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A Highly Diastereoselective Synthesis of α-Hydroxy-β-amino Acid Derivatives via a Lewis Acid Catalyzed Three-Component Condensation Reaction

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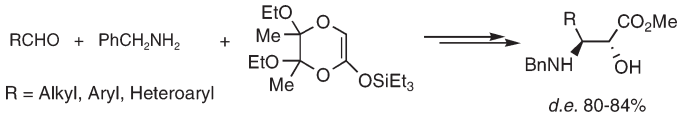
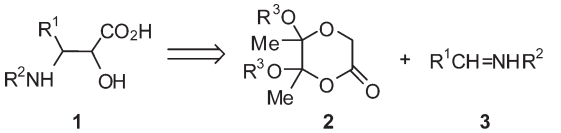


A very efficient three-component synthesis of a series of *syn* α-hydroxy-β-amino esters, obtained in high diastereoselection and yield, was realized starting from an aldehyde, benzylamine, and the ketene silyl acetals derived from Ley's lactones. The synthetic protocol was optimized and the above compounds were obtained without the isolation of intermediates. The origin of the observed diastereoselection was investigated through a computational model of the key reaction step.

Introduction

α-Hydroxy-β-amino acids **1** (Scheme 1) are synthetic targets of many researchers because they are present in molecules of great biological interest such as ornicorrugatin, a new lipopeptidic siderophore;[1] KRI-1314,[2] a potent human renin inhibitor polypeptide; amastatin,[3] a tetrapeptide with immunoregulatory, antitumor, and antibacterial activity; microginin;[4] threo-β-benzyloxyaspartate (TBOA),[5] the first nontransportable blocker for all subtypes of excitatory amino acid transporters (EAATs); and most of all, taxane derivatives.[6] In this last case, since the α-hydroxy-β-amino propanoic acid plays an important role in the interaction with the bioreceptor as well as in increasing the bioavailability of the molecule, several SAR studies were performed including modifications of the skeleton and of the functional groups linked to the heteroatoms.

SCHEME 1. Retrosynthesis of α-Hydroxy-β-amino Acids



As a result of the importance of these amino acids, different synthetic methods have appeared over the years based on the homologation of chiral amino acids, the enantioselective introduction of amino and hydroxy groups from olefinic acids, the Staudinger reaction between ketenes and imines to give β-lactams, that are then hydrolyzed to the corresponding amino acids, and the aldimine-type coupling with an enolate of an ester or a ketene acetal.[7]

Ley's acetals **2**[8] have attracted our attention since they are protected α-hydroxy acids efficiently obtained through a cheap synthesis, in multigram scale, and in enantiopure form.[8j] It is well-known that acetals **2** react with different electrophiles under basic conditions with high diastereoselectivity. Furthermore, the "one-pot" deprotection to reveal both hydroxy and

(1) Matthijs, S.; Budzikiewicz, H.; Schafer, M.; Wathelet, B.; Cornelis, P. *Z. Naturforsch., C: J. Biosci.* **2008**, *63*, 8–12.
(2) Iizuka, K.; Kamijo, T.; Harada, H.; Akahane, K.; Kubota, T.; Umeyama, H.; Ishida, T.; Kiso, Y. *J. Med. Chem.* **1990**, *33*, 2707–2714.
(3) Blomgren, H.; Wasserman, J. *Cancer Lett.* **1981**, *11*, 303–308.
(4) Okino, T.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *Tetrahedron Lett.* **1993**, *34*, 501–504.
(5) Shimamoto, K. *Chem. Rec.* **2008**, *8*, 182–199.
(6) (a) Ke, B.; Qin, Y.; Zhao, F.; Qu, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4783–4785. (b) Ganesh, T.; Yang, C.; Norris, A.; Glass, T.; Bane, S.; Ravindra, R.; Banerjee, A.; Metaferia, B.; Thomas, S. L.; Giannakakou, P.; Alcaraz, A. A.; Lakdawala, A. S.; Snyder, J. P.; Kingston, D. G. I. *J. Med. Chem.* **2007**, *50*, 713–725. (c) Thoret, S.; Gueritte, F.; Guenard, D.; Dubois, J. *Org. Lett.* **2006**, *8*, 2301–2304. (d) Chen, J.; Kuznetsova, L. V.; Ungreanu, I. M.; Ojima, I. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; John Wiley & Sons, Inc.: Hoboken, NJ, 2005; pp 447−476. (e) Spletstoser, J. T.; Flaherty, P. T.; Himes, R. H.; Georg, G. I. *J. Med. Chem.* **2004**, *47*, 6459–6465. (f) Liu, C.; Tamm, M.; Notzel, M. W.; de Meijere, A.; Schilling, J. K.; Kingston, D. G. I. *Tetrahedron Lett.* **2003**, *44*, 2049–2052. and references therein. (g) Kingston, D. G. I.; Jagtap, P. J.; Yuan, H.; Samala, L. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C., Eds.; Springer-Verlag: Wien & New York, 2002; Vol. 84, pp 53−225. (h) Georg, G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mejillano, M. R.; Burke, C. T. *J. Med. Chem.* **1992**, *35*, 4230–4237.

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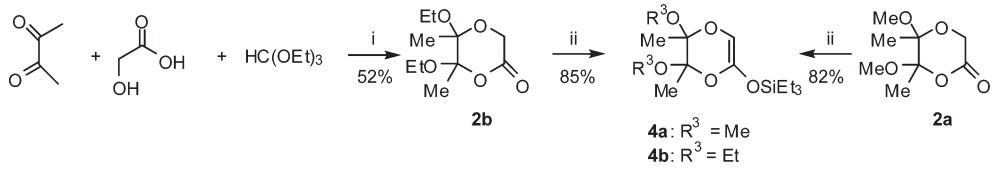
SCHEME 2. Synthesis of Acetal 2b and of Ketene Silyl Acetals 4a,b[a]



[a]Reagents and conditions: (i) cat. H_2SO_4, 50 °C, 1 h. (ii) LHMDS, Et_3SiCl, THF −78 °C, 10 min, then 25 °C, 20 h.

carboxylic groups is easily performed, affording a large number of compounds of biological interest.

Despite their different applications, to our knowledge, the condensation of compounds **2** with imine derivatives **3**, which could be a simple route to access isoserine derivatives **1** (Scheme 1), has not been reported so far.

Syn isomers are generally needed when amino acid moieties **1** are present in compounds of biological interest. In principle, this stereochemical feature is in contrast with the results found by the condensation of **2** with an aldehyde,[8d,g] which gives as the main isomer the *anti* dihydroxy acid. So, a versatile procedure to give isoserine derivatives and to direct the diastereoselection toward the *syn* isomer was our challenge. These synthetic targets have been accomplished by using a very efficient three-component condensation protocol, promoted by Lewis acids, between an aldehyde, an amine, and a ketene silyl acetal derived from Ley's lactones, without isolation of intermediates.

Results

The preparation of **2a** is reported in the literature[8c] starting from 2,3-dimethoxybutadiene and glycolic acid in dichloromethane at 25 °C and using $Ph_3P \cdot HBr$ as a catalyst. The same procedure could be adopted to obtain the new lactone **2b**, but the preparation of the starting 2,3-diethoxybutadiene[9] gave poor yield and low reproducibility. The above procedure was modified and a very efficient "one-pot" protocol was realized starting directly from a mixture of 2,3-butandione, glycolic acid, and ethyl orthoformate operating in the presence of catalytic H_2SO_4 at 50 °C (1 h). Compound **2b** was directly obtained in 52% yield. (Scheme 2)

In a first experiment the enolate of **2a**, generated with LHMDS in THF at −78 °C,[8c] was made to react with *N*-benzylidene-benzylamine (**3a**). The reaction was unsuccessful, and only the starting materials were recovered. The use of different bases (*t*BuOK or LDA in THF at −78 °C) failed also.

The Mannich-like reaction of **2a** and **3a** catalyzed by Lewis acids was then investigated. According to a known procedure,[10] $TiCl_4$ was used, but **2a** decomposed. In order to decrease the acidity of the Lewis acid, both $Ti(i\text{-}PrO)_4$ and $InCl_3$ were tested, but only traces of products were detected by ^1H NMR. The acid-catalyzed condensation of imines and ketene silyl acetals represents a known alternative synthetic procedure.[7k,n,11] Therefore, the ketene silyl acetals **4** were prepared and tested (Scheme 2).

The preparation of the ketene trimethylsilyl acetal of **2a** was reported in literature:[8b,12] To achieve a better stability, the ketene triethylsilyl acetal **4a** was prepared in 82% yield from **2a** by generating its enolate with LHMDS in THF at −78 °C and then by addition of the silylating agent. The above protocol was modified for an efficient synthesis of the new compound **4b** (85%), i.e., the solution of **2b** and triethylsilylchloride in THF at −78 °C was initially prepared, and then the base was added (Scheme 2).

Initially, the reaction of **4a** and imine **3a** was studied by using several Lewis acids[13] in MeCN at −30 °C (1 h, **3a**/**4a**/cat. 1:1:0.5 ratio) (Scheme 3). As reported in Table 1, the reaction was not operative in absence of a catalyst (entry 1), whereas in the presence of a Lewis acid diastereomers **5a** and **6a** were obtained together with lactone **2a** deriving from the hydrolysis of **4a**. The best diastereoselection was found with

(7) (a) Guo, Z.; Shi, T.; Jiang, J.; Yang, L.; Hu, W. *Org. Biomol. Chem.* **2009**, *7*, 5028–5033. and references therein. (b) Cariou, C. C. A.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2008**, *73*, 9762–9764. (c) Bodkin, J. A.; Bacskay, G. B.; McLeod, M. D. *Org. Biomol. Chem.* **2008**, *6*, 2544–2553. (d) Hata, S.; Tomioka, K. *Tetrahedron* **2007**, *63*, 8514–8520. (e) Torssell, S.; Somfai, P. *Adv. Synth. Catal.* **2006**, *348*, 2421–2430. (f) Li, F.; Schwardt, O.; Jäeger, V. *Synthesis* **2006**, 2173–2182. (g) Wang, Y.; He, Q.-F.; Wang, H.-W.; Zhou, X.; Huang, Z.-Y.; Qin, Y. *J. Org. Chem.* **2006**, *71*, 1588–1591. and references therein. (h) Feske, B. D.; Kaluzna, I. A.; Stewart, J. D. *J. Org. Chem.* **2005**, *70*, 9654–9657. (i) Martin-Zamora, E.; Ferrete, A.; Llera, J. M.; Muñoz, J. M.; Pappalardo, R. R.; Fernandez, R.; Lassaletta, J. M. *Chem.—Eur. J.* **2004**, *10*, 6111–6129. (j) Aggarwal, V. K.; Vasse, J.-L. *Org. Lett.* **2003**, *5*, 3987–3990. (k) Ha, H.-J.; Ahn, Y.-G.; Woo, J.-S.; Lee, G. S.; Lee, W. K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1667–1672. and references therein. (l) Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem.* **1997**, *62*, 7364–7375. (m) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2385–2391. (n) Hattori, K.; Miyata, M.-; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1152–1152. (o) Kobayashi, Y.; Takemoto, Y.; Kamijo, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853–1868.

(8) (a) Maddes, M. L.; Tackett, M. N.; Watanabe, H.; Brennan, P. E.; Spilling, C. D.; Scott, J. S.; Osborn, D. P.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 591–597. (b) Ley, S. V.; Dixon, D. J.; Guy, R. T.; Rodriguez, F.; Sheppard, T. D. *Org. Biomol. Chem.* **2005**, *3*, 4095–4107. (c) Ley, S. V.; Diez, E.; Dixon, D. J.; Guy, R. T.; Michel, P.; Nattrass, G. L.; Sheppard, T. D. *Org. Biomol. Chem.* **2004**, *2*, 3608–3617. (d) Ley, S. V.; Dixon, D. J.; Guy, R. T.; Palomero, M. A.; Polara, A.; Rodríguez, F.; Sheppard, T. D. *Org. Biol. Chem.* **2004**, *2*, 3618–3627. (e) Diez, E.; Dixon, D. J.; Ley, S. V.; Polara, A.; Rodríguez, F. *Synlett* **2003**, *8*, 1186–1188. (f) Dixon, D. J.; Ley, V. S.; Rodriguez, F. *Org. Lett.* **2001**, *3*, 3753–3755. (g) Dixon, D. J.; Ley, S. V.; Polara, A.; Sheppard, T. D. *Org. Lett.* **2001**, *3*, 3749–3752. (h) Ley, V. S.; Michel, P. *Synlett* **2001**, *11*, 1793–1795. (i) Ley, V. S.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. *J. Chem Rev.* **2001**, *101*, 53–80. (j) Diez, E.; Dixon, D. J.; Ley, S. V. *Angew. Chem., Int. Ed.* **2001**, *40*, 2906–2909.

(9) Pozzo, J.-L.; Clavier, G. M.; Colomes, M.; Bouas-Laurent, H. *Tetrahedron* **1997**, *53*, 6377–6390.

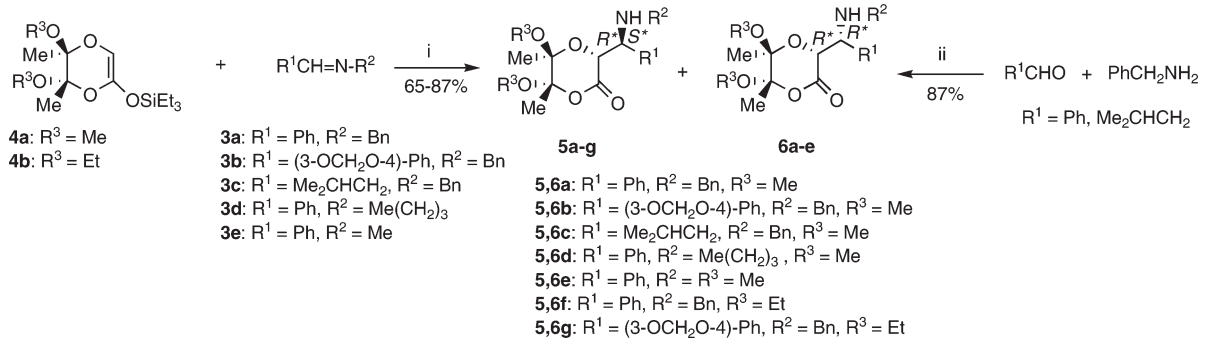
(10) (a) Periasamy, M.; Suresh, S.; Ganesan, S. S. *Tetrahedron: Asymmetry* **2006**, *17*, 1323–1331. (b) Silveira, C. C.; Vieira, A. S.; Braga, A. L.; Russowsky, D. *Tetrahedron* **2005**, *61*, 9312–9318.

(11) (a) Wang, S.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2007**, *48*, 6449–6452. (b) Xiao, J.; Loh, T.-P. *Synlett* **2007**, 815–817. and references therein. (c) Akiyama, T.; Suzuki, A.; Fuchibe, K. *Synlett* **2005**, *6*, 1024–1026. (d) Jaber, N.; Assié, M.; Fiaud, J.-C.; Collin, J. *Tetrahedron* **2004**, *60*, 3075–3083. (e) Jacobsen, M. F.; Skrydstrup, T. *J. Org. Chem.* **2003**, *68*, 7112–7114. (f) Saaby, S.; Nakama, K.; Lie, M. A.; Hazell, R. G.; Jorgensen, K. A. *Chem.—Eur. J.* **2003**, *9*, 6145–6154. (g) Allef, P.; Kunz, H. *Tetrahedron: Asymmetry* **2000**, *11*, 375–378. (h) Cozzi, P. G.; Di Simone, B.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 1691–1694. (i) Mukaiyama, T.; Kashiwagi, K.; Matsui, S. *Chem. Lett.* **1989**, 1397–1400. (j) Ojima, I.; Inaba, S.; Nagai, M. *Synthesis* **1981**, *7*, 545–547.

(12) Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182–5191.

(13) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem.—Eur. J.* **2000**, *6*, 3491–3494.

SCHEME 3. Preparation of Intermediates 5/6 by Mannich-like Condensation[a]



[a]Reagents and conditions: (i) Method A: $InCl_3$, MeCN, −30 °C, 1 h. (ii) Method B: activated molecular sieves, MeCN, 25 °C, 1 h, then **4a**, $InCl_3$, −30 °C, 1 h.

TABLE 1. Synthesis of 5/6a: Lewis Acid Effect on Diastereoselection

entry[a]	catalyst	**5a**:**6a**:**2a**
1	*b*	*c*
2	$ZnCl_2$	2.8:1:0.7[d,e]
3	$CoCl_2$	2.7:1:0.7[d,e]
4	$NbCl_5$	2.8:1:0.6[d,e]
5	$InCl_3$	4:1:0.7[d,e,f]
6	$SnCl_2$	3.3:1:0.4[d,f]
7	$Y(OTf)_3$	2.5:1:1[d]
8	$PdCl_2$	1:2:3[d,e]
9	$Eu(OTf)_3$	2.2:1:1.2[d,e]
10	$CeCl_3$	1.8:1:5.5[d]
11	$MgBr_2$	4.6:1:0.85[d,f]

[a]Reaction conditions: MeCN, −30 °C, 1 h, **3a**/**4a**/cat., 1:1:05. [b]Reaction time: 24 h. [c]Recovered starting materials. [d]Diastereomeric ratio calculated by ^{1}H NMR. [e]Diastereomeric ratio calculated by HPLC. [f]Isolated compounds.

TABLE 2. Synthesis of 5/6a: Solvent and Temperature Effect on Diastereoselection

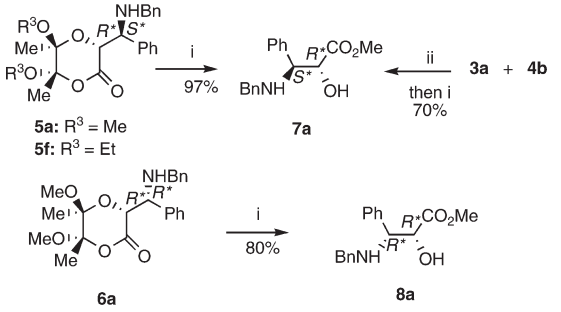
entry[a]	solvent	catalyst/°C	**5a**:**6a**:**2a**
1	MeCN	$InCl_3$/−30	4:1:0.7[b,c]
2	DCM	$InCl_3$/−30	4.5:1:2.2[b,c]
3	THF	$InCl_3$/−30	2.35:1:1[b]
4	DMA	$InCl_3$/−30	*d*
5	toluene	$InCl_3$/−30	*d*
6	DCM	$InCl_3$/−70	*d*
7	MeCN	$InCl_3$/25	2.1:1:0.6[b]
8	MeCN	$SnCl_2$/−30	3.3:1:0.4[b]
9	DCM	$SnCl_2$/−30	3.6:1:2.9[b]
10	THF	$SnCl_2$/−30	4:1:3.1[b]
11	MeCN	$SnCl_2$/25	2.5:1:1.1[b]

[a]Reaction conditions: 1 h, **3a**/**4a**/cat., 1:1:05. [b]Diastereomeric ratio calculated by ^{1}H NMR. [c]Diastereomeric ratio calculated by HPLC. [d]Recovered starting materials.

$InCl_3$ (entry 5), $SnCl_2$ (entry 6), and $MgBr_2$ (entry 11), which gave a mixture of **5a** and **6a** in comparable yield ($InCl_3$, 65%; $SnCl_2$, 67%; $MgBr_2$, 66%; isolated compounds).

The deprotection of the hydroxy and carboxylic functions was performed at once, according to a known procedure,[8d] by using trimethylsilylchloride in methanol. Starting from pure compounds **5a** and **6a**, methyl esters 2*R**,3*S**-**7a** and 2*R**,3*R**-**8a** (Scheme 4) were obtained, respectively, whose stereochemistry was confirmed by comparing their ^{1}H NMR spectra with those of the known compounds.[7l] This allowed us to unequivocally assign the relative configuration to the corresponding stereocenter on intermediates **5a** and **6a**. This stereochemical result appears very interesting since our challenge was to obtain the *syn* adducts **7**.

SCHEME 4. Methanolysis of Adducts 5 and 6[a]



[a]Reagents and conditions: (i) MeOH/Me_3SiCl (0.5 M), 25 °C, 10 min. (ii) $InCl_3$, MeCN, −30 °C, 1 h, then (i).

In order to improve the diastereoselection of the process, further studies were performed by evaluating the effect of the variation of the solvent, temperature, and the stoichiometry of both the catalyst and the reagents. According to the above results, $InCl_3$ and $SnCl_2$ were selected, and their efficacy was evaluated in different solvents (Table 2). A strong solvent effect is evident for $InCl_3$ (entries 1−5). Replacing MeCN by DCM, the diastereomeric ratio increased, but decomposition of **4a** to lactone **2a** was also observed even if anhydrous conditions were employed. The use of a coordinating solvent such as THF decreased the diastereoselection, while DMA and toluene were ineffective in the formation of the reaction products. A similar trend was observed using $SnCl_2$ with the exception of THF, which increased the diastereoselection but also the decomposition of the reagent **4a**.

No positive effects on de were found by increasing the temperature (entries 7 and 11), while when operating at lower temperature (entry 6) in DCM the reaction failed.

As reported in Table 3, decreasing the stoichiometry of the catalyst induced a negative effect on the diastereoselection.

Finally, experiments using a 2:1 or 1:2 ratio of **3a**/**4a** were carried out in MeCN at −30 °C, but similar results were found without improvement in diastereoselection (**5a/6a/2a**, 3.6:1:0.5; 4.1:1:2.9, respectively).

In summary, the above results indicated that the best reaction conditions giving the highest diastereoselection and minimizing the degradation of **4** are as follows: 1:1 ratio

TABLE 3. Synthesis of 5/6a: Influence of Catalyst Stoichiometry on Diastereoselection

entry[a]	catalyst (eqiv)	5a:6a:2a
1	$InCl_3$ (0.5)	4:1:0.7[b,c]
2	$InCl_3$ (0.2)	2.6:1:0.6[b,c]
3	$InCl_3$ (0.1)	1.23:1:0.8[b]
4	$SnCl_2$ (0.5)	3.3:1:0.4[b]
5	$SnCl_2$ (0.2)	2.1:1:0.7[b]

[a]Reaction conditions: 1 h, **3a/4a**: 1:1, MeCN, −30 °C. [b]Diastereomeric ratio calculated by ^{1}H NMR. [c]Diastereomeric ratio calculated by HPLC.

of **3a/4a**, in the presence of 0.5 molar equiv of $InCl_3$ or $SnCl_2$, at −30 °C in MeCN.

To verify the generality of this synthetic protocol and to evaluate the steric effect of the imine substituent on the diastereoselection, a series of imines **3b−e** was prepared according to general procedures. Their reaction with **4a** under standard conditions gave the expected compounds **5b−e** and **6b−e** (Scheme 3) as reported in Table 4 (entries 2−5).

TABLE 4. Yields and Diastereomeric Distribution of Compounds 5/6

Entry	Products	Yield %	5:6
1	**5a/6a**: R^1 = Ph; R^2 = Bn; R^3 = Me	65[a,c]	4:1[e]
		87[b,c]	4.4:1[e]
2	**5b/6b**: R^1 =  ; R^2 = Bn; R^3 = Me	70[a,c]	5.3:1[e]
3	**5c/6c**: R^1 = Me_2CHCH_2; R^2 = Bn; R^3 = Me	74[a,c]	5:1[e]
		87[b,c]	5.3:1[e]
4	**5d/6d**: R^1 = Ph; R^2 = $(CH_2)_3Me$; R^3 = Me	68[a,c]	3.2:1[e]
5	**5e/6e**: R^1 = Ph; R^2 = R^3 = Me	65[a,c]	3.9:1[e]
6	**5f/6f**: R^1 = Ph; R^2 = Bn; R^3 = Et	74[a,d]	11:1[e,f]
7	**5g/6g**: R^1 =  ; R^2 = Bn; R^3 = Et	87[a,d]	13:1[e]

[a]Method A (see Experimental Section). [b]Method B (see Experimental Section). [c]Isolated compounds (mixture of diastereomers). [d]Yield referred to the isolated main isomer **5**. [e]Diastereomeric ratio calculated via ^{1}H NMR. [f]Diastereomeric ratio calculated via HPLC.

In general the de ranged between 60% and 69%, and the substituent on the starting aldehyde seemed to have little influence on the diastereoselection. Instead, the substituent on the starting amine is of importance since a decrease of the de was found when a *N*-alkyl substituent (entries 4 and 5) was used instead of the benzyl one.

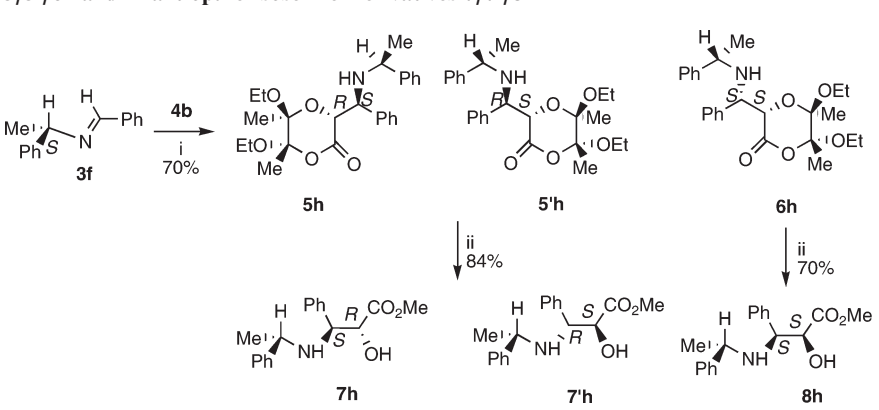
To evaluate the bulkiness of the Ley's lactone ether functions, the ketene triethylsilyl acetal **4b** was made to react with **3a** (Scheme 3). Products **5f** and **6f** were obtained with an improved diastereoselectivity (de 83%; Table 4, entry 6). The isolation of compounds **5/6f** was quite difficult despite the fact that the ^{1}H NMR and HPLC analyses of the crude reaction mixture showed a high purity. Actually, compound **5f** was isolated in very low yields (20−30%) after chromatography on silica gel or on neutral alumina, thus indicating that the ethoxy lactone is unstable under these conditions. Pure **5f** was successfully isolated in 74% yield by using flash cartridge chromatography. Similar results were obtained from **4a** and imine **3b**, and isomers **5g** and **6g** were obtained (Table 4, entry 6). The conversion of intermediate **5f** into ester **7a** confirmed the assigned stereochemistry (Scheme 4).

The possibility to use imines containing a chiral auxiliary was evaluated, and both *N*-benzylidene-(*R*)-*tert*-butylsulfinamide[14] and *N*-benzylidene-(*S*)-α-methylbenzylamine (**3f**)[15] were made to react with **4a** and **4b**, respectively. The first imine did not give the condensation products. Instead, by using **3f**, the formation of three stereoisomers was detected by ^{1}H NMR (4:5.4:1). Their purification on silica gel allowed isolation of the main quasi-enantiomers **5 h/5′h**, which are not separable, in good yield (62%), but in low diastereoselection (de 14%). The third diastereomer **6h** was also isolated in 8% yield (Scheme 5, see Supporting Information for discussion). The methanolysis of **5 h/5′h** gave the corresponding isoserine esters 2*R*,3*S*-**7h** (minor isomer) and 2*S*,3*R*-**7′h** (major isomer), not separable, belonging to the *syn* series, as confirmed by literature.[7n] Accordingly, **6h** was transformed into **8h**, which was characterized by 2*S*,3*S* absolute configuration.[7n] In this case, a partial epimerization occurred as shown by ^{1}H NMR spectrum.

Aiming to ameliorate the synthetic protocol, further experiments were done by reducing the synthetic steps without intermediate isolation.

The direct transformation of compounds **5/6**, derived from Mannich condensation, to the corresponding esters **7** and **8** was performed. As an example, the condensation of **3a** and **4b** followed by methanolysis gave pure diastereomer **7a** (70%) (Scheme 4).

SCHEME 5. Adducts 5/5′/6h and Enantiopure Isoserine Derivatives 7/7′/8h[a]

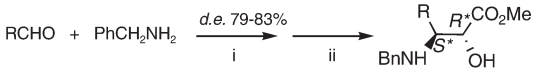


[a]Reagents and conditions: (i) $InCl_3$, MeCN, −30 °C, 1 h. (ii) $MeOH/Me_3SiCl$ (0.5 M), 25 °C, 10 min.

A three-component reaction starting from an aldehyde, benzylamine, and **4a** was then studied. Imine **3a** was generated *in situ* from benzaldehyde in MeCN and in the presence of molecular sieves. After 1 h, the mixture was cooled to −30 °C, and then the catalyst and **4a** were added. Compounds **5a/6a** were isolated with an improved overall yield and diastereoselection (**5/6a**: 87%, 4.4:1). In an analogous way, staring from isovaleraldehyde, via intermediate **3c**, diastereomers **5c/6c** (87%, 5.3:1) were obtained.

The final goal was the direct synthesis of esters **7a**−**g** without any intermediate isolation (Scheme 6). According to the above protocol, by using a series of aldehydes, benzylamine, and **4b** as starting reagents, intermediates **5/6** were generated. Finally, the crude reaction mixture was quenched with a MeOH/TMSCl solution, and the pure main *syn* isomers **7a**−**g** were isolated in good yields and diastereoselection.

SCHEME 6. Direct α-Hydroxy-β-amino Esters 7 Synthesis by a Three-Component Reaction[a]



7a: R = Ph, 74%
7b: R = (3-OCH_2O-4)-Ph, 70%
7c: R = Me_2CHCH_2, 68%
7d: R = *p*-NO_2Ph, 74%
7e: R = *p*-MeOPh, 72%
7f: R = *p*-ClPh, 73%
7g: R = tiophenyl, 73%

7a-g

[a]Reagents and conditions: (i) activated molecular sieves, MeCN, 25 °C, 1 h, then **4b**, $InCl_3$, −30 °C, 1 h. (ii) MeOH/Me_3SiCl (0.5 M), 25 °C, 10 min.

Theoretical Investigation of the Reaction Mechanism

The stereochemical result of the condensation of compounds **4** and the imines **3** differs from that found for the products obtained by the condensation of Ley's lactone and aldehydes in basic conditions, where the major diastereomer is the *anti* adduct, while in our case the major diastereomer is the *syn* adduct. Interestingly, the reported acid-catalyzed condensation of imines and ketene silyl acetals afforded *syn* isoserine derivatives[7k] by using the *Z* ketene silyl acetals, which have an opposite geometry with respect to compounds **4**.

To investigate the origin of the observed diastereoselectivity, the reaction mechanism of the key step addition of compound **4** to imine **3** was investigated through DFT calculations. Every calculation was performed with the recently developed MPW1B95 functional,[16] as the popular B3LYP functional evidenced some shortcomings, especially in estimating reaction barrier heights and in describing van der Waals interactions, which might be important when two transition states leading to diastereomers being compared.[16g,h] This decision was also driven by our previous experience with modeling reactions paths where weak interactions were found to be important in determining the final regiochemical outcome[17] and was verified through preliminary calculations performed with the B3LYP functional, which provided poor results compared to experiments.

The R^2 substituent did not significantly affect the regiochemical outcome, as experimentally evidenced in Table 4. Indeed, comparable **5**/**6** ratios were observed for entry 1 (4.1:1, R^2 = Bn) and entry 5 (3.9:1, R^2 = Me), evidence also explained by conformational searches performed on **5a** and **6a** at the molecular mechanic level, showing that the benzyl group was located far away from the reaction centers in all conformers lying in an energy range of 5 kcal/mol from the most stable one. For the above reasons, the most computationally comfortable reaction of **3e** with **4a** was chosen as a representative model. For simplicity, the Lewis acid was modeled as an hydrogen cation, thus avoiding the use of complex basis sets that would be necessary for the correct treatment of post-transition metals,[18] while the triethylsilyl moiety of **4a** was replaced with a trimethylsilyl group to reduce CPU time and improve convergence. This approximation is not expected to affect the model predictability, as preliminary calculations conducted by replacing the alkylsilyl moiety with a hydrogen, thus making the location of transition states easier, provided comparable results in terms of diastereoselectivity predictions. The modeled reactants, transition states (TSs), and products will be hereafter referred as **3e** (imine) and **M4a**, **TS-M5e** and **TS-M6e** (where the "M" indicates that the trimethylsilyl has been used instead of the triethylsilyl group, as explained above), and **5e** (2*R*,3*S* stereochemistry) and **6e** (2*R*,3*R* stereochemistry), respectively. The solvent was included in both geometry optimizations and energy calculations through the CPCM solvation model for MeCN.

Reactants, TSs, and products were fully optimized at the CPCM-MPW1B95/6-31+G(d,p) level, while single point energy evaluations were conducted with the more sophisticated 6-311+G(3df,2p) basis set. Several conformations were optimized for either reactants, TSs, and products, but only the most favored conformations will be reported and discussed. The geometry of the located TSs is represented in Figure 1, and relative energies and relevant distances are reported in Table 5.

As reported in Table 5, **TS-M5e** was found to be 3.2 kcal/mol more stable than **TS-M6e**, while reaction energies show that product **6e** is thermodynamically favored over **5e** by 1.1 kcal/mol. Equilibrium between **5** and **6** could be possible through a retrocondensation reaction, but the low reaction temperatures experimentally adopted, together with the high-energy barrier expected for the retrocondensation, suggest that the reaction is mainly under kinetic control. This observation is supported by the fact that conducting the

(14) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.
(15) Rogalska, E.; Belzecki, C. *J. Org. Chem.* **1984**, *49*, 1397–1402.
(16) (a) Dybala-Defratyka, A.; Paneth, P.; Pu, J.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 2475–2486. (b) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 6908–6918. (c) Boese, A. D.; Martin, J. M. L. *J. Chem. Phys.* **2004**, *121*, 3405–3416. (d) Zhao, Y.; Pu, J.; Lynch, B. J.; Truhlar, D. G. *Phys. Chem. Chem. Phys.* **2004**, *6*, 673–676. (e) Zhao, Y.; Truhlar, D. G. *Phys. Chem. Chem. Phys.* **2005**, *7*, 2701–2705. (f) Pu, J.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 773–778. (g) Lynch, B. J.; Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 1643–1649. (h) Zhao, Y.; González-García, N.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 2012–2018. (I) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 5656–5667.
(17) (a) Contini, A.; Leone, S.; Menichetti, S.; Viglianisi, C.; Trimarco, P. *J. Org. Chem.* **2006**, *71*, 5507–5514. (b) Borsini, E.; Broggini, G.; Contini, A.; Zecchi, G. *Eur. J. Org. Chem.* **2008**, 2808–2816. (c) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Contini, A. *J. Phys. Org. Chem.* **2009**, *22*, 1048–1057.
(18) This choice was supported by the experimental observation that the reaction proceeds with a similar diastereoselection, even though with very low yield, by using different protic acids (i.e., p-TSA and 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate, see Supporting Information) as the catalyst.

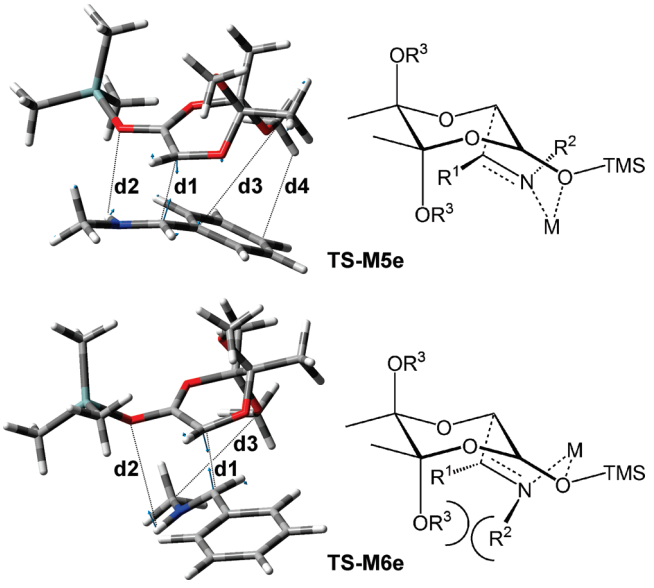


FIGURE 1. Structure of **TS-M5e** and **TS-M6e**. Displacement vectors for the unique imaginary frequency are shown, together with relevant distances.

TABLE 5. Relative Activation and Reaction Energies (kcal/mol) and Selected Distances (Å) for TS-M5e and TS-M6e[a]

	5e	6e
$\Delta E^{\ddagger}$	5.0	8.2
ΔE	−25.1	−26.2
d_1	2.23	2.03
d_2	2.73	3.34
d_3	4.13	3.72

[a]Relative energies computed as the sum of total free energies in solution obtained from single point calculations with the 6-311+(3df,2p) basis set and ZPE correction resulted from thermochemical analyses with the 6-31+G(d,p) basis. Reactant's energy is the sum of isolated reactants energies. Relative energies have been computed for the balanced reaction by including a water molecule in the reactants and trimethylsilanol in the products.

reaction at higher temperature results in a loss of diastereoselectivity (see Table 2).

Concerning geometrical parameters, the forming C−C bond length (*d*1, Figure 1) resulted 2.23 Å and 2.03 Å in the *syn* **TS-M5e** and in the *anti* **TS-M6e**, respectively. Thus, according to the Hammond's postulate, **TS-M6e** is "later" (higher activation barrier, shorter length for the forming bonds) than **TS-M5e**. Conversely, the *d*2 distance between the enolether oxygen and the nitrogen-coordinated Lewis acid (modeled as a proton) was 2.73 Å for **TS-M5e** and 3.34 Å for **TS-M6e**. Accordingly, as shown in Figure 1, although both TSs assume a fused six-membered ring bicyclic conformation with a *cis* junction at the C2−C3 carbons of **4a**, the energetically favored **TS-M5e** adopts a rather regular "chair-like" conformation, with quite similar *d*1 and *d*2 distances, while the least favored **TS-M6e** adopts a distorted "boat-like" conformation with a difference between *d*1 and *d*2 of more than 1 Å. This means that in **TS-M5e** a stabilizing interaction involving all three N−H−O atoms occurs, whereas in **TS-M6e** this interaction is lost. The highest stability of **TS-M5e** with respect to **TS-M6e** could be ascribed to a stabilizing C−H/π interaction between the methoxy hydrogens and the phenyl group (see *d*4 distance, Figure 1, 2.83 Å), but this interaction can only be operative when R^1 is aromatic (entries 1, 2, 4−7, Table 4), while a good diastereoselection was also obtained for entry 3 (**5/6c** = 5:1, Table 4) where R^1 = *i*-Bu. More reasonably, the lower **TS-M5e** energy with respect to **TS-M6e** is due to the different steric hindrance occurring at the TS levels. In fact, the *d*3 distance (which describes the hindrance occurring between the R^3 group of **4a** and R^1 or R^2 for **TS-M5** and **TS-M6**, respectively) measured between the C5-linked methoxy group and the C1-phenyl and *N*-methyl carbons is 4.13 and 3.72 Å, respectively. This observation is experimentally supported by the fact that by replacing the methoxy with an ethoxy group the obtained diastereoselection was greatly enhanced (entries 6 and 7, Table 4). Moreover, these findings are also supported by the modest diastereoselection observed when the chiral imine **3f** (R^2 = (*S*)-CH(Me)Ph) was used in the formation of isomers **5h/5h′**. The far chiral moiety in the **TS-M5e**-like TS gave a low diastereoselection in the *syn* series. Instead, a single enantiomer was obtained in the *anti* series, according to the **TS-M6e**-like TS.

Conclusion

In conclusion, a very efficient three-component synthesis of a series of 2*R**,3*S**-α-hydroxy-*β*-amino esters **7**, obtained in high diastereoselection and yields, was realized. This synthetic protocol made it possible to obtain the target compounds while avoiding the isolation of the single intermediates.

The key reaction step has been modeled and is predicted to be under kinetic control, with the observed diastereoselection resulting mainly from the steric factors within the two different TSs.

Experimental Section

Theoretical Calculations. Products **5e** and **6e** were initially obtained from a conformational search performed in vacuum at the molecular mechanic level using the MMFF94s force field implemented in MOE.[19] All conformers within 3 kcal/mol from the most favored were optimized at the MPW1B95/6-31+G(d,p) level of theory,[16] and only the most stable for each product was further considered. Reactants **3e** and **M4a** and transition states **TS-M5e** and **TS-M6e** were then constructed and fully optimized at the same level of theory. Several conformations and relative orientations of reacting groups were considered for each TS, but only the lowest energy structures were further considered. Vibrational frequencies were computed at the same level of theory in order to define optimized geometries as minima (no imaginary frequencies) or TSs (a unique imaginary frequency corresponding to the vibrational stretching of the forming/breaking bonds) and to calculate ZPVE and thermochemical corrections to electronic energies (1 atm, 298.15 K, unscaled frequencies). Single point calculations were performed at the MPW1B95/6-311+G(3df,2p). All calculations were performed in solution (MeCN) using the CPCM solvent model,[20] and basis sets using Cartesian *d* and *f* functions were always requested. The default united atom topological model UA0, implemented in Gaussian09,[21] was adopted for the construction

(19) *MOE V. 2009.10*; Chemical Computing Group Inc.: Montreal, Canada, http://www.chemcomp.com.

(20) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669–681.

(21) Frisch, M. J. et al. *Gaussian 09, Revision A.02*; Gaussian, Inc.: Wallingford, CT, 2009.

of the molecular cavity (an extra sphere was added on the proton modeling the Lewis acid in TS structures). All quantum-chemical calculations were performed with the Gaussian09 software package.

One-Pot Procedure for the Preparation of 5,6-Diethoxy-5,6-dimethyl[1,4]dioxan-2-one (2b). 2,3-Butandione (4.6 mL, 46.22 mmol) and glycolic acid (3.07 g, 40.40 mmol) were dissolved in triethyl orthoformate (40 mL), and a catalytic amount of H_2SO_4 was added. The reaction mixture was heated at 50 °C for 1 h. A saturated solution of $NaHCO_3$ (10 mL) was added, and the mixture was extracted with AcOEt (3 × 30 mL). The organic layers were dried over Na_2SO_4 and the crude reaction mixture was chromatographed on silica gel (cyclohexane/AcOEt, 10:1), affording pure compound **2b** (52%) after crystallization. White solid, mp 37 °C (CH_2Cl_2/pentane, 0 °C). IR (NaCl) ν_{max} 1752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.32, 4.23 (AB system, J = 16.6, 2H), 3.79−3.69 (m, 2H), 3.58 (q, J = 7.2, 2H), 1.53 (s, 3H), 1.41 (s, 3H), 1.21 (t, J = 6.9, 3H), 1.99 (t, J = 7.0, 3H); ^{13}C NMR ($CDCl_3$) δ 168.1, 105.2, 97.8, 60.5, 58.8, 57.3, 18.8, 17.9, 15.7, 15.3. MS (ESI) m/z 341.4 $[M + 23]^+$. Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.78; H, 8.52.

5,6-Dimethoxy-5,6-dimethyl-([1,4]dioxen-2-yloxy)triethylsilane (4a). Lactone **2a** (3.23 g, 17 mmol) was dissolved in anhydrous THF (35 mL), and the mixture was cooled to −78 °C under N_2. A solution of LHMDS (4.52 g, 27 mmol) in THF (10 mL) was added dropwise. After stirring for 10 min, TESCl (4 mL, 26 mmol) was added. The solution was warmed to 25 °C, and the stirring was continued overnight. THF was removed under reduced pressure, and *n*-pentane (50 mL) was added to the mixture. A solid was formed and filtered through Celite. After solvent evaporation, the crude compound was distilled in vacuum (120 °C, 0.8 mmHg). Pure compound **4a** was obtained (4.26 g, 82%) as a colorless oil. IR (NaCl) ν_{max} 1719, 1149, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.52 (s, 1H), 3.37 (s, 3H), 3.22 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H), 1.06−0.94 (m, 9H), 0.75−0.67 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 143.9, 104.3, 96.6, 90.4, 49.5, 48.6, 17.6, 17.1, 6.6, 4.8. MS (ESI) m/z 327.1 $[M + 23]^+$. Anal. Calcd for $C_{14}H_{28}O_5Si$: C, 55.23; H, 9.27. Found: C, 55.05; H, 9.10.

5,6-Diethoxy-5,6-dimethyl-([1,4]dioxin-2-yloxy)triethylsilane (4b). Silyl derivative **4b** (4.8 g, 85%) was prepared according to the above synthetic protocol except for the base that was added to the mixture of **2b** (3.7 g, 17 mmol) and TESCl. Colorless oil (130 °C, 0.8 mmHg). IR (NaCl) ν_{max} 1721, 1149, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.50 (s, 1H), 3.68−3.63 (m, 2H), 3.51 (q, J = 7.0, 2H), 1.46 (s, 3H), 1.40 (s, 3H), 1.22−1.03 (m, 6H), 1.02−0.88 (m, 9H), 0.75−0.63 (m, 4H), 0.55 (q, J = 10.8, 2H); ^{13}C NMR ($CDCl_3$) δ 143.8, 104.3, 100.2, 96.4, 57.4, 56.6, 18.4, 17.9, 15.9, 15.7, 6.6, 4.9. MS (ESI) m/z 355.2 $[M + 23]^+$. Anal. Calcd for $C_{16}H_{32}O_5Si$: C, 57.79; H, 9.70. Found: C, 57.60; H, 9.58.

Preparation of Compounds 5 and 6. *Method A.* Imine **3** (0.66 mmol) was dissolved in dry MeCN (1.2 mL) under nitrogen and stirring. The reaction mixture was cooled at −30 °C, and anhydrous $InCl_3$ (73 mg, 0.33 mmol) was added in one portion. After stirring at this temperature for 10 min, a solution of silyl derivative **4** (0.66 mmol) in dry MeCN (1 mL) was added dropwise. In the case of imine **3c**, $InCl_3$ was added to the solution of the two reagents. The reaction mixture was stirred for 1 h and then quenched with a saturated solution of $NaHCO_3$ (1 mL). The crude material was extracted with AcOEt (3 × 5 mL), and the collected organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuum, and the crude material was purified by silica gel flash chromatography. Compounds **5/6f**, **5/6g**, and **5/6h** were chromatographed by flash cartridge chromatography (SiO_2; *n*-hexane/Et_2O, 7:2; flow, 30 mL/min). In the first two cases, only isomers **5f** and **5g** were isolated, respectively. A mixture of quasi-enantiomers **5/5′h**, which cannot be separated, was isolated together with diastereomer **6h**. *Method B.* In a two-necked round-bottomed flask equipped with a magnetic stirring bar and a nitrogen inlet, the aldehyde (benzaldehyde, 60 μL, 0.59 mmol; isovaleraldehyde, 63 μL, 0.59 mmol) and amine (benzylamine, 79 μL, 0.59 mmol) were dissolved in MeCN (1.5 mL) in the presence of molecular sieves (60 mg, activated at 200 °C in vacuum for 2 h). After 1 h, the reaction mixture was cooled to −30 °C, and anhydrous $InCl_3$ (65.3 mg, 0.29 mmol) was added in one portion. After stirring at this temperature for 10 min, a solution of ketene triethylsilyl acetal **4a** (180.2 mg, 0.59 mmol) in dry MeCN (1 mL) was added dropwise. The reaction mixture was stirred for 1 h and worked up as reported in Method A. Compounds **5/6a** and **5/6c** were isolated, respectively.

(3*R,5*S**,6*S**)-3-(1′-*N*-Benzylamino-1′-phenyl-methyl)-5,6-dimethoxy-5,6-dimethyl[1,4]dioxan-2-one (5a, 6a).** Column chromatography: AcOEt/cyclohexane, 1:5. Method A: **5a**, 52%; **6a**, 13%. Method B: **5a**, 71%; **6a**, 16%.

Data for 1′*S-5a.** 108 °C (*n*-pentane/CH_2Cl_2). IR (KBr) ν_{max} 3372, 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.22 (m, 10H), 4.31, 4.28 (AB system, J = 2.9, 2H), 3.60, 3.51 (AM system, J = 13.2, 2H), 3.21 (s, 3H), 3.14 (s, 3H), 3.00−2.00 (br, 1H, exch.), 1.47 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.2, 140.8, 139.7, 128.7, 128.6, 128.5, 127.2, 105.1, 98.6, 75.7, 63.6, 51.1, 50.1, 49.5, 18.4, 17.2. MS (ESI) m/z 386.0 $[M + 1]^+$. Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.30; H, 7.24; N, 3.50.

Data for 1′*R-6a.** Pale yellow oil. IR (NaCl) ν_{max} 3318, 1748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41−7.26 (m, 10H), 4.54, 4.30 (AB system, J = 2.7, 2H), 3.75, 3.56 (AM system, J = 13.2, 2H), 3.33 (s, 3H), 2.77 (s, 3H), 2.76 (brs, 1H, exch.), 1.37 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.1, 140.5, 138.4, 129.7, 128.7, 128.2, 127.8, 127.4, 105.1, 98.6, 74.7, 63.4, 51.5, 49.6, 49.5, 18.3, 17.2. MS (ESI) m/z 386.2 $[M + 1]^+$. Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.38; H, 7.19; N, 3.51.

General Procedure for the Methanolysis of Compounds 5 and 6. Compound **5a,f,h** or **6a,h** (0.225 mmol) was dissolved in a 0.5 M solution of TMSCl in MeOH (1.0 mL, 0.5 mmol) under stirring at 25 °C for 10 min. The solvent was evaporated, and the residue was crystallized, giving pure compound (**7a**: 97% from **5a**, 95% from **5f**; **8a**: 80% from **6a**; **7/7′h**: 84% from **5/5′h**; **8h**: 70% from **6h**).

One-Pot Preparation of Methyl 3-(Amino)-2-hydroxy-propionate Derivatives. *Method C.* The reaction between **3a** and **4b** was performed according to Method A. The ^1H NMR analysis of the crude reaction mixture showed the presence of the diastereomer **5f** and only traces amount of **6f** (HPLC: ASCENTIS SI, 3 μm, 150 × 4.6 mm, 0.8 mL/min, λ = 210 nm, *n*-hexane/*i*PrOH, 98:2; **5f/6f**, 92:8). The crude reaction mixture was treated with MeOH/TMSCl according to the above-reported procedure, and methyl ester derivative **7a** (60%) was obtained after recrystallization. A further batch of compound **7a** (10%) was isolated after column chromatography on silica gel (cyclohexane/AcOEt, 4:1). Total yield: 70%. *Method D.* Operating as reported in Method B, starting from the corresponding aldehyde (0.59 mmol) and benzylamine (79 μL, 0.59 mmol), imines **3** were generated, and then compound **4b** (196.4 mg, 0.59 mmol) was added. The crude reaction mixture containing compounds **5/6** was treated with MeOH/TMSCl according to the above-reported procedure, and methyl ester derivatives **7a−g** were isolated after flash silica gel column chromatography (**7a,f,g**: AcOEt/cyclohexane, 1:4; **7b**: AcOEt/*n*hexane, 1:6; **7c**: Et_2O/*n*-hexane, 1:4; **7d,e**: AcOEt/cyclohexane, 1:3).

Methyl 3-(Benzylamino)-2-hydroxy-3-phenyl-propionate (7/8a): de 83%. Data for (2*R,3*S**)-7a.** 74%. Mp 107 °C (*n*-pentane/Et_2O), (107−108 °C).[71] ^1H NMR ($CDCl_3$) δ 7.41−7.22 (m, 10H), 4.26, 3.95 (AX system, J = 4.1, 2H), 3.77, 3.49 (AM system, J = 13.2, 2H), 3.70 (s, 3H), 1.60 (br, 2H, exch.).

Data for (2*R,3*R**)-8a.** 10%. Mp 99 °C (*n*-pentane/CH_2Cl_2), (98−99 °C).[71] ^{1}H NMR ($CDCl_3$) δ 7.38−7.22 (m, 10H), 4.54, 4.06 (AX system, J = 4.0, 2H), 3.78, 3.61 (AM system, J = 12.8, 2H), 3.60 (s, 3H), 3.00−2.00 (br, 2H, exch.).

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Supporting Information Available: Spectroscopic discussion for compounds **5/6a**. Experimental: general and starting materials. Column chromatography conditions and spectroscopic characterization of **5/6b**−**h**, **6b**−**e**, **7b**−**h**, and **8h**. Further computational details: Cartesian coordinates and energies of the mentioned stationary points. Complete ref 21. Further discussion for the reaction of **4b** with imine **3f**. Copies of ^{1}H and ^{13}C NMR spectra. HPLC spectra for crude reaction mixtures affording **5a/6a** and **5f/6f**. This material is available free of charge via the Internet at http://pubs.acs.org.