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Diastereoselective Protocols for the Synthesis of 2,3-*trans*- and 2,3-*cis*-6-Methoxy-morpholine-2-carboxylic Acid Derivatives

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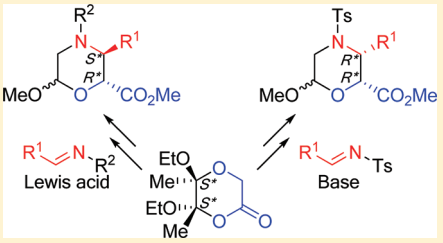
Supporting Information

ABSTRACT: Two diastereoselective and straightforward protocols for the high-yielding synthesis of 2,3-*trans*- and 2,3-*cis*-6-methoxy-3-substituted morpholine-2-carboxylic esters were realized in few steps, through the condensation between 5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one and an appropriate imine, which is the key reaction to control the C2−C3 relative stereochemistry, followed by a methanolysis/ring-closure tandem reaction sequence. In particular, 2,3-*trans*-morpholines derive from the *R**,*S**-product of the acid condensation of *N*-functionalized alkylimines with the silylketene acetal of the above lactone, whereas 2,3-*cis*-morpholines derive from the *R**,*R**-product of basic condensation of an *N*-tosylimines with the lactone.



INTRODUCTION

The design and synthesis of polyfunctionalized new building blocks for the preparation of original foldamers[1] represent an attractive research field. Foldamers, artificial oligomers inspired by biopolymers, have a strong tendency to adopt a specific compact conformation through noncovalent interactions between nonadjacent monomer units. Depending on their structure, they mimic the ability of peptides, nucleic acids, or polysaccharides to fold into an ordered state in solution. To obtain foldamers, a powerful strategy is the use of rigid monomers that leads to conformational constraints locking the backbone conformation. In this context, the morpholine ring represents an interesting template used for the preparation of a new class of foldamers named "morpholinos".[2] Furthermore, morpholine-3-carboxylic acid could act as proline surrogates inducing β conformation on peptides.[3]

Substituted morpholines have also attracted considerable interest due to their presence in several biologically active compounds.[4] 2-Alkoxymorpholines are structural components of drugs, such as the potent antitumor agent nemorubicin[5] and aprepitant,[6] a compound used for the prevention of chemotherapy-induced nausea and vomiting. 6-Alkoxymorpholine-3-carboxylic acid derivatives are prepared and used in a wide range of applications by Guarna et al.[3,7] On the contrary, to our knowledge, only one example of a 6-alkoxymorpholine-2-carboxylic acid derivative is reported in a paper concerning the purification of paclitaxel.[8]

Considering all these findings regarding the biological importance of this nucleus, our challenge was to obtain a straightforward and diastereoselective synthesis of new 6-methoxymorpholine-2-carboxylic acid templates. These compounds, constrained β-amino acid derivatives containing both the isoserine skeleton and an acetal function, are attractive precursors for peptidomimetics and morpholinos synthesis.

Our diastereoselective strategy for the preparation of the morpholine derivatives (Figure 1) employs, as a key reaction,

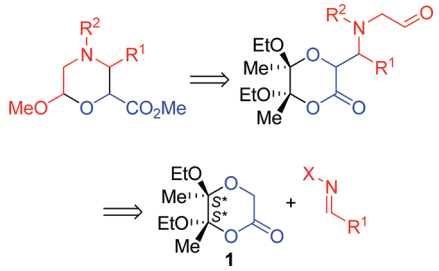


Figure 1. Retrosynthetic scheme for the preparation of 6-methoxy-morpholine-2-carboxylic acid derivatives.

the condensation between 5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one (**1**) or its silylketene acetal and a suitable *N*-substituted imine, followed by a methanolysis/ring-closure tandem reaction sequence. Depending on the imine *N*-substituent and on the condensation conditions, it was possible to obtain 2,3-*trans*- or 2,3-*cis*-substituted morpholines containing the C-6 anomeric carbon as a third stereocenter.

RESULTS AND DISCUSSION

Recently, we reported on the preparation of isoserine derivatives through an acid-catalyzed stereoselective Mannich-like condensation between the silylketene acetal **2** derived from lactone **1** and different imines.[9] This protocol allowed control of the reciprocal 2*R**,3*S**-stereochemistry of the masked isoserines.

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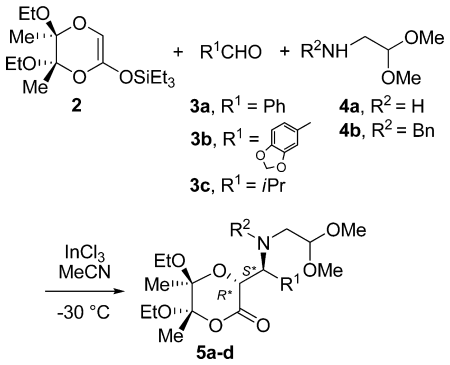
According to this strategy, 2,3-*trans*-6-methoxymorpholine-2-carboxylic acids were efficiently synthesized in two steps via the key intermediates **5** (Scheme 1), which contain the set of atoms

Scheme 1. Synthesis of Adducts 5a−d



necessary to obtain the morpholine skeleton. Adducts **5a−c** (R^2 = H) were prepared through a three-component one-pot protocol,[10] by allowing equimolar amounts of the silylketene acetal **2**, aldehydes **3a,b**, and aminoacetaldehyde dimethylacetal **4a** to react under Lewis acid conditions (Table1). $InCl_3$

Table 1. Synthesis of Compounds 5a−e

entry	R^1	R^2	product[a]	yield (%)	dr (%)[b]
1	Ph	H	**5a**	100[c]	97:3
2	Ar[d]	H	**5b**	97[c]	98:2
3	*i*Pr	H	**5c**	94[c]	90:10
4	*i*Pr	Bn	**5d**	77[e]	100:0
5	H	Bn	**5e**[f]	97[e]	

[a]Reaction conditions: silylketene acetal **2** (1 mmol), aldehyde **3a−c** (1 mmol), 2,2-dimethoxyethanamine **4a,b** (1 mmol), $InCl_3$ (0.25 + 0.25 mmol), MeCN (2 mL), −30 °C, 1 h. [b]*R**,*S**-adduct as major diastereoisomer (NMR analysis). [c]Crude product. [d]Ar = 3,4-$(OCH_2O)C_6H_3$. [e]Purified product. [f]Reaction conditions: silylketene acetal **2** (1 mmol), *N*-benzyl-2,2-dimethoxy-*N*-(methoxymethyl)-ethanamine (**6**) (1 mmol), $InCl_3$ (0.5 mmol), MeCN (2.5 mL), −30 °C, 1 h.

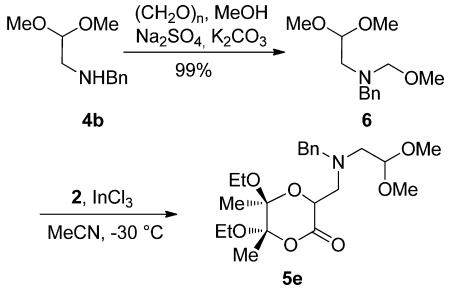
catalyzed the in situ formation of the corresponding imine and the subsequent C−C bond construction. *β*-Aryl-substituted (*R**,*S**)-*β*-aminolactones **5a,b** were obtained in almost quantitative yield and up to 98% diastereomeric purity (Table 1, entries 1 and 2). Very good yields and dr of compound **5c** (entry 3) were also obtained from aliphatic isobutyraldehyde.

Mannich-like condensation reactions between esters and iminium ions generated in situ from enolizable aldehydes and a secondary amine are very rare,[11,12] owing to the formation of enamines as byproduct. On the contrary, following our three-component protocol, it was also possible to react the enolizable isobutyraldehyde (**3c**) with *N*-benzylaminoacetaldehyde dimethylacetal[13] (**4b**) and **2** (Scheme 1). This condensation afforded in good yield and excellent dr (Table 1, entry 4) the expected product **5d** bearing the *N*-benzyl group, a versatile substituent for the preparation of *N*-protected morpholines.

The relative *R**,*S**-configuration of compounds **5a−d** was indirectly assigned by NMR analysis of the corresponding morpholine derivatives (see compounds **13a−d**, in Scheme 5 below).

In order to synthesize the *β*-unsubstituted adduct **5e** (Scheme 2), the *N*,*O*-acetal **6** was prepared from **4b**,

Scheme 2. Synthesis of Compound 5e



paraformaldehyde, and MeOH, under basic anhydrous conditions.[14] Compound **6** in the presence of $InCl_3$ gave the corresponding *N*-benzyl immonium chloride that, in turn, reacted with **2** affording **5e** in nearly quantitative yield (Table 1, entry 5) .

With the purpose of preparing 2,3-*cis*-morpholine derivatives, we studied the condensation step between **1** and imines to obtain *R**,*R**-adducts, precursors of the target compounds.

Since it is well-known that the condensation of lactones such as **1** with aldehydes under basic conditions affords the *R**,*R**-*β*-hydroxy adducts as main diastereoisomers[15] and that the *N*-arylsulfonyl-activated C═N bond is polarized similarly to the C═O bond, we tested the reactivity of **1** with *N*-tosylimines, aiming to obtain a similar stereochemical result. Actually, the condensation of the lithium enolate of **1** with the preformed *N*-tosylimines **7a,b** bearing an aromatic ring (Scheme 3) gave in very good yield the *R**,*R**-adducts **9a,b** as sole diastereoisomers.[16]

N-Tosylimines derived from aliphatic enolizable aldehydes suffer from poor stability, and the *N*-tosylimine of isobutyraldehyde was generated in situ from [2-methyl-1-(phenylsulfonyl)-propyl]tosylamide (**8**) (Scheme 3), by using 2 mol equiv of LHMDS. The condensation between the formed *N*-tosylimine and the lithium enolate of lactone **1** gave *β*-tosylamido lactone **9c** as pure the *R**,*R**-diastereoisomer.

The *R**,*R**-stereochemistry was indirectly determined by acid-catalyzed methanolysis at 25 °C of both **9a** and **9b** into the corresponding known isoserine derivatives **12a,b**[17] (Scheme 4). This latter synthesis is of general interest, since it represents a highly diastereoselective and efficient two-step protocol to obtain isoserine derivatives characterized by the 2*R**,3*R**-configuration.

The stereochemical outcome of the above condensation reactions can be explained as follows. As regards the reaction under acid conditions, the *R**,*S**-stereochemistry of the intermediate **5** is in agreement with the transition state proposed for the condensation of **2** with *N*-benzylimines.[9] In addition, a higher diastereoselectivity was found in this case, probably due to extra coordination of the indium cation to the acetal side-chain methoxy group (Figure 2, **A**). As a result, an additional stabilization of the transition state occurs, increasing the diastereoisomeric ratio in favor of the above *R**,*S**-adduct **5**. In contrast, a Zimmerman−Traxler transition state model[18] (Figure 2, **B**) can be proposed to account for the diastereoselective formation of the *R**,*R**-*N*-tosyl-adduct **9** under basic conditions.

Unlike adducts **5**, intermediates **9** do not bear an *N*-chain containing a masked aldehyde necessary for the cyclization to the target 6-methoxymorpholine derivatives and thus were subjected to further transformations. To introduce directly the

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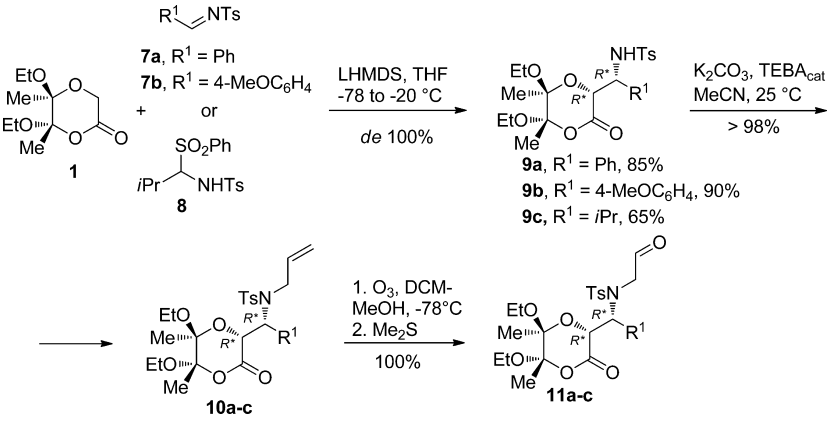
Scheme 3. Synthesis of *N*-Tosyl-aminoacetaldehydes 11a−c



Scheme 4. Synthesis of 2*R,3*R**-Isoserine Derivatives 12a,b**

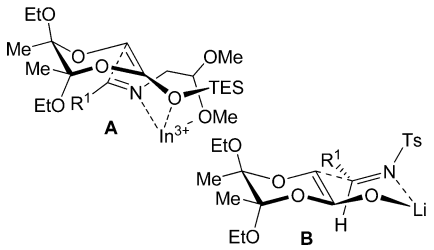


Figure 2. Transition states for the major diastereoisomers: **A** leading to *R***S**-**5**; **B** leading to *R***R**-**9**.

acetaldehyde backbone, the *N*-alkylation of compounds **9** with bromoacetaldehyde dimethylacetal was initially tested under several homogeneous and heterogeneous phase transfer catalysis (PTC) conditions, but only byproducts were obtained,[19] probably because of the steric hindrance of the acetal group. The *N*-alkylation with the less hindered and more activated allyl bromide, from which the carbonyl function can be easily generated by ozonolysis, proceeded under solid−liquid PTC optimized conditions,[20] to give the *N*-allyl-tosylamido derivatives **10a−c** in practical quantitative yields (Scheme 3). Also the ozonolysis of **10a−c** was very efficient, giving the pure aldehydes **11a−c** in quantitative yields.

Finally, the target diastereoisomeric morpholines **13** and **14** were prepared from the corresponding intermediates *R**,*S**-**5** and *R**,*R**-**11** by methanolysis in the presence of trimethylsilyl chloride, as source of anhydrous HCl (Scheme 5). Under these conditions, adducts **5a−e** were directly used as crude compounds and gave intermediates **C**, which in turn cyclized to **13a−e**, isolated in excellent yields (Table 2). Compounds **13a,b** were isolated as pure β-anomers (entries 1−3), while **13c−e** were obtained as inseparable α:β mixtures (entries 4 and 5). In all cases, as demonstrated by NMR analyses, the 2-methoxycarbonyl group in the morpholines **13a−d** lies in the equatorial position, *trans* to the equatorial R[1].

Starting from *R**,*R**-**11**, through the intermediate **D**, 2,3-*cis*-6-methoxymorpholine esters **14a−c** were formed as a mixture of α,β-anomers (96−98% total yields) that were separated by column chromatography (entries 6−8). Interestingly, anomers **14** interconverted, when left in solution. As an example, after 1 month in $CDCl_3$ solution α-**14a** gave 76:24 α,β-ratio, whereas β-**14a** gave 20:80 α,β-ratio. It is worth noting that the formation of α,β-anomeric mixtures of morpholines **13** and **14** is not a stereochemical drawback, in the perspective of obtaining modified nucleosides to be used in the synthesis of morpholinos' foldamers. In fact, as well-known also for the condensation of a sugar unit with a nucleobase, these transformations are realized under strong acidic conditions, which promote the equilibration of the two anomeric forms, allowing the formation of only, or in prevalence, one anomeric nucleoside.[21]

Scheme 5. Synthesis of Methyl 6-Methoxy-morpholine-2-carboxylic Esters 13 and 14

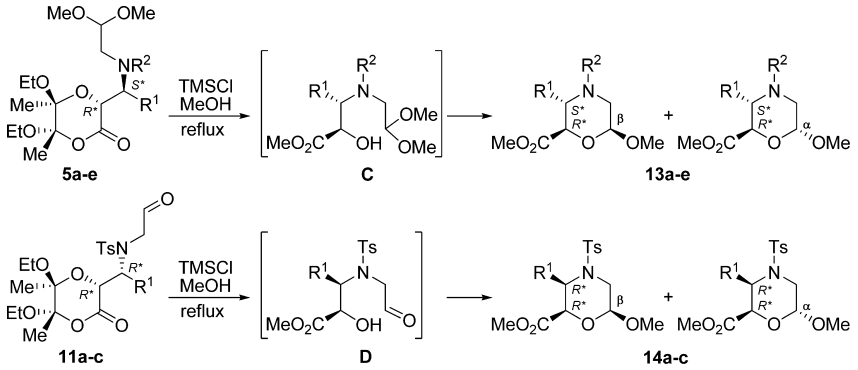


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Table 2. Methyl 6-Methoxy-morpholine-2-carboxylic Esters 13 and 14

entry	R^1	R^2	product[a]	yield (%)[b]	α:β	entry	R^1	product[c]	α (%)[b]	β (%)[b]
1	Ph	H	**13a**	98	0:100	6	Ph	**14a**	47	51
2	Ar[d]	H	**13b**	87	0:100	7	4-MeOPh	**14b**	23	74
3	*i*Pr	H	**13c**	82	20:80[e]	8	*i*Pr	**14c**	77	19
4	*i*Pr	Bn	**13d**	87	25:75[e]					
5	H	Bn	**13e**	94	40:60[e]					

[a]Reaction conditions: crude **5a−e** (1 mmol), TMSCl 1.3 M in MeOH (13 mmol), reflux, 4 h. [b]Purified product. [c]Reaction conditions: pure **11a−c** (1 mmol), TMSCl 0.25 M in MeOH (2.5 mmol), 25 °C, 16 h. [d]Ar = 3,4-$(OCH_2O)C_6H_3$. [e]Isolated as inseparable mixture of anomers.

NMR experiments (^{1}H, ^{13}C, COSY, HETCOR, and NOESY) confirmed the structure and the stereochemistry assigned to morpholine compounds, as detailed for selected compounds (Figure 3).

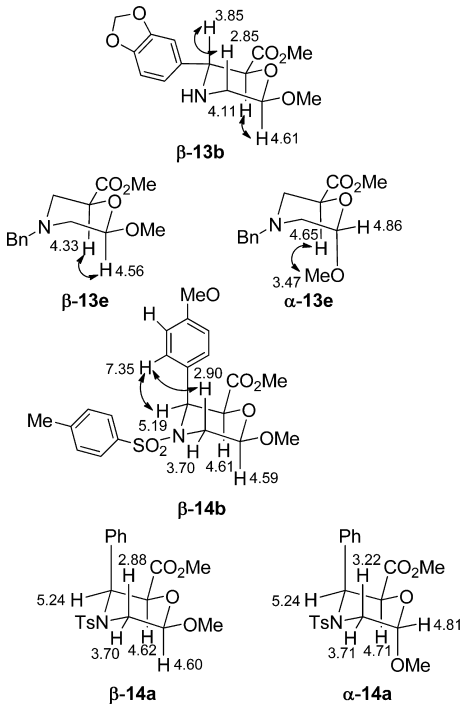

Figure 3. Selected NMR data for morpholines **13** and **14**.

The NOESY experiment on morpholine β-**13b** showed H-2/H-6 spatial proximity, indicating that carboxy and methoxy groups are in the equatorial position. A H-3/H-5 NOE was found, demonstrating that the aryl is in the equatorial position, *trans* to the carboxylic group. The position of the methoxy group in the anomeric couple β-**13e**/α-**13e** was unequivocally assigned, since in the β-anomer is present a positive H-2/H-6 NOE, which is absent in the α-anomer. As a confirmation, in the anomer α-**13e** a weak MeO/H-2 NOE was found, showing their *cis* relationship. These data, together with the *J* values, are indicative of an equatorial position of the carboxylic function in both anomers.

The main difference between *trans*-**13** and *cis*-**14** morpholines is related to the H-3 chemical shift, that of *cis*-compounds being at lower field, probably due to the deshielding effect of the SO_2 group. Hereafter NMR data of compound β-**14b** are first described, since NOE information from aromatic protons are of relevance to define the spatial disposition of the substituents. The H-2/H-3 *cis* relationship was demonstrated by the observed small *J* value (3.8 Hz), as well as the β-configuration by the H-6/H-5 *J* values ($J_{ax,ax}$ = 9.3, $J_{ax,eq}$ = 2.8 Hz). Moreover, the H-6 chemical shift is very close to that of H-2, thus preventing detection of a NOE between these nuclei. Information on the spatial disposition of the substituents is given from the NOE between H-5_{ax} and the *o*-protons of the *p*-MeOPh group, indicating their axial position. As a consequence, the equatorial position was assigned to the ester function (Figure 3). According to these data, the chemical shifts and the spatial disposition of the substituents are shown in Figure 3 for compounds β-**14a** (H-2/H-3, $J_{ax,eq}$ = 3.9 Hz; H-5/H-6, $J_{ax,ax}$ = 9.4 Hz, $J_{ax,eq}$ = 2.8 Hz) and α-**14a** (H-2/H-3, $J_{ax,eq}$ = 3.9 Hz; H-5/H-6, $J_{eq,ax}$ = 2.5 Hz, $J_{eq,eq}$ = 0 Hz).

CONCLUSION

In summary, starting from lactone **1**, a series of 2,3-*trans*- and 2,3-*cis*-3-substituted 6-methoxy-morpholine-2-carboxylic esters were prepared in high yields and diastereoselectivity by two straightforward, efficient synthetic protocols. Since the related Ley's acetals[15a,22] are efficiently obtained in enantiopure form through an inexpensive synthesis and in multigram scale, the procedures here reported open the way to the preparation of optically pure 6-methoxy-morpholine derivatives, putative polyfunctionalized templates for the preparation of both new peptidomimetics and morpholinos. In addition, a highly diastereoselective and efficient protocol to 2*R**,3*R**-isoserine derivatives has been realized.

EXPERIMENTAL SECTION

All reactions were carried out using flame-dried glassware, equipped with magnetic stirring. Isolated yields refer to homogeneous materials (TLC, HPLC, NMR). Reagent-grade commercially available reagents and solvents were used; anhydrous solvents were used as purchased. TLC was performed using 0.25 mm silica gel precoated plates and visualized by UV-254 light and CAM staining. Silica-gel (particle size 0.040−0.063 mm) was used for flash column chromatography (FCC). Melting points are corrected; IR spectra are reported in frequency of absorption (cm^{-1}). NMR spectra were recorded at 300.13 or 200.00 MHz for ^{1}H and 75.00 or 50.00 MHz for ^{13}C; TMS was used as external reference; δ are in ppm, and *J* are in Hz. Characterization data for 5,6-diethoxy-5,6-dimethyl[1,4]dioxan-2-one (**1**),[9] 5,6-diethoxy-5,6-dimethyl-([1,4]dioxin-2-yloxy)triethylsilane (**2**),[9] and the *N*-tosyl derivative **8**[23] completely matched the literature data.

Synthesis of Compounds 5a−e: General Procedures for the Mannich Condensation. *Method A.* In a dried two-necked round-bottomed flask, aldehyde **3a−c** (1 mmol) and 2,2-dimethoxyethanamine (**4a**) (105 mg, 1 mmol) or *N*-benzyl-2,2-dimethoxyethanamine (**4b**) (195 mg, 1 mmol) were dissolved in dry MeCN (2 mL) under nitrogen atmosphere. The solution was cooled at −30 °C, and $InCl_3$ (55 mg, 0.25 mmol) was added. After 10 min, the silylketene acetal **2** (201 mg, 1 mmol) dissolved in MeCN (0.5 mL) and additional $InCl_3$ (55 mg, 0.25 mmol) were added. The reaction mixture was stirred for 1 h and then quenched with saturated $NaHCO_3$ (1 mL). *Method B.* *N*-Benzyl-2,2-dimethoxy-*N*-(methoxymethyl)ethanamine **6** (239 mg, 1 mmol) and silyl derivative **2** (201 mg, 1 mmol) were dissolved in dry MeCN (2.5 mL) under nitrogen atmosphere. The solution was cooled

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at −30 °C, and then anhydrous $InCl_3$ (110 mg, 0.5 mmol) was added in one portion. The reaction mixture was stirred for 1 h and then quenched with saturated $NaHCO_3$ (1 mL). (*Workup valid for both Method A and Method B*) The crude was filtered through a Celite pad and extracted with AcOEt (3 × 10 mL), and the collected organic phases were washed with brine, dried over Na_2SO_4, and concentrated under vacuum, giving the crude **5a−e**. Compounds **5a−c** were unstable on silica gel and were used without further purification, whereas compounds **5d,e** were purified by FCC. Yield, chromatographic eluent (**5d,e**), and physical and analytical data of compounds **5a−e** are as follows.

(3*R,5*S**,6*S**)-3-[(*S**)-(2,2-Dimethoxyethylamino)(phenyl)methyl]-5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one (5a).** *Method A*, 411 mg, 100%; de 94%; clear oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37−7.23 (m, 5H), 4.35 (dd, 1H, *J* = 6.1, 4.5 Hz), 4.28 (d, 1H, *J* = 2.9 Hz), 4.22 (d, 1H, *J* = 2.9 Hz), 3.81−3.40 (m, 3H), 3.29 (s, 3H), 3.28 (s, 3H), 3.26−3.18 (m, 1H), 2.60 (dd, 1H, *J* = 12.5, 6.5 Hz), 2.60 (dd, 1H, *J* = 12.5, 4.5 Hz), 2.24 (bs, 1H), 1.50 (s, 3H), 1.40 (s, 3H), 1.25−1.18 (m, 3H), 1.10−1.03 (m, 3H). Used as a crude in the following reaction.

(3*R,5*S**,6*S**)-3-[(*S**)-Benzo[*d*][1,3]dioxol-5-yl(2,2-dimethoxyethylamino)methyl]-5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one (5b).** *Method A*, 442 mg, 97%; de 96%; clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91−6.90 (m, 1H), 6.80−6.75 (m, 2H), 5.94 (s, 2H), 4.34 (dd, 1H, *J* = 6.3, 4.5 Hz), 4.18 (s, 2H), 3.78−3.61 (m, 3H), 3.49−3.44 (m, 1H), 3.29 (s, 3H), 3.28 (s, 3H), 2.56 (dd, 1H, *J* = 12.6, 6.3 Hz), 2.45 (dd, 1H, *J* = 12.3, 4.5 Hz), 2.23 (bs, 1H), 1.49 (s, 3H), 1.40 (s, 3H), 1.23−1.19 (m, 3H), 1.10−1.06 (m, 3H). Used as a crude in the following reaction.

(3*R,5*S**,6*S**)-3-[(*S**)-1-(2,2-Dimethoxyethylamino)-2-methylpropyl]-5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one (5c).** *Method A*, 355 mg, 94%; de 80%; clear oil. ^{1}H NMR (200 MHz, $CDCl_3$) major diastereoisomer δ 4.36−4.28 (m, 2H), 3.80−3.46 (m, 4H), 3.34 (s, 3H), 3.33 (s, 3H), 2.85 (dd, 1H, *J* = 7.4, 2.3 Hz), 2.75 (d, 2H, *J* = 5.5 Hz), 1.98−1.85 (m, 1H), 1.65 (bs, 1H), 1.50(s, 3H,), 1.43 (s, 3H), 1.26−1.15 (m, 6H), 1.00−0.92 (m, 6H). Used as a crude in the following reaction.

(3*R,5*S**,6*S**)-3-[(*S**)-1-(Benzyl(2,2-dimethoxyethyl)amino)-2-methylpropyl]-5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one (5d).** *Method A*, FCC (AcOEt/hexane 1:8); 291 mg, 77%; de > 99%; clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 4.41 (d, 1H, *J* = 2.7 Hz), 4.24 (t, 1H, *J* = 7.2 Hz), 4.04 (d, 1H, *J* = 14.7 Hz), 3.86−3.53 (m, 5H), 3.24 (s, 3H), 3.17 (s, 3H), 3.09−2.99 (m, 2H), 2.89 (dd, 1H, *J* = 14.5, 7.5 Hz), 2.25−2.10 (m, 1H), 1.53(s, 3H,), 1.41 (s, 3H), 1.21−1.19 (m, 6H), 1.07 (d, 3H, *J* = 9.9 Hz), 0.93 (d, 3H, *J* = 9.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 141.1, 129.0 (2C), 128.0 (2C), 126.5, 105.5, 105.2, 98.3, 70.6, 68.0, 58.5, 57.2, 57.1, 53.8, 53.7, 53.0, 28.9, 21.1, 20.9, 18.7, 17.9, 15.3, 15.1; IR (neat) 3062, 2832, 1745, 1278, 1126 cm^{-1}. Anal. Calcd for $C_{25}H_{41}NO_7$: C, 64.22; H, 8.84; N, 3.00. Found: C, 64.07; H, 8.98; N, 2.87.

(3*R,5*S**,6*S**)-3-[(Benzyl(2,2-dimethoxyethyl)amino)-methyl]-5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one (5e).** *Method B*, FCC (AcOEt/hexane 1:8); 413 mg, 97%; de 95%; clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.21 (m, 5H), 4.48 (t, 1H, *J* = 5.2 Hz), 4.36 (t, 1H, *J* = 6.0 Hz), 3.87 (s, 2H), 3.74−3.52 (m, 4H), 3.33 (s, 3H), 3.30 (s, 3H), 3.16 (d, 2H, *J* = 6.0 Hz), 2.80 (d, 2H, *J* = 5.2 Hz), 1.49 (s, 3H), 1.41 (s, 3H), 1.18 (t, 3H, *J* = 7.0 Hz), 1.10 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.5, 139.7, 129.1 (2C), 128.3 (2C), 127.1, 104.9, 104.2, 98.0, 70.8, 59.7, 58.4, 57.3, 57.1, 56.1, 54.1, 53.6, 18.8, 18.0, 15.6, 15.4; IR (neat) 3057, 2821, 1724, 1255, 1122 cm^{-1}. Anal. Calcd for $C_{22}H_{35}NO_7$: C, 62.10; H, 8.29; N, 3.29. Found: C, 62.29; H, 8.16; N, 3.40.

***N*-Benzyl-2,2-dimethoxy-*N*-(methoxymethyl)ethanamine (6).** Anhydrous Na_2SO_4 (240 mg, 1.7 mmol) and anhydrous K_2CO_3 (276 mg, 2 mmol) were added to a solution of *N*-benzyl-2,2-dimethoxyethanamine (390 mg, 2 mmol) and paraformaldehyde (104 mg, 4 mmol) in dry methanol (7 mL). The mixture was stirred at 25 °C for 24 h, then filtered through a Na_2SO_4 pad, and concentrated under reduced pressure. The resulting white solid was suspended in Et_2O, and undissolved excess paraformaldehyde was filtered through a Na_2SO_4 pad. After evaporation of the solvent under vacuum the product **6** was used without further purification: 237 mg, 99%; clear liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 4.42 (t, 1H, *J* = 5.3 Hz), 4.13 (s, 2H), 3.91 (s, 2H), 3.10 (s, 6H), 3.26 (s, 3H), 2.87 (d, 2H, *J* = 5.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 128.7, 128.1, 126.8, 104.0, 87.2, 56.5, 55.2, 55.1, 53.4, 53.3. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.06; H, 9.05; N, 5.63.

Synthesis of Compounds 9a−c. In a flame-dried two-neck round-bottom flask, a LHMDS/THF (1 M) solution (1.3 mL, 1.3 mmol) was added dropwise to a solution of 5,6-diethoxy-5,6-dimethyl[1,4]dioxan-2-one **1** (218 mg, 1 mmol) in dry THF (1 mL), at −78 °C, under N_2. A solution of compound **7a,b** (1 mmol) or *N*-tosyl derivative **8** (1 mmol) in THF (3 mL) was added after 15 min. The reaction mixture was stirred for further 2 h, and then the resulting solution was warmed at −20 °C and stirred for 20 h, (TLC analysis, hexane/AcOEt 7:3). The reaction mixture was quenched at −78 °C with NH_4Cl_{sat} (1 mL), and the crude was extracted with AcOEt (3 × 4 mL), washed with brine (3 × 2 mL), and dried over anhydrous Na_2SO_4. After solvent removal and precipitation with hexane, **9a−c** were isolated as pure products.

***N*-{(*S**)-[(2*S**,5*S**,6*S**)-5,6-Diethoxy-5,6-dimethyl-3-oxo-1,4-dioxan-2-yl](phenyl)methyl}-4-methylbenzenesulfonamide (9a).** Yield 406 mg, 85%; white solid, mp 154−155 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55 (d, 2H, *J* = 8.3 Hz), 7.26−7.08 (m, 7H), 5.68 (d, 1H, *J* = 8.7 Hz), 4.94 (dd, 1H, *J* = 4.0, 8.7 Hz), 4.43 (d, 1H, *J* = 4.0 Hz), 3.61−3.24 (m, 3H) 3.01−2.84 (m, 1H), 2.34 (s, 3H) 1.38 (s, 3H), 1.37 (s, 3H), 1.14 (t, 3H, *J* = 7.0 Hz), 0.71 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 143.1, 137.1, 135.5, 129.3 (2C), 128.9 (2C), 127.7 (2C), 127.5 (2C), 127.1, 105.6, 98.4, 73.2, 58.1, 57.8, 57.2, 21.3, 18.4, 17.4, 15.0, 14.9; IR (nujol) 3240, 1746, 1322, 1158 cm^{-1}. Anal. Calcd for $C_{24}H_{31}NO_7S$: C, 60.36; H, 6.54; N, 2.93. Found: C, 60.18; H, 6.49; N, 3.06.

***N*-{(*S**)-[(2*S**,5*S**,6*S**)-5,6-Diethoxy-5,6-dimethyl-3-oxo-1,4-dioxan-2-yl](4-methoxyphenyl)methyl}-4-methylbenzenesulfonamide (9b).** Yield 457 mg, 90%; white solid, mp 167−168 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57−7.53 (m, 2H), 7.13−7.02 (m, 4H), 6.64−6.60 (m, 2H), 5.63 (d, 1H, *J* = 8.5 Hz), 4.89 (dd, 1H, *J* = 4.0, 8.6 Hz), 4.41 (d, 1H, *J* = 3.9 Hz), 3.71 (s, 3H), 3.60−3.26 (m, 3H), 3.05−2.89 (m, 1H), 2.35 (s, 3H), 1.37 (s, 6H), 1.13 (t, 3H, *J* = 7.0 Hz), 0.75 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 159.2, 143.0, 137.3, 130.1, 129.3 (2C), 128.1 (2C), 127.1 (2C), 113.2 (2C), 105.6, 98.4, 73.3, 58.2, 57.5, 57.3, 55.1, 21.4, 18.4, 17.5 15.0. IR (nujol) 3198, 1737, 1308, 1243 cm^{-1}. Anal. Calcd for $C_{25}H_{33}NO_8S$: C, 59.15; H, 6.55; N, 2.76. Found: C, 58.93, H, 6.30, N, 2.63.

***N*-{(*S**)-1-[(2*S**,5*S**,6*S**)-5,6-Diethoxy-5,6-dimethyl-3-oxo-1,4-dioxan-2-yl]-2-methylpropyl}-4-methylbenzenesulfonamide (9c).** Yield 288 mg, 65%; white solid, mp 130−131 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.82−7.790 (m, 2H), 7.30−7.28 (m, 2H), 4.82 (d, 1H, *J* = 10.6 Hz), 4.05 (d, 1H, *J* = 3.3 Hz), 3.79−3.58 (m, 3H), 3.50−3.40 (m, 1H), 3.17−3.07 (m, 1H), 2.40 (s, 3H), 1.87−1.76 (m, 1H), 1.46 (s, 3H), 1.35 (s, 3H), 1.14 (t, 3H, *J* = 7.0 Hz), 1.00 (t, 3H, *J* = 7.0 Hz), 0.93 (d, 3H, *J* = 6.7 Hz), 0.81 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 143.4, 137.9, 129.7 (2C), 127.1 (2C), 105.7, 98.1, 72.5, 58.7, 58.3, 56.9, 29.7, 21.5, 21.4, 18.3 (2C), 17.8, 17.5, 14.9. IR (nujol) 3257, 1742, 1335 cm^{-1}. Anal. Calcd for $C_{21}H_{33}NO_7S$: C, 56.86; H, 7.50; N, 3.16. Found: C, 56.69; H, 7.60; N, 3.02.

General Procedure for the Allylation of Compounds 9a−c. In a screw cap vial, a heterogeneous mixture of sulfonamide **9a−c** (1 mmol), benzyltriethylammonium chloride (23.0 mg, 0.1 mmol), allyl bromide (182 mg, 1.5 mmol), and anhydrous potassium carbonate (276 mg, 2 mmol) was vigorously stirred at room temperature in anhydrous acetonitrile (10 mL) for 5 h. The crude was then diluted with dichloromethane (20 mL) and filtered through a Celite pad. After evaporation of the solvent under reduced pressure and purification of the crude by FCC (AcOEt/hexane 1:4) the *N*-allyl sulfonamides **10a−c** were obtained.

***N*-Allyl-*N*-[(*S**)-(2*S**,5*S**,6*S**)-(5,6-diethoxy-5,6-dimethyl-3-oxo-1,4-dioxan-2-yl)-(phenyl)methyl]-4-methyl-benzensulfonamide (10a).** Yield 512 mg, 99%; white solid, mp 127−128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82−7.78 (m, 2H), 7.39−7.16 (m, 7H),

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5.57 (d, 1H, J = 4.2 Hz), 5.40−5.23 (m, 1H), 4.96−4.81 (m, 3H), 3.96−3.92 (m, 2H), 3.70−3.46 (m, 4H), 2.44 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H), 1.24−1.16 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.3, 143.3, 137.8, 135.4, 135.2, 129.9 (2C), 129.7 (2C), 128.2 (2C), 128.1 (2C), 127.6, 116.8, 106.3, 98.8, 73.3, 59.8, 58.3, 57.3, 48.6, 21.6, 18.5, 17.9, 15.3, 15.0. Anal. Calcd for $C_{27}H_{35}NO_7S$: C, 62.65; H, 6.82; N, 2.71. Found: C, 62.57; H, 6.95; N, 2.65.

***N*-Allyl-*N*-{(*S**)-[(2*S**,5*S**,6*S**)(5,6-diethoxy-5,6-dimethyl-3-oxo-[1,4]dioxan-2-yl)-(4-methoxy-phenyl)-methyl]}-4-methyl-benzenesulfonamide (10b).** Yield 542 mg, 99%; white solid, mp 114−115 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82−7.78 (m, 2H), 7.33−7.26 (m, 4H), 6.71−6.66 (m, 2H), 5.49 (d, 1H, J = 4.2 Hz), 5.44−5.24 (m, 1H), 4.99−4.89 (m, 2H), 4.85 (d, 1H, J = 4.2 Hz), 3.96−3.91 (m, 2H), 3.74 (s, 3H), 3.69−3.46 (m, 4H), 2.44 (s, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.20 (t, 3H, J = 7.0 Hz), 1.19 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 159.3, 143.3, 138.0, 135.6, 131.2 (2C), 129.6 (2C), 127.6 (2C), 116.6, 113.52 (2C), 109.5, 106.2, 98.8, 73.6, 59.4, 58.2, 57.3, 55.1, 48.5, 21.5, 18.4, 17.9, 15.4, 14.9. Anal. Calcd for $C_{28}H_{37}NO_8S$: C, 61.41; H, 6.81; N, 2.56. Found: C, 61.36; H, 6.92; N, 2.53.

***N*-Allyl-*N*-{(*S**)-(2*S**,5*S**,6*S**)-[1-(5,6-diethoxy-5,6-dimethyl-3-oxo-[1,4]dioxan-2-yl)-2-methyl-propyl]}-4-methyl-benzene-sulfonamide (10c).** Yield 479 mg, 99%; white solid, mp 105−106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.77 (m, 2H), 7.28−7.26 (m, 2H), 6.09−5.96 (m, 1H), 5.18 (dd, 1H, J = 17.1, 1.2 Hz), 5.09 (dd, 1H, J = 10.2, 1.2 Hz), 4.41 (d, 1H, J = 10.8 Hz), 3.96−3.88 (m, 3H), 3.73−3.61 (m, 2H), 3.48−3.38 (m, 1H), 3.01−2.91 (m, 1H), 2.38 (s, 3H), 2.23−2. 2.10 (m, 1H), 1.44 (s, 3H), 1.35 (s, 3H), 1.67 (t, 3H, J = 6.9 Hz), 0.97−0.94 (m, 6H), 0.80 (t, 3H, J = 5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 143.1, 137.6, 136.4, 129.6, 127.3, 116.8, 105.8, 98.5, 72.3, 64.7, 58.1, 57.3, 47.5, 27.2, 21.4, 20.7, 19.5, 18.5, 17.6, 14.8, 14.4. Anal. Calcd for $C_{24}H_{37}NO_7S$: C, 59.60; H, 7.71; N, 2.90. Found: C, 59.52; H, 7.80; N, 2.87.

General Procedure for the Synthesis of Aldehydes 11a−c by Ozonolysis of Compounds 10a−c. A solution of *N*-allyl derivatives **10a−c** (1 mmol) in anhydrous methanol (10 mL) and dichloromethane (10 mL) was saturated with ozone at −78 °C under nitrogen atmosphere, then dimethylsulfide (31 mg, 2.5 mmol) was added, and the mixture was allowed to warm overnight. After solvents evaporation, purification of the crude by FCC (AcOEt/hexane 1:4), aldehydes **11a−c** were obtained.

***N*-{(*S**)-[(*SR**,5*S**,6*S**)-5,6-Diethoxy-5,6-dimethyl-3-oxo-1,4-dioxan-2-yl]-(phenyl)methyl}-4-methyl-*N*-(2-oxoethyl)-benzensulfonamide (11a).** Yield 514 mg, 99%; white solid, mp 160−162 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.85−7.78 (m, 2H), 7.39−7.12 (m, 7H), 5.64 (d, 1H, J = 4.1 Hz), 4.82 (d, 1H, J = 4.1 Hz), 3.93−3.37 (m, 6H), 2.47 (s, 3H), 1.50 (s, 3H), 1.45 (s, 3H), 1.24−1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 166.8, 144.6, 137.0, 134.5, 130.3, 129.8, 128.9, 127.7, 106.8, 99.4, 73.6, 60.0, 58.6, 57.7, 54.6, 21.8, 18.7, 17.9, 15.5, 15.2. Anal. Calcd for $C_{26}H_{33}NO_8S$: C, 60.10; H, 6.40; N, 2.70. Found: C, 60.00; H, 6.48; N, 2.62.

***N*-{(*S**)-[(2*S**,5*S**,6*S**)-5,6-Diethoxy-5,6-dimethyl-3-oxo-1,4-dioxan-2-yl](4-methoxyphenyl)methyl}-*N*-(2-oxoethyl)4-methyl-benzenesulfonamide (11b).** Yield 544 mg, 99%; white solid, mp 155.5−157 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.81−7.79 (m, 2H), 7.36−7.33 (m, 2H), 7.26−7.23 (m, 2H), 6.69−6.66 (m, 2H), 5.59 (d, 1H, J = 3.9 Hz), 4.79 (d, 1H, J = 4.2 Hz), 3.89−3.39 (m, 9H), 2.45 (s, 3H), 1.48 (s, 3H), 1.43 (s, 3H), 1.20−1.15 (m, 6H). Anal. Calcd for $C_{27}H_{35}NO_9S$: C, 59.00; H, 6.42; N, 2.55. Found: C, 58.75; H, 6.62; N, 2.69.

***N*-[(*S**)-1-((2*S**,5*S**,6*S**)-5,6-Diethoxy-5,6-dimethyl-3-oxo-1,4-dioxan-2-yl)-2-methylpropyl)-4-methyl-*N*-(2-oxoethyl)-benzenesulfonamide (11c).** Yield 481 mg, 99%; white solid, mp 133−134 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.80−7.77 (m, 2H), 7.31−7.26 (m, 2H), 4.38 (d, 1H, J = 10.2 Hz), 4.08 (d, 1H, J = 19.9 Hz), 3.90 (s, 1H) 3.71−3.61 (m, 3H), 3.48−3.39 (m, 1H), 2.29−2.88 (m, 1H), 2.40 (s, 3H), 2.07−2.04 (m, 1H), 1.43 (s, 3H), 1.30 (s, 3H), 1.29−0.87 (m, 12H). Anal. Calcd for $C_{23}H_{35}NO_8S$: C, 56.89; H, 7.26; N, 2.88. Found: C, 56.77; H, 7.39; N, 2.72.

General Procedure for the Synthesis of (2*R,3*R**)-*N*-Tosyl-isoserine Methyl Esters 12a,b.** Compound **9a,b** (1 mmol) was dissolved in a 0.25 M solution of TMSCl in MeOH (2.0 mL, 1 mmol) and stirred at 25 °C overnight. The solvent was then evaporated, and the residue was diluted with AcOEt and washed with brine. ^{1}H and ^{13}C NMR spectra of compounds **12a,b** completely matched the literature data.[23]

(2*R,3*R**)-Methyl 2-Hydroxy-3-(4-methylphenylsulfonamido)-3-phenylpropanoate (12a).** Yield 332 mg, 95%; pale yellow wax. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53−7.49 (d, 2H), 7.14−6.97 (m, 7 H), 5.75 (d, 1H, J = 9.5 Hz), 4.83 (dd, 1H, J = 9.5, 3.7 Hz), 4.52 (d, 1H, J= 3.7 Hz), 3.65 (s, 3H), 2.97 (bs, 1H), 2.32 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.7, 143.4, 137.8, 135.2, 129.5, 128.5, 128.4, 127.6, 127.2, 73.8, 59.4, 52.8, 21.6.

(2*R,3*R**)-Methyl 2-Hydroxy-3-(4-methoxyphenyl)-3-(4-methylphenylsulfonamido)propanoate (12b).** Yield 360 mg, 95%; pale yellow wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.51 (m, 2H), 7.10−7.07 (m, 2H), 6.93−6.90 (m, 2H), 6.65−6.62 (m, 2H), 5.58 (d, 1H, J = 9.5 Hz), 4.78 (dd, 1H, J = 9.5, 3.5 Hz), 4.49 (d, 1H, J = 3.5 Hz), 3.72 (s, 3H), 3.65 (s, 3H), 2.82 (bs, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 159.3, 142.9, 137.6, 129.2, 128.7, 127.3, 127.0, 113.6, 73.9, 58.8, 55.13, 52.6, 21.3.

General Procedure for the One-Pot Mannich Condensation/Morpholine Ring Closure. Synthesis of Products 13a−e. Mannich condensation was carried out according to *Method A* or *Method B* starting from 1 mmol of reagents, affording crude intermediates **5a−e** (1 h). Then the solvent was removed at reduced pressure, and a 1.3 M solution of TMSCl in MeOH (10 mL, 13 mmol) was added. The mixture was refluxed for 4 h, the solvent was removed under vacuum, and the crude was treated with propylene oxide (87 mg, 1.5 mmol) in MeOH (5 mL) and refluxed for 1 h. After solvents evaporation and purification of the crude by FCC, morpholines **13a−e** were isolated. Yield, chromatographic eluent, and physical and analytical data are as follows.

(2*S,3*R**,6*R**)-Methyl 6-Methoxy-3-phenylmorpholine-2-carboxylate (13a).** FCC (AcOEt/hexane 1:4); 246 mg, 98%; de > 99%; clear wax. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39−7.26 (m, 5H), 4.64 (dd, 1H, J = 8.3, 2.5 Hz), 4.19 (d, 1H, J = 8.8 Hz), 3.94 (d, 1H, J = 8.8 Hz), 3.54 (s, 3H), 3.52 (s, 3H), 3.16 (dd, 1H, J = 11.4, 2.5 Hz), 2.88 (dd, 1H, J = 11.5, 8.3 Hz), 1.88 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.8, 138.0, 128.7 (2C), 128.6 (2C), 128.0, 100.8, 80.4, 61.8, 56.8, 51.9, 49.8; IR (neat) 3325, 1743, 1446, 1031 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.98; H, 7.00; N, 5.31

(2*S,3*R**,6*R**)-Methyl 3-(Benzo[*d*][1,3]dioxol-5-yl)-6-methoxymorpholine-2-carboxylate (13b).** FCC (AcOEt/hexane 1:3); 257 mg, 87%; de > 99%; yellow solid, mp 133−135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, 1H, J = 1.4 Hz), 6.79 (dd, 1H, J = 8.0, 1.5 Hz), 6.72 (d, 1H, J = 8.0 Hz), 5.94 (s, 2H), 4.61 (dd, 1H, J = 8.4, 2.4 Hz), 4.11 (d, 1H, J = 8.8 Hz), 3.85 (d, 1H, J = 8.9 Hz), 3.57 (s, 3H), 3.53 (s, 3H), 3.14 (dd, 1H, J = 11.4, 2.4 Hz), 2.85 (dd, 1H, J = 11.4, 8.4 Hz), 1.91 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 148.1, 147.8, 132.3, 121.6, 108.5, 108.2, 101.5, 101.1, 81.0, 61.7, 57.0, 52.2, 50.2; IR (nujol) 3317, 1738, 1490, 1249, 1029 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.82; H, 5.91; N, 4.61

(2*S,3*R**)-Methyl 3-Isopropyl-6-methoxymorpholine-2-carboxylate (13c).** FCC (AcOEt/hexane 1:4); 252 mg, 82%; de 80%; clear wax. Anomeric mixture: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.54 (m, 1H$_\alpha$), 4.43 (dd, 1H$_\beta$, J = 7.8, 2.6 Hz), 4.29 (d, 1H$_\alpha$, J = 9.7 Hz), 4.07 (d, 1H$_\beta$, J = 8.4 Hz), 3.77 (s, 3 + 3H), 3.47 (s, 3H$_\beta$), 3.39 (s, 3H$_\alpha$)3.10 (dd, 1H$_\beta$, J = 12.4, 2.6 Hz), 3.01−2.99 (m, 2H$_\alpha$), 2.81−2.775 (m, 1 + 1H), 2.70 (dd, 1H$_\beta$, J = 12.4, 7.9 Hz), 2.53 (bs, 1 + 1H), 1.89−1.66 (m, 1 + 1H), 1.0−0.90 (m, 6 + 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (β-anomer) 169.8, 100.2, 77.1, 60.2, 56.6, 52.2, 48.6, 28.0, 20.2, 16.7; IR (neat) 3349, 1745, 1448, 1067 cm^{-1}. Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 54.99; H, 9.03; N, 6.13.

(2*S,3*R**)-Methyl 4-Benzyl-3-isopropyl-6-methoxymorpholine-2-carboxylate (13d).** FCC (AcOEt/hexane 1:4); 267 mg, 87%; de 75%; clear wax. Anomeric mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.26 (m, 5 + 5H), 5.01 (dd, 1H$_\beta$, J = 7.2, 5.1 Hz), 4.50

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(dd, 1H$_{\alpha'}$ J = 5.4, 3.6 Hz), 4.38 (d, 1H$_{\beta}$, J = 5.1 Hz), 4.16 (d, 1H$_{\alpha'}$ J = 4.8 Hz), 4.06 (d, 1H$_{\alpha'}$ J = 13.5 Hz), 3.95−3.82 (m, 2H$_{\beta}$ + 1H$_{\alpha}$), 3.77 (s, 3 + 3H), 3.46 (s, 3H), 3.43 (s, 3H), 2.89 (dd, 1H$_{\alpha'}$, J = 12.6, 3.0 Hz), 2.81−2.60 (m, 5H), 2.28 (dd, 1H$_{\alpha'}$, J = 12.6, 6.0 Hz), 2.18−2.07 (m, 1 + 1H), 1.05−0.94 (m, 6 + 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (β-anomer) 172.6, 139.4, 128.6, 128.2, 127.1, 95.7, 71.3, 65.2, 60.7, 56.0, 52.1, 47.7, 28.3, 20.5, 19.8; δ (α-anomer) 172.0, 139.0, 128.9, 128.2, 127.1, 99.2, 71.9, 63.5, 59.2, 56.0, 52.1, 50.9, 27.9, 19.3, 18.9. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56. Found: 66.10; H, 8.47; N, 4.28.

(2*S)-Methyl 4-Benzyl-6-methoxymorpholine-2-carboxylate (13e).** FCC (AcOEt/hexane 1:4), 249 mg, 94%; de 60%; clear wax. Anomeric mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5 + 5H), 4.86 (t, 1H$_{\alpha'}$ J = 2.4 Hz), 4.65 (dd, 1H$_{\alpha'}$ J = 9.4, 2.9 Hz), 4.56 (dd, 1H$_{\beta}$, J = 8.3, 2.2 Hz), 4.33 (dd, 1H$_{\beta}$, J = 10.3, 2.5 Hz), 3.76 (s, 3H), 3.57−3.54 (m, 10H), 3.47 (s, 3H), 3.01−2.97 (m, 1 + 1H), 2.88 (d, 1H$_{\beta}$, J =10.9 Hz), 2.74 (d, 1H$_{\alpha'}$ J = 11.7 Hz), 2.42 (dd, 1H$_{\alpha'}$ J = 8.9, 2.7 Hz), 2.38 (dd, 1H$_{\alpha'}$, J = 11.2, 9.6 Hz), 2.21 (t, 1H$_{\beta}$, J =11.7 Hz), 2.05 (dd, 1H$_{\beta}$, J =10.9, 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (anomeric mixture) 171.1, 170.0, 137.2, 136.9, 129.7, 129.6, 128.8, 128.7, 127.9, 127.8, 100.9$_{\beta}$, 97.8$_{\alpha}$, 73.3$_{\beta}$, 69.2$_{\alpha'}$, 63.1, 62.8, 57.1, 56.5$_{\beta}$, 56.1, 55.8$_{\alpha}$, 54.2$_{\alpha}$. 54.0$_{\beta}$, 52.6. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: 63.11; H, 7.40; N, 5.00.

Synthesis of Morpholines 14a−c. Aldehyde **11a−c** (1 mmol) was added to a 0.25 M solution of TMSCl in MeOH (10 mL, 2.5 mmol). The reaction mixture was stirred at 25 °C overnight. The solvent was evaporated, and the crude was purified by flash column chromatography (AcOEt/hexane 1:3) giving the pure α- and β-anomers **14a−c**.

(2*R,3*R**)-Methyl 6-Methoxy-3-phenyl-4-tosylmorfoline-2-carboxylate (14a).** β-**14a**, 203 mg, 50%; white solid, mp 129−130 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42−7.06 (m, 9 H), 5.24 (d, 1H, J = 3.9 Hz), 4.64−4.57 (m, 2H), 3.70 (dd, 1H, J = 13.1 Hz, J = 2.8 Hz), 3.60 (s, 3H), 3. 51 (s, 3H), 2.88 (dd, 1H, J = 13.0, 9.4 Hz), 2.33 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.5, 143.6, 136.4, 134.8, 129.7, 128.5, 128.4, 127.9, 127.4, 100.6, 76.0, 57.1, 56.0, 52.2, 43.9, 21.6; IR (nujol) 3436, 1758, 1354, 1165 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NO_6S$: C, 59.24; H, 5.72; N, 3.45. Found: C, 59.00; H, 5.88; N, 3.21. α-**14a**: 187 mg, 46%; white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.56 (m, 2H), 7.49−7.44 (m, 2H), 7.26−7.15 (m, 5H), 5.24 (d, 1H, J = 3.9 Hz), 4.86 (d, 1H, J = 2.4 Hz), 4.71 (d, 1H, J = 3.9 Hz), 3.71 (d, 1H, J = 14.1 Hz), 3.54 (s, 3H), 3.28 (s, 3H), 3.22 (dd, 1H, J = 14.1, 2.5 Hz), 2.38 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.8, 143.4, 137.1, 135.0, 129.6, 129.3, 129.2, 128.5, 127.9, 96.3, 68.8, 55.9, 55.0, 52.3, 43.3, 21.6. Anal. Calcd for $C_{20}H_{23}NO_6S$: C, 59.24; H, 5.72; N, 3.45. Found: 59.02; H, 5.90; N, 3.24.

(2*R,3*R**)-Methyl 6-Methoxy-3-(4-methoxyphenyl)-4-tosylmorpholine-2-carboxylate (14b).** β-**14b**, 322 mg, 74%; white wax . ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42−7.30 (m, 4 H), 7.11−7.07 (m, 2 H), 6.70−6.66 (m, 2 H), 5.19 (d, 1H, J = 4.0 Hz), 4.61−4.55 (m, 2H), 3.77 (s, 3H), 3.70 (dd, 1H, J = 13.0, 2.6 Hz), 3. 62 (s, 3H), 3. 54 (s, 3H), 2.90 (dd, 1H, J = 13.0, 9.3 Hz), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 160.0, 143.8, 136.4, 131.2, 129.7, 127.7, 127.0, 114.0, 100.7, 76.3, 57.4, 55.7, 55.6, 52.5, 44.0, 21.8; IR (nujol) 2748, 1745, 1344, 1250 cm^{-1}. Anal. Calcd for $C_{21}H_{25}NO_7S$: C, 57.92; H, 5.79; N, 3.22. Found: C, 57.67; H, 5.93; N, 3.03. α-**14b**, 100 mg, 23%; white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61−7.56 (m, 2 H), 7.41−7.38 (m, 2H), 7.19−7.16 (m, 2H), 6.75−6.72 (m, 2H), 5.19 (d, 1H, J = 3.7 Hz), 4.84 (d, 1H, J = 1.5 Hz), 4.70 (d, 1H, J = 3.8 Hz), 3.76−3.67 (m, 4H), 3. 54 (s, 3H), 3. 52 (s, 3H), 3.24 (dd, 1H, J = 14.1, 2.4), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 159.5, 143.1, 136.4, 130.3, 129.1, 127.7, 126.8, 113.7, 96.1, 76.6, 57.4, 68.8, 55.2, 52.2, 43.0, 21.5. Anal. Calcd for $C_{21}H_{25}NO_7S$: C, 57.92; H, 5.79; N, 3.22. Found: C, 57.60; H, 5.95; N, 2.98.

(2*R,3*R**)-Methyl 3-Isopropyl-6-methoxy-4-tosylmorpholine-2-carboxylate (14c).** β-**14c**, 71 mg, 19%; white solid, mp 108−109 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.72 (m, 2H), 7.33−7.31 (m, 2H), 4.18 (dd, 1H, J = 9.8, 3.0 Hz), 4.11 (d, 1H, J = 2.4), 3.88 (dd, 1H, J = 6.9, 2.4 Hz), 3.75−3.71 (m, 4H), 3.48 (s, 3H), 2.89 (dd, 1H, J = 9.9, 14.7 Hz), 2.34 (s, 3H), 2.27−2.20 (m, 1H), 0.87−0.84 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 143.8, 137.8, 130.0, 127.3, 99.5, 74.6, 59.6, 56.7, 52.0, 44.1, 25.7, 21.5, 20.4, 20.0; IR (nujol) 3403, 1764, 1330, 1121 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_6S$: C, 54.97; H, 6.78; N, 3.77. Found: C, 54.85; H, 6.88; N, 3.68. α-**14c**, 293 mg, 79%; clear wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.72 (m, 2H), 7.26−7.23 (m, 2H), 4.61 (d, 1H, J = 2.6 Hz), 4.13 (d, 1H, J = 2.6 Hz), 3.82−3.71 (m, 5H), 3.29 (dd, 1H, J = 15.2, 2.6 Hz), 3.02 (s, 3H), 2.40 (s, 3H), 2.30−2.15 (m, 1H), 0.96 (d, 3H J = 6.6 Hz), 0.85 (d, 3H J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 143.3, 137.7, 129.2, 128.0, 96.1, 67.4, 59.9, 54.5, 52.2, 43.8, 25.4, 21.7, 20.7, 20.1. Anal. Calcd for $C_{17}H_{25}NO_6S$: C, 54.97; H, 6.78; N, 3.77. Found: C, 54.81; H, 6.90; N, 3.63.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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