography, or recrystallization.

***rac*-(2*S*,1′*S*)-, (2*R*,1′*S*)-2,5-Dihydro-2-(1-phenylethyl)-3-methoxydihydrofuran (19a,b).** Cyclization of crude adduct **9** (1.63 g, 8.00 mmol, **a**:**b** = 81:19) provided 1.47 g of crude cyclization product (**a**:**b** = 83:17). Kugelrohr distillation (75 °C/0.01 Torr) yielded 1.16 g (60% based on the amount of aldehyde **3**) of dihydrofuran **19** (**a**:**b** = 85:15) as a colorless liquid. ^{1}H NMR **19a**: 7.34–7.15 (m, 5 H), 4.76 (m_c, 1 H), 4.64 (dd, J = 1.6, 3.2 Hz, 1 H), 4.58 (m_c, 2 H), 3.67 (s, 3 H), 3.06 (dq, J = 2.3, 7.2 Hz, 1 H), 1.23 (d, J = 7.2 Hz, 3 H). **19b**: 3.54 (s, 3 H), 1.42 (d, J = 7.2 Hz). ^{13}C NMR **19a**: 158.7 (s), 144.4 (s), 128.0, 127.9, 126.0 (3d), 91.2 (d), 85.4 (d), 73.4 (t), 57.4 (q), 42.3 (d), 13.5 (q). ^{13}C NMR **19b**: 90.7 (d, C(4)), 85.8 (d, C(2)), 73.1 (t, C(5)), 57.0 (q, OMe), 42.8 (d, C(1′)), 17.3 (q, Me). IR (film): 3100–3000 (=C—H), 3000–2800 (C—H), 1660 (C=C). Anal. Calcd for $C_{13}H_{16}O_2$ (204.27): C, 76.44; H, 7.89. Found: C, 76.80; H, 7.35.

***rac*-2-(*N*,*N*-Dibenzylamino)-2,5-dihydro-3-methoxyfuran (20).** Cyclization of adduct **10** (1.00 g, 3.20 mmol) provided 911 mg of crude product; recrystallization (methanol) afforded 465 mg (41% based on the amount of aldehyde **4**) of **20** as pale red crystals, mp 53–55 °C. ^{1}H NMR: 7.39–7.17 (m, 10 H), 4.76 (m_c, 1 H), 4.60 (m, 3H), 3.73 (d, J = 13.9 Hz, 2 H), 3.66 (d, J = 13.9 Hz, 2 H), 3.53 (s, 3 H), 2.79 (dd, J = 2.3, 14.0 Hz, 1 H), 2.63 (dd, J = 6.6, 14.0 Hz, 1 H). ^{13}C NMR: 157.3 (s), 139.9 (s), 128.9, 128.0, 126.6 (3d), 90.4 (d), 81.4 (d), 72.7 (t), 58.8 (t), 57.3 (q), 56.0 (t). IR (KBr): 3100–3000 (=C—H), 3000–2740 (C—H), 1660 (C=C). Anal. Calcd for $C_{20}H_{23}NO_2$ (309.41): C, 77.64; H, 7.49; N, 4.53. Found: C, 78.04; H, 7.48; N, 4.45.

(2*S*,1′*S*)-, (2*R*,1′*S*)-2-[1-(*N*,*N*-Dibenzylamino)ethyl]-2,5-dihydro-3-methoxyfuran (21a,b). Cyclization of adduct **11** (646 mg, 2.00 mmol, **a**:**b** = 95:5) provided 603 mg of crude product (**a**:**b** = 95:5); recrystallization (methanol) afforded 528 mg (77% based on the amount of aldehyde **5**) of **21a** as colorless crystals, mp 69–70 °C, $[\alpha]^{20}_D$ = +21.5° ($CHCl_3$, c = 1.0). ^{1}H NMR **21a**: 7.39–7.14 (m, 10 H), 4.98 (ddd, J = 1.7, 3.3, 6.6 Hz, 1 H), 4.63 (m_c, 2 H), 4.56 (dd, J = 1.3, 3.3 Hz, 1 H), 3.78 (d, J = 14.3 Hz, 2 H), 3.69 (d, J = 14.3 Hz, 2 H), 3.51 (s, 3 H), 3.02 (dq, J = 1.3, 6.9 Hz, 1 H), 1.01 (d, J = 6.9 Hz, 3 H). ^{1}H NMR **21b**: 3.55 (s, 3 H), 1.19 (d, J = 6.9 Hz, 3 H). ^{13}C NMR **21a**: 156.9 (s), 140.9 (s), 128.5, 128.0, 126.4 (3d), 90.3 (d), 83.5 (d), 73.8 (t), 57.3 (d), 54.7 (q), 54.6 (t), 8.3 (q). ^{13}C NMR **21b**: 157.1 (s), 140.2 (s), 90.2 (d), 72.2 (t), 8.6 (q). IR (KBr): 3120–3000 (=C—H), 3000–2660 (C—H), 1660 (C=C). Anal. Calcd for $C_{21}H_{25}NO_2$ (323.43): C, 77.98; H, 7.79; N, 4.33. Found: C, 77.95; H, 7.73; N, 4.31.

(2*S*,1′*S*)-, (2*R*,1′*S*)-2-[1-(*N*,*N*-Dibenzylamino)-2-phenylethyl]-2,5-dihydro-3-methoxyfuran (22a,b). Cyclization of adduct **12** (1.13 g, 2.50 mmol, **a**:**b** = 89:11) provided 1.06 g of crude product (**a**:**b** = 89:11); chromatography (chromatotron, hexane/EtOAc 10:1) yielded 721 mg (62% based on the amount of aldehyde **6**) of **22** (**a**:**b** = 83:17) as a pale yellow oil. ^{1}H NMR **22a**: 7.33–7.14 (m, 15 H), 5.12 (m_c, 1 H), 4.70 (m_c, 2 H), 4.53 (dd, J = 1.5, 3.2 Hz, 1 H), 3.89 (d, J = 14.3 Hz, 2 H), 3.61 (d, J = 14.3 Hz, 2 H), 3.43 (s, 3 H), 3.26 (ddd, J = 0.7, 5.0, 9.2 Hz, 1 H), 2.93 (dd, J = 9.2, 14.3 Hz, 1 H), 2.71 (dd, J = 5.0, 14.3 Hz, 1 H). ^{1}H NMR **22b**: no signals could be assigned. ^{13}C NMR **22a**: 156.9 (s), 140.8, 140.5 (2s), 129.6, 128.7, 127.9, 127.8, 126.6, 125.5 (6d), 90.6 (d), 80.8 (d), 72.8 (t), 60.4 (d), 57.4 (q), 54.5 (t), 31.3 (t). ^{13}C NMR **22b**: 129.3, 129.0, 126.4, 125.8 (4d), 90.0 (d), 82.8 (d), 72.8 (t), 60.4 (d), 57.0 (q), 55.7 (t). IR (film): 3080–3000 (=C—H), 3000–2780 (C—H), 1655 (C=C). Anal. Calcd for $C_{27}H_{29}NO_2$ (399.53): C, 81.16; H, 7.32; N, 3.51. Found: C, 80.83; H, 7.36; N, 3.43.

***rac*-(2*S*,1′*S*)-2-[1-(*N*,*N*-Dibenzylamino)-2,5-dihydro-2-(*tert*-butyldimethylsiloxy)ethyl]-3-methoxyfuran (23a).**[12] Cyclization of primary adduct **13** (2.42 g, 5.00 mmol, **a**:**b** = 86:14) provided 1.55 g of crude product; an accurate determination of the diastereomer ratio was not possible. Chromatography (chromatotron, hexane/EtOAc 5:1) afforded 101 mg (4% based on the amount of aldehyde **5**) of *rac*-dihydrofuran **23a** as a pale yellow oil. ^{1}H NMR: 7.35–7.14 (m, 10 H), 4.94 (ddd, J = 1.6, 3.2, 7.2 Hz, 1H), 4.62–4.58 (m, 2 H), 4.55 (m_c, 1 H), 3.96 (dd, J = 7.9, 10.8 Hz, 1 H), 3.93 (d, J = 14.3 Hz, 2 H), 3.80 (d, J = 14.3 Hz, 2 H), 3.74 (dd, J = 4.8, 10.8 Hz, 1 H), 3.12 (ddd, J = 1.7, 4.8, 7.9 Hz, 1 H), 0.91 (s, 9 H), 0.23, 0.00 (2s, 6 H). ^{13}C NMR: 157.0 (s), 140.8 (s), 128.5, 128.0, 126.2 (3d), 89.9 (d), 82.0 (d), 73.4 (t), 61.0 (d), 59.9 (t), (q), 54.0 (t), 25.8 (q), 18.1 (s), -5.7 (q). IR: 3080–3000 (=C—H), 3000–2780 (C—H), 1660 (C=C). Anal. Calcd for $C_{27}H_{39}NO_3Si$ (453.70): C, 71.48; H, 8.68; N, 3.09. Found: C, 71.63; H, 8.95; N, 3.13.

(2*S*,1′*S*)-, (2*R*,1′*S*)-2,5-Dihydro-2-[1-(*N*,*N*-dibenzylamino)-3-methylbutyl]-3-methoxyfuran (24a,b). Cyclization of **14** (2.42 g, 5.00 mmol, **a**:**b** = 80:20) afforded 2.48 g of crude product (**a**:**b** = 80:20); purification by column chromatography (silica gel, hexane/EtOAc 10:1) provided 1.38 g (43% based on the amount of amino aldehyde **8**) of dihydrofuran **29** (**a**:**b** = 80:20) as a pale yellow oil. ^{1}H NMR **24a**: 7.36–7.16 (m, 10 H), 5.13 (m, 1 H), 4.66, 4.61, 4.58, (3m_c, 3 H), 3.93 (d, J = 13.7 Hz, 2 H), 3.47 (d, J = 13.7 Hz, 2 H), 3.56 (s, 3 H), 2.89 (ddd, J = 0.8, 3.5, 10.2 Hz, 1 H), 1.79 (ddd, J = 3.5, 6.6, 14.1 Hz, 1 H), 1.60 (ddd, J = 3.7, 10.2, 14.1 Hz, 1 H), 0.91 (d, octet, J = 3.7, 6.6 Hz, 1 H), 0.84, 0.38 (2d, J = 6.6 Hz, 6 H). ^{1}H NMR **24b**: 4.70, 4.63 (2m_c, 2 H), 3.86 (d, J = 13.7 Hz, 2 H), 3.57 (d, J = 13.7 Hz, 2 H), 3.55 (s, 3 H), 2.89 (ddd, J = 3.0, 6.0, 8.0 Hz, 1 H), 0.85, 0.77 (2d, J = 6.4 Hz, 6 H). ^{13}C NMR **24a**: 157.1 (s), 140.6 (s), 128.3, 127.7, 126.3 (3d), 90.0 (d), 79.7 (d), 73.7 (t), 57.1, 56.4 (q, d), 54.3 (t), 34.1 (t), 23.9 (q), 21.1 (d). ^{13}C NMR **24b**: 141.0 (s), 128.9, 128.2, 126.9 (3d), 83.7 (d), 72.4 (t), 56.8, 55.9 (d, q), 55.1 (t), 34.7 (t), 24.7, 23.0, 22.4 (2q, d). IR (film): 3100–3000 (=C—H), 3000–2720 (C—H), 1660 (C=C). Anal. Calcd for $C_{24}H_{31}NO_2$ (365.51): C, 78.87; H, 8.55; N, 3.83. Found: C, 78.94; H, 8.70; N, 3.72.

Hydrolysis of 3-Methoxy-2,5-dihydrofurans. General Procedure Analogous to That Described in Ref 7. A solution of the 2,5-dihydrofuran in 2 mL/mmol of a mixture of 2 N H_2SO_4 and THF (1:1) was heated for 3 h under reflux. After cooling to rt, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution. The removal of the organic layer was followed by extraction of the remaining aqueous layer with Et_2O (3 × 10 mL). The combined ethereal extracts were dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by chromatography or recrystallization.

***rac*-(2*S*,1′*S*)-, (2*R*,1′*S*)-4,5-Dihydro-2-(1-phenylethyl)-3-(2*H*)-furanone (25a,b).** Hydrolysis of **19** (323 mg, 1.80 mmol,

a:b = 85:15) yielded 263 mg of crude product (a:b = 86:14). Kugelrohr distillation (75 °C/0.01 Torr) followed by chromatography (chromatotron, hexane/EtOAc 5:1) afforded 146 mg (46%) of **25** (a:b = 86:14). ^{1}H NMR **25a**: 7.35–7.18 (m, 5 H), 4.26 (dt, J = 3.7, 9.4 Hz, 1 H), 3.99 (dt, J = 7.2, 9.4 Hz, 1 H), 3.86 (d, J = 2.9 Hz, 1 H), 3.25 (dq, J = 2.9, 7.2 Hz, 1 H), 2.45 (ddd, J = 3.7, 7.2, 18.1 Hz, 1 H), 2.33 (td, J = 9.4, 18.1 Hz, 1 H), 1.26 (d, J = 7.2 Hz, 3 H). **25b**: 1.45 (d, J = 7.3 Hz, 3 H). ^{13}C NMR **25a**: 215.6 (s), 143.3 (s), 128.4, 127.4, 126.7 (3d), 83.7 (d), 64.6 (t), 41.1 (d), 37.6 (t), 15.2 (q). ^{13}C NMR **25b**: 128.7, 128.1, 126.8 (3d), 83.6 (d), 41.4 (d), 37.2 (t), 18.1 (q). IR (film): 3080–3000 (=C—H), 3000–2800 (C—H), 1750 (C=O). Anal. Calcd for $C_{12}H_{14}O_2$ (190.24): C, 75.76; H, 7.42. Found: C, 75.93; H, 7.74.

***rac*-2-[(*N*,*N*-Dibenzylamino)methyl]-4,5-dihydro-3(2*H*)-furanone (26).** Hydrolysis of **20** (309 mg, 1.10 mmol) afforded 303 mg of crude product. Purification by chromatography (chromatotron, hexane/EtOAc 5:1) yielded 145 mg (45%) of **26** as a colorless oil: ^{1}H NMR: 7.36–7.17 (m, 10 H, phenyl), 4.15 (td, J = 6.6, 9.3 Hz, 1 H), 3.97–3.89 (m, 2 H), 3.71 (d, J = 13.9 Hz, 2 H), 3.66 (d, J = 13.9 Hz, 2 H), 2.85 (dd, J = 2.6, 14.2 Hz, 1 H), 2.71 (dd, J = 7.4, 14.2 Hz, 1 H), 2.33 (m_c, 2 H). ^{13}C NMR: 214.7 (s), 139.0 (s), 128.7, 128.0, 127.0 (3d), 79.2 (d), 64.1 (t), 53.2 (t), 50.3 (t), 36.7 (t). IR (film): 3100–3000 (=C—H), 3000–2700 (C—H), 1750 (C=O). Anal. Calcd for $C_{19}H_{21}NO_2$ (295.38): C, 77.25; H, 7.17; N, 4.74. Found: C, 76.98; H, 6.99; N, 4.48.

(2*S*,1′*S*)-, (2*R*,1′*S*)-2-[1-(*N*,*N*-Dibenzylamino)ethyl]-4,5-dihydro-3(2*H*)-furanone (27a). Hydrolysis of **21a** (490 mg, 1.50 mmol) yielded 435 mg of crude product. After purification by recrystallization (methanol), 366 mg (79%) of **27a** were obtained as colorless crystals, mp 80 °C, $[\alpha]^{20}_D$ = −99.6° ($CHCl_3$, c = 2.0). ^{1}H NMR: 7.41–7.14 (m, 10 H), 4.35 (dt, J = 4.3, 9.0 Hz, 1 H), 4.06 (d, J = 2.2 Hz, 1 H), 4.01 (dt, J = 7.4, 9.0 Hz, 1 H), 3.72 (d, J = 14.2 Hz, 2 H), 3.66 (d, J = 14.2 Hz, 2 H), 3.20 (dq, J = 2.2, 6.9 Hz, 1 H), 2.34 (m_c, 2 H), 1.01 (d, J = 6.9 Hz, 3 H). ^{13}C NMR: 215.2 (s), 140.2 (s), 128.5, 128.2, 126.8 (3d), 81.2 (d), 64.7 (t), 54.7 (t), 54.5 (d), 36.8 (t), 10.7 (q). IR (KBr): 3120–3000 (=C—H), 3000–2800 (C—H), 1745 (C=O). Anal. Calcd for $C_{20}H_{23}NO_2$ (309.41): C, 77.64; H, 7.49; N, 4.53. Found: C, 77.73; H, 7.55; N, 4.47.

(2*S*,1′*S*)-, (2*R*,1′*S*)-2-[1-(*N*,*N*-Dibenzylamino)-2-phenylethyl]-4,5-dihydro-3(2*H*)-furanone (28a,b). Hydrolysis of **22** (1.00 g, 2.50 mmol, a:b = 92:8) yielded 953 mg of crude product (a:b = 92:8). Purification by chromatography (chromatotron, hexane/EtOAc 5:1) afforded 584 mg (61%) of **28** (a:b = 93:7) as a yellow oil. ^{1}H NMR **28a**: 7.32–6.95 (m, 15 H), 4.25 (dt, J = 2.8, 9.4 Hz, 1 H), 3.95 (dt, J = 6.9, 9.4 Hz, 1 H), 4.05 (s, 1 H), 3.89 (d, J = 14.2 Hz, 2 H), 3.54 (2d, J = 14.2 Hz, 2 H), 3.48 (m_c, 1 H), 2.96 (dd, J = 8.4, 13.8 Hz, 1 H), 2.60 (dd, J = 7.0, 13.8 Hz, 1 H), 2.18 (ddd, J = 2.8, 6.9, 18.1 Hz, 1 H), 1.88 (td, J = 9.4, 18.1 Hz, 1 H). ^{13}C NMR **28a**: 215.6 (s), 139.7, 138.7 (2s), 130.0, 128.6, 128.1, 127.9, 126.8, 126.1 (6d), 79.4 (d), 64.7 (t), 60.9 (d), 53.3 (t), 36.1 (t), 33.3 (t). ^{13}C NMR **28b**: 81.0 (d), 64.2 (t), 60.5 (d), 38.0 (t), 31.9 (t). IR 3100–3000 (=C—H), 3000–2800 (C—H), 1750 (C=O). Anal. Calcd for $C_{26}H_{27}NO_2$ (385.51): C, 81.01; H, 7.06; N, 3.63. Found: C, 80.72; H, 6.93; N, 3.37.

(2*S*,1′*S*)-, (2*R*,1′*S*)-2-[1-(*N*,*N*-Dibenzylamino)-3-methylbutyl]-4,5-dihydro-3(2*H*)-furanone (29a,b). Hydrolysis of **24** (485 mg, 1.00 mmol, a:b = 80:20) yielded 374 mg of crude product (a:b = 80:20). After chromatography (chromatotron, hexane/EtOAc 10:1), 285 mg (81%) of **29** (a:b = 82:18) was obtained as a pale yellow oil. ^{1}H NMR **29a**: 7.33 (m_c, 10 H), 4.33 (dt, J = 4.3, 8.7 Hz, 1 H), 4.19 (d, J = 1.2 Hz, 1 H), 4.06 (dt, J = 2.0, 8.7 Hz, 1 H), 3.93 (d, J = 13.8 Hz, 2 H), 3.36 (d, J = 13.8 Hz, 2 H), 3.13 (ddd, J = 1.2, 3.5, 10.2 Hz, 1 H), 2.44–2.38 (m, 2 H), 1.78 (m_c, 2 H), 0.81, 0.40 (2d, J = 6.5 Hz, 6 H), 0.59 (m_c, 1 H). ^{1}H NMR **29b**: 4.26 (dt, J = 3.6, 9.2 Hz, 1 H), 3.90 (d, J = 13.9 Hz, 2 H), 3.63 (d, J = 13.9 Hz, 2 H), 3.02 (ddd, J = 4.5, 6.5, 7.6 Hz, 1 H), 0.83, 0.71 (2d, J = 6.5 Hz, 6 H). ^{13}C NMR **29a**: 216.5 (s), 140.0 (s), 129.1, 128.2, 126.8 (3d), 78.6 (d), 64.8 (t), 57.0 (d), 54.8 (t), 37.0, 36.9 (2t), 24.7 (q), 21.0 (d). ^{13}C NMR **29b**: 215.2 (s), 128.8 (d), 81.7 (d), 64.2 (t), 55.9 (d), 55.3 (t), 38.0 (t), 34.7 (t), 24.7, 22.8, 22.7 (2q, d). IR (film): 3080–3000 (=C—H), 3000–2700 (C—H), 1750 (C=O). Anal. Calcd for $C_{23}H_{29}NO_2$ (351.49): C, 78.60; H, 8.32; N, 3.99. Found: C, 78.34; H, 8.31; N, 3.86.

$NaBH_4$ Reduction of 3(2*H*)-Dihydrofuranones. General Procedure. The dihydrofuranone was added in portions at rt to a stirred solution of 2 equiv $NaBH_4$ in 2 mL/mmol of EtOH. Stirring was continued at rt for 18 h after the addition of dihydrofuranone was completed. The reaction mixture was quenched with 2 N HCl until the colorless precipitate was dissolved, and then the mixture was extracted with Et_2O (5 × 2 mL/mmol). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and dried with Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by chromatography.

(2*S*,3*R*,1′*S*)-, (2*S*,3*S*,1′*S*)-2-[1-(*N*,*N*-Dibenzylamino)ethyl]-tetrahydrofuran-3-ol (30a,b). Reduction of **27a** (1.85 g, 6.00 mmol) yielded 1.77 g (95%) of tetrahydrofuranol **30** (a:b = 92:8) as a colorless oil; further purification was not necessary. ^{1}H NMR **30a**: 7.33 (m_c, 10 H), 4.51 (t, J = 3.6 Hz, 1 H), 3.91, 3.88 (2t, J = 8.0 Hz, 2 H)), 3.71 (d, J = 11.7 Hz, 2 H), 3.41 (d, J = 11.7 Hz, 2 H), 3.69 (m, 2 H), 3.01 (s, br, 1 H), 2.03 (dd, J = 6.0, 8.0 Hz, 1 H), 1.87 (ddd, J = 3.6, 6.0, 8.0 Hz, 1 H), 1.30 (d, J = 6.5 Hz, 3 H). ^{1}H NMR **30b**: 2.71 (s, br, 1 H), 1.20 (d, J = 7.0 Hz, 3 H). ^{13}C NMR **30a**: 138.5 (s), 129.1, 128.8, 127.7 (3d), 85.3 (d), 71.7 (d), 66.4 (t), 54.3 (t), 53.5 (d), 34.4 (t), 9.3 (q). IR (KBr): 3600–3140 (OH), 3100–3000 (=C—H), 3000–2740 (C—H). Anal. Calcd for $C_{20}H_{25}NO_2$ (311.42): C, 77.14; H, 8.09; N, 4.50. Found: C, 76.80; H, 7.89, N, 4.45.

(2*S*,3*R*,1′*S*)-, (2*S*,3*S*,1′*S*)-2-[1-(*N*,*N*-Dibenzylamino)-2-phenylethyl]tetrahydrofuran-3-ol (31a,b). Reduction of **28** (2.00 mmol, 770 mg, a:b = 98:2) afforded 875 mg of crude product (a:b = 78:22). Purification by chromatography (chromatotron, hexane/EtOAc 10:1) yielded 445 mg (57%) of tetrahydrofuranol **31** (a:b = 95:5) as a colorless solid, mp 90–91 °C. ^{1}H NMR **31a**: 7.42–7.07 (m, 15 H), 4.45 (ddd, J = 1.6, 3.4, 5.3 Hz, 1 H), 3.93 (q, J = 8.0 Hz, 1 H), 3.80 (dd, J = 3.4, 9.0 Hz, 1 H), 3.70 (d, J = 13.3 Hz, 2 H), 3.50 (d, J = 13.3 Hz, 2 H), 3.68 (dt, J = 4.6, 8.0 Hz, 1 H), 3.32 (ddd, J = 5.0, 6.4, 9.0 Hz, 1 H), 3.16 (m_c, 2 H), 2.03 (dtd, J = 5.3, 8.0, 14.0 Hz, 1 H), 1.87 (dddd, J = 1.6, 4.6, 8.0, 14.0 Hz, 1 H). ^{13}C NMR **31a**: 142.0, 139.6 (2s), 130.0, 129.2, 128.8, 128.6, 127.7, 126.1 (6d), 84.5 (d), 71.9 (d), 66.4 (t), 60.0 (d), 54.9 (t), 34.6, 34.5 (2t). ^{13}C NMR **31b**: 141.5, 139.6 (2s), 129.9, 129.3, 129.0, 127.2, 122.6 (5d), 85.0 (d), 75.5 (d), 66.4 (t), 62.0 (d), 54.8 (t), 33.9, 29.9 (2t). IR (KBr): 3540–3320 (OH), 3080–3000 (=C—H), 3000–2760 (C—H). Anal. Calcd for $C_{26}H_{29}NO_2$ (387.52): C, 80.59; H, 7.54; N, 3.61. Found: C, 80.31; H, 7.77; N, 3.49.

Addition of Methylmagnesium Bromide to 3(2*H*)-Dihydrofuranones. General Procedure. A solution of 3(2*H*)-dihydrofuranone in 5 mL/mmol of Et_2O was cooled to −78 °C. At this temperature, 3 equiv of methylmagnesium bromide (1 M ethereal solution) were added dropwise. The reaction mixture was stirred overnight and allowed to reach rt during this time. Quenching with 2 mL/mmol of 5% H_2SO_4 was followed by addition of 1 mL/mmol of CH_2Cl_2. After removal of the organic layer and extraction of the aqueous layer with CH_2Cl_2 (2 × 1 mL/mmol), the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by the method mentioned in the individual experiment.

(2*S*,3*R*,1′*S*)-, (2*S*,3*S*,1′*S*)-2-[1-(*N*,*N*-Dibenzylamino)ethyl]-3-methyltetrahydrofuran-3-ol (32a,b). Methylation of **27a** (618 mg, 2.00 mmol) afforded 425 mg of crude product (a:b = 85:15). Purification by chromatography (chromatotron, hexane/Et_2O 2:1) yielded 379 mg (66%) of tetrahydrofuranol **32** (a:b = 92:8) as a colorless oil. ^{1}H NMR **32a**: 7.33–7.21 (m, 10 H), 5.74 (s, br, 1 H), 3.80 (d, J = 13.2 Hz, 2 H), 3.71 (ddd, J = 5.8, 8.0, 9.0 Hz, 1 H), 3.58 (q, J = 8.0 Hz, 1 H), 3.51 (d, J = 9.1 Hz, 1 H), 3.37 (d, J = 13.2 Hz, 2 H), 3.04 (qd, J = 6.5, 9.1 Hz, 1 H), 1.76 (m_c, 2 H), 1.37 (s, 3 H), 1.22 (d, J = 6.5 Hz, 3 H). ^{1}H NMR **32b**: 1.25 (s, 3 H), 1.01 (d, J = 6.9 Hz, 3 H). ^{13}C NMR **32a**: 138.0 (s), 129.3, 128.5, 127.4 (3d), 84.4 (d), 78.8 (s), 65.5 (t), 54.3 (d), 54.0 (t), 41.5 (t), 28.5 (q), 8.8 (q). ^{13}C NMR **32b**: 141.6 (s), 129.8, 128.5, 126.7 (3d), 81.1 (d), 64.6 (t), 54.6 (t), 36.8 (t), 11.0 (q). IR (KBr): 3580–3320 (OH), 3080–3000 (=C—H), 3000–2780 (C—H). Anal. Calcd for $C_{21}H_{27}NO_2$ (325.45): C, 77.50; H, 8.36; N, 4.30. Found: C, 76.85; H, 8.23; N, 4.10.

(2*S*,3*R*,1′*S*)-2-[1-(*N*,*N*-Dibenzylamino)-2-phenylethyl]-3-methyltetrahydrofuran-3-ol (33a). Methylation of **31** (770 mg, 2.00 mmol, a:b = 98:2) afforded 776 mg of crude product (a:b = 91:9). Recrystallization (Et_2O) yielded 672 mg (84%) of **33a**

as a colorless solid, mp 143–144 °C, $[\alpha]^{20}_D$ = +10.5° ($CHCl_3$, *c* = 1.1). ^{1}H NMR: 7.21 (m_c, 10 H), 7.19 (m_c, 5 H), 4.12 (s, br, 1 H), 3.74 (d, *J* = 6.0 Hz, 1 H), 3.67 (s, 4 H), 3.74–3.67 (m, 2 H), 3.29 (q, *J* = 6.0 Hz, 1 H), 3.11, 3.03 (2dd, *J* = 6.0, 14.3 Hz, 2 H), 1.86, 1.77 (2dt, *J* = 6.0, 13.4 Hz, 2 H), 1.29 (s, 3 H). ^{13}C NMR: 141.8, 140.2 (2s), 129.6, 129.0, 128.3, 128.2, 127.1, 125.7 (6d), 83.3 (d), 79.0 (s), 65.8 (t), 60.3 (d), 54.4 (t), 41.2 (t), 33.1 (t), 26.9 (q). IR (KBr): 3480 (OH), 3080–3000 (=C—H), 3000–2780 (C—H). Anal. Calcd for $C_{27}H_{31}NO_2$ (401.55): C, 80.76; H, 7.78; N, 3.49. Found: C, 80.44; H, 7.91; N, 3.41.

(2*S*,3*R*,1′*S*)-, (2*S*,3*S*,1′*S*)-2-[1-(*N*-Benzylamino)ethyl]tetrahydrofuran-3-ol (34a,b). Palladium black (370 mg) was added to a mixture of methanol (96 mL), formic acid (4 mL), and of tetrahydrofuranol **30** (1.30 g, 4.2 mmol, **a**:**b** = 92:8). After the mixture stirred for 18 h at rt, the catalyst was filtered off, and the solvent was evaporated. The residue was dissolved in water. After extraction with Et_2O (2 × 10 mL), the aqueous layer was neutralized with K_2CO_3. Extraction was repeated with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with water (10 mL) and dried with Na_2SO_4. The solvent was removed in vacuo to afford 360 mg (39%) of tetrahydrofuranol **34** (**a**:**b** = 95:5) as a colorless liquid. Further purification was not necessary. ^{1}H NMR **34a**: 7.27 (m_c, 5 H), 4.51 (q, *J* = 3.0 Hz, 1 H), 4.23 (s, br, 2 H), 4.07 (q, *J* = 8.1 Hz, 1 H), 3.89 (m_c, 1 H), 3.88 (d, *J* = 13.0 Hz, 1 H), 3.66 (d, *J* = 13.0 Hz, 1 H), 3.55 (t, *J* = 3.0 Hz, 1 H), 3.45 (dq, *J* = 3.0, 6.7 Hz, 1 H), 1.97 (m_c, 2 H), 1.25 (d, *J* = 6.7 Hz, 3 H). ^{13}C-NMR **34a**: 139.3 (s), 128.5, 128.1, 127.2 (3d), 84.3 (d), 72.4 (d), 66.9 (t), 53.1 (d), 51.0 (t), 36.0 (t), 16.0 (q). ^{13}C NMR **34b**: 140.1 (s), 128.2, 127.4, 126.8 (3d), 87.8 (d), 74.6 (d), 66.7 (t), 55.4 (d), 51.3 (t), 34.2 (t), 17.4 (q). IR (film): 3580–3210 (OH, NH), 3100–3000 (=C—H), 3000–2760 (C—H). Anal. Calcd for $C_{13}H_{19}NO_2$ (221.30): C, 70.56; H, 8.65; N, 6.33. Found: C, 70.45; H, 8.59; N, 6.30.

(2*S*,3*R*,1′*S*)-, (2*S*,3*S*,1′*S*)-2-(1-Aminoethyl)tetrahydrofuran-3-ol (35a,b). Palladium black (500 mg) was added to a solution of tetrahydrofuranol **30** (1.31 g, 4.20 mmol, **a**:**b** = 92:8) in methanol (50 mL). The mixture was stirred 4 d at rt under slight hydrogen pressure. The catalyst was filtered off, and the solvent was evaporated in vacuo. The residue was purified by fractionated sublimation (90 °C/0.06 Torr) to yield 440 mg (80%, **a**:**b** = 87:13) of **35** as a colorless solid, mp 105–109 °C. ^{1}H NMR **35a**: 4.51 (q, *J* = 3.8 Hz, 1 H), 4.11 (q, *J* = 8.0 Hz, 1 H), 4.11 (m_c, 1H), 3.58 (dq, *J* = 3.8, 6.7 Hz, 1 H), 3.45 (t, *J* = 3.8 Hz, 1 H), 3.34 (m, 3 H), 2.0 (m_c, 2 H), 1.28 (d, *J* = 6.7 Hz, 3 H). **35b**: 4.19 (dt, *J* = 4.2, 7.0 Hz, 1 H), 2.95 (quint, *J* = 6.5 Hz, 1 H), 1.16 (d, *J* = 6.5 Hz, 3 H). ^{13}C-NMR **35a**: 83.8 (d), 72.6 (d), 66.8 (t), 47.4 (d), 35.9 (t), 18.9 (q). ^{13}C NMR **35b**: 89.8 (d), 73.3 (d), 66.5 (t), 49.1 (d), 35.2 (t), 20.6 (q). IR (KBr): 3660–3180 (OH, NH_2), 3000–2500 (C—H). Anal. Calcd for $C_6H_{13}NO_2$ (131.17): C, 54.94; H, 9.99; N, 10.68. Found: C, 55.10; H, 9.95; N, 10.61.

(6*S*,5*S*,1*S*)-4-*N*-Benzyl-5-methyl-2,7-dioxa-4-azabicyclo[4.3.0]nonan-3-one (36). To a cooled (−20 °C) solution of **34** (480 mg, 2.17 mmol, **a**:**b** = 95:5) were added simultaneously 50% aqueous NaOH (5 mL) and trichloromethyl chloroformate (429 mg, 4.17 mmol). The cooling bath was removed, and stirring was continued at rt for 1.5 h. The reaction mixture was quenched with water (5 mL). After removal of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried with $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by chromatography (chromatotron, hexane/EtOAc 2:1) to afford 139 mg (41%, single diastereomer) of **36** as colorless oil, $[\alpha]^{20}_D$ = +21.6° ($CHCl_3$, *c* = 1.0). ^{1}H NMR ([d_6]-acetone): 7.39–7.24 (m, 5 H), 5.07 (m_c, 1 H), 4.32 (d, *J* = 15.5 Hz, 1 H), 4.22 (d, *J* = 15.5 Hz, 1 H), 3.98–3.95 (m, 1 H), 3.94 (d, *J* = 1.8 Hz, 1 H), 3.86 (dt, *J* = 3.7, 8.6 Hz, 1 H), 3.58 (dq, *J* = 1.8, 6.8 Hz, 1 H), 2.30–2.12, 2.18–2.09 (2m, 2 H), 1.19 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR ($CDCl_3$): 152.5 (s), 136.6 (s), 128.3, 127.7, 127.3 (3d), 78.6, 78.2 (2d), 66.7 (t), 52.2 (d), 50.8 (t), 34.5 (t), 17.2 (q). IR (KBr): 3080–3000 (=C—H), 3000–2820 (C—H), 1685 (C=O). Anal. Calcd for $C_{14}H_{17}NO_3$ (247.29): C, 68.00; H, 6.93; N, 5.66. Found: C, 67.87; H, 6.89; N, 5.61.

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