Tandem Protocol for the Stereoselective Synthesis of Different Polyfunctional β-Amino Acids and 3-Amino-Substituted Carbohydrates

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Conjugate addition of homochiral amidocuprates or lithium amides based on (*R*)-*N*-(1-phenylethyl)-(trimethylsilyl)amine to α,β-unsaturated esters proceeds stereoselectively and allows the synthesis of β-amino acids. Trapping of the intermediate ester enolate with D_2O affords the corresponding deuterated compounds. *anti*-α-Alkyl-β-amino acids are obtained stereoselectively after transmetalation of the lithium/copper ester enolate to the titanium ester enolate and trapping with carbon electrophiles. Both diastereomers of β-homothreonine, other precursors of 3-amino-substituted carbohydrates, and stereoselectively in position 2 deuterated analogues are formed from enantiomerically pure γ-alkoxy-substituted enoates. The product distribution observed is complementary to published results regarding 1,4-addition to γ-silyloxy-substituted enoates. The *anti*/*syn* selectivity can be explained by assuming transition state geometries where the delivery of the nitrogen nucleophile is controlled by lithium "chelation" between reagent and substrate. In one case the product configuration can be controlled by the reagent irrespective of the substrate stereochemistry; in other cases the topicity of the addition is complementary to published results. For instance, *erythro*- or *threo*-configured 2,3-dideoxy-3-aminopentoses are accessible via this route.

Although being less abundant than the corresponding α-amino acids, β-amino acids occur in nature both in free form and bound in peptides. They tend to be stronger bases and weaker acids compared to α-amino acids. Peptides containing β-amino acids have a different skeleton atom pattern, and the incorporation of β-amino acids into biologically active peptides may enhance activity and metabolic stability.[1]

3-Amino-2,3-dideoxyaldoses belong to a class of biologically relevant carbohydrates. Some of them are known as components of glycoside and polysaccharide antibiotics (e.g. daunosamine, acosamine, ristosamine).[2] Nucleosides with 3′-amino-substituted carbohydrate moieties often show antiviral[3] or cancerostatic[4] properties. 3′-Amino-2′,3′-dideoxycytidine inhibits DNA replication.[5] 3-Amino-3-deoxyaldoses and their precursors have been obtained via Michael addition of amines to homochiral α,β-unsaturated aldehydes,[6] lactones,[7] or esters,[2,8] carrying suitably protected hydroxy groups.

The most versatile methodology for the asymmetric synthesis of β-amino acids and α-derivatized β-amino acids published so far relies on conjugate addition of nitrogen nucleophiles to α,β-unsaturated esters.[9] This type of reaction allows subsequent α-derivatization of the corresponding β-amino ester enolate with electrophiles. Michael addition of the achiral (amido)cuprate derived from *N*-benzyl-(trimethylsilyl)amine to 2,4-dienoates proceeds highly regio- and diastereoselectively. Subsequent aldol reactions of the enolate can be performed with excellent stereoselectivity.[10] The stereoselectivity of the trapping reaction strongly depends on the double bond geometry[11] of the intermediate ester enolate, which is

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(11) For simplicity, all metals (including Li) are here defined to have higher priority than carbon in the description of *Z* and *E* ester enolates. Hence, the lithium ester enolate and the corresponding silyl ketene acetal are both regarded e.g. as *Z* configured.

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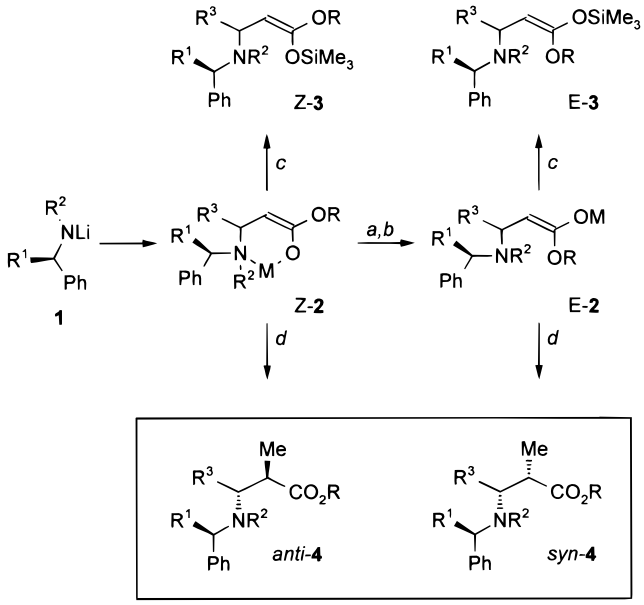
Scheme 1[a]



[a] Key: (a) MeOH; (b) LDA; (c) TMSCl; (d) MeI.

governed by the conformational preference of the enoate. The *s-cis* and *s-trans* conformers of methyl cinnamate are nearly equally populated in the gas phase at 4 K, whereas in solution a slight preference for the *s-cis* conformer of uncomplexed methyl cinnamate was found.[12] The Michael addition of metal amides to uncomplexed α,*β*-unsaturated esters at low temperature is supposed to proceed via this conformation giving perferentially the intermediate *Z*-configured ester enolate, as shown by several examples (e.g. lithium amides,[13,14] lithium/copper amides[10,15,16]). While the ester enolate *Z*-**2** is involved in the tandem addition e.g. of lithium *N*-benzyl(trimethylsilyl)amide to enoates and ester enolate trapping with alkyl halides, the corresponding ester enolate *E*-**2** is formed on deprotonation of the corresponding *β*-amino acid esters (Scheme 1). The configuration of the ester enolates was proved by O-silylation.[13]

However, divergent results regarding the diastereoselectivity of ester enolate alkylation reactions have been published. Methylation of *Z*-**2** obtained on Michael addition of the achiral lithium *N*-benzyl(trimethylsilyl)-amide proceeds with only marginal stereoselectivity (Table 1, entry 1), while a 69:31 selectivity favoring the *anti* isomer is observed upon alkylation of *E*-**2** (entry 2).[13] In contrast, tandem addition of lithium dibenzylamide/ester enolate methylation results in very good *syn* selectivity (entry 3). In this case, the stepwise protocol affords only a marginal excess of the *anti* isomer (entry 4). Products are obtained diastereoselectively according to the literature via a stepwise reaction sequence consisting of Michael addition e.g. of lithiated *N*-benzyl[(*R*)-(1-phenylethyl)]amine to α,*β*-unsaturated esters, quenching, ester enolate formation, and alkylation. Chiral recognition in enolate alkylation obviously is influenced by the distant (*R*)-(1-phenylethyl)amino group. Here, the stepwise protocol [(α*R*,*E*)-**2**: entry 6] represents the matched case with better *anti* selectivity compared to the tandem protocol [(α*R*,*Z*)-**2**: entry 5].[17a]

Table 1. Comparison of *Anti/Syn* Selectivities (%) of Ester Enolate Methylation

entry	enolate type	M	R^1	R^2	R^3	*anti*	*syn*
1	*Z*-**2** (tandem)[a]	Li	H	$SiMe_3$	Me	47	53
2	*E*-**2** (stepwise)[a]	Li	H	$SiMe_3$	Me	69	31
3	*Z*-**2** (tandem)[b]	Li	H	Bzl	Ph	5	95
4	*E*-**2** (stepwise)[b]	Li	H	Bzl	Ph	60	40
5	*Z*-**2** (tandem)[b]	Li	Me	Bzl	Ph	58	42
6	*E*-**2** (stepwise)[b]	Li	Me	Bzl	Ph	97	3

[a] Reference 13. [b] Reference 17a.

The counterion of the intermediate ester enolate also seems to profoundly influence the stereoselectivity of its reaction with electrophiles. Tandem Michael addition of a homochiral lithium amide with subsequent ester enolate methylation proceeds with moderate *anti* selectivity,[17a] while the analogous reaction with the magnesium amide is reported to be highly *syn* selective.[17b]

We are interested in *β*-amino acids as building blocks for analogs of pharmacologically active peptides.[18] Connected with our studies on peptide modification by nonproteinogenic or non-natural amino acids, we elaborated a stereoselective route toward *β*-amino acid derivatives via conjugate addition of homochiral amidocuprates to readily available α,*β*-unsaturated methyl or ethyl esters. (Scheme 2) This method for the synthesis of *β*-amino acid derivatives is based on enantiomerically pure lithium *N*-(1-phenylethyl)(trimethylsilyl)amide (**1a**) and the corresponding lithium (amido)cuprates as homochiral nitrogen nucleophiles,[15] because it is cheap and readily available in both enantiomeric forms in sufficient enantiomeric purity. While our investigation was in progress, the *in situ* generation of this amine was reported;[19] however, no systematic examination of the corresponding amidocuprate has been published yet.

The acid-sensitive N−Si bond is easily cleaved by flash-chromatography or by treatment with dilute acid. Hydrogenolysis of the *N*-(1-phenylethyl)-substituted *β*-amino acid esters usually proceeds smoothly with palladium catalysts and hydrogen or via transfer hydrogenation.[19] However, in the case of *β*-aryl-substituted *β*-amino acid derivatives, where two *N*-benzyl moieties are present in the substrate, a lower yield of the product often is observed because of the formation of the corresponding 3-arylpropionate.

The intermediate lithium/copper ester enolates only slowly react with deuterium oxide to give α-deuterated compounds. (Scheme 2) The α-deuterated derivatives are obtained stereoselectively (de >90%) in good yields with nearly quantitative deuterium incorporation (>95%, according to ^{1}H NMR analysis) as a consequence of the tandem protocol. There are numerous examples that a stepwise protocol (e.g. deprotonation of an ester with LDA and enolate trapping with D_2O) often results in a moderate degree of deuteration, because e.g. diisopropylamine

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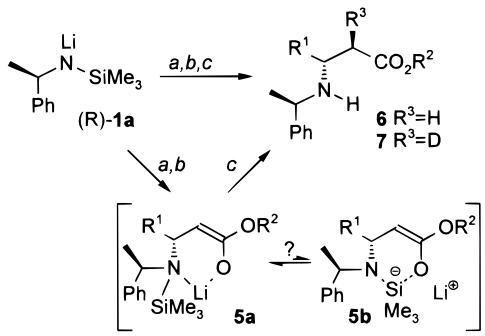
Scheme 2[a]



[a] Key: (a) CuI, 0.2 equiv of HMPA; (b) (*E*)-$R^1CH{=}CHCO_2R^2$; (c) R^3 = H, NH_4Cl_{aq}, or R^3 = D, D_2O, and then NH_4Cl_{aq}.

Table 2. Tandem Michael Addition of (Amido)cuprates/ Enolate Trapping with Electrophiles

entry	R^1	R^2	R^3	yield (%)[a]	predominant diastereomer		diastereomer ratio
1	Me	Et	H	54	(α*R*,3*R*)	**6a**	80:20
2	Et	Et	H	46	(α*R*,3*R*)	**6b**	>99:1
3	^{i}Pr	Et	H	50	(α*R*,3*S*)	**6c**	99:1
4	Ph	Me	H	54	(α*R*,3*S*)	**6d**	>99:1
5	Me	Et	D	53	(α*R*,2*R*,3*R*)	**7a**	83:17:-:-
6	Et	Et	D	47	(α*R*,2*R*,3*R*)	**7b**	99:1:-:-
7	^{i}Pr	Et	D	49	(α*R*,2*R*,3*S*)	**7c**	98:2:-:-
8	Ph	Me	D	54	(α*R*,2*R*,3*S*)	**7d**	95:5:-:-
9	Me	Et	Me	45	(α*R*,2*R*,3*R*)	**9a**	50:25:25:-
10	Et	Et	Me	44		**9b**	54:37:9:-
11	Ph	Me	Me	40	(α*R*,2*R*,3*S*)	**9c**	62:33:5:-
12	Me	Et	Bzl	44		**10a**	42:36:19:3
13	Ph	Me	Bzl	44	(α*R*,2*R*,3*S*)	**10c**	90:10:-:-
14	Ph	Me	Allyl	51	(α*R*,2*R*,3*S*)	**11**	88:12:-:-
15	Ph	Me	CH_2CO_2Et	49	(α*R*,2*R*,3*S*)	**12**	86:12:2:-

[a] Isolated yield.

formed upon lithium enolate generation with LDA may act as an acid.[20] Therefore, the tandem 1,4-addition/ deuteration seems to be especially suited for the synthesis of α-deuterated *β*-amino acids. The stereochemistry of the deuterated product **7d** is (2*R*,3*S*) as revealed by the coupling constant of ca. 2 Hz between 2-H and 3-H in the corresponding *β*-lactam, thus indicating *anti* configuration (*vide infra*, Scheme 4). In contrast, trapping of the intermediate lithium enolate formed upon addition of lithium *N*-benzyl[(*R*)-(1-phenylethyl)]amide to *tert*-butyl cinnamate e.g. with iodomethane is reported to give only moderate diastereoselectivity.[17a] The high *anti* selectivity on deuteration of the lithium/copper enolate (→**7**, Scheme 2 and Table 2, entries 5−8) is explained by steric hindrance of the chelate complex. An additional possible explanation of the high stereoselectivity would be a coordinative stabilization of the ester enolate by the oxophilic silicon substituent (**5b**)[19] strongly favoring *re*-face attack of the deuteron. However, ^{29}Si NMR measurements with the corresponding lithium enolate rule out the presence of a pentacoordinate silicon species (Figure 1). The spectrum of the reaction mixture shows a major peak at 1.31 ppm besides a small signal at −10.5 ppm corresponding to residual lithium *N*-(1-phenylethyl)-(trimethylsilyl)amide. A pentacoordinate silicon species stabilized by intramolecular N-donor coordination usually resonates at considerably higher field.[21]

The intermediate lithium/copper ester enolates do not react with carbon electrophiles under similar reaction

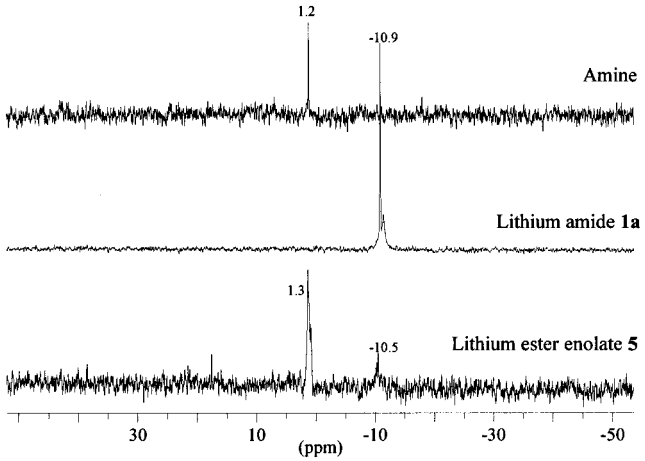
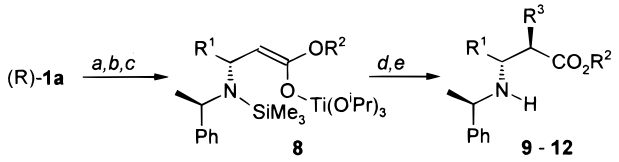


Figure 1. ^{29}Si NMR spectra of *N*-(trimethylsilyl)(1-phenylethyl)amine, of lithium *N*-(trimethylsilyl)(1-phenylethyl)amide (**1a**), and of the reaction mixture of the conjugate addition to methyl cinnamate, recorded in THF-d_8 at 70.459 MHz and 258 K with TMS as an external standard.

Scheme 3[a]



[a] Key: (a) CuI, 0.2 equiv of HMPA; (b) (*E*)-$R^1CH{=}CHCO_2R^2$; (c) $ClTi(O^iPr)_3$; (d) R^3X, 1 equiv of HMPA; (e) NH_4Cl_{aq}.

conditions, presumably because of the existence of sterically demanding bi- or oligonuclear copper complexes of still unknown structure. Alternatively, a migration of the trimethylsilyl group from nitrogen to oxygen and the formation of a *O*-trimethylsilyl ketene acetal intermediate might be feasible. However, this seems to be unlikely, as this species should give rise to a ^{29}Si NMR signal at > 20 ppm.[22]

In the course of our investigation we found that transmetalation of this type of ester enolate from copper to titanium with chlorotriisopropoxytitanium enhances the reactivity toward carbon electrophiles. (Scheme 3 and Table 2, entries 9−15) Trapping with carbon electrophiles is then possible after additional activation with 1 equiv of HMPA. This route provides access to a variety of α-alkyl-substituted *β*-amino acids in a one-pot reaction; the stereoselectivity varies from good to excellent values. Therefore, in some cases this method complements the published procedures.

Except for crotonates, the diastereoselectivity of the Michael addition is quantitative, considering the fact that the enantiomeric excess of the chiral auxiliary used is ≥96%. The topicity of the first reaction step, i.e. the conjugate addition of the lithium (amido)cuprate, was proven by comparison of the optical rotation index of methyl (3*S*)-3-amino-3-phenylpropionate {R^1 = Ph, R^3 = H: $[\alpha]_D^{20}$ −18.4 (*c* 1.8, $CHCl_3$)} with a literature value[23] {$[\alpha]_D^{20}$ −18.2 (*c* 1.46, $CHCl_3$)}. Consequently, chirality

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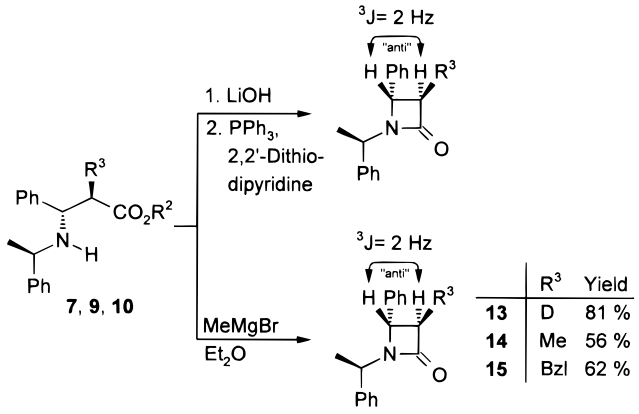
Scheme 4



at C-2 of the α-alkyl derivatives is then revealed by the relative stereochemistry at C-2 and C-3 of the corresponding *β*-lactams, which were obtained via two independent methods: ester saponification and ring closure with triphenylphosphane/2,2′-dithiodipyridine[24] or by Grignard reagent mediated *β*-lactam cyclization[25] (Scheme 4).

The coupling constants between *H*C-2 and *H*C-3 of the *β*-lactam derivatives **13**−**15** are measured to be 2 Hz proving the *anti* relationship of these protons.

In cases where the de value after protonation of the enolate approximates 100% (Table 2, compounds **6b**,**c**), the ratio of the α-alkylated diastereomers represents a measure for the stereoselectivity of the alkylation reaction. We found that methylation of the mononuclear titanated ester enolates favors the 2,3-*anti*-configured products [R^1 = Me, (50 + 25):(25 + 0); R^1 = Et, (54 + 9):(37 + 0); R^1 = Ph, (62 + 5):(33 + 0)]. Hence, the *anti* selectivity of the tandem Michael addition/*Z*-enolate methylation can be slightly enhanced by titanation (cf. Table 1, entries 1 and 5) but still remains insufficient. However, reactions with other carbon electrophiles, e.g. benzylation, allylation, or ethoxycarbonylmethylation, proceed with good to excellent stereoselectivity.

Comparison of four different possible transition states reveals that formation of the *anti* product by attack of the electrophile from the lower side tentatively is favored (**A**, **B**, Scheme 5).

We further investigated the influence of an additional chiral center present in *γ*-alkoxy-substituted enoates on the stereoselectivity of the lithium amide addition.[26] According to the literature, the 1,4-addition of achiral primary amines proceeds with *syn* selectivity.[8,27] Analogously, the addition of organolithiums to both *E*- and *Z*-configured O-MOM-protected *γ*-hydroxy enoates is reported to be *syn* selective.[28]

We found pronounced solvent effects on the *syn*/*anti* ratio of additions using the chiral lithium amide **1a**. The stereoselectivity in most cases is considerably improved

Scheme 5

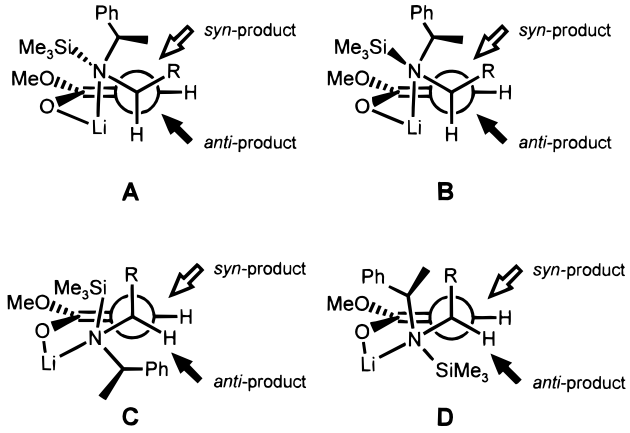


Table 3. *Anti/Syn* Selectivities of the Conjugate Addition to 16

entry			R^1	R^2	solvent		*anti* (%)	*syn* (%)
1	(*S*)-**1a**	(*S*)-**16a**	Me	MOM	ether	**17a**	96	4
2	(*S*)-**1a**	(*S*)-**16a**	Me	MOM	THF	**17a**	92	8
3	(*R*)-**1a**	(*S*)-**16a**	Me	MOM	ether	**18a**	14	86
4	(*R*)-**1a**	(*S*)-**16a**	Me	MOM	THF	**18a**	62	38
5	1b	(*S*)-**16a**	Me	MOM	ether	**19a**	32	68
6	1b	(*S*)-**16a**	Me	MOM	THF	**19a**	50	50
7	(*S*)-**1a**	(*R*)-**16b**	Ph	MOM	ether	**17b**	1	99
8	(*S*)-**1a**	(*R*)-**16b**	Ph	MOM	THF	**17b**	50	50
9	(*R*)-**1a**	(*R*)-**16b**	Ph	MOM	ether	**18b**	12	88
10	(*R*)-**1a**	(*R*)-**16b**	Ph	MOM	THF	**18b**	69	31
11	(*S*)-**1a**	(*S*)-**16c**	$CH_2OC(CH_3)_2$		ether	**17c**	5	95
12	(*S*)-**1a**	(*S*)-**16c**	$CH_2OC(CH_3)_2$		THF	**17c**	50	50
13	(*R*)-**1a**	(*S*)-**16c**	$CH_2OC(CH_3)_2$		ether	**18c**	10	90
14	(*R*)-**1a**	(*S*)-**16c**	$CH_2OC(CH_3)_2$		THF	**18c**	50	50

with ether instead of THF as solvent. Similarly, the addition of the achiral lithium amide **1b** to the enoate **16a** is *syn* selective in ether, while in THF no selectivity is observed (Table 3, entries 5 and 6).

The combination of (*S*)-**1a** with (*S*)-**16a** (matched pair, Table 3, entry 1) provides *anti*-**17a**, while *syn*-**18a** predominates for (R)-**1a**/(S)-**16a** (mismatched pair, Table 3, entry 3). The application of the homochiral lithium amides turned out to be favorable, because the product configuration at C-3 is completely reagent controlled and independent of the substrate stereochemistry, if ether is used as solvent (Scheme 6).

The *syn* selectivity described only recently by Yamamoto et al.[27] for the addition of the achiral lithium amide **1b** to *γ*-(trialkylsilyl)oxy- or *γ*-trityloxy-substituted enoates (*syn*:*anti* 54:46 for OTBDMS to 90:10 for OTIPS; *syn*:*anti* 100:0 for OTrt) can be explained by close analogy to the Felkin−Anh model.[29] Despite the similarity between the addition of a nucleophile to an α-chiral carbonyl group and the corresponding 1,4-addition to a *γ*-chiral α,*β*-unsaturated carbonyl group, the latter reaction should have different steric requirements. Structure **E** (Scheme 7) represents a close analog to the Felkin−Anh model,[29] where the C=O moiety has been replaced by the *E*-configured C=$CHCO_2R^1$ group.[28] The medium size group (CH_3) occupies the *inside* position, the electronegative oxygen substituent (OR^2) is oriented perpendicularly to the double bond, and the small substituent (H) is placed in the *outside* position. Because of the presence of the *O*-trialkylsilyl group of the substrate, Yamamoto et al.

(24) Kobayashi, S.; Iimori, T.; Izawa, T.; Ohno, M. *J. Am. Chem. Soc.* **1981**, *103*, 2406.

(25) (a) Shustov, G. V.; Rauk, A. *Tetrahedron: Asymmetry* **1996**, *7*, 699. (b) Davies, S. G.; Fenwick, D. R. *J. Chem. Soc., Chem. Commun.* **1995**, 1109.

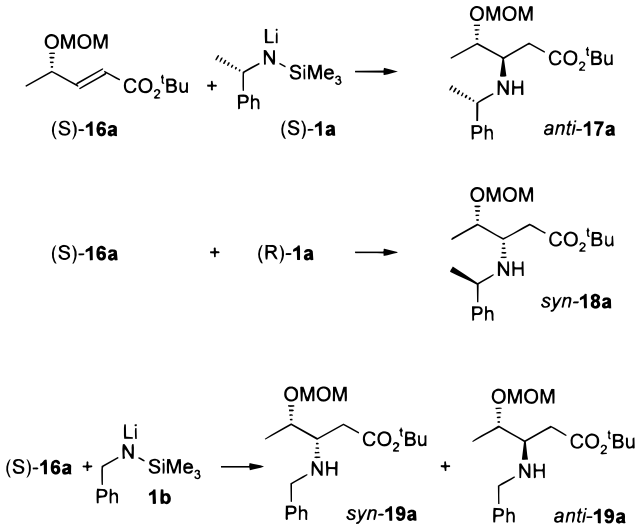
(26) Körner, M.; Findeisen, M.; Sewald, N. *Tetrahedron Lett.* **1998**, *39*, 3463.

(27) Asao, N.; Shimada, T.; Sudo, T.; Tsukada, N.; Yazawa, K.; Gyoung, Y. S.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 6274.

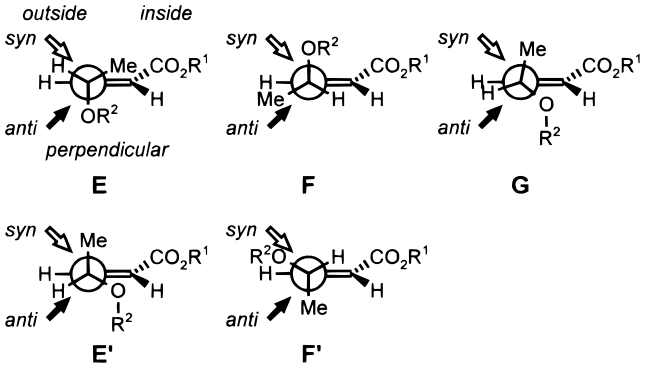
(28) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652 and references cited.

(29) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1997**, *1*, 61.

Scheme 6



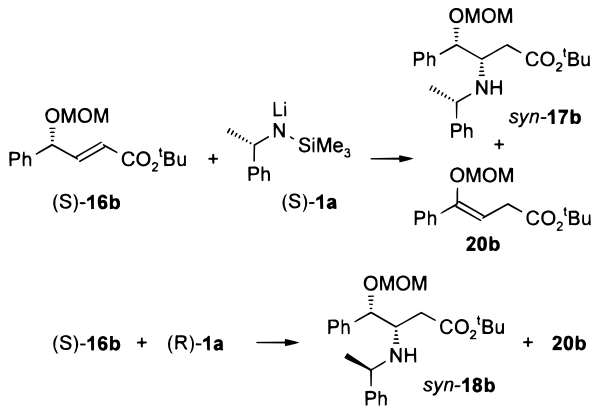
Scheme 7



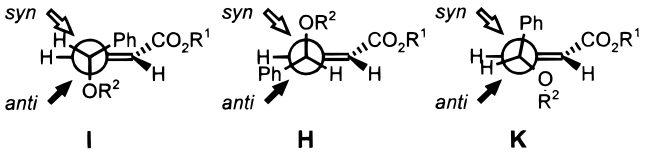
exclude the possibility of a "chelated" transition state, where the delivery of the nucleophile is assisted by lithium co-ordination between reagent nitrogen and substrate oxygen (**E**, *anti*). This model suitably explains *syn* selectivity, but seems to be valid only for *E*-configured α,β-unsaturated esters, because the *inside* position of *Z* enoates is sterically more hindered. A modified Felkin−Anh model **F** has also been suggested[28] but seems to be more appropriate for *Z*-configured esters. Furthermore, divergent results regarding the *syn*/*anti* selectivity of organocuprate additions to enoates had been observed which led to the development of a different model **G**.[28] This has been proposed also on the basis of *ab initio* studies.[30] According to these theoretical studies, transition state conformers with electron-withdrawing (electronegative) groups oriented perpendicularly are electronically disfavored.

A "chelation"-controlled delivery of the nucleophile (**E**, *anti*, or **F**, *syn*) cannot be excluded in the case of the reaction **1a** + **16a** involving MOM-protected derivatives in ether as solvent, taking into account the pronounced solvent dependence of the stereoselectivity. The reagent control of the stereoselectivity observed can be explained by transition state conformers **E** (*anti*; cf. Table 3, entry 1) and **F** (*syn*; cf. Table 3, entry 3), respectively, assuming the above mentioned reagent delivery by lithium coordination between reagent and substrate. Chiral recognition between substrate **16** and lithium amide **1a** efficiently outweighs the predominance of a certain transition state conformer (**E**/**F**). On addition of the achiral nucleophile **1b** to **16a** we found only marginal *syn* preference (Table 3, entry 5). This is in accordance with the findings of Yamamoto et al. regarding the addition of lithium dibenzylamide to γ-methoxy butanoate (*anti*:*syn* 37:63), where chelation-controlled delivery in transition state model **F′** (*syn*) is used to account for *syn* preference.[27] In contrast, the addition of lithium dibenzylamide to γ-((triisopropylsilyl)oxy) butanoate is described to proceed *anti* selectively, which has been explained by chelation control on the basis of structural arguments and increased hardness of the nucleophile compared to the *N*-silyl derivative **1b**.[27] However, the latter argument does not seem to be valid, as the reagent controlled *anti*/*syn* selectivity of the 1,4 addition of **1a** to **16a** presumably depends on steric effects of the reagent/substrate interaction and not likely on a change between chelation control and nonchelation control.

Scheme 8



Scheme 9



Substrate control dominates the stereoselectivity for the phenyl-substituted γ-alkoxy enoates **16b** (Scheme 8 and Table 3, entries 7 and 9). Regardless of the configuration of reagent **1a**, *syn* products are obtained with high selectivity, provided the reaction is performed in ether. The reaction of (*S*)-**1a** with (*R*)-**16b** proceeds slowly but with excellent stereoselectivity. However, the yields are only in a medium range, because a double bond isomerization takes place under the reaction conditions applied to give compound **20b**.

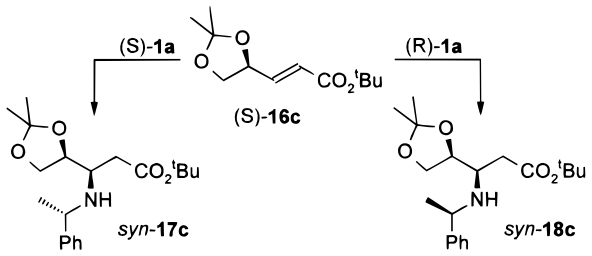
While the reaction of **1a** with the MOM-protected derivatives **16b** is *syn* selective, *anti* products are formed exclusively with the corresponding *O*-silyl-protected γ-hydroxy enoates.[27] Consequently, the addition **1a** + **16b** proceeds via "chelation"-controlled delivery (model **H**, *syn*), while with *O*-silyl protection "nonchelation" delivery (**H**, *anti*) suitably explains the experimental results.[27] **I** and **K** are energetically disfavored (Scheme 9).

The 1,3-dioxolan-4-yl residue like in **16c** usually favors *syn* selectivity in the addition of nucleophiles.[8a,31] This

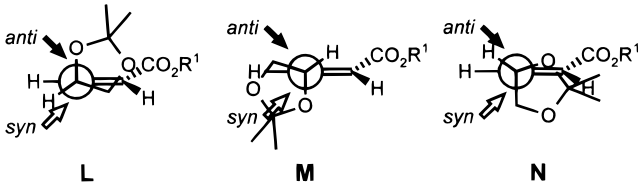
(30) Dorigo, A. E., Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 6524.

(31) Mulzer, J.; Kappert, M.; Huttner, G.; Jibril, I. *Angew. Chem.* **1984**, *96*, 726; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 704.

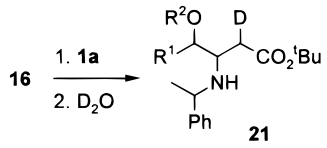
Scheme 10



Scheme 11



Scheme 12



	R^1	R^2	
21a	Me	MOM	αS,2S,3R,4S
21b	Me	MOM	αR,2R,3S,4S
21c	Ph	MOM	αS,2R,3S,4S
21d	Ph	MOM	αR,2R,3S,4S
21e	CH_2O-$C(CH_3)_2$		αS,2S,3R,4S
21f	CH_2O-$C(CH_3)_2$		αR,2S,3R,4S

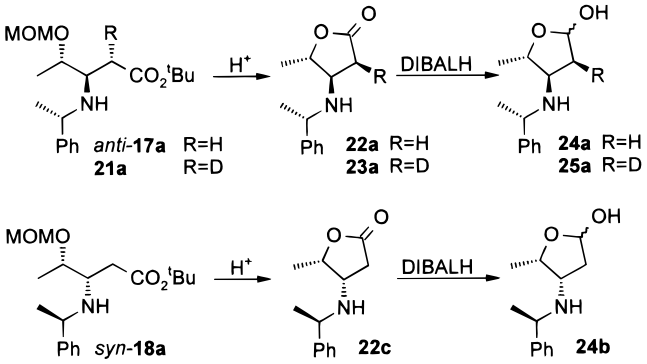
type of stereocontrol by the substrate predominates also in the case of **1a** (Scheme 10 and Table 3, entries 11 and 13). The stereoselectivity drops to zero if THF is used as solvent (Table 3, entries 12 and 14). Only conformer **L** suitably explains the experimental results; formation of *syn* products via **M** is highly disfavored by the heterocycle. However, chelation-controlled reagent delivery should result in the formation of the *anti* isomer, which has not been observed. Probably the rigid dioxolan ring lowers the coordinative ability, or alternatively, the second oxygen atom in the flexible MOM derivatives **16a**,**b** also plays a role (Scheme 11).

The intermediate ester enolates can be trapped with D_2O as a deuteron source to give stereospecifically deuterated products **21**. 1,2-*Anti* induction dominates for the deuteration reaction as proven by NMR analysis of a corresponding β-lactam.[32] While the deuterium incorporation in **21a**,**b** is practically complete (>95% D), insufficient deuteration is observed in the case of the derivatives **21c**−**e** (80−90% D). Byproduct **20b** could explain the result observed for **21c**, as it possesses acidic α-protons, which would be able to protonate the intermediate ester enolate. However, no conclusive explanation for the incomplete deuterium incorporation in products **21d**,**e** can be provided yet (Scheme 12).

The derivatives **17**−**19** and **21** can be easily converted into the γ-lactones **22**/**23** upon treatment with acid (Scheme 13). Exclusive formation of the γ-lactones takes place also with the dihydroxy derivatives **17c** and **18c**,

(32) Körner, M. Ph.D. Thesis, University of Leipzig, 1998.

Scheme 13



which is proven by an IR absorption at ≈1780 cm^{-1}. The γ-lactones were used for stereochemical assignment of all polyfunctional compounds **17**−**19** by nOe difference spectra (Scheme 14, 400 MHz).

DIBALH reduction of the γ-lactones affords the corresponding lactols **24** and **25**, respectively (Scheme 13). Comparison of the ^1H NMR data in DMSO-d_6 with those of analogous compounds[33] reveals a mixture of α and β anomers both for **24a**,**b** and **25a**.

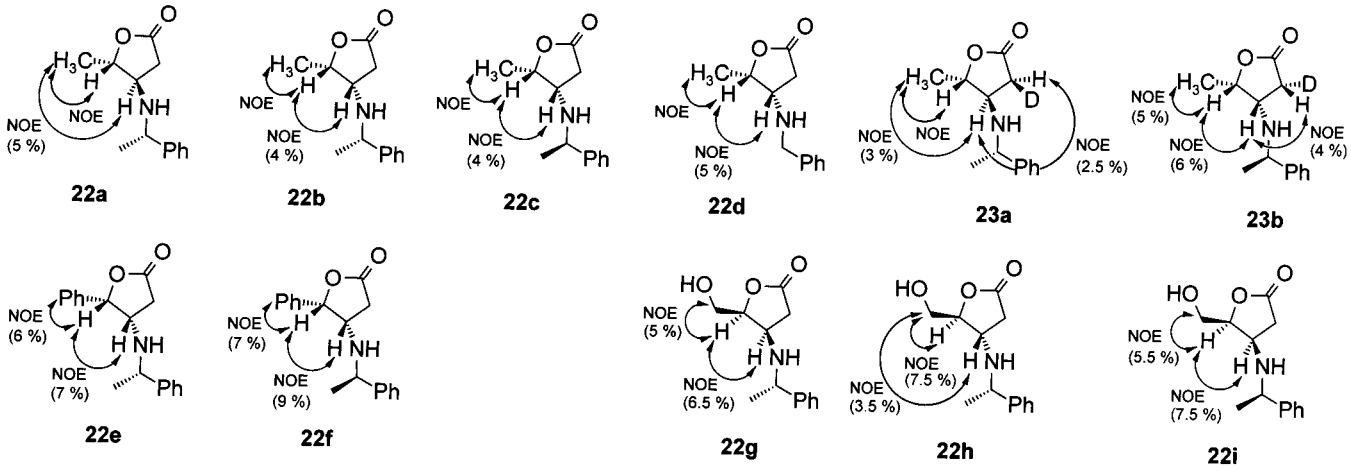
In summary, the tandem protocol presented here enables the synthesis of *anti*-α-deuterio-β-amino acids and *anti*-α-alkyl-β-amino acids including polyfunctional derivatives by 1,4-addition of homochiral nitrogen nucleophiles to γ-alkoxy enoates. Double stereoinduction is observed with chiral substrates. Both diastereomers of β-homothreonine (*anti*-**17a**, *syn*-**18a**) and other precursors of 3-amino-substituted carbohydrates as well as stereoselectively in position 2 deuterated analogues have been synthesized in a reagent- or substrate-controlled manner, depending on the nature of the substrate. The topicity observed is complementary to previous results. The *anti*/*syn* selectivity can be explained assuming transition states where the delivery of the nitrogen nucleophile is controlled by lithium chelation between reagent and substrate. Reagent control in the case of substrate **16a** is accounted for by different transition state geometries. The strategy described enables the straightforward stereoselective synthesis of 2,3-dideoxy-3-aminoaldoses in *erythro* or *threo* configuration, either in the D or L series, and their stereospecifically 2-deuterated derivatives.

Experimental Section

All reactions were performed under dry oxygen-free argon atmosphere in flame-dried glassware. Most reagents were commercially available and of synthetic grade. (*R*)-(1-Phenylethyl)amine with an ee value of ≥96% was used without further purification. Diethyl ether and tetrahydrofuran were distilled immediately before use from sodium benzophenone ketyl. Analytical TLC was performed using silica gel 60 F_{254} plates on aluminum foil; silica gel 60 (32−60 μm) was used for flash chromatography. Melting points were determined with an apparatus according to Tottoli and are uncorrected. Diastereomeric ratios were determined by GC-MS with a 30 m HP-5 MS capillary column, temperature program: (a) 70 °C, 2 min, 70 °C → 270 °C, 25 °C/min or (b) 90 °C, 6 min, 90 °C → 270 °C, 12 °C/min with EI mode for mass detection after aqueous workup and filtration through silica gel. The dr values were verified by ^1H NMR integration where possible.

(33) (a) Fronza, G.; Fuganti, C.; Grasselli, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 885. (b) Hirama, M.; Shigemoto, T.; Itô, S. *J. Org. Chem.* **1987**, *52*, 3342.

Scheme 14



NMR spectra routinely were recorded in $CDCl_3$ at 200 MHz (^{1}H) and 50 MHz (^{13}C), respectively, at 297 K unless otherwise mentioned and were calibrated against internal standards (TMS and/or solvent; δ values in ppm, J values in Hz). IR spectra were recorded as liquid film unless otherwise stated; the data are given in wavenumbers (cm^{-1}).

***N*-[(*R*)-1-Phenylethyl](trimethylsilyl)amine.** A 20.91 mL (15.18 g, 150 mmol) amount of triethylamine was added with stirring to a solution of 12.89 mL (12.12 g, 100 mmol) of (*R*)-(+)-(1-phenylethyl)amine in hexane. The mixture was refluxed for 10 min, and 19.04 mL (16.30 g, 150 mmol) of chlorotrimethylsilane was added. After the mixture was cooled to rt (room temperature), stirring was continued for 24 h. The precipitated triethylammonium chloride was removed by filtration and washed with 25 mL of hexane. Excess chlorotrimethylsilane and hexane were evaporated at ambient pressure; the residual colorless liquid was distilled in vacuo to give 15.26 g (79.0 mmol, 79%) of *N*-[(*R*)-1-phenylethyl]-(trimethylsilyl)amine with bp 82 °C/14 mbar. IR: ν 3380. $[\alpha]_D^{20}$: +54.4 (*c* 1.1, hexane). ^{1}H NMR: δ 0.65 (s, 9H), 1.39 (d, *J* 6.5, 3H), 1.51 (br s, 1H), 4.14 (q, *J* 6.5, 1H), 7.29−7.32 (m, 5H). ^{13}C NMR: δ 0.40, 29.10, 51.10, 125.32, 125.65, 127.66, 148.81. Anal. Calcd for $C_{11}H_{19}NSi$ (193.36): C, 68.34; H, 9.98; N, 7.17. Found: C, 68.55; H, 9.83; N, 7.36.

General Procedure for the Synthesis of α-Deuterated β-Amino Acid Esters. A 2.5 mL volume of a 1.6 M solution (4.0 mmol) of *n*-BuLi in hexane was added to a solution of 0.77 g (4.0 mmol) of *N*-[(*R*)-1-phenylethyl](trimethylsilyl)amine in 8 mL of diethyl ether at −20 °C. The mixture was cooled to −78 °C; then 0.38 g (2.0 mmol) of CuI was added with stirring, and the suspension was kept at −78 °C for 10 min. After addition of 0.24 mL (0.23 g, 1.4 mmol) of triethyl phosphite and 2.0 mmol of the α,β-unsaturated ester stirring was continued for 1 h. The reaction mixture was quenched with 1.0 mL of D_2O to achieve α-deuteration, and stirring was continued for 2 h at room temperature, followed by extraction of the mixture with diethyl ether (2 × 50 mL). The combined organic layers were evaporated to about 50 mL, and the residue was stirred with 40 mL of 1 N HCl to achieve complete desilylation. Then Na_2CO_3 was added and the mixture was subsequently extracted with diethyl ether (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated in vacuo. The products were obtained analytically pure after flash chromatography.

Ethyl(2*R*,3*R*)-2-Deuterio-3-[(*R*)-(1-phenylethyl)amino]-butanoate (7a). Yield: 0.23 g (50 %). Deuteration: >95%. dr: 83:17:0:0. R_f = 0.32 (1:1 EtOAc/hexane). IR: ν 2950, 1720. ^{1}H NMR (major isomer): δ 1.03 (d, *J* 6.6, 3H), 1.26 (t, *J* 7.2, 3H), 1.31 (d, *J* 6.5, 3H), 1.54 (br s, 1H), 2.40 (d, *J* 6.5, 1H), 2.98 (m, 1H), 3.86 (q, *J* 6.5, 1H), 4.15 (q, *J* 7.2, 2H), 7.22−7.25 (m, 5H). ^{13}C NMR (major isomer): δ 14.64, 21.73, 25.01, 40.45 (t, J_{CD} 20 Hz), 48.20, 55.61, 60.41, 126.93, 127.22, 128.78, 146.50, 172.44. GC-MS (a): t_R 8.34 min. Anal. Calcd for $C_{14}H_{20}DNO_2$ (236.33): C, 71.15; H/D, 8.96; N, 5.93. Found: C, 71.32; H/D, 8.93; N, 5.91.

Ethyl(2*R*,3*R*)-2-Deuterio-3-[(*R*)-(1-phenylethyl)amino]-pentanoate (7b). Yield: 0.24 g (47%). Deuteration: >95%. dr: 99:1:0:0. R_f = 0.33 (1:5 EtOAc/hexane). $[\alpha]_D^{20}$ +55.3 (*c* 1.0, $CHCl_3$). IR: ν 1740. ^{1}H NMR: ν 0.85 (t, *J* 7.3, 3H), 1.26 (t, *J* 7.0, 3H), 1.30 (d, *J* 6.5, 3H), 1.37−1.44 (m, 2H), 1.54 (br s, 1H), 2.36 (d, *J* 5.5, 1H), 2.73 (ddd, *J* 6.2, 1H), 3.87 (q, *J* 6.5, 1H), 4.11 (q, *J* 7.0, 2H), 7.26−7.33 (m, 5 H). ^{13}C NMR: δ 10.34, 14.30, 24.86, 27.96, 38.06 (t, J_{CD} 20 Hz), 53.56, 55.14, 60.18, 126.71, 128.24, 129.06, 146.08, 172.56. GC-MS (a): t_R 8.60 min. Anal. Calcd for $C_{15}H_{22}DNO_2$ (250.36): C, 71.96; H/D, 9.26; N, 5.59. Found: C, 72.13; H/D, 9.12; N, 5.14.

Ethyl (2*R*,3*S*)-2-Deuterio-4-methyl-3-[(*R*)-(1-phenylethyl)amino]pentanoate (7c). Yield: 0.26 g (49%). Deuteration: >95%. dr: 98:2:0:0. R_f = 0.33 (EtOAc/hexane 1:4). IR: ν 3320, 1720. $[\alpha]_D^{20}$: +51.3 (*c* 1.1, $CHCl_3$). ^{1}H NMR (360 MHz): δ 0.80 (d, *J* 6.7, 3H), 0.87 (d, *J* 6.7, 3H), 1.26 (t, *J* 7.1, 3H), 1.31 (d, *J* 6.4, 3H), 1.66 (m, 1H), 1.76 (br s, 1H), 2.33 (br d, *J* 6.3, 1H), 2.63 (dd, *J* 6.3/5.5, 1 H), 3.85 (q, *J* 6.4, 1H), 4.13 (q, *J* 7.1, 2H), 7.19−7.34 (m, 5H). ^{13}C NMR (90 MHz): δ 14.24, 18.41, 18.67, 24.81, 31.36, 35.76 (t, J_{CD} 20 Hz), 55.48, 57.60, 60.17, 126.78, 126.88, 128.23, 146.23, 173.00. GC-MS (b): t_R 23.5 min. Anal. Calcd for $C_{16}H_{24}DNO_2$ (264.38): C, 72.69; H/D, 9.53; N, 5.30. Found: C, 72.74; H/D, 9.37; N, 5.18.

Ethyl (2*R*,3*S*)-2-Deuterio-3-phenyl-3-[(*R*)-(1-phenylethyl)amino]propanoate (7d). Yield: 0.30 g (51%). Deuteration: >95%. dr: 95:5:0:0. R_f = 0.27 (1:4 EtOAc/hexane). IR: ν 3310, 1720. $[\alpha]_D^{20}$: +19.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (360 MHz): δ 1.17 (t, *J* 7.0, 3H), 1.34 (d, *J* 6.6, 3H), 1.95 (br s, 1H), 2.70 (br d, *J* 8.0, 1H), 3.66 (q, *J* 6.6, 1H), 4.07 (q, *J* 7.0, 2H), 4.17 (d, *J* 8.0 Hz), 7.13−7.41 (m, 10H). ^{13}C NMR (90 MHz): δ 14.14, 22.25, 42.37 (t, J_{CD} 20 Hz), 54.58, 56.80, 60.34, 126.56, 126.78, 126.99, 127.30, 128.38, 128.49, 142.72, 145.93, 171.70. GC-MS (b): t_R 28.2 min. Anal. Calcd for $C_{19}H_{22}DNO_2$ (298.40): C, 76.47; H/D, 7.77; N, 4.69. Found C, 76.64; H/D, 7.80; N, 5.05.

General Procedure for the Tandem Michael Addition/Enolate Trapping of (Amido)cuprates Based on 1a. A 2.5 mL volume of a 1.6 M solution (4.0 mmol) of *n*-BuLi in hexane was added to a solution of 0.77 g (4.0 mmol) of *N*-[(*R*)-1-phenylethyl](trimethylsilyl)amine in 8 mL of diethyl ether at −20 °C. The mixture was cooled to −78 °C; then 0.38 g (2.0 mmol) of CuI and 0.035 mL (0.2 mmol) of HMPA were added with stirring and the suspension was kept at −78 °C for 10 min. Stirring was continued at −78 °C for 1 h after addition of 2.0 mmol of the α,β-unsaturated ester. The intermediate enolate was then transmetalated by addition of 0.52 g (2.0 mmol) of chlorotriisopropoxytitanium, and stirring was continued at −78 °C for 1 h. The reaction mixture was quenched with a mixture of 10.0 mmol of the electrophile and 1.75 mL (10.0 mmol) of HMPA at −78 °C. After the mixture was stirred for 3 h at the same temperature (the reaction

progress can be monitored by GC-MS), saturated ammonium chloride solution (50 mL) was added, followed by extraction of the mixture with diethyl ether (2 × 50 mL). Benzylation requires longer reaction times and excess of electrophile: 30.0 mmol of benzyl bromide, 30.0 mmol of HMPA, addition at −78 °C, after warming to rt stirring continued for 36 h. The combined organic layers were stirred with 40 mL of 1 N HCl to achieve complete desilylation. Aqueous Na_2CO_3 was added, and the mixture was subsequently extracted with diethyl ether (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The crude reaction mixture was filtered through silica gel; the products were obtained analytically pure after flash chromatography.

Ethyl (2*R*,3*R*)-2-Methyl-3-[(*R*)-(1-phenylethyl)amino]-butanoate (9a). Yield: 0.22 g (45%). dr: 50:25:25:0. R_f = 0.16 (1:5 EtOAc/petroleum ether). IR: ν 1730. ^{1}H NMR (400 MHz, mixture of diastereomers, major isomer in italics): δ *0.95*/1.00/1.05 (*d*/d/d, *J 6.5*/6.5/6.3, 3H), *1.13*/1.11/1.14 (*d*/d/d, *J 7.0*/6.8/7.2, 3H), *1.25*/1.30/1.20 (*t*/t/t, *J 7.1*/7.1/7.1, 3H), *1.31*/1.32/1.33 (*d*/d/d, *J 6.5*/6.3/6.5, 3H), 1.60 (br, 1H), *2.57*/2.70/2.40 (*dq*/dq/dq, *J 6.7, 6.7*/4.3, 7.0/7.2, 7.2, 1H), *2.94*/2.77/2.45 (*dq*/dq/dq, *J 6.4, 6.4*/4.4, 6.6/5.2, 7.2, 1H), *3.84*/3.95/3.92 (*q*/q/q, *J 6.6*/6.6/6.6, 1H), 4.07−4.22 (m, 2H), 7.23−7.36 (m, 5H). ^{13}C NMR (major diastereomer): δ 12.27, 14.74, 18.29, 24.70, 45.11, 52.87, 55.82, 60.58, 127.07, 127.30, 128.84, 146.88, 176.27. GC-MS (a): t_R 8.49/8.55 min. Anal. Calcd for $C_{15}H_{23}NO_2$ (249.35): C, 72.25; H, 9.30; N, 5.62; O, 13.00. Found: C, 72.27; H, 9.14; N, 5.55; O, 13.04.

Ethyl (2*R*,3*R*)-2-Methyl-3-[(*R*)-(1-phenylethyl)amino]-pentanoate (9b). Yield: 0.23 g (44%). dr: 54:37:9:0. R_f = 0.28 (1:4 EtOAc/petroleum ether). IR: ν 1730. ^{1}H NMR (400 MHz, mixture of diastereomers, major isomer in italics): δ *0.80*/0.87/0.88 (*t*/t/t, *J 7.4*/7.4/7.4, 3H), *1.13*/1.08/1.05 (*d*/d/d, *J 6.8*/7.0/7.0, 3H), 1.25 (t, *J* 7.2, 3H), 1.27−1.33 (m, 3H), 1.33−1.47 (m, 3H), 2.50−2.80 (m, 2H), *3.83*/3.92/3.87 (*q*/q/q, *J 6.5*/6.5/6.5, 1H), 4.06−4.21 (m, 2H), 7.22−7.37 (m, 5H). ^{13}C NMR (major diastereomer): δ 10.67, 11.67, 14.46, 24.35, 25.12, 42.10, 55.41, 57.96, 60.57, 127.31, 127.34, 128.73, 146.46, 176.37. GC-MS (a): t_R 8.18 min. $C_{16}H_{25}NO_2$ (263.38).

Methyl (2*R*,3*S*)-2-Methyl-3-phenyl-3-[(*R*)-(1-phenylethyl)amino]propanoate (9c). Yield: 0.24 g (40%). dr: 62:33:5:0. R_f = 0.15 (1:5 EtOAc/petroleum ether). IR: ν 3350, 1720. Major isomer: $[\alpha]_D^{20}$: +16.8 (*c* 1.4, $CHCl_3$). ^{1}H NMR: δ 0.94 (d, *J* 7.0, 3H), 1.27 (d, *J* 6.5, 3H), 1.84 (br, 1H), 2.68 (dq, *J* 9.9, 7.0, 1H), 3.53 (q, *J* 6.5, 1H), 3.76 (s, 3H), 3.89 (d, *J* 9.9, 1H), 7.17−7.34 (m, 10H). ^{13}C NMR: δ 15.02, 21.91, 47.46, 51.60, 54.58, 63.23, 126.63, 126.87, 127.44, 127.58, 128.32, 128.56, 141.46, 146.45, 176.26. GC-MS (a): t_R 9.92 min. Anal. Calcd for $C_{19}H_{23}NO_2$ (297.40): C, 76.74; H, 7.80; N, 4.71; O, 10.76. Found: C, 76.99; H, 7.99; N, 4.59; O, 10.80.

Ethyl (2*R*,3*R*)-2-Benzyl-3-[(*R*)-(1-phenylethyl)amino]-butanoate (10a). Yield: 0.29 g (44%). dr: 42:36:19:3. R_f = 0.18 (1:5 EtOAc/petroleum ether). IR: ν 3320, 1730. ^{1}H NMR (major isomer): δ 1.04 (d, *J* 6.5, 3H), 1.11 (t, *J* 7.2, 3H), 1.27 (d, *J* 6.5, 3H), 1.39 (br, 1H), 2.76−2.97 (m, 4H), 3.87 (q, *J* 6.5, 1H), 4.02 (q, *J* 7.2, 2H), 7.21−7.34 (m, 5H). ^{13}C NMR (major isomer): δ 14.63, 19.16, 24.55, 34.01, 52.48, 53.55, 55.88, 60.55, 126.60, 127.09, 127.35, 128.85 (2×), 129.40, 140.72, 146.83, 174.89. GC-MS (a): t_R 10.96/10.90/11.06 min. Anal. Calcd for $C_{21}H_{27}NO_2$ (325.45): C, 77.50; H, 8.36; N, 4.30; O, 9.83. Found: C, 77.48; H, 8.27; N, 4.48; O, 9.77.

Methyl (2*R*,3*S*)-2-Benzyl-3-phenyl-3-[(*R*)-(1-phenylethyl)amino]propanoate (10c). Yield: 0.33 g (44%). dr: 90:10:0:0. R_f = 0.35 (1:3 EtOAc/petroleum ether). IR: ν 3320, 1730. $[\alpha]_D^{20}$: +85.1 (*c* 0.9, $CHCl_3$). ^{1}H NMR: δ 1.24 (d, *J* 6.6, 3H), 1.76 (br, 1H), 2.52 (dd, *J* 12.4, 3.2, 1H), 2.74−3.00 (m, 2H), 3.54 (q, *J* 6.6, 1H), 3.58 (s, 3H), 3.96 (d, *J* 8.4, 1H), 7.01−7.39 (m, 15H). ^{13}C NMR: δ 22.02, 36.24, 51.38, 54.56, 55.84, 62.26, 126.29, 126.62, 126.91, 127.41, 127.57, 128.34 (2×), 128.65, 128.75, 139.26, 141.63, 146.46, 174.80. GC-MS (a): t_R 12.71 min. Anal. Calcd for $C_{25}H_{27}NO_2$ (373.50): C, 80.40; H, 7.29; N, 3.75. Found: C, 79.99; H, 7.66; N, 3.65.

Methyl (2*R*)-2-{(*S*)-Phenyl-[(*R*)-(1-phenylethyl)amino]-methyl}pent-4-enoate (11). Yield: 0.33 g (51%). dr: 88:12:0:0. R_f = 0.34 (1:4 EtOAc/petroleum ether). IR: ν 3320, 1740. $[\alpha]_D^{20}$: +6.4 (*c* 0.9, $CHCl_3$). ^{1}H NMR: δ 1.25 (d, *J* 6.5, 3H), 1.77 (br, 1H), 1.95 (m, 1H), 2.23 (m, 1H), 2.70 (m, 1H), 3.52 (q, *J* 6.3, 1H), 3.74 (s, 3H), 3.92 (d, *J* 9.6, 1H), 4.94 (m, 1H), 4.96 (m, 1H), 5.64 (m, 1H), 7.19−7.34 Hz (m, 10H). ^{13}C NMR: δ 22.40, 34.85, 51.90, 54.02, 54.97, 62.51, 117.17, 127.07, 127.35, 127.89, 127.98, 128.77, 129.11, 135.62, 141.97, 146.92, 175.31. GC-MS (a): t_R 10.16/9.91 min. Anal. Calcd for $C_{21}H_{25}NO_2$ (323.44): C, 77.98; H, 7.79; N, 4.33; O, 9.89. Found: C, 78.08; H, 7.71; N, 4.29; O, 9.77.

1-Methyl4-Ethyl(2*R*)-2-{(*S*)-Phenyl-[(*R*)-(1-phenylethyl)-amino]methyl}butandioate (12). Yield: 0.36 g (49%). dr: 86:12:2:0. R_f = 0.23 (1:5 EtOAc/petroleum ether). IR: ν 1740, 1680. $[\alpha]_D^{20}$: −2.2 (*c* 0.9, $CHCl_3$). ^{1}H NMR: δ 1.19 (t, *J* 7.0, 3H), 1.25 (d, *J* 6.5, 3H), 1.82 (br, 1H), 2.32 (dd, *J* 16.8, 4.4, 1H), 2.65 (dd, *J* 16.8, 10.4, 1H), 3.13 (ddd, *J* 10.4, 8.6, 4.4, 1H), 3.55 (q, *J* 6.5, 1H), 3.72 (s, 3H), 3.94 (d, *J* 8.6, 1H), 4.04 (q, *J* 7.0, 2H), 7.16−7.32 (m, 10H). ^{13}C NMR: δ 14.12, 22.29, 34.00, 48.37, 51.75, 54.52, 60.62, 61.50, 126.53, 126.93, 127.41, 127.72, 128.36, 128.65, 140.68, 146.08, 171.88, 174.24. GC-MS (a): t_R 11.21 min. Anal. Calcd for $C_{22}H_{27}NO_4$ (369.46): C, 71.52; H, 7.37; N, 3.79. Found: C, 71.55; H, 7.24; N, 3.97.

General Procedure for β-Lactam Formation. (a) Saponification with Subsequent Cyclization. A 21 mg amount of lithium hydroxide monohydrate (0.5 mmol) was added at 0 °C to a solution of the β-amino acid ester (0.1 mmol) in 8.0 mL of MeOH/H_2O (3:1, v/v). The mixture was stirred at 5 °C for 20 h. The solvent was evaporated in vacuo, the residue was dissolved in H_2O, and the solution was acidified to pH 2 with 1 M HCl. The solvent was evaporated in vacuo, and the residue was redissolved in water and lyophilized. The crude β-amino acid hydrochloride and 14 μL triethylamine (0.1 mmol) were dissolved in 15.0 mL of absolute acetonitrile. A 31.5 mg amount of triphenylphosphine (0.12 mmol) and 26.4 mg of 2,2′-dithiodipyridine (0.12 mmol) were added, and the mixture was refluxed for 8 h. The solvent was evaporated in vacuo, and the residue was purified by flash-chromatography (eluent chloroform).

(b) Ester Cyclization. A 1 mL amount of a 1.0 M solution of methylmagnesium bromide (1.0 mmol) in absolute ether was added to a solution of the β-amino acid ester (1.0 mmol) in absolute ether. The mixture was refluxed, and the reaction progress was monitored by GC-MS. After addition of 50 mL of aqueous NH_4Cl, the organic layer was separated and the aqueous layer was extracted with ether (2 × 50 mL). The organic layers were pooled, dried over $MgSO_4$, and evaporated in vacuo. The products were obtained analytically pure after flash chromatography.

(3*R*,4*S*)-3-Deuterio-4-phenyl-1-[(*R*)-1-phenylethyl]azetidin-2-one (13). Yield (b): 0.20 g (81%). R_f = 0.27 ($CHCl_3$). IR: ν 1740, 1670, 1630. $[\alpha]_D^{20}$: −15.8 (*c* 1.4, $CHCl_3$). ^{1}H NMR: δ 1.30 (d, *J* 7.3, 3H), 2.81 (br d, *J* 2.5, 1H), 4.29 (d, *J* 2.5, 1H), 5.04 (q, *J* 7.3, 1H), 7.24−7.36 (m, 10H). ^{13}C NMR: δ 19.24, 46.50 (m), 52.73, 53.87, 127.21, 127.80, 128.20, 128.91, 129.10, 129.22, 140.26, 140.40, 167.89. GC-MS (a): t_R 9.84 min. $C_{17}H_{16}DNO$ (252.34).

(3*R*,4*S*)-3-Methyl-4-phenyl-1-[(*R*)-1-phenylethyl]azetidin-2-one (14). Yield (b): 0.15 g (56%). R_f = 0.23 ($CHCl_3$), 0.52 (1:1 EtOAc/petroleum ether). $[\alpha]_D^{20}$: −2.1 (*c* 1.0, $CHCl_3$). IR: ν 1750. ^{1}H NMR: δ 1.24 (d, *J* 7.3, 3H), 1.30 (d, *J* 7.3, 3H), 3.01 (dq, *J* 2.1, 7.3 Hz), 3.80 (d, *J* 2.1, 1H), 5.06 (q, *J* 7.3, 1H), 7.19−7.37 (m, 10H). ^{13}C NMR: δ 13.10, 19.13, 52.26, 54.95, 62.69, 127.26, 127.74, 128.14, 128.81, 129.09, 129.16, 140.02, 140.55, 171.72. GC-MS (a): t_R 9.75 min. $C_{18}H_{19}NO$ (265.36).

(3*R*,4*S*)-3-Benzyl-4-phenyl-1-[(*R*)-1-phenylethyl]azetidin-2-one (15). Yield (b): 0.21 g (62%). R_f = 0.46 (1:1 EtOAc/petroleum ether). $[\alpha]_D^{20}$: −14.5 (*c* 1.0, $CHCl_3$). IR: ν 1750. ^{1}H NMR: δ 1.26 (d, *J* 7.2, 3H), 2.90−3.10 (m, 2H), 3.29 (m, 1H), 3.96 (d, *J* 2.2, 1H), 4.95 (q, 1H, *J* 7.2), 6.98−7.29 (m, 15H). ^{13}C NMR: δ 19.26, 34.16, 52.39, 59.82, 60.44, 127.04, 127.29, 127.65, 128.01, 128.75, 129.01, 129.00, 129.12, 129.64, 138.19, 139.76, 140.25, 170.37. GC-MS (a): t_R 12.96 min. $C_{24}H_{23}NO$ (341.45).

General Procedure for the Conjugate Addition of 1 to γ-Alkoxy Enoates 16. A 193 mg (1.0 mmol) amount of *N*-[(*R*)-1-phenylethyl](trimethylsilyl)amine or 178 mg (1.0 mmol) of *N*-benzyl(trimethylsilyl)amine, respectively, in 25 mL of ether was lithiated at −20 °C under an inert gas atmosphere with 625 μL (1.0 mmol, 1.6 M in hexane) of *n*-BuLi. A 0.5 mmol amount of ester (108 mg of **16a**, 139 mg of **16b**, 114 mg of **16c**), dissolved in 2 mL of ether, was added slowly at low temperature, and stirring was continued for a further 4−8 h. Saturated NH_4Cl was added, and the mixture was allowed to reach rt and was then extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with water, saturated $NaHCO_3$, and brine and then evaporated. The crude product was purified by flash chromatography.

Addition of (*S*)-1a to (*S*)-16a. Yield: 160 mg (95%). dr: 96:4.

Major Isomer tert-Butyl (3R,4S)-4-[(methoxy)methoxy]-3-[(1′S)-(1′-phenylethyl)amino]pentanoate (*anti*-17a). R_f = 0.18 (1:5 EtOAc/petroleum ether). $[\alpha]_D^{20}$: −36.0 (*c* 1.0, $CHCl_3$). IR: ν 3336, 1725. ^{1}H NMR: δ 1.12 (d, *J* 6.4, 3H), 1.32 (d, *J* 6.5, 3H), 1.45 (s, 9H), 1.66 (br s, 1H), 2.34 (dd_{ABX}, *J* 14.8, 6.4, 1H), 2.42 (dd_{ABX}, *J* 14.8, 5.7, 1H), 2.81 (ddd, *J* 6.4, 5.7, 4.3, 1H), 3.27 (s, 3H), 3.69 (dq, *J* 4.3, 6.4, 1H), 3.88 (q, *J* 6.5, 1H), 4.48 (d_{AB}, *J* 16.4, 1H), 4.56 (d_{AB}, *J* 16.4, 1H), 7.20−7.32 (m, 5H). ^{13}C NMR: δ 17.47, 25.00, 28.60, 36.54, 55.72, 55.86, 56.88, 75.17, 80.67, 95.80, 127.34, 127.38, 128.76, 146.48, 172.42. GC-MS (a): t_R 9.64 min. Anal. Calcd for $C_{19}H_{31}NO_4$ (337.46): C, 67.62; H, 9.26; N, 4.15. Found: C, 67.22; H, 9.29; N, 4.40.

***tert*-Butyl (3*S*,4*S*)-4-[(Methoxy)methoxy]-3-[(1′*S*)-(1′-phenylethyl)amino]pentanoate (*syn*-17a).** R_f = 0.11 (1:5 EtOAc/petroleum ether). ^{1}H NMR: δ 1.18 (d, *J* 6.4, 3H), 1.32 (d, *J* 6.5, 3H), 1.42 (s, 9H), 2.18 (dd, *J* 14.9, *J* 8.0, 1H), 2.42 (dd, *J* 14.9, *J* 4.9, 1H), 2.59 (br s, 1H), 2.98 (ddd, *J* 8.0, 4.9, 3.8, 1H), 3.27 (s, 3H), 3.87 (q, *J* 6.5, 1H), 3.89 (m, 1H), 4.52 (d, *J* 22.0, 1H), 4.55 (d, *J* 22.0, 1H), 7.20−7.35 (m, 5H). GC-MS (a): t_R 9.59 min.

Addition of (*R*)-1a to (*S*)-16a. Yield: 125 mg (74%). dr: 86:14.

Major Isomer *tert*-Butyl (3*S*,4*S*)-4-[(Methoxy)methoxy]-3-[(1′*R*)-(1′-phenylethyl)amino]pentanoate (*syn*-18a). R_f = 0.09 (1:6 EtOAc/petroleum ether). $[\alpha]_D^{20}$: +47.4 (*c* 1.0, $CHCl_3$). IR: ν 3345, 1726. ^{1}H NMR: δ 1.10 (d, *J* 6.2, 3H), 1.33 (d, *J* 6.6, 3H), 1.44 (s, 9H), 1.60 (br s, 1H), 2.34 (dd, *J* 14.7, *J* 6.3, 1H), 2.46 (dd, *J* 14.7, *J* 6.4, 1H), 2.80 (ddd, *J* 6.4, 6.3, 3.4, 1H), 3.33 (s, 3H), 3.60 (dq, *J* 3.4, 6.2, 1H), 3.88 (q, *J* 6.6, 1H), 4.55 (d, *J* 15.4, 1H), 4.59 (d, *J* 15.4, 1H), 7.15−7.30 (m, 5H). ^{13}C NMR: δ 16.53, 25.40, 28.50, 37.30, 55.92, 56.10, 56.95, 75.14, 80.75, 95.90, 127.38, 127.43, 128.78, 146.41, 172.61. GC-MS: t_R 9.64 min. Anal. Calcd for $C_{19}H_{31}NO_4$ (337.46): C, 67.62; H, 9.26; N, 4.15. Found: C, 66.89; H, 8.92; N, 4.37.

***tert*-Butyl (3*S*,4*S*)-4-[(Methoxy)methoxy]-3-[(1′*R*)-(1′-phenylethyl)amino]pentanoate (*anti*-18a).** R_f = 0.05 (1:6 EtOAc/petroleum ether). ^{1}H NMR: δ 1.10 (d, *J* 6.4, 3H), 1.30 (d, *J* 6.4, 3H), 1.43 (s, 9H), 2.21 (dd, *J* 14.9, *J* 7.7, 1H), 2.31 (dd, *J* 14.9, *J* 5.5, 1H), 2.85 (ddd, *J* 7.7, 5.5, 2.9, 1H), 3.89 (dq, *J* 6.4, 2.9, 1H), 3.97 (q, *J* 6.4, 1H), 4.64 (d, *J* 11.7, 1H), 4.67 (d, *J* 11.7, 1H), 7.18−7.35 (m, 5H). GC-MS (a): t_R 9.68 min.

Addition of 1b to (*S*)-16a. Yield: 144 mg (89%). dr: 68:32.

***tert*-Butyl(4*S*)-3-(Benzylamino)-4-[(methoxy)methoxy]-pentanoate (*syn/anti*-19a).** IR: ν 3337, 1726. Major isomer (*syn*): R_f = 0.06 (1:5 EtOAc/petroleum ether). $[\alpha]_D^{20}$: +8.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 1.19 (d, *J* 6.6, 3H), 1.44 (s, 9H), 1.61 (br s, 1H), 2.34 (dd, *J* 15.2, 7.4, 1H), 2.49 (dd, *J* 15.2, 5.4, 1H), 3.09 (ddd, *J* 7.4, 5.4, 4.3, 1H), 3.35 (s, 3H), 3.76 (d, *J* 13.0, 1H), 3.82 (dq, *J* 6.6, 4.3, 1H), 3.86 (d, *J* 13.0, 1H), 4.62 (d, *J* 14.3, 1H), 4.66 (d, *J* 14.3, 1H), 7.21−7.37 (m, 5H). ^{13}C NMR: δ 16.20, 28.50, 37.38, 52.33, 55.94, 58.91, 74.62, 80.90, 95.85, 127.39, 128.67, 128.82, 141.14, 172.69. GC-MS (b): t_R 17.87 min. Minor isomer (*anti*): R_f = 0.05 (1:5 EtOAc/petroleum ether). ^{1}H NMR: δ 1.19 (d, *J* 6.4, 3H), 1.45 (s, 9H), 1.76 (br s, 1H), 2.36 (dd, *J* 15.1, 7.4, 1H), 2.45 (dd, *J* 15.1, 5.4, 1H), 3.05 (ddd, *J* 7.4, 5.4, 4.2, 1H), 3.35 (s, 3H), 3.82 (m, 3H), 4.62 (d, *J* 11.0, 1H), 4.66 (d, *J* 11.0, 1H), 7.20−7.38 (m, 5H). ^{13}C NMR: δ 17.00, 28.50, 37.28, 52.02, 55.94, 59.20, 74.37, 80.82, 95.85, 127.36, 128.67, 128.82, 141.14, 172.67. GC-MS (b): t_R 17.91 min. Anal. Calcd for $C_{18}H_{29}NO_4$ (323.43): C, 66.84; H, 9.04; N, 4.33. Found: C, 66.92; H, 8.64; N, 4.78.

Addition of (*S*)-1a to (*R*)-16b. Yield: 54 mg (27%). dr: 99:1.

Major Isomer *tert*-Butyl (3*S*,4*S*)-4-[(Methoxy)methoxy]-3-[(1′*S*)-(1′-phenylethyl)amino]-4-phenylbutanoate (*syn*-17b). R_f = 0.09 (1:10 EtOAc/petroleum ether). $[\alpha]_D^{20}$: +46.0 (*c* 1.0, $CHCl_3$). IR: ν 3341, 1726. ^{1}H NMR: δ 1.24 (d, *J* 6.4, 3H), 1.39 (s, 9H), 1.74 (br s, 1H), 1.92 (dd, *J* 15.1, 7.2, 1H), 2.42 (dd, *J* 15.1, 5.8, 1H), 3.21 (ddd, *J* 7.2, 5.8, 4.5, 1H), 3.30 (s, 3H), 3.86 (q, *J* 6.4, 1H), 4.55 (s, 2H), 4.87 (d, *J* 4.5, 1H), 7.25−7.36 (m, 10H). ^{13}C NMR: δ 24.67, 28.46, 38.59, 56.22, 56.33, 57.36, 76.47, 80.67, 95.08, 127.44, 127.97, 128.16, 128.17, 128.63, 128.79, 139.34, 146.20, 172.22. GC-MS (a): t_R 11.51 min. Anal. Calcd for $C_{24}H_{33}NO_4$ (399.53): C, 72.15; H, 8.33; N, 3.51. Found: C, 71.79; H, 8.02; N, 3.49.

***tert*-Butyl 4-[(Methoxy)methoxy]-4-phenylbut-3-enoate (20b).** R_f = 0.04 (1:10 EtOAc/petroleum ether). ^{1}H NMR: δ 1.47 (s, 9H), 3.30 (d, *J* 7.2, 2H), 3.50 (s, 3H), 4.82 (s, 2H), 5.47 (t, *J* 7.2, 1H), 7.30−7.48 (m, 5H). GC-MS (a): t_R 9.06 min.

Addition of (*R*)-1a to (*R*)-16b. Yield: 78 mg (39%). dr: 88:12.

Major Isomer *tert*-Butyl (3*S*,4*S*)-4-[(Methoxy)methoxy]-3-[(1′*R*)-(1′-phenylethyl)amino]-4-phenylbutanoate (*syn*-18b). R_f = 0.03 (1:10 EtOAc/petroleum ether). $[\alpha]_D^{20}$: +36.0 (*c* 1.0, $CHCl_3$). IR: ν 3345, 1725. ^{1}H NMR: δ 1.27 (d, *J* 6.6, 3H), 1.44 (s, 9H), 2.21 (dd, *J* 15.0, 5.4, 1H), 2.50 (dd, *J* 15.0, 7.0, 1H), 2.60 (br s, 1H), 3.07 (ddd, *J* 7.0, 5.4, 4.8, 1H), 3.35 (s, 3H), 3.83 (q, *J* 6.6, 1H), 4.53 (d_{AB}, *J* 10.2, 1H), 4.56 (d_{AB}, *J* 10.2, 1H), 4.71 (d, *J* 4.8, 1H), 7.05−7.35 (m, 10H). ^{13}C NMR: δ 25.17, 28.51, 37.75, 55.72, 56.38, 57.40, 79.37, 80.78, 95.21, 127.05, 127.20, 128.06, 128.13, 128.56, 128.76, 139.52, 145.89, 172.15. GC-MS (a): t_R 11.41 min. $C_{24}H_{33}NO_4$ (399.53).

***tert*-Butyl (3*R*,4*S*)-4-[(Methoxy)methoxy]-3-[(1′*R*)-(1′-phenylethyl)amino]-4-phenylbutanoate (*anti*-18b).** R_f = 0.05 (1:10 EtOAc/petroleum ether). IR: ν 3345, 1725. ^{1}H NMR: δ 1.32 (d, *J* 6.4, 3H), 1.41 (s, 9H), 1.90 (br s, 1H), 2.17 (dd, *J* 15.0, 4.8, 1H), 2.32 (dd, *J* 15.0, 8.4, 1H), 3.02 (ddd, *J* 8.4, 4.8, 3.7, 1H), 3.45 (s, 3H), 4.07 (q, *J* 6.4, 1H), 4.61 (d_{AB}, *J* 10.3, 1H), 4.64 (d_{AB}, *J* 10.3, 1H), 4.97 (d, *J* 3.7, 1H), 7.05−7.38 (m, 10H). GC-MS (a): t_R 11.47 min.

Addition of (*S*)-1a to (*S*)-16c. Yield: 131 mg (75%). dr: 95:5.

Major Isomer *tert*-Butyl (3*R*)-3-[(4′*S*)-2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl-3-[(1″*S*)-(1″-phenylethyl)amino]propanoate (*syn*-17c). R_f = 0.28 (1:4 EtOAc/petroleum ether). $[\alpha]_D^{20}$: −32.0 (*c* 1.06, $CHCl_3$). IR: ν 3343, 1726. ^{1}H NMR: δ 1.31 (s, 3H), 1.35 (d, *J* 6.6, 3H), 1.37 (s, 3H), 1.45 (s, 9H), 2.15 (br s, 1H), 2.31 (dd, *J* 14.8, 5.1, 1H), 2.46 (dd, *J* 14.8, 6.2, 1H), 2.81 (ddd, *J* 6.2, 5.1, 5.1, 1H), 3.75 (dd, *J* 8.0, 7.0, 1H), 3.88 (dd, *J* 8.0, 6.6, 1H), 3.93 (q, *J* 6.6, 1H), 4.08 (ddd, *J* 7.0, 6.6, 5.1, 1H), 7.20−7.35 (m, 5H). ^{13}C NMR: δ 25.60, 25.71, 26.85, 28.58, 37.52, 54.21, 55.61, 66.59, 78.19, 81.06, 109.52, 127.30, 127.40, 128.84, 146.03, 171.82. GC-MS (a): t_R 9.95 min. Anal. Calcd for $C_{20}H_{31}NO_4$ (349.47): C, 68.73; H, 8.94; N, 4.00. Found: C, 68.65; H, 9.20; N, 3.49.

***tert*-Butyl (3*S*)-3-[(4′*S*)-2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl-3-[(1″*S*)-(1″-phenylethyl)amino]propanoate (*anti*-17c).** R_f = 0.38 (1:4 EtOAc/petroleum ether). $[\alpha]_D^{20}$: −12.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 1.31 (d, 6.4, 3H), 1.33 (s, 3H), 1.42 (s, 3H), 1.43 (s, 9H), 1.72 (br s, 1H), 2.33−2.36 (m, 2H), 2.98 (m, 1H), 3.79 (dd, *J* 8.0, 5.9, 1H), 3.92 (q, *J* 6.4, 1H), 4.01 (dd, *J* 8.0, 6.4, 1H), 4.11 (m, 1H), 7.20−7.32 (m, 5H). ^{13}C NMR: δ 24.86, 25.56, 27.02, 28.57, 37.66, 55.33, 55.60, 67.82, 77.33, 80.92, 109.55, 127.12, 127.43, 128.89, 146.57, 172.15. GC-MS (a): t_R 9.87 min.

Addition of (*R*-1a) to (*S*)-16c. Yield: 143 mg (82%). dr: 90:10.

Major Isomer *tert*-Butyl (3*R*)-3-[(4′*S*)-2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl-3-[(1″*R*)-(1″-phenylethyl)amino]pro-

panoate (*syn*-18c). R_f = 0.17 (1:5 EtOAc/petroleum ether). $[\alpha]_D^{20}$: +24.0 (*c* 1.0, $CHCl_3$). IR: ν 3336, 1725. ^{1}H NMR (400 MHz): δ 1.33 (s, 3H), 1.35 (d, *J* 6.6, 3H), 1.41 (s, 3H), 1.44 (s, 9H), 1.72 (br s, 1H), 2.25 (dd, *J* 15.2, 6.8, 1H), 2.35 (dd, *J* 15.5, 5.6, 1H), 3.11 (ddd, *J* 6.8, 5.6, 5.1, 1H), 3.84 (dd, *J* 8.1, 7.1, 1H), 3.99 (q, *J* 6.6, 1H), 4.02 (dd, *J* 8.1, 6.5, 1H), 4.23 (ddd, *J* 6.6, 6.5, 5.1, 1H), 7.20−7.35 (m, 5H). ^{13}C NMR: δ 24.67, 25.75, 26.93, 28.55, 38.22, 53.97, 55.99, 66.64, 78.35, 81.08, 109.62, 127.14, 127.34, 128.85, 146.55, 172.00. GC-MS (a): t_R 9.97 min. Anal. Calcd for $C_{20}H_{31}NO_4$ (349.47): C, 68.73; H, 8.94; N, 4.00. Found: C, 68.37; H, 8.78; N, 4.50.

***tert*-Butyl (3*S*)-3-[(4′*S*)-2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl-3-[(1″*R*)-(1″-phenylethyl)amino]propanoate (*anti*-18c).** R_f = 0.09 (1:6 EtOAc/petroleum ether). ^{1}H NMR (400 MHz): δ 1.36 (s, 3H), 1.36 (d, *J* 6.7, 3H), 1.38 (s, 3H), 1.47 (s, 9H), 1.72 (br s, 1H), 2.32 (dd, *J* 14.7, *J* 4.9, 1H), 2.47 (dd, *J* 14.7, *J* 6.4, 1H), 2.82 (ddd, *J* 6.4, 5.3, 4.9, 1H), 3.76 (dd, *J* 8.1, *J* 6.9, 1H), 3.89 (dd, *J* 8.1, *J* 6.6, 1H), 3.93 (q, *J* 6.7, 1H), 4.09 (ddd, *J* 6.7, 6.6, 5.3, 1H), 7.20−7.35 (m, 5H). GC-MS (a): t_R 9.92 min.

General Procedure for the Tandem Addition/Deuteration. A 193 mg (1.0 mmol) amount of *N*-[(*R*)-1-phenylethyl]-(trimethylsilyl)amine in 25 mL of ether was lithiated at −20 °C under an inert gas atmosphere with 625 μL (1.0 mmol, 1.6 M in hexane) of *n*-BuLi. A 0.5 mmol amount of ester (108 mg of **16a**, 139 mg of **16b**, 114 mg of **16c**), dissolved in 2 mL of ether, was added slowly at low temperature, and stirring was continued for a further 4−8 h. A 100 μL (5.0 mmol) volume of D_2O was added at −78 °C and the mixture was allowed to reach rt within 2 h. Saturated NH_4Cl solution was added, and the mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with water, saturated $NaHCO_3$, and brine and then evaporated. The crude product was purified by flash chromatography.

Tandem Addition of (*S*)-1a to (*S*)-16a/Deuteration. Yield: 150 mg (89%). dr: 96:4. Deuteration: >95%.

Major Isomer *tert*-Butyl (2*S*,3*R*,4*S*)-2-Deuterio-4-[(methoxy)methoxy]-3-[(1′*S*)-(1′-phenylethyl)amino]pentanoate (21a). R_f = 0.16 (1:4 EtOAc/petroleum ether). $[\alpha]_D^{20}$: −28.6 (*c* 1.0, $CHCl_3$). IR: ν 3333, 1722. ^{1}H NMR: δ 1.12 (d, *J* 6.4, 3H), 1.31 (d, *J* 6.4, 3H), 1.45 (s, 9H), 1.60 (br s, 1H), 2.35 (br d, *J* 6.1, 1H), 2.80 (dd, *J* 6.1, 4.3, 1H), 3.27 (s, 3H), 3.69 (dq, *J* 4.3, 6.4, 1H), 3.88 (q, *J* 6.4, 1H), 4.50 (d_{AB}, *J* 16.5, 1H), 4.54 (d_{AB}, *J* 16.5, 1H), 7.20−7.35 (m, 5H). ^{13}C NMR: δ 17.46, 24.99, 28.60, 36.25 (t, J_{CD} 19.1), 55.72, 55.87, 56.82, 75.15, 80.68, 95.80, 127.34, 127.37, 128.76, 146.47, 172.42. GC-MS (a): t_R 9.64 min. Anal. Calcd for $C_{19}H_{30}DNO_4$ (338.47): C, 67.42; H/D, 9.23; N, 4.14. Found: C, 67.41; H/D, 9.12; N, 4.23.

Tandem Addition of (*R*)-1a to (*S*)-16a/Deuteration. Yield: 130 mg (77%). dr: 86:14. Deuteration: >95%.

Major Isomer *tert*-Butyl (2*R*,3*S*,4*S*)-2-Deuterio-4-[(methoxy)methoxy]-3-[(1′*R*)-(1′-phenylethyl)amino]pentanoate (21b). R_f = 0.17 (1:5 EtOAc/petroleum ether). $[\alpha]_D^{20}$: +50.0 (*c* 1.0, $CHCl_3$). IR: ν 3346, 1725. ^{1}H NMR: δ 1.09 (d, *J* 6.2, 3H), 1.32 (d, *J* 6.6, 3H), 1.43 (s, 9H), 1.59 (br s, 1H), 2.34 (br d, *J* 6.0, 1H), 2.79 (dd, *J* 5.5, 3.5, 1H), 3.33 (s, 3H), 3.60 (dq, *J* 3.5, 6.2, 1H), 3.87 (q, *J* 6.6, 1H), 4.56 (d_{AB}, *J* 15.4, 1H), 4.59 (d_{AB}, *J* 15.4, 1H), 7.20−7.36 (m, 5H). ^{13}C NMR: δ 16.53, 25.39, 28.50, 37.20 (t), 55.93, 56.10, 56.90, 75.13, 80.77, 95.90, 127.40, 127.44, 128.78, 146.40, 172.62. GC-MS (a): t_R 9.55 min. Anal. Calcd for $C_{19}H_{30}DNO_4$ (338.47): C, 67.42; H/D, 9.23; N, 4.14. Found: C, 67.23; H/D, 9.10; N, 4.50.

Tandem Addition of (*S*)-1a to (*S*)-16b/Deuteration. Yield: 50 mg (25%). dr: 99:1. Deuteration: >80%.

Major Isomer *tert*-Butyl (2*R*,3*S*,4*S*)-2-Deuterio-4-[(methoxy)methoxy]-3-[(1′*S*)-(1′-phenylethyl)amino]-4-phenylbutanoate (21c). R_f = 0.15 (1:10 EtOAc/petroleum ether). IR: ν 3330, 1724. ^{1}H NMR: δ 1.24 (d, *J* 6.5, 3H), 1.41 (s, 9H), 1.85 (br s, 1H), 1.91 (br d, *J* 7.3, 1H), 3.21 (dd, *J* 7.3, 4.4, 1H), 3.31 (s, 3H), 3.85 (q, *J* 6.5, 1H), 4.56 (s, 2H), 4.87 (d, *J* 4.4, 1H), 7.23−7.38 (m, 10H). ^{13}C NMR: δ 24.81, 28.57, 38.46 (t), 56.26, 56.38, 57.39, 78.16, 80.66, 95.11, 127.36, 127.40, 127.94, 128.12, 128.60, 128.76, 139.36, 146.27, 172.16. GC-MS (a): t_R 11.35 min. Anal. Calcd for $C_{24}H_{32}DNO_4$ (400.54): C, 71.97; H/D, 8.30; N, 3.50. Found: C, 71.58; H/D, 7.84; N, 3.90.

Tandem Addition of (*R*)-1a to (*S*)-16b/Deuteration. Yield: 72 mg (36%). dr: 88:12. Deuteration: >80%.

Major Isomer *tert*-Butyl (2*R*,3*S*,4*S*)-2-Deuterio-4-[(methoxy)methoxy]-3-[(1′*R*)-(1′-phenylethyl)amino]-4-phenylbutanoate (21d). IR: ν 3346, 1725. ^{1}H NMR: δ 1.27 (d, *J* 6.6, 3H), 1.43 (s, 9H), 2.21 (br d, *J* 5.4, 1H), 2.89 (br s, 1H), 3.06 (dd, *J* 5.4, 4.8, 1H), 3.35 (s, 3H), 3.83 (q, *J* 6.6, 1H), 4.52 (d, *J* 10.1, 1H), 4.57 (d, *J* 10.1, 1H), 4.71 (d, *J* 4.8, 1H), 7.05−7.35 (m, 10H). GC-MS (a): t_R 11.26 min. $C_{24}H_{32}DNO_4$ (400.54).

Tandem Addition of (*S*)-1a to (*S*)-16c/Deuteration. Yield: 131 mg (75%). dr: 95:5. Deuteration: >80%.

Major Isomer *tert*-Butyl (2*S*,3*R*)-2-Deuterio-3-[(4′*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl-3-[(1″*S*)-(1″-phenylethyl)amino]propanoate (21e). R_f = 0.21 (1:5 EtOAc/ petroleum ether). IR: ν 3342, 1725. ^{1}H NMR: δ 1.31 (s, 3H), 1.35 (d, *J* 6.6, 3H), 1.36 (s, 3H), 1.45 (s, 9H), 1.79 (br s, 1H), 2.29 (br d, *J* 5.0, 1H), 2.80 (dd, *J* 5.1, 5.0, 1H), 3.75 (dd, *J* 8.0, 7.0, 1H), 3.87 (dd, *J* 8.0, 6.6, 1H), 3.92 (q, *J* 6.6, 1H), 4.08 (ddd, *J* 7.0, 6.6, 5.1, 1H), 7.18−7.33 (m, 5H). ^{13}C NMR: δ 25.62, 25.74, 26.87, 28.60, 37.52 (t), 54.19, 55.61, 66.61, 78.18, 81.06, 109.53, 127.32, 127.42, 128.86, 146.05, 171.84. GC-MS (a): t_R 9.86 min. Anal. Calcd for $C_{20}H_{30}DNO_4$ (350.48): C, 68.54; H/D, 8.92; N, 4.00. Found: C, 68.44; H/D, 8.77; N, 4.13.

Tandem Addition of (*R*)-1a to (*S*)-16c/Deuteration. Yield: 140 mg (80%). dr: 90:10. Deuteration: >80%.

Major Isomer *tert*-Butyl (2*S*,3*R*)-2-Deuterio-3-[(4′*S*)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl-3-[(1″*R*)-(1″-phenylethyl)amino]propanoate (21f). R_f = 0.09 (1:6 EtOAc/ petroleum ether). IR: ν 3332, 1724. ^{1}H NMR: δ 1.31 (d, *J* 6.6, 3H), 1.33 (s, 3H), 1.39 (s, 3H), 1.42 (s, 9H), 1.73 (br s, 1H), 2.29 (br d, *J* 6.6, 1H), 3.08 (dd, *J* 6.6, 5.1, 1H), 3.81 (dd, *J* 8.1, 7.3, 1H), 3.96 (q, *J* 6.6, 1H), 3.99 (dd, *J* 8.1, 6.6, 1H), 4.20 (ddd, *J* 7.3, 6.6, 5.1, 1H), 7.17−7.34 (m, 5H). ^{13}C NMR: δ 24.56, 25.64, 26.83, 28.45, 37.83 (t), 53.86, 55.92, 66.59, 78.30, 81.08, 109.64, 127.17, 127.37, 128.88, 146.57, 172.11. GC-MS (a): t_R 9.83 min. $C_{20}H_{30}DNO_4$ (350.48).

General Procedure for Deprotection/Lactonization of 17−19 and 21. A 0.5 mmol amount of the β-amino acid ester **17**−**19** and **21** was stirred in 10 mL of 6 N hydrochloric acid (A) or 4.0 mL of trifluoroacetic acid (B) for 3 h at rt. The pH was then adjusted to >8, and the mixture was extracted (3×) with 30 mL of ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and evaporated in vacuo. The products were obtained analytically pure after flash chromatography.

(4*R*,5*S*)-5-Methyl-4-[(1′*S*)-(1′-phenylethyl)amino]tetrahydrofuran-2-one (22a) (from *anti*-17a). Yield: 74 mg (67%). R_f = 0.19 (1:2 EtOAc/petroleum ether). $[\alpha]_D^{20}$: −178.0 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): (3435, 1777. ^{1}H NMR: δ 1.27 (d, *J* 6.2, 3H), 1.36 (d, *J* 6.6, 3H), 1.78 (br s, 1H), 2.33 (dd, *J* 17.4, 7.3, 1H), 2.74 (dd, *J* 17.4, 7.3, 1H), 2.96 (ddd, *J* 7.3, 7.3, 6.6), 3.80 (q, *J* 6.6, 1H), 4.23 (dq, *J* 6.6, 6.2, 1H), 7.20−7.36 (m, 5H). ^{13}C NMR: δ 19.44, 25.36, 36.78, 57.00, 59.12, 82.51, 126.98, 127.95, 129.21, 144.71, 175.68. GC-MS (a): t_R 8.96 min. Anal. Calcd for $C_{13}H_{17}NO_2$ (219.28): C, 71.20; H, 7.81; N, 6.39. Found: C, 70.70; H, 7.56; N, 6.26.

(4*S*,5*S*)-5-Methyl-4-[(1′*S*)-(1′-phenylethyl)amino]tetrahydrofuran-2-one (22b) (from *syn*-17a). R_f = 0.12 (1:2 EtOAc/ petroleum ether). ^{1}H NMR (400 MHz): δ 1.28 (d, *J* 6.8, 3H), 1.33 (d, *J* 6.8, 3H), 1.47 (br s, 1H), 2.16 (dd, *J* 17.3, *J* 7.2, 1H), 2.37 (dd, *J* 17.3, 7.6, 1H), 3.41 (ddd, *J* 7.6, 7.2, 6.0), 3.68 (q, *J* 6.8, 1H), 4.60 (dq, *J* 6.0, 6.8, 1H), 7.20−7.30 (m, 5H). ^{13}C NMR: δ 14.99, 24.64, 35.93, 55.01, 57.35, 79.71, 126.96, 128.01, 129.26, 145.42, 175.81. GC-MS (a): t_R 9.13 min. $C_{13}H_{17}NO_2$ (219.28).

(4*S*,5*S*)-5-Methyl-4-[(1′*R*)-(1′-phenylethyl)amino]tetrahydrofuran-2-one (22c) (from *syn*-18a). Yield: 71 mg (65%). R_f = 0.13 (1:2 EtOAc/petroleum ether). $[\alpha]_D^{20}$: +102.0 (*c* 1.0, $CHCl_3$). IR: ν 3324, 1776. ^{1}H NMR (400 MHz): δ 1.36 (d, *J* 6.8, 3H), 1.37 (d, *J* 6.4, 3H), 1.54 (br s, 1H), 2.51 (dd, *J*

17.2, *J* 4.8, 1H), 2.59 (dd, *J* 17.2, 6.4, 1H), 3.26 (ddd, *J* 6.4, 6.0, 4.8), 3.77 (q, *J* 6.4, 1H), 4.50 (dq, *J* 6.0, 6.8, 1H), 7.20−7.30 (m, 5H). ^{13}C NMR: δ 15.06, 25.39, 36.09, 54.72, 56.29, 80.09, 127.07, 127.85, 129.15, 145.00, 176.29. GC-MS (a): t_R 9.12 min. Anal. Calcd for $C_{13}H_{17}NO_2$ (219.28): C, 71.20; H, 7.81; N, 6.39. Found: C, 70.79; H, 7.72; N, 6.90.

(4*S*,5*S*)-4-(Benzylamino)-5-methyltetrahydrofuran-2-one (22d) (from *syn*-19a). Yield: 69 mg (67%). R_f = 0.07 (1:2 EtOAc/petroleum ether). $[\alpha]_D^{20}$: +14.2 (*c* 0.52, $CHCl_3$). IR: ν 3333, 1776. ^{1}H NMR (400 MHz): δ 1.40 (d, *J* 6.6, 3H), 1.50 (br s, 1H), 2.49 (dd, *J* 17.2, 5.5, 1H), 2.66 (dd, *J* 17.2, 7.0, 1H), 3.56 (ddd, *J* 7.0, 5.8, 5.5), 3.72 (d_{AB}, *J* 13.2, 1H), 3.84 (d_{AB}, *J* 13.2, 1H), 4.68 (dq, *J* 6.6, 5.8, 1H), 7.20−7.30 (m, 5H). ^{13}C NMR: δ 14.98, 36.03, 52.30, 56.60, 79.90, 127.90, 125.50, 129.09, 139.82, 175.93. GC-MS (a): t_R 9.23 min. $C_{12}H_{15}NO_2$ (205.26).

(4*S*,5*S*)-5-Phenyl-4-[(1′*S*)-(1′-phenylethyl)amino]tetrahydrofuran-2-one (22e) (from *syn*-17b). Yield: 115 mg (82%). R_f = 0.10 (1:5 EtOAc/petroleum ether). $[\alpha]_D^{20}$: +12.5 (*c* 0.56, $CHCl_3$). IR: ν 3344, 1778. ^{1}H NMR: δ 1.00 (d, *J* 6.6, 3H), 1.53 (br s, 1H), 2.31 (dd, *J* 17.3, 4.9, 1H), 2.62 (dd, *J* 17.3, 6.9, 1H), 3.27 (q, *J* 6.6, 1H), 3.67 (ddd, *J* 6.9, 5.5, 4.9, 1H), 5.56 (d, *J* 5.5, 1H), 7.14−7.47 (m, 10 H). ^{13}C NMR: δ 24.70, 37.44, 56.89, 56.89, 84.38, 126.77, 127.08, 127.78, 129.11, 129.25, 129.33, 135.32, 145.58, 176.42. GC-MS (a): t_R 11.26 min. $C_{18}H_{19}NO_2$ (281.35).

(4*S*,5*S*)-5-Phenyl-4-[(1′*R*)-(1′-phenylethyl)amino]tetrahydrofuran-2-one (22f) (from *syn*-18b). Yield: 120 mg (85%). R_f = 0.07 (1:5 EtOAc/petroleum ether). $[\alpha]_D^{20}$: −42.1 (*c* 0.38, $CHCl_3$). IR: ν 3328, 1778. ^{1}H NMR: δ 1.16 (d, *J* 6.7, 3H), 1.40 (br s, 1H), 2.60 (dd_{ABX}, *J* 17.0, 3.9, 1H), 2.69 (dd_{ABX}, *J* 17.0, 5.0, 1H), 3.46 (ddd, *J* 5.2, 5.0, 3.9, 1H), 3.61 (q, *J* 6.7, 1H), 5.47 (d, *J* 5.2, 1H), 6.94−6.99 (m, 2H), 7.23−7.45 (m, 8H). ^{13}C NMR: δ 24.84, 36.75, 55.02, 55.58, 84.04, 126.46, 126.76, 127.75, 129.11, 129.14, 129.20, 134.76, 144.82, 176.62. GC-MS (a): t_R 11.20 min. $C_{18}H_{19}NO_2$ (281.35).

(4*R*,5*S*)-5-(Hydroxymethyl)-4-[(1′*S*)-(1′-phenylethyl)amino]tetrahydrofuran-2-one (22g) (from *syn*-17c). Yield: 100 mg (85%). R_f = 0.14 (25:1 $CHCl_3$/MeOH). $[\alpha]_D^{20}$: −78.6 (*c* 1.85, $CHCl_3$). IR ($CHCl_3$): ν 3435, 1778. ^{1}H NMR (400 MHz): δ 1.39 (d, *J* 6.5, 3H), 2.27 (br s, 1H), 2.57 (dd, *J* 17.3, 7.4, 1H), 2.69 (dd, *J* 17.3, 8.0, 1H), 3.51 (ddd, *J* 8.0, 7.4, 7.4, 1H), 3.80 (q, *J* 6.5, 1H), 3.93 (dd, *J* 12.5, 3.9, 1H), 4.00 (dd, *J* 12.5, 3.5, 1H), 4.37 (ddd, *J* 7.4, 3.9, 3.5, 1H), 7.20−7.35 (m, 5H). ^{13}C NMR: δ 25.20, 36.25, 53.81, 57.17, 62.27, 81.61, 127.11, 128.19, 129.37, 144.33, 176.05. GC-MS (a): t_R 9.98 min. Anal. Calcd for $C_{13}H_{17}NO_3$ (235.28): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.46; H, 7.07; N, 5.84.

(4*S*,5*S*)-5-(Hydroxymethyl)-4-[(1′*S*)-(1′-phenylethyl)amino]tetrahydrofuran-2-one (22h) (from *anti*-17c). R_f = 0.07 (25:1 $CHCl_3$/MeOH). $[\alpha]_D^{20}$: −14.4 (*c* 1.25, $CHCl_3$). IR ($CHCl_3$): ν 3430, 1778. ^{1}H NMR (400 MHz): δ 1.38 (d, *J* 6.6, 3H), 1.94 (br s, 1H), 2.14 (dd, *J* 17.8, 6.0, 1H), 2.58 (dd, *J* 17.8, 8.0, 1H), 3.41 (ddd, *J* 8.0, 6.0, 4.9, 1H), 3.67 (dd, *J* 12.3, 4.1, 1H), 3.83 (q, *J* 6.6, 1H), 3.87 (dd, *J* 12.3, 3.5, 1H), 4.32 (ddd, 4.9, 4.1, 3.5), 7.20−7.35 (m, 5H). ^{13}C NMR: δ 24.48, 37.60, 54.34, 57.16, 63.17, 85.94, 127.04, 128.07, 129.32, 145.16, 176.70. GC-MS (a): t_R 10.01 min. $C_{13}H_{17}NO_3$ (235.28).

(4*R*,5*S*)-5-(Hydroxymethyl)-4-[(1′*R*)-(1′-phenylethyl)amino]tetrahydrofuran-2-one (22i) (from *syn*-18c). Yield: 64 mg (54%). R_f = 0.20 (15:1 $CHCl_3$/MeOH). $[\alpha]_D^{20}$: +13.3 (*c* 0.75, $CHCl_3$). IR ($CHCl_3$): ν 3430, 1778. ^{1}H NMR (400 MHz): δ 1.40 (d, *J* 6.7, 3H), 2.33 (dd, *J* 17.5, 9.0, 1H), 2.42 (dd, *J* 17.5, 8.6, 1H), 2.89 (br s, 2H), 3.71 (ddd, *J* 9.0, 8.6, 7.3, 1H), 3.78 (q, *J* 6.7, 1H), 3.97 (dd, *J* 12.7, 3.9, 1H), 4.04 (dd, *J* 12.7, 3.1, 1H), 4.54 (ddd, *J* 7.3, 3.9, 3.1, 1H), 7.20−7.35 (m, 5H). ^{13}C NMR: δ 24.39, 36.67, 54.57, 58.20, 62.34, 81.83, 126.87, 128.11, 129.32, 145.14, 176.26. GC-MS (a): t_R 10.04 min. Anal. Calcd for $C_{13}H_{17}NO_3$ (235.28): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.10; H, 7.37; N, 5.84.

(4*S*,5*S*)-5-(Hydroxymethyl)-4-[(1′*R*)-(1′-phenylethyl)amino]tetrahydrofuran-2-one (22k) (from *anti*-18c). R_f = 0.10 (15:1 $CHCl_3$/MeOH). ^{1}H NMR: δ 1.36 (d, *J* 6.6, 3H), 2.12 (br s, 1H), 2.40 (dd, *J* 17.4, 6.6, 1H), 2.80 (dd, *J* 17.4, 7.8, 1H), 3.28 (ddd, *J* 7.8, 6.6, 5.8, 1H), 3.56 (dd, *J* 12.2, 4.2, 1H), 3.75 (dd, *J* 12.2, 3.5, 1H), 3.80 (q, *J* 6.6, 1H), 4.19 (ddd, 5.8, 4.2, 3.5), 7.20−7.35 (m, 5H). ^{13}C NMR: δ 25.17, 36.99, 54.07, 56.96, 63.10, 86.02, 127.03, 128.09, 129.31, 144.54, 176.07. GC-MS (a): t_R 10.07 min. $C_{13}H_{17}NO_3$ (235.28).

(3*S*,4*R*,5*S*)-3-Deuterio-5-methyl-4-[(1′*S*)-(1′-phenylethyl)amino]tetrahydrofuran-2-one (23a) (from 21a). Yield: 88 mg (80%). R_f = 0.16 (1:2 EtOAc/petroleum ether). $[\alpha]_D^{20}$: −132.6 (*c* 0.95, $CHCl_3$). ^{1}H NMR: δ 1.27 (d, *J* 6.4, 3H), 1.35 (d, *J* 6.6, 3H), 2.27 (br s, 1H), 2.71 (dt, *J* 7.2, J_{HD} 2.4, 1H), 2.94 (dd, *J* 7.2, 6.0, 1H), 3.79 (q, *J* 6.6, 1H), 4.22 (dq, *J* 6.0, 6.4, 1H), 7.20−7.30 (m, 5H). ^{13}C NMR: δ 19.35, 25.27, 36.35 (t, J_{CD} 20), 56.91, 58.95, 82.53, 126.98, 127.98, 129.25, 144.76, 175.87. GC-MS (a): t_R 8.94 min. Anal. Calcd for $C_{13}H_{16}DNO_2$ (220.29): C, 70.88; H/D, 7.78; N, 6.36. Found: C, 71.00; H, 8.12; N, 5.90.

(3*R*,4*S*,5*S*)-3-Deuterio-5-methyl-4-[(1′*R*)-(1′-phenylethyl)amino]tetrahydrofuran-2-one (23b) (from 21b). Yield: 91 mg (83%). R_f = 0.15 (1:2 EtOAc/petroleum ether). $[\alpha]_D^{20}$: +92.0 (*c* 1.0, $CHCl_3$). IR: ν 3323, 1773. ^{1}H NMR: δ 1.35 (d, *J* 6.6, 3H), 1.36 (br s, 1H), 1.37 (d, *J* 6.6, 3H), 2.56 (dt, *J* 6.8, J_{HD} 2.4, 1H), 3.24 (dd, *J* 6.8, 5.8, 1H), 3.77 (q, *J* 6.6, 1H), 4.50 (dq, *J* 6.6, 5.8, 1H), 7.22−7.38 (m, 5H). ^{13}C NMR: δ 14.96, 25.30, 35.74 (t, J_{CD} 20), 54.59, 56.21, 80.08, 127.09, 127.89, 129.19, 145.00, 176.44. GC-MS (a): t_R 9.00 min. Anal. Calcd for $C_{13}H_{16}DNO_2$ (220.29): C, 70.88; H/D, 7.78; N, 6.36. Found: C, 70.51; H, 7.75; N, 6.41.

General Procedure for the DIBALH Reduction of the Lactones 22 and 23. A 311 μL amount of diisobutylaluminum hydride (1.75 mmol) was added slowly to a solution of the lactone **22** or **23** (0.5 mmol) in 20 mL of CH_2Cl_2 at −78 °C. Stirring was continued at low temperature for a further 3 h. After hydrolysis with 402 μL of trifluoroacetic acid (5.25 mmol), the mixture was allowed to reach rt. A 1.5 mL volume of water and 636 mg of $NaHCO_3$ (6.0 mmol) were added, and the organic layer was separated. A little water was added to the aqueous residue, which was subsequently extracted twice with 25 mL of CH_2Cl_2. The organic layers were pooled, washed with minute amounts of saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated. The crude products were purified chromatographically.

(4*R*,5*S*)-2-Hydroxy-5-methyl-4-[(1′*S*)-(1′-phenylethyl)amino]tetrahydrofuran (24a) (from 22a). Yield: 95 mg (86%). Anomer ratio α:β ≈ 2:1. R_f = 0.17 (10:1 $CHCl_3$/MeOH). IR: ν 3400−3150. ^{1}H NMR (400 MHz, DMSO-d_6): major anomer (α), δ 1.01 (d, *J* 6.2, 3H), 1.23 (d, *J* 6.6, 3H), 1.58 (ddd, *J* 13.0, *J* 6.3, 3.1, 1H), 2.15 (ddd, *J* 13.0, *J* 7.7, 5.4, 1H), 2.36 (ddd, *J* 7.7, 6.3, 6.3, 1H), 3.75 (q, *J* 6.6, 1H), 3.79 (dq, *J* 6.3, 6.2, 1H), 5.20 (m, 1H), 6.00 (br d, *J* 4.0, 1H), 7.18−7.37 (m, 5H); minor anomer (β), δ 1.11 (d, *J* 6.2, 3H), 1.22 (d, *J* 6.5, 3H), 1.67 (dddd, *J* 12.2, *J* 9.0, 5.4, *J* 0.9, 1H), 1.92 (ddd, *J* 12.2, *J* 6.8, 1.6, 1H), 2.67 (ddd, *J* 7.3, 6.8, 5.4, 1H), 3.54 (dq, *J* 7.3, 6.2, 1H), 3.73 (q, *J* 6.5, 1H), 5.22 (ddd, *J* 9.0, 5.0, 1.6, 1H), 5.90 (dd, *J* 5.0, *J* 0.9, 1H), 7.15−7.38 (m, 5H). ^{13}C NMR (DMSO-d_6) major anomer (α), δ 19.21, 25.35, 40.20, 56.05, 61.67, 77.43, 97.03, 126.76, 126.85, 128.47, 146.19; minor anomer (β), δ 21.00, 25.64, 40.96, 56.36, 60.59, 79.27, 97.16, 126.76, 126.85, 128.47, 146.48. GC-MS (a): t_R 8.32 min. $C_{13}H_{19}NO_2$ (221.30).

(4*S*,5*S*)-2-Hydroxy-5-methyl-4-[(1′*R*)-(1′-phenylethyl)amino]tetrahydrofuran (24b) (from 22c). Yield: 60 mg (54%). Anomer ratio α:β ≈ 1:1. R_f = 0.16 (20:1 $CHCl_3$/MeOH). ^{1}H NMR (DMSO-d_6): anomeric mixture, α-anomer, δ 1.05 (d, *J* 6.4, 3H), 1.21 (d, *J* 6.4, 3H), 1.65−1.97 (m, 3H), 2.90 (ddd, *J* 6.1, 6.0, 5.4, 1H), 3.77 (q, *J* 6.4, 1H), 3.95 (dq, *J* 6.1, 6.4, 1H), 5.29 (ddd, *J* 9.5, 5.0, 2.5, 1H), 5.82 (d, *J* 9.5, 1H), 7.14−7.35 (m, 5H); β-anomer, δ 1.16 (d, *J* 6.4, 3H), 1.21 (d, *J* 6.4, 3H), 1.65−1.97 (m, 3H), 2.68 (m, 1H), 3.71 (dq, *J* 5.4, 6.4, 1H), 3.76 (q, *J* 6.4, 1H), 5.17 (m, 1H), 6.10 (br d, *J* 7.3, 1H), 7.14−7.35 (m, 5H). ^{13}C NMR (DMSO-d_6) (anomeric mixture): δ = 16.39, 17.57, 25.95, 26.04, 39.00, 40.50, 56.03, 56.26, 57.00, 57.23, 75.36, 77.53, 96.79, 97.87, 127.49, 127.56, 127.62, 129.18, 129.20, 146.97, 147.18. GC-MS (a): t_R 8.36 min. $C_{13}H_{19}NO_2$ (221.30).

(3*S*,4*R*,5*S*)-3-Deuterio-2-hydroxy-5-methyl-4-[(1′*S*)-(1′-phenylethyl)amino]tetrahydrofuran (25a) (from 23a). Yield: 78 mg (70%). Anomer ratio α:$\beta \approx$ 2:1. $R_f = 0.11$ (10:1 $CHCl_3$/MeOH). IR: ν 3400−3250. ^{1}H NMR (400 MHz, DMSO-d_6): major anomer (α), δ 1.01 (d, *J* 6.1, 3H), 1.23 (d, *J* 6.6, 3H), 2.13 (dd, *J* 7.7, 5.8, 1H), 2.35 (dd, *J* 7.7, 6.3, 1H), 3.75 (q, *J* 6.6, 1H), 3.79 (dq, *J* 6.3, 6.1, 1H), 5.21 (br d, *J* 5.8, 1H), 6.00 (br s, 1H), 7.15−7.38 (m, 5H); minor anomer (β), δ 1.11 (d, *J* 6.2, 3H), 1.22 (d, *J* 6.5, 3H), 1.90 (dd, *J* 6.8, 1.5, 1H), 2.66 (dd, *J* 7.3, 6.8, 1H), 3.53 (dq, *J* 7.3, 6.2, 1H), 3.73 (q, *J* 6.5, 1H), 5.22 (dd, *J* 4.9, 1.5, 1H), 5.89 (d, *J* 4.9, 1H), 7.15−7.38 (m, 5H). ^{13}C NMR (DMSO-d_6): major anomer (α), δ 19.20, 25.35, 56.04, 61.62, 77.41, 96.99, 126.76, 126.85, 128.47, 146.20 (the signal of C3 is hidden below the solvent signal); minor anomer (β), δ 21.01, 25.65, 56.35, 60.53, 79.25, 97.12, 126.76, 126.85, 128.47, 146.52 (the signal of C3 is hidden below the solvent signal). GC-MS (a): t_R 8.33 min. Anal. Calcd for $C_{13}H_{18}DNO_2$ (222.31): C, 70.24; H, 9.07; N, 6.30. Found: C, 70.29; H, 9.08; N, 6.07.

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