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Influence of Amino Acid Stereocenters on the Formation of Bicyclic *N,O*-Acetals

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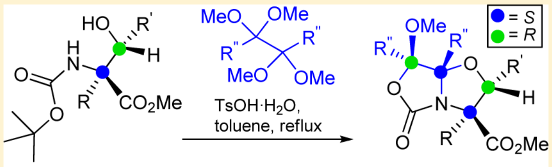
Supporting Information

ABSTRACT: In recent years, our group has reported the highly diastereoselective acid-catalyzed *N,O*-acetalization/intramolecular transcarbamoylation cascade of reactions between protected *α*-amino acid derivatives (Ser and Thr) and tetramethoxyalkanes. The resulting oligocyclic *N,O*-acetals have been used as excellent chiral building blocks for asymmetric transformations such as diastereoselective alkylation of the *α*-position. We now evaluate the scope of the reaction with related non-natural *α*-amino acid derivatives. A combined experimental and theoretical study reveals the key influence of the *α*-carbon substitution (serine versus *α*-methylserine) and the relative configuration of *α*-/*β*-carbons (threonine versus *allo*-threonine) in the thermodynamic stability of the products and, as a consequence, the stereochemical outcome of the reaction. Notably, the complete diastereoselectivity achieved with natural amino acid precursors is completely lost with their non-natural analogues.



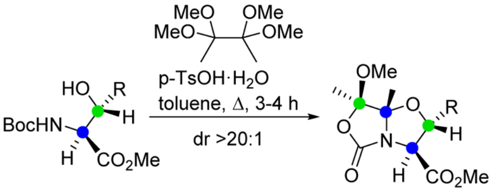
cascade acid-catalyzed acetalization-transcarbamoylation reaction
only good diastereoselectivities with natural amino acids
L-Ser (R = R' = H) and L-Thr (R = H, R' = Me) derivatives

INTRODUCTION

The use of 1,2-diacetals as special structural motifs for applications in natural product synthesis is well-known. For example, they can work as chemoselective protecting groups, provide reactivity control through torsional effects, and act as chiral auxiliaries in a variety of reactions or as desymmetrization agents in several processes.[1] Nevertheless, relatively little attention has been focused on the use of their analogues: the *N,O*-diacetals. In this context, five-membered-ring *N,O*-acetals derived from L-serine or L-serinal (i.e., Garner aldehyde)[2] or from *α*-methylserine[3] have been used as three-carbon building blocks in organic synthesis. However, due to the propensity of some of these materials to polymerize, racemize, and form hydrates, the compounds must be freshly prepared and their storage is not recommended. To overcome these problems, particularly in terms of scale-up, we recently developed an alternative approach to prepare stable and readily available chiral five-ring *N,O*-acetal derivatives from adequately protected serine or threonine. This approach involves the incorporation of a new ring in their structures by generation of chiral bicyclic *N,O*-acetal systems, which favor the diastereoselectivity of subsequent alkylation reactions.[4]

We have previously described that commercially available Boc-protected serine (**1a**) and threonine (**1b**) methyl esters react smoothly with 2,2,3,3-tetramethoxybutane (TMB) in the presence of *p*-toluenesulfonic acid (TsOH·H_2O) to give chiral bicyclic *N,O*-acetals **2a**,**b** on a multigram scale with high yields and in a highly stereoselective way (Scheme 1 and Figure 1).[4] These chiral building blocks have shown a superior reactivity toward diastereoselective alkylation at the *α*-position with several electrophiles, allowing the synthesis of enantiopure *α*-alkylserines,[4a,b] *α*-alkylthreonines,[4c] and Tn antigen mimics.[4d] As theoretically proposed for serine derivative **2a**, the structural restraints imposed by the bicyclic structure force the enolate generated after deprotonation to adopt a highly pyramidalized geometry, which leads to a complete retention of configuration in the alkylation process.[4a]

Scheme 1. Synthesis of Chiral Bicyclic *N,O*-Acetals from Natural Amino Acid Derivatives[a]



R=H (Ser): **1a**
R=Me (Thr): **1b**

R=H (Ser): **2a-II** (75%)
R=Me (Thr): **2b-II** (69%)

[a]The absolute configuration of stereocenters is represented by colored dots (blue *S*; green *R*).

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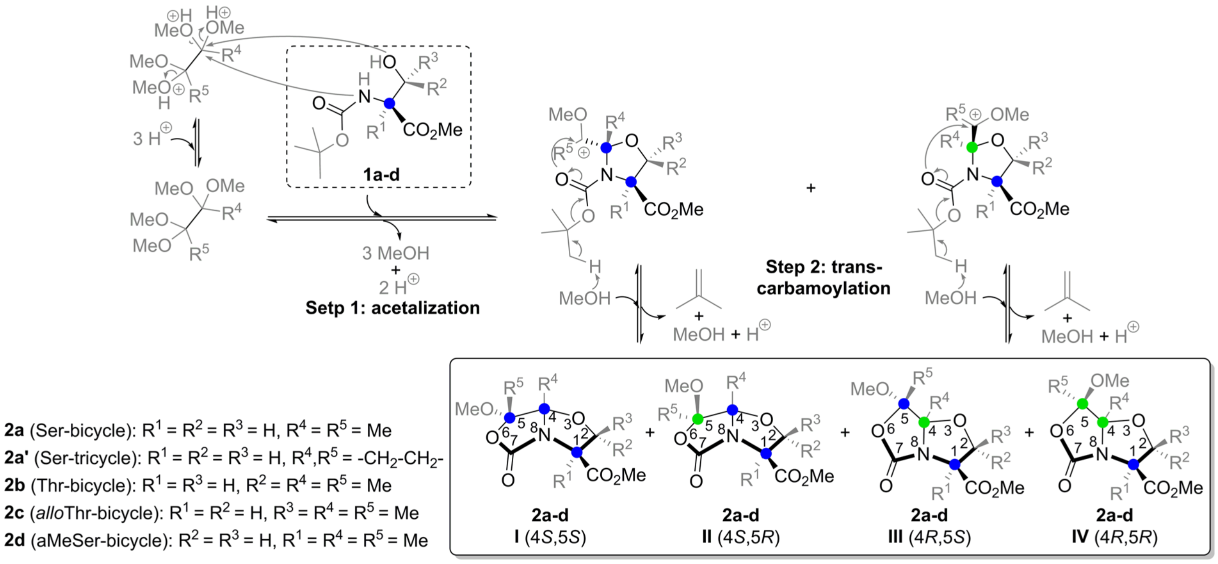


Figure 1. Proposed mechanism for the acid-catalyzed formation of *N*,*O*-acetals **2a**−**d** from hydroxyamino acid derivatives **1a**−**d**. The four possible diastereomers of the bicyclic and tricyclic Ser, Thr, *allo*Thr, and αMeSer derivatives studied in this work are displayed. The absolute configuration of stereocenters is represented by colored dots (blue *S*; green *R*).

RESULTS AND DISCUSSION

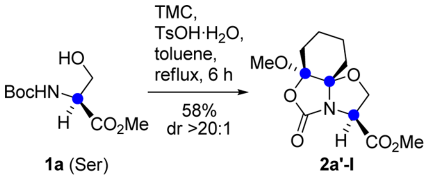
Once the synthetic utility of these building blocks has been demonstrated, we were interested in revisiting the stereoselective (but not trivial) formation of these bicyclic compounds. Though there are 8 possible diastereoisomeric products from the reaction with Ser derivative **1a** and 16 from the reaction with Thr derivative **1b**, only 1 diastereoisomer was obtained from either starting material, despite the drastic conditions required (prolonged heating in refluxing toluene under acidic conditions) and the expected participation of carbocations in the formation of the *N*,*O* and *O*,*O*-acetals (see a proposed abbreviated reaction mechanism in Figure 1). Irrespective of the presence of a methyl group at the β position, the configuration of the new stereocenters followed the same pattern in both the Ser- and Thr-derived bicycles (**2a-II** and **2b-II**, respectively); that is, the *N*,*O*- and *O*,*O*-acetalic carbons (henceforth C4 and C5; see Figure 1) showed *S* and *R* configurations, respectively. To explain these results, we postulated that the configuration of the α-carbon of the starting amino acid derivative remains unaltered during the whole process, guiding the stereocontrolled ring-closure cascade by means of thermodynamic control (i.e., greater stability of the final bicycles possessing certain configurations and conformations).[4a]

To further test this hypothesis, we explored the scope of this methodology by varying both the acetalization reagent (acyclic or cyclic) and the substitution pattern in the hydroxyamino acid substrate, which led to significant changes in the stereochemical outcome of the reaction that were not anticipated. However, before discussing the experimental results, it is necessary to describe the geometries of all the possible bi- or tricyclic adducts (depending on the substrate) that can be formed in the acetalization reaction. Taking into account that the amino acid original stereocenters remain unaltered along the reaction, as experimentally observed, up to four diastereomeric forms (**I**−**IV**) are possible depending on the absolute configuration of acetalic carbons C4 and C5. As can be seen in Figure 1, the configuration of carbon C4 determines the curvature of the bicyclic products, placing the bridgehead substituent (typically a methyl group) and the ester group in a *syn* (convex structures **I** and **II**) or *anti* (concave structures **III** and **IV**) disposition. On the other hand, the absolute configuration of C5 arranges the bridgehead substituent and methoxy group in a *syn* (structures **II** and **III**) or *anti* (structures **I** and **IV**) disposition.

With respect to the hydroxyamino acid moiety, C1 always shows an *S* configuration, whereas C2 can be nonstereogenic (**2a**, **2a′**, and **2d**) or stereogenic (*R* in **2b** and *S* in **2c**). In order to rationalize the experimental results, the relative stability of each possible structure, which depends on the distinct substitution patterns, will be discussed later on. Attending to this nomenclature, the bicyclic *N*,*O*-acetals previously obtained from protected Ser and Thr were **2a-II** and **2b-II**.

Experimental Results. As a first approach, the role of the acetalization reagent was analyzed by reducing its conformational flexibility. Thus, when protected serine **1a** and 1,1,2,2-tetramethoxycyclohexane (TMC) were reacted in the presence of $TsOH \cdot H_2O$,[1] a single product was obtained, although in moderate yield (58%; Scheme 2). X-ray diffraction[5] and NMR analysis, including NOE experiments of this compound (**2a′-I**), confirmed its tricyclic structure (Figure 2) but, remarkably, an opposite configuration at carbon C5 (*S*) was found with respect to previous examples. This structural change was imposed by the cyclohexane ring, which forces both alkyl substituents at the acetalic positions to adopt a *syn* configuration. Of note, the X-ray diffraction structure of this compound revealed an unusual

Scheme 2. Synthesis of Chiral Tricyclic *N*,*O*-Acetal from Boc-L-Ser-OMe[a]



[a]The absolute configuration of stereocenters is represented by colored dots (blue *S*).

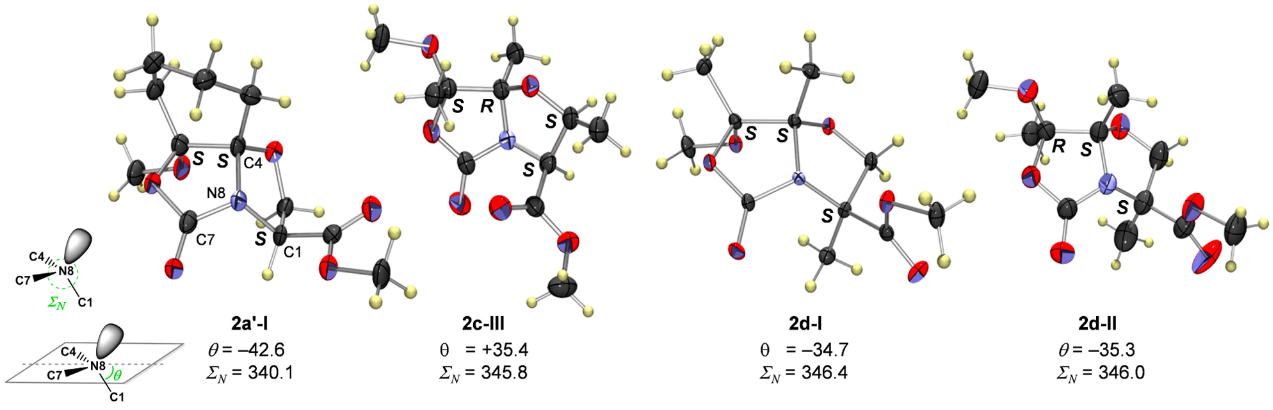
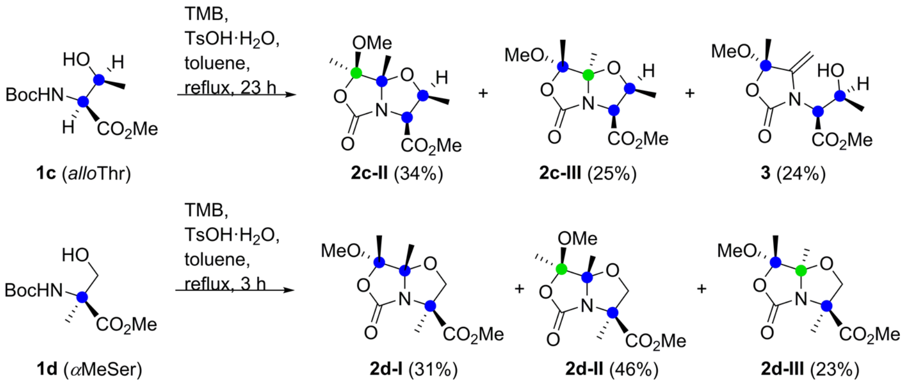


Figure 2. X-ray diffraction structures of bicycles **2a′-I**, **2c-III**, **2d-I**, and **2d-II**. $\sum_N$ and θ angles are given in degrees.

Scheme 3. Synthesis of Chiral Bicyclic *N*,*O*-Acetals from Non-Natural Amino Acid Derivatives[a]



[a]The absolute configuration of stereocenters is represented by colored dots (blue *S*; green *R*).

twist-boat conformation for the cyclohexane ring, as a result of the torsional restraints imposed by the fused tricyclic structure. It is worth mentioning that, to the best of our knowledge, although the close octahydro-2*H*-oxazolo[3,2-i]indole substructure has been previously obtained,[6] this is the first time that the heterotricyclic substructure included in compound **2a′-I** has been synthesized.

On the other hand, a significant drop in diastereoselectivity was observed when the configuration of the *β*-carbon of Thr was changed from *R* to *S*: that is, by reacting protected *allo*Thr **1c** with acyclic TMB under the standard conditions (Scheme 3). In this case, the conversion was high (82%), but a rather complex mixture of products was obtained, which was very difficult to separate and only a few compounds could be identified after exhaustive purification by column chromatography. In contrast to our previous results with natural amino acid derivatives, a mixture of *N*,*O*-bicyclic acetals (**2c**) was formed in the reaction together with an unexpected alkene (**3**).[7] Although up to three *allo*Thr-derived bicycles were detected in the ^{1}H NMR spectrum of distinct chromatographic fractions, the structures of only two of them could be fully established by NMR (**2c-II**) and X-ray diffraction analysis (**2c-III**, Figure 2). Of note, whereas the major compound (**2c-II**, 34%) shows an stereochemistry analogous to that of the major products obtained from Ser and Thr derivatives, the significant minor bicyclic product (**2c-III**, 25%) shows the reverse stereochemistry at both newly formed stereocenters C4 and C5.

Given the impact of the *β*-carbon configuration on diastereoselectivity observed for Thr and *allo*Thr, we were intrigued about the consequences of placing a methyl group on the *α*-carbon of Ser. Hence, protected *α*-methylserine (*α*MeSer) **1d** was reacted with TMB in the presence of TsOH·H_2O in refluxing toluene (Scheme 3). As in the case of *allo*Thr, the reaction mixture was rather complex and the stereoselectivity obtained in the formation of the bicyclic products was also very poor. In this case, no alkene products were detected and up to three major diastereomers could be isolated. The structure of these compounds was determined by NMR (**2d-III**) and X-ray diffraction analysis (**2d-I** and **2d-II**, Figure 2). Again, the major product obtained in this reaction (**2d-II**) showed the same configuration at the new stereocenters as those obtained as single diastereomers from protected Ser and Thr. However, the presence of the methyl group in the *α*-position favors the formation of other diastereomers in similar proportions and makes the reaction synthetically impractical.[8]

Given the low yields and the broad distribution of products obtained in the *N*,*O*-acetalization reaction with non-natural amino acid derivatives, it is clear that the high stereoselectivity observed originally with Boc-protected Ser and Thr methyl esters cannot be easily extrapolated to other substrates. These results, although synthetically unsatisfactory, raise the interesting question of why only natural amino acids provide high levels of stereoselection. In view of these and previous[4a] observations, we anticipated that the different stabilities of the final diastereomeric bi- or tricycles as a function of their

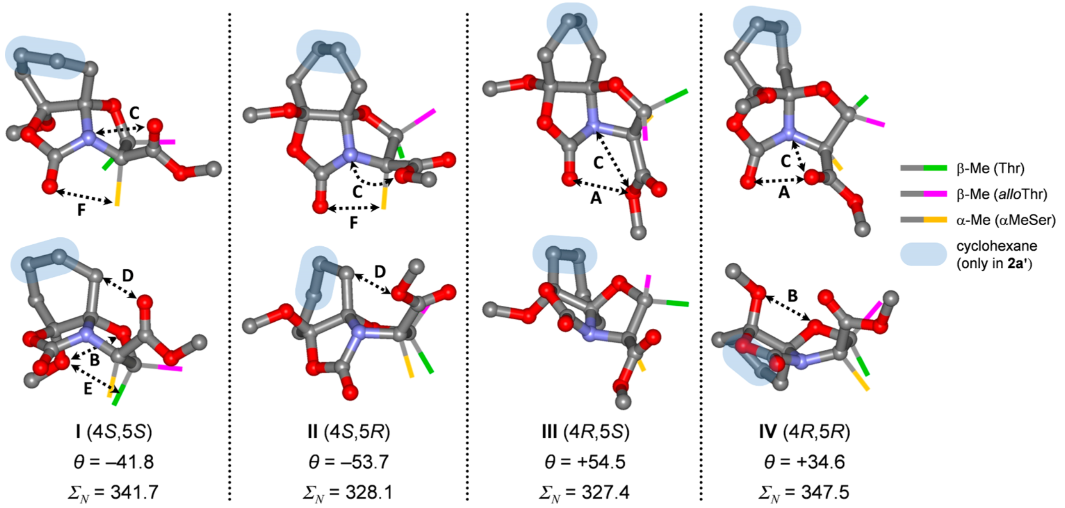


Figure 3. Minimum-energy geometries (two orientations) of tricycle **2a**′ calculated at the B3LYP/6-31+G(d) level. For illustrative purposes, the *α*- and *β*-methyl groups corresponding to the Thr (**2b**), *allo*Thr (**2c**), and *α*MeSer (**2d**) analogues have been attached schematically through colored lines. The most significant steric interactions are indicated with arrows and capital letters (**A**−**H**; see Table 2 and the text).

absolute configurations, are the main sources of stereocontrol in this thermodynamically controlled reaction.

Computational Analysis. In order to rationalize the experimental results described above, and assuming thermodynamic control for these acid-catalyzed acetalizations due to the harsh conditions employed (excess of TMB and prolonged heating),[4a] we evaluated the thermal stability of all the possible stereoisomers of the final bi- and tricycles **2a**−**d**. To this end, we first optimized the structures of all possible diastereomers through DFT methods and then evaluated the most important steric interactions occurring between selected functional groups through the NBO partition scheme (see Computational Details). Given that the acetalization reactions were carried out in dilute solutions of a nonpolar solvent such as toluene (ca. 0.15 M on a multigram scale), performing the calculations in the gas phase constitutes a reasonable approximation. As an example, Figure 3 shows the minimum energy structures calculated for each diastereomer (**I**−**IV**) of the Ser-derived tricycle **2a**′. Just for visualization purposes, we added methyl groups to these structures in order to represent the steric interactions analyzed for Ser, Thr, *allo*Thr, and *α*MeSer (all of the computed geometries can be found in the Supporting Information). In line with our previous observations[4b] and as confirmed in the X-ray diffraction structures depicted in Figure 2, one of the most remarkable geometrical features found in all the calculated bicycles is the highly nonplanar character of the bridgehead carbamate N atom, measured in terms of the out-of-plane angle (*θ*) between the bond vector N8−C1 and the plane N8−C4−C7, and the sum of the three valence angles around N ($\sum_N$).

This high pyramidalization is the result of the conformational restraints imposed by the bicyclic structure and makes N8 formally stereogenic.[9] This characteristic hybridization of N8 has been proposed to have a key influence on the stereochemical outcome of subsequent reactions such as the diastereoselective alkylation of these substrates.[4a,b]

Table 1 summarizes the distribution of diastereomeric bi- and tricycles (**2a**−**d**) based on the Boltzmann distribution obtained from the Gibbs free energies (Δ*G*) of all calculated conformers and stereoisomers. Although these bicyclic and even tricyclic species are quite rigid, some conformational flexibility arises from the puckering of the oxazolidine ring and the presence of rotatable bonds in the methyl ester group (see the Supporting Information for details). As can be seen through these data, a good agreement with the experimental results was obtained in all cases; the calculations reproduced the experimental observation that natural amino acid derivatives provide excellent diastereoselectivities in the formation of bi- and tricyclic *N*,*O*-acetals, while non-natural analogues do not. Thus, diastereomeric form **II** (4*S*,5*R*) is, by far, the most stable configuration of stereocenters for Ser- and Thr-derived bicyclic *N*,*O*-acetals (>90%). In addition, the conformational restraints introduced by the cyclohexane ring fully invert the stability of diastereomers **II** (4*S*,5*R*) and **I** (4*S*,5*S*), making the latter the exclusive expected diastereoisomer in the case of tricyclic **2a**′. For *α*MeSer (**2d**) up to three diastereomers, **I** (4*S*,5*S*), **II** (4*S*,5*R*) and **III** (4*R*,5*S*), are of comparable stability and, in agreement with experimental results, **2d-II** is the most populated species. The only discrepancy is observed in the *allo*Thr derivative (**2c**), for which diastereomers **I** (4*S*,5*S*) and **II** (4*S*,5*R*) are of comparable stability whereas experimentally **2c-II** and **2c-III** are the major compounds. This disagreement between the experimental and calculated distributions of

Table 1. Experimental (exptl) and Calculated (calcd) Populations at the B3LYP/6-31+G(d) Level of the Four Diastereomers of Compounds 2a−d[a]

	diastereomeric ratio (%)							
	I (4*S*,5*S*)		**II** (4*S*,5*R*)		**III** (4*R*,5*S*)		**IV** (4*R*,5*R*)	
structure	exptl	calcd	exptl	calcd	exptl	calcd	exptl	calcd
2a (Ser-bicycle)	<5	7.1	**>95**	**90.3**	<5	2.5	<5	0.1
2a′ (Ser-tricycle)	**>95**	**99.9**	<5	0.0	<5	0.1	<5	0.0
2b (Thr-bicycle)	<5	0.7	**>95**	**98.2**	<5	0.9	<5	0.1
2c (*allo*Thr-bicycle)	nd	**57.6**	**34**	39.7	25	2.5	nd	0.1
2d (*α*MeSer-bicycle)	31	30.0	**46**	**41.0**	23	27.2	nd	1.8

[a]Major compounds are shown in boldface. nd = not determined.

products encouraged us to test whether thermodynamic equilibrium was fully reached in this reaction. This question is especially relevant in this case, because the time required to reach full conversion from the *allo*Thr derivative **1c** is considerably longer (23 h) than that from Ser, Thr, and αMeSer derivatives (3–6 h). We assayed the thermodynamic equilibration of purified samples of diastereomers **2c-II** and **2c-III** in the presence of TsOH and TMB. In agreement with the calculated higher stability of **2c-I**, a slight enrichment of this product in the reaction mixture was observed by GC upon prolonged heating. However, most of the starting material underwent decomposition and significant formation of alkene **3** was observed. The complex reaction mixtures resulting from these experiments could not be readily analyzed by NMR spectroscopy or GC chromatography, due to extensive overlap of signals and elution peaks. These results showed the relevance of thermodynamic control in this reaction and suggest that, when prolonged reaction times and high temperatures are needed (as in the case of *allo*Thr derivatives), thermodynamic equilibration might not be achieved. This failure to reach equilibrium could be due to the presence of a secondary decomposition pathway to form alkene **3**, which has not been observed during the analogous reactions of other hydroxyamino acids.

Given that no significant attractive intramolecular interactions are expected to take place within these quite rigid compounds, the main factors governing the stability of each diastereomer should be essentially steric (except in the case of **2a′**, in which the stability is determined by torsional strains imposed by the tricyclic core). In an effort to gain some insights into these observed preferences in the formation of *N*,*O*-acetals, the most important steric interactions were estimated through NBO calculations (see Computational Details). These repulsive interactions between occupied orbitals were collected and summed in pairs of functional groups, and the results are summarized in Table 2. Before proceeding with the analysis of the results, it is worth noting that the NBO method belongs to a family of theoretical constructs based on the arbitrary decomposition and localization of the electron density onto atoms and atom pairs, which sometimes can be problematic. Furthermore, the pairwise steric exchange energies calculated for these systems are quite small, and within the range of the—also very small—differences in the total energy. Therefore, these energy values may be close to the accuracy limit of the method. For this reason, and given the inherent lack of accuracy of any energy partition scheme, these data should only be considered semiquantitatively.

According to these data, steric interactions occurring between the ester and carbamate carbonyl (type A) are dominant in diastereomers **III** and **IV** of all derivatives, whereas repulsions between the bridgehead N atom and the ester group (type C) appear (although to a minor extent) only in diastereomers **I** and **II**. An exception to this general trend is found in *allo*Thr (**2c**) and αMeSer (**2d**) derivatives, in which type C repulsions are of similar magnitude in all diastereomeric forms. This might be roughly related to the more equally populated distribution of isomers calculated for these compounds (Table 1), which is also found experimentally. Other weaker interactions take place only in certain diastereomers, such as those between exo- and endocyclic ethers (type B) in diastereomers **I** and **IV** and those between the ester and the bridgehead alkyl groups (type D) in isomer **I**. Again, a deviation to this tendency is observed in *allo*Thr (**2c**) and αMeSer (**2d**) adducts, in which isomer **II** also exhibits significant type D repulsive interactions.

Table 2. Sum of Repulsive Interactions (Pairwise Steric Exchange Energies in kcal mol^{-1}) Derived from NBO Calculations Carried out on the Minimum Energy Structures of Each Diastereomer (I–IV) of Bicycles 2a–d at the B3LYP/6-31+G(d) Level[a]

structure	**I** (4*S*,5*S*)	**II** (4*S*,5*R*)	**III** (4*R*,5*S*)	**IV** (4*R*,5*R*)
2a (Ser)				
interactions A			3.3	2.5
interactions B	0.7			0.7
interactions C	0.9	0.7		
interactions D	1.2			
total	*2.8*	*0.7*	*3.3*	*3.2*
2b (Thr)				
interactions A			3.2	2.5
interactions B	0.8			0.6
interactions C	0.9	0.7		
interactions D	1.3	0.2		
interactions E	1.2			
total	*4.2*	*0.9*	*3.2*	*3.1*
2c (*allo*Thr)				
interactions A			2.2	1.9
interactions B	0.6			0.9
interactions C	0.9	0.8	0.9	0.8
interactions D	1.4	2.2		
total	*2.9*	*3.0*	*3.1*	*3.6*
2d (αMeSer)				
interactions A			3.2	3.2
interactions B	0.6			0.6
interactions C	1.2	1.0	1.3	0.2
interactions D	0.3	0.8		
interactions F	4.1	5.8	0.2	
interactions G		0.3	0.7	0.8
interactions H	8.8	8.8	11.2	9.5
total	*15.0*	*16.7*	*16.6*	*14.3*

[a] See Figure 3 and Computational Details.

Notably, the presence of a methyl group in the β position has a negligible effect in generating any significant interactions with other functional groups in *allo*Thr (**2c**) and Thr (**2b**) derivatives; only weak repulsions between the β-methyl and the exocyclic ether groups (type E) appear in diastereomer **II**.

In contrast, the presence of a methyl group in the α-position of the αMeSer derivative (**2d**) generates important steric interactions with the cyclic carbamate group (type F) in isomers **I** and **II**. Other weaker interactions involving the α-methyl group in **2d** are those taking place with the bridgehead methyl group (type G) only in isomers **III** and **IV**. Together with these, subtle differences in the steric interactions occurring between the geminal α-methyl and ester groups (type H) compensate type F repulsions and contribute to make diastereomeric forms **III** and **IV** of **2d** less stable.

■ CONCLUSIONS

The diastereoselective formation of bicyclic and tricyclic *N*,*O*-acetals has been systematically studied both experimentally and theoretically. It has been demonstrated that suitably protected Ser and Thr derivatives provide excellent diastereoselectivities in the acetalization/ring-closure sequence of reactions, which allows the stereocontrolled formation of up to three new stereogenic atoms (two carbons and one nitrogen). Moreover, the nature of the acetalization reagent (i.e. cyclic or acyclic tetramethoxyalkanes) determines the absolute configuration of the *O*,*O*-acetal present in the methoxyoxazolidin-2-one ring, whereas the other stereogenic atoms remain unaltered. However, the high stereoselection achieved with natural amino acid derivatives is completely lost when amino acids that are non-natural (αMeSer) or rarely present in nature (*allo*Thr) are subjected to the acetalization reaction under the same conditions. In these cases, a complex mixture of compounds is obtained. Computational studies carried out on all possible bicyclic and tricyclic structures derived from Ser, Thr, *allo*Thr, and αMeSer precursors reproduced semi-quantitatively the diastereomeric ratios obtained for all derivatives. The thermodynamic stability of the different diastereomers, which in turn determines the distribution of products obtained experimentally, is determined by the subtle balance of steric interactions occurring between the different functional groups on each structure, as suggested by NBO calculations.

■ EXPERIMENTAL SECTION

Synthetic General Procedures. Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using silica gel 60 (230−400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in $\mathrm{CDCl_3}$ with TMS as the internal standard, and chemical shifts are reported in ppm on the δ scale and coupling constants in Hz. The assignment of all separate signals in the ^{1}H NMR spectra was made on the basis of coupling constants, selective proton−proton homonuclear decoupling experiments, and COSY and HSQC experiments. Melting points were determined on a melting point apparatus and are uncorrected. Optical rotations were measured on a polarimeter in 1.0 and 0.5 dm cells of 3.4 and 1.0 mL capacity, respectively. Microanalyses were carried out on a analyzer and are in good agreement with the calculated values. Electrospray mass spectra were recorded on a microQTof spectrometer; accurate mass measurements were achieved using sodium formate as an external reference.

General Procedure for the Acetalization−Transcarbamoylation Reactions. A round-bottomed flask was charged with 1.0 equiv of *N*-Boc protected α-amino acid **1a−d**, tetramethoxyalkane (2−3 equiv), $\mathrm{TsOH{\cdot}H_2O}$ (0.1 equiv), and toluene. The typical concentration of the amino acid derivatives in toluene was around 0.15 M (ca. 46 mmol of substrate in 300 mL of solvent). The solution was heated under reflux, stirred, and monitored by TLC. When the reaction was complete, the mixture was cooled down to room temperature, diluted with diethyl ether, and quenched with saturated $\mathrm{NaHCO_3}$. The aqueous phase was extracted with more diethyl ether. The organic layers were combined, washed with brine, and dried over anhydrous $\mathrm{Na_2SO_4}$. The solvent was evaporated, and the different products were purified by column chromatography (hexane/ethyl acetate).

Reaction between Protected Amino Acid 1a and 1,1,2,2-Tetramethoxycyclohexane. Following the general procedure described above, compound **2a′-I** was obtained as a yellow pale solid (1.079 g, 3.98 mmol, 58%), after column chromatographic purification (hexane/ethyl acetate, 7/3): $[\alpha]_D^{25} = +19.0°$ (c 0.92, $\mathrm{CHCl_3}$); mp 92 °C; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.58−1.73 (m, 4H, $\mathrm{CH_2}$), 1.79−1.99 (m, 2H, $\mathrm{CH_2}$), 2.07−2.13 (m, 2H, $\mathrm{CH_2}$), 3.49 (s, 3H, $\mathrm{OCH_3}$), 3.80 (s, 3H, $\mathrm{CO_2CH_3}$), 4.27 (dd, J = 8.6, 3.9 Hz, 1H, $\mathrm{CH_2}$), 4.33 (t, J = 8.2 Hz, 1H, $\mathrm{CH_2}$), 4.76 (dd, J = 7.8, 3.9 Hz, 1H, CH); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 17.8 ($\mathrm{CH_2}$), 18.4 ($\mathrm{CH_2}$), 28.2 ($\mathrm{CH_2}$), 30.0 ($\mathrm{CH_2}$), 51.2 ($\mathrm{OCH_3}$), 52.9 ($\mathrm{CO_2CH_3}$), 59.3 (CH), 69.8 ($\mathrm{CH_2}$), 99.5 ($\mathrm{CNCH_2OCH_2}$), 107.2 ($\mathrm{CCH_2OCH_3}$), 154.1 ($\mathrm{NCO_2}$), 170.3 ($\mathrm{CO_2CH_3}$); HRMS ESI (m/z) 294.0946 [M + Na$^+$], calcd for $\mathrm{C_{12}H_{17}NO_6Na^+}$ 294.0948.

Reaction between Protected Amino Acid 1c and 1,1,2,2-Tetramethoxybutane. Following the general procedure described above, a mixture of compounds **2c-II**, **2c-III**, and **3** was obtained, which could be separated and purified by column chromatography (hexane/ethyl acetate, 7/3).

*Compound **2c-II**:* colorless oil (34%); $[\alpha]_D^{25} = -12.4°$ (c 0.34, $\mathrm{CHCl_3}$); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.35 (d, J = 6.5 Hz, 3H, $\mathrm{CHC}H_3$), 1.55 (s, 3H, $\mathrm{CH_3}$), 1.57 (s, 3H, $\mathrm{CH_3}$), 3.46 (s, 3H, $\mathrm{OCH_3}$), 3.79 (s, 3H, $\mathrm{CO_2CH_3}$), 4.41−4.55 (m, 1H, $\mathrm{C}H\mathrm{CH_3}$), 4.87 (d, J = 8.2 Hz, 1H, $\mathrm{C}H\mathrm{CO_2CH_3}$); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 16.3 ($\mathrm{CH_3}$), 18.2 ($\mathrm{CHCH_3}$), 21.2 ($\mathrm{CH_3}$), 51.3 ($\mathrm{OCH_3}$), 52.2 ($\mathrm{CO_2CH_3}$), 64.6 ($\mathrm{CHCO_2CH_3}$), 76.2 ($\mathrm{CHCH_3}$), 101.9 ($\mathrm{CNCH_3OCH}$), 108.9 ($\mathrm{CCH_3OCH_3}$), 159.9 ($\mathrm{NCO_2}$), 168.8 ($\mathrm{CO_2CH_3}$); HRMS ESI (m/z) 282.0949 [M + Na$^+$], calcd for $\mathrm{C_{11}H_{17}NO_6Na^+}$ 282.0948.

*Compound **2c-III**:* yellow pale solid (25%); $[\alpha]_D^{25} = +78.4°$ (c 1.11, $\mathrm{CHCl_3}$); mp 115 °C; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.27 (d, J = 6.3 Hz, 3H, $\mathrm{CHC}H_3$), 1.40 (s, 3H, $\mathrm{CH_3}$), 1.65 (s, 3H, $\mathrm{CH_3}$), 3.42 (s, 3H, $\mathrm{OCH_3}$), 3.72 (s, 3H, $\mathrm{CO_2CH_3}$), 4.12 (d, J = 6.7 Hz, 1H, $\mathrm{C}H\mathrm{CO_2CH_3}$), 4.71−4.77 (m, 1H, $\mathrm{C}H\mathrm{CH_3}$); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 15.2 ($\mathrm{CHCH_3}$), 17.0 ($\mathrm{CH_3}$), 19.4 ($\mathrm{CH_3}$), 52.1 ($\mathrm{OCH_3}$), 52.4 ($\mathrm{CO_2CH_3}$), 61.3 ($\mathrm{CHCO_2CH_3}$), 79.1 ($\mathrm{CHCH_3}$), 100.4 ($\mathrm{CNCH_3OCH}$), 110.3 ($\mathrm{CCH_3OCH_3}$), 155.0 ($\mathrm{NCO_2}$), 168.0 ($\mathrm{CO_2CH_3}$); HRMS ESI (m/z) 282.0948 [M + Na$^+$], calcd for $\mathrm{C_{11}H_{17}NO_6Na^+}$ 282.0948.

*Compound **3**:* colorless oil (24%); $[\alpha]_D^{25} = +16.6°$ (c 0.82, $\mathrm{CHCl_3}$); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.31 (d, J = 6.5 Hz, 3H, $\mathrm{CHC}H_3$), 1.67 (s, 3H, $\mathrm{CH_3}$), 3.28 (s, 3H, $\mathrm{OCH_3}$), 3.79 (s, 3H, $\mathrm{CO_2CH_3}$), 4.04 (s, 1H, OH), 4.14 (d, J = 6.5 Hz, 1H, $\mathrm{C}H\mathrm{CO_2CH_3}$), 4.38 (s, 2H, $\mathrm{C{=}CH_2}$), 4.52−4.63 (m, 1H, $\mathrm{C}H\mathrm{CH_3}$); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 19.6 ($\mathrm{CHCH_3}$), 26.4 ($\mathrm{CH_3}$), 50.8 ($\mathrm{OCH_3}$), 52.9 ($\mathrm{CO_2CH_3}$), 60.7 ($\mathrm{CHCO_2CH_3}$), 65.6 ($\mathrm{CHCH_3}$), 84.7 ($\mathrm{C{=}CH_2}$), 106.5($\mathrm{CCH_3OCH_3}$), 143.8 ($\mathrm{C{=}CH_2}$), 154.2 ($\mathrm{NCO_2}$), 169.3 ($\mathrm{CO_2CH_3}$); HRMS ESI (m/z) 282.0944 [M + Na$^+$], calcd for $\mathrm{C_{11}H_{17}NO_6Na^+}$ 282.0948.

Reaction between Protected Amino Acid 1d and 1,1,2,2-Tetramethoxybutane. Following the general procedure described above, a mixture of compounds **2d-I**, **2d-II**, and **2d-III** was obtained, which could be separated and purified by column chromatography (hexane/ethyl acetate, 7/3).

*Compound **2d-I**:* colorless oil (31%); $[\alpha]_D^{25} = +35.9°$ (c 0.92, $\mathrm{CHCl_3}$); mp 70 °C; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.49 (s, 3H, $\mathrm{CH_3}$), 1.55 (s, 3H, $\mathrm{CH_3}$), 1.72 (s, 3H, $\mathrm{CH_3}$), 3.44 (s, 3H, $\mathrm{OCH_3}$), 3.79 (s, 3H, $\mathrm{CO_2CH_3}$), 4.01 (d, J = 8.2 Hz, 1H, $\mathrm{CH_2}$), 4.61 (d, J = 8.1 Hz, 1H, $\mathrm{CH_2}$); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 15.2 ($\mathrm{CH_3}$), 17.9 ($\mathrm{CH_3}$), 22.4 ($\mathrm{CH_3}$), 50.3 ($\mathrm{OCH_3}$), 53.1 ($\mathrm{CO_2CH_3}$), 65.4 ($\mathrm{CHCO_2CH_3}$), 80.2 ($\mathrm{CH_2}$), 101.1 ($\mathrm{CNCH_3OCH_2}$), 108.5 ($\mathrm{CCH_3OCH_3}$), 154.1 ($\mathrm{NCO_2}$), 172.7 ($\mathrm{CO_2CH_3}$); HRMS ESI (m/z) 282.0947 [M + Na$^+$], calcd for $\mathrm{C_{11}H_{17}NO_6Na^+}$ 282.0948.

*Compound **2d-II**:* colorless solid (46%); the physical properties are the same as those described previously in the literature.[4a] In addition to this, we were able to find single monocrystals suitable for X-ray diffraction analysis: $[\alpha]_D^{25} = -92.8°$ (c 1.00, $\mathrm{CHCl_3}$); HRMS ESI (m/z) 282.0950 [M + Na$^+$], calcd for $\mathrm{C_{11}H_{17}NO_6Na^+}$ 282.0948.

*Compound **2d-III**:* colorless oil (23%); $[\alpha]_D^{25} = +49.5°$ (c 1.02, $\mathrm{CHCl_3}$); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.41 (s, 3H, $\mathrm{CH_3}$). 1.54 (s, 3H, $\mathrm{CH_3}$), 1.59 (s, 3H, $\mathrm{CH_3}$), 3.41 (s, 3H, $\mathrm{OCH_3}$), 3.71 (s, 3H, $\mathrm{CO_2CH_3}$), 3.95 (d, J = 9.5 Hz, 1H, $\mathrm{CH_2}$), 4.41 (d, J = 9.5 Hz, 1H, $\mathrm{CH_2}$); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 17.0 ($\mathrm{CH_3}$), 19.1 ($\mathrm{CH_3}$), 23.0 ($\mathrm{CH_3}$), 51.8 ($\mathrm{OCH_3}$), 52.9 ($\mathrm{CO_2CH_3}$), 64.8 ($\mathrm{CHCO_2CH_3}$), 79.1 ($\mathrm{CH_2}$), 102.1 ($\mathrm{CNCH_3OCH_2}$), 109.2 ($\mathrm{CCH_3OCH_3}$), 155.6 ($\mathrm{NCO_2}$), 171.2 ($\mathrm{CO_2CH_3}$); HRMS ESI (m/z) 282.0946 [M + Na$^+$], calcd for $\mathrm{C_{11}H_{17}NO_6Na^+}$ 282.0948.

X-ray Crystallography. The diffraction data for the crystalline compounds **2a′-I**, **2c-III**, **2d-I**, and **2a-II** were collected at −173 °C on a diffractometer with a CCD detector using Mo Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods and refined by a full-matrix least-squares procedure with the SHELXL suite of programs.[6] Hydrogen atoms were located from mixed methods (electron-density maps and theoretical positions).

*Crystal data for **2a′-I**:* $\mathrm{C_{12}H_{17}NO_6}$, M_w = 271.27, colorless prism, 0.60 × 0.30 × 0.05 mm, T = 173 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 6.0540(7) Å, b = 9.9480(14) Å, c = 20.4270(3) Å, V = 1230.2 (3) Å^3, d_{calcd} = 1.465 g cm^{-3}, $F(000)$ = 576, λ = 0.71073 Å (Mo Kα), μ = 0.118 mm^{-1}, θ range 3.63−27.44°, 6937 collected reflections, 2747 unique reflections, full-matrix least squares (SHELXL97),[6] R1 = 0.0913, wR2 = 0.1901 (R1 = 0.1589, wR2 =

0.2263, all data), goodness of fit 1.098, residual electron density between 0.429 and −0.371 e Å^{-3}.

Crystal data for 2c-III: $C_{11}H_{17}NO_6$, M_w = 259.26, colorless prism, 0.35 × 0.25 × 0.15 mm, T = 173 K, monoclinic, space group $P2_1$, Z = 2, a = 6.5512(5) Å, b = 10.8875(12) Å, c = 9.1118(8), β = 105.048(5)°, V = 627.62 (10) Å^3, d_{calcd} = 1.372 g cm^{-3}, $F(000)$ = 276, λ = 0.71073 Å (Mo Kα), μ = 0.112 mm^{-1}, θ range 4.40−27.88°, 3480 collected reflections, 2038 unique reflections, full-matrix least squares (SHELXL97),[6] R1 = 0.0421, wR2 = 0.0968, (R1 = 0.0579, wR2 = 0.1035, all data), goodness of fit 1.088, residual electron density between 0.286 and −0.258 e Å^{-3}.

Crystal data for 2d-I: $C_{11}H_{17}NO_6$, M_w = 259.26, colorless prism, 0.70 × 0.70 × 0.25 mm, T = 100 K, monoclinic, space group $P2_1$, Z = 2, a = 5.7610(2) Å, b = 15.9190(8) Å, c = 6.7360(3) Å, β = 97.770(2)°, V = 612.08(5) Å^3, d_{calcd} = 1.407 g cm^{-3}, $F(000)$ = 276, λ = 0.71073 Å (Mo Kα), μ = 0.115 mm^{-1}, θ range 3.05−27.51°, 4573 collected reflections, 2587 unique reflections, full-matrix least squares (SHELXL97),[6] R1 = 0.0315, wR2 = 0.0721 (R1 = 0.0350, wR2 = 0.0749, all data), goodness of fit 1.080, residual electron density between 0.253 and −0.144 e Å^{-3}.

Crystal data for 2d-II: $C_{11}H_{17}NO_6$, M_w = 259.26, colorless prism, 0.30 × 0.30 × 0.12 mm, T = 173 K, monoclinic, space group $P2_1$, Z = 2, a = 5.8457(4) Å, b = 7.8597(5) Å, c = 13.8602(9) Å, β = 96.640(4)°, V = 632.54(7) Å^3, d_{calcd} = 1.361 g cm^{-3}, $F(000)$ = 276, λ = 0.71073 Å (Mo Kα), μ = 0.111 mm^{-1}, θ range 3.51−28.21°, 5469 collected reflections, 1664 unique reflections, full-matrix least squares (SHELXL97),[6] R1 = 0.0436, wR2 = 0.1124 (R1 = 0.0604, wR2 = 0.1263, all data), goodness of fit 0.969, residual electron density between 0.160 and −0.187 e Å^{-3}.

Further details on the crystal structures are available from the CIF data in the Supporting Information.

Computational Details. All calculations were carried out using the B3LYP hybrid functional[10] with the 6-31+G(d) basis set. Full geometry optimizations were carried out using the Gaussian 09 package.[11] The possibility of different conformations involving rotamers and ring isomers was taken into account for all structures. BSSE corrections were not considered in this work. Frequency analyses were carried out at the same level used in the geometry optimizations, and the nature of the stationary points was determined in each case according to the appropriate number of negative eigenvalues of the Hessian matrix. Scaled frequencies were not considered, since significant errors in the calculated thermodynamic properties are not found at this theoretical level.[12] Gibbs free energies (ΔG) calculated at 388.15 K (reflux temperature of toluene at atmospheric pressure) were used for the discussion on the relative stabilities of the considered structures. Steric interactions were evaluated by means of the pairwise steric exchange energies for disjointed interactions.[13] These quantities were calculated through a natural bond orbital/natural localized molecular orbital (NBO/NLMO) analysis using the NBO 5.G program[14] and upgraded Gaussian 09 as interface. These repulsive interactions were estimated by means of the localized σ, π, and n valence orbitals. Hard data on Cartesian coordinates and electronic energies, as well as entropies, enthalpies, Gibbs energies, and lowest frequencies of the different conformations of all structures considered, are available as Supporting Information.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures, tables, and CIF files giving spectroscopic characterization data for all new compounds, crystal structure data, and computational data. 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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