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Dual Amino Acids

Stereoselective Synthesis of α,α′-Dihydroxy-β,β′-diaryl-β-amino Acids by Mannich-Like Condensation of Hydroarylamides

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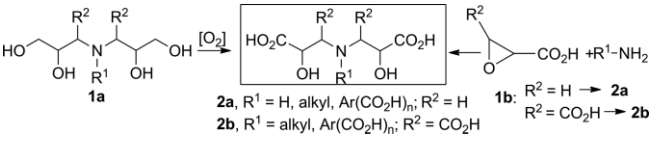
Abstract: *Dual* α,α′-Dihydroxy-β-amino acids are highly interesting tools for several industrial applications. Nevertheless, only few derivatives are reported in the literature and knowledge concerning the substitution pattern as well as their enantioselective syntheses are lacking. Herein, we report on the preparation of enantiopure α,α′-dihydroxy-β,β′-diaryl-β-amino acid (*dual*) derivatives by an efficient Mannich-like condensation of hydroarylamides with 5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one (triethylsilyl)ketene acetal. The synthetic protocol has been optimized affording the *dual* compounds in very good yields and with different aryl substitution patterns. Taking advantage of the "double stereodifferentiation" concept, a highly stereoselective reaction was performed: of the 16 possible isomers, only two diastereoisomers (*d.r.* up to 93:7) formed. Insights into the high stereocontrol of this condensation were given.

Introduction

Over the last two decades, there has been increasing interest in the chemistry of β-amino acid derivatives since these non-proteinogenic molecules have been extensively used to build new bioactive poly-functionalized molecules,[1] peptidomimetics and foldamers[2] and materials.[3] Focusing on α-hydroxy-β-amino acids, they are particularly profitable as pharmaceutical compounds.[4] As documented by several patents, the parent *dual* α-hydroxy-β-amino acid derivatives **2** (Scheme 1) have found industrial application as chelating agents in detergents,[5] bleaching processes for photography,[6] electrostratographic toner preparation,[7] biological treatment of waste water,[8] to prevent corrosion processes, and in formulations for skin care products[9] and biocides.[10] On the other hand, *dual* amino acids could be very appealing for the preparation of peptidomimetic with exotic architectures.

Nevertheless, only few racemic *duals* **2** are described in the literature. In the known structures, both $C_β$/$C_{β'}$ are unsubstituted (**2a**) or bear an additional carboxylic function (**2b**). The simplest *duals* **2a** have been prepared via tertiary *N*,*N*-*bis*(2,3-dihydroxy-propyl)amines **1a**, through O_2 oxidation of the hydroxy-methylene groups,[11] or by amine nucleophilic ring-opening of glycidic acid derivatives **1b** (R^2 = H). This protocol applied to the oxirane-2,3-dicarboxylic acid produces the more polar compounds **2b** (R^2 = CO_2H).[12] It is to be point out that the above compounds are produced in racemic form and diastereoisomeric mixture.



Scheme 1. *Dual* α-hydroxy-β-amino acids **2a,b** from literature.

The paucity of the substitution pattern in the known *dual* α-hydroxy-β-amino acids **2a,b** and the large number of applications of these structurally simple derivatives, focused our ongoing studies on exotic β-amino acids[13] toward the synthesis of new chiral β,β′-diaryl *duals* **2c** (Scheme 2), adopting an original challenging strategy in term of protocol and stereochemistry control. To include the glycolic acid moiety into the target structure, two molecules of the lactone **3** were condensed in the presence of $InCl_3$ with a molecule of *N*,*N*′-diarylidene-1-arylmethanediamine (or hydroarylamide) **4**.

The $InCl_3$ promoted Mannich-like reaction was optimized, mostly in term of reagents ratio. Different hydroarylamides **4** were tested making this procedure general for the preparation of *dual* compounds **2c**. Even if four stereocenters were generated during the condensation process, by using the enantiopure lactone a highly stereoselective control was achieved. Actually, of the 16 possible isomers, only two diastereoisomers were formed, being one of them the largely major product (*d.r.* up to 93:7). Studies performed to rationalize this behavior indi-

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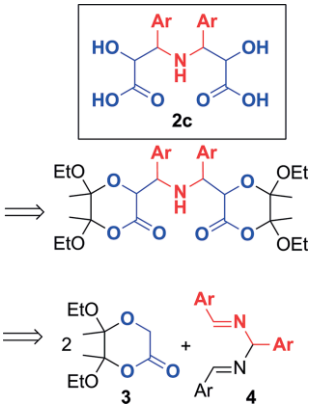


Scheme 2. Retrosynthetic scheme for the synthesis of *dual* α-hydroxy-β-amino acids **2c**.

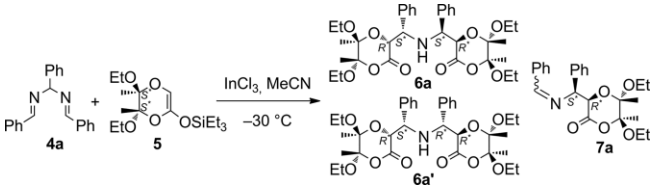
cated, most probably, that a double stereodifferentiation drives these excellent stereochemical results.

Results and Discussion

To access natural and unnatural isoserines, several smart synthetic methods have been developed.[14] Recently, we described the use of acid catalyzed Mannich-like condensation reactions of imines and the racemic "Ley's lactone"[15] analogous (triethylsilyl)ketene acetal **5**, for the diastereoselective synthesis of α-hydroxy-β-amino acid derivatives[13c] and 3-substituted morpholine-2-carboxylic esters.[13d]

Here, we apply the above strategy to the synthesis of *dual* compounds **2c**, using hydroarylamides **4**[16] as imine counterpart. Initially, this condensation was studied (Table 1) by adding $InCl_3$ to a solution of racemic TES-acetal **5** and hydrobenzamide (**4a**) (*Method A*).

Table 1. Screening of the reaction conditions for the reaction of racemic **5** with hydrobenzamide **4a**.[a]



Entry	**4a/5**/$InCl_3$[b]	method[c]	*t* [min][d]	**6a** [%]	**6a′** [%]	**7a** [%]
1	1:1:0.5	A	90	25	11	16
2	1:0.5:0.25	A	30	6[e]	7[e]	59[e]
3	1:2:0.5	A	90	35	7	42
4	1:2:1	A[f]	30	50	6	15
5	1:2:2	A	90	45	13	16
6	1:2:1	B	10	18	7	63
7	1:0.5:0.5	B	10	7[e]	–	58[e]
8	1:3:2	B	10	60	2	18

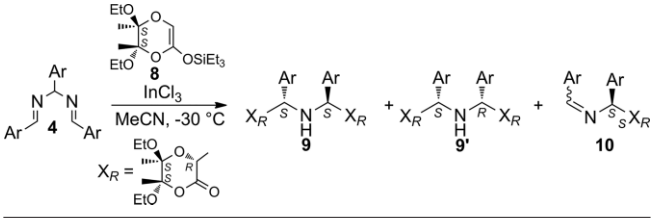
[a] In all the reactions, solutions (1 mol L^{-1}) of **4a**, **5** and $InCl_3$ in MeCN were used. [b] Molar equivalent ratio. [c] *Method A*: the hydrobenzamide (**4a**) and TES-acetal **5** solutions were mixed at 25 °C; this mixture cooled to –30 °C was stirred for 10 min, then the $InCl_3$ solution was added. *Method B*: $InCl_3$ and **4a** solutions were mixed at 25 °C and the resulting mixture was stirred at –30 °C until some solid crystallized (1 h). The TES-acetal **5** solution was then added and the mixture was stirred at –30 °C for further 10 min. [d] Time from the addition of the last reagent (*Method A*: $InCl_3$; *Method B*: TES-acetal **5**). [e] Referred to **5**. [f] The reaction carried out under the conditions of entry 4, but at 25 °C, gave only decomposition products.

In the reaction between equimolar amount of **4a** and **5** with sub-stoichiometric $InCl_3$ (entry 1), *dual* **6a/6a′** mixture and imine **7a** were the most abundant components of the crude, together with benzaldehyde and lactone **3** as by-products. With an excess of hydrobenzamide (entry 2), only **7a** was obtained in good yield. With a reversed **4a/5** molar ratio (entry 3), a substantial increase of both **5** conversion (84 %) and *duals* yield (42 %) was reached. The reaction did not proceed with $InCl_3$ 10 % molar, whereas by increasing it to 1 molar equivalent (entry 4) *duals* were the major products. When excess of both **5** and $InCl_3$ (entry 5) was used, a large quantity of lactone **3** formed together with the target compounds **6**.

The reaction is strongly dependent on the addition order of reagents, as proved by the dramatic effect found when TES-acetal **5** was added at –30 °C to a solution of hydrobenzamide/$InCl_3$ (*Method B*): in all cases, starting materials were rapidly consumed (entries 6–8). Condensations carried out using excess of either **5** (entry 6) or **4a** (entry 7) gave similar results, the imine **7a** being the major product (58–63 %). The goal in obtaining **6a**/**6a′** in good yields (62 %) was reached by operating with a large excess of both TES-acetal **5** and $InCl_3$ (entry 8).

The generality of the above procedure was proved by applying the more efficient conditions (*Method B*) to a series of hydroarylamides **4** and using a masked enantiopure glycolic acid derivative (Table 2).

Table 2. Stereoselective condensation of hydroarylamides **4** with enantiopure (5*S*,6*S*)-TES-acetal **8**.[a]



	4	Ar	*duals* [%]		imine [%]
1	**4a**[b]	Ph	**9a** (63)	**9a′** (5)	**10a** (18)
2	**4a**[b,c]	Ph	**ent-9a** (62)	**ent-9a′** (5)	**ent-10a** (18)
3	**4b**[b]	4-MeC_6H_4	**9b** (51)	**9b′** (8)	**10b** (24)
4	**4c**[b]	4-$MeOC_6H_4$	**9c** (47)	**9c′** (6)	**10c** (25)
5	**4d**[b]	4-FC_6H_4	**9d** (43)	**9d′** (7)	**10d** (50)
6	**4d**[c]	4-FC_6H_4	**ent-9d** (43)	**ent-9d′** (6)	**ent-10d** (48)
7	**4e**[b]	4-BrC_6H_4	**9e** (60)	**9e′** (8)	**10e** (26)
8	**4a**[d]	Ph	**9a** (20)	**9a′** (9)	**10a** (66)
9	**4b**[d]	4-MeC_6H_4	**9b** (23)	**9b′** (3)	**10b** (68)
10	**4c**[d]	4-$MeOC_6H_4$	**9c** (25)	–	**10c** (65)
11	**4d**[d]	4-FC_6H_4	**9d** (18)	**9d′** (2)	**10d** (75)
12	**4d**[c,d]	4-FC_6H_4	**ent-9d** (19)	–	**ent-10d** (72)
13	**4e**[d]	4-BrC_6H_4	**9e** (28)	**9e′** (3)	**10e** (60)

[a] *Method B* was applied, using solutions (1 mol L^{-1}) of **4, 8** and $InCl_3$ in MeCN. [b] **4**:**8**/$InCl_3$, 1:3:2 molar ratio. [c] In the condensation, (5*R*,6*R*)-(triethylsilyl)ketene acetal **11** was used instead of **8**. [d] **4**:**8**/$InCl_3$, 1:2:1 molar ratio.

Even if the synthesis of the 5,6-dimethoxy Ley's lactone derived (5*S*,6*S*)-(triethylsilyl)ketene acetal was reported in the literature,[15b] we decided to prepare and use the new chiral 5,6-diethoxy parent **8**, that we expected to be more effective in the

Mannich condensation diastereoselectivity control, analogously to the racemic acetal **5**. The synthesis and the tricks to obtain **8** in very good yields, operating in batch conditions, are reported in the Supporting Information (Scheme S1).

The reaction between **4** and **8** was performed by modulating the reagents molar ratio in order to control the inherent selectivity of the reaction.

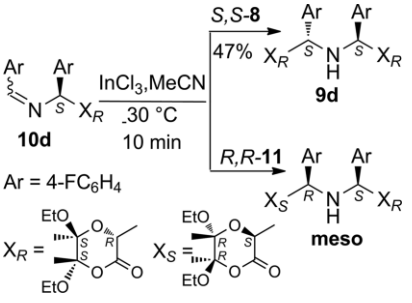
High conversions (78–94 %) of **4** and good yields (50–68 %) of enantiopure *duals* **9**/**9′** were reached by using the **4**/**8**/$InCl_3$ molar ratio 1:3:2 (entries 1, 3–5, 7). Both electrondonating (entries 3,4) and electronwithdrawing substituents (entries 5,7) were tolerated on the hydroarylamide moiety. Together with *dual* compounds, relevant amounts of imines **10** (18–50 %) were isolated. In all cases, *dual* **9** was prevalent over the diastereoisomer **9′** (*d.r.* up to 93:7), demonstrating the high diastereoselectivity of this Mannich-like condensation. As expected, when (5*R*,6*R*)-(triethylsilyl)ketene acetal **11** was used instead of **8**, a similar products distribution was found, the enantiomeric *dual* **ent-9** being the major product (entries 2, 6).

The above protocol was applied to hydroarylamides derived from the more sterically demanding 1-naphthaldehyde and from salicylaldehyde. The reaction fails in the first case and in the second one gave only by-products, probably due to the presence of the acid phenolic group.

Finally, by changing the molar ratio (**4**/**8**/$InCl_3$, 1:2:1, entries 8–13), imines **10** were isolated as major product (60–75 %), accompanied by minor amounts of **9** (18–28 %) and **9′** (2–9 %).

In conclusion, by using *Method B,* it is possible to tune the formation of dual compounds **9**/**9′** or imines **10**, valuable tools for other condensation reactions, simply by changing the molar ration between the reagents.

To verify whether imines **10** was an intermediate in the *duals* construction and to rationalize the stereochemical result of the above reaction, **10d** was made to react with both (5*S*,6*S*)-(triethylsilyl)ketene acetal **8** and its enantiomer (5*R*,6*R*)-(triethylsilyl)ketene acetal **11** (Scheme 3). In the first case, the diastereoisomer **9d** was isolated as the sole condensation product. On the other hand, **10d** did not react with **11** to form the **meso** diastereoisomer (Scheme 3). This behavior shows that the second condensation was strongly dependent on the stereochemistry of the nucleophile, and that a significant mismatch was operative between **10d** and **11**.

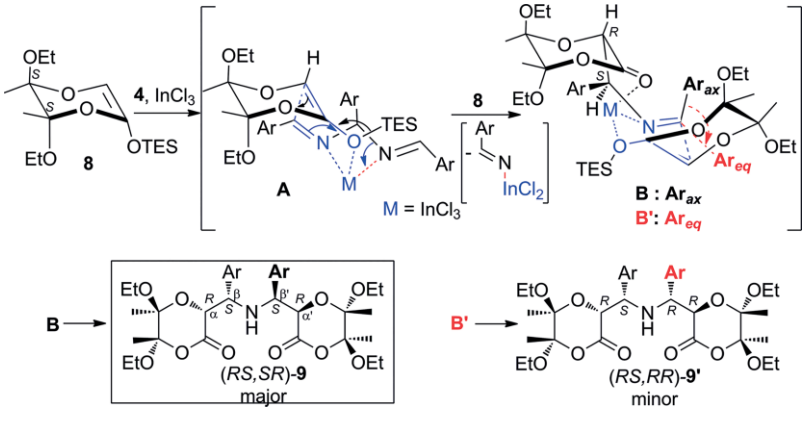


Scheme 3. Match and mismatch in the condensation of imine **10d** with TES-acetals *S*,*S*-**8** and *R*,*R*-**11**.

This reaction demonstrates that the imine **10**, far for being only a condensation by-product, can be a useful intermediate for the preparation of both *duals* and other non-symmetric double Mannich-like condensation products.

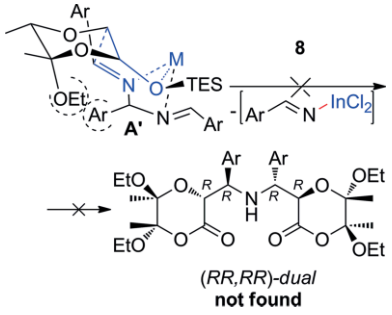
To rationalize the stereoselectivity of this reaction, we propose a mechanism (Scheme 4) that takes into account the transition state assumed for analogous condensations of **5** with different imines.[13c,13d] In this hypothesis, the stereochemistry of the two (*S*,*S*)-lactone units fixed the *R* configuration of the two new Cα/Cα′ stereocenters of the products. Therefore, even if four new stereocenters formed, only three diastereoisomers can form.[17] Nevertheless, only *duals* **9** (the major diastereoisomer) and **9′** have been isolated. To explain this behavior, we have hypothesized that a first condensation of **8** with **4** formed complex **A**, driving the (*R*)-C_α and (*S*)-C_β configuration (Scheme 4). Then, after *N*-indium-imine derivative elimination from **A**, a second molecule of silylketene acetal **8** was coordinated. Two diastereoisomeric intermediates, differing from the imine geometry, can be formed. The *Z complex* **B** (black), presenting the Ar_{ax} group in the less hindered *pseudo*-axial position, can evolve to the major *dual* **9**. The minor stereoisomer **9′** formed via intermediate *E complex* **B′** (red), in which the Ar_{eq} group is flipped into the more hindered *pseudo*-equatorial position. Our stereochemical result is in accord with the "double stereodifferentiation" concept.[18] Actually, as demonstrated in Scheme 3, the second condensation forming complex **B** occurs between **8** and the intermediate imine **10**, bearing the (*S*,*S*)-lactone scaffold.

The formation of the (*RR*,*RR*)-*dual* diastereoisomer, via the boat-conformed complex **A′** (Scheme 5), could also be ex-



Scheme 4. Mechanism of the Mannich-like condensation.

pected, but this compound did not form, most likely because the steric crowding in **A′** prevents the first Mannich-like condensation.



Scheme 5. Stereochemical forbidden (*RR*,*RR*)-*dual* diastereoisomer.

The absolute configuration of diastereoisomers **9** was unequivocally assigned by X-ray crystallography of the major diastereoisomers **9e** (Figure 1) and **9a** (Figure S1 in the supporting Information).

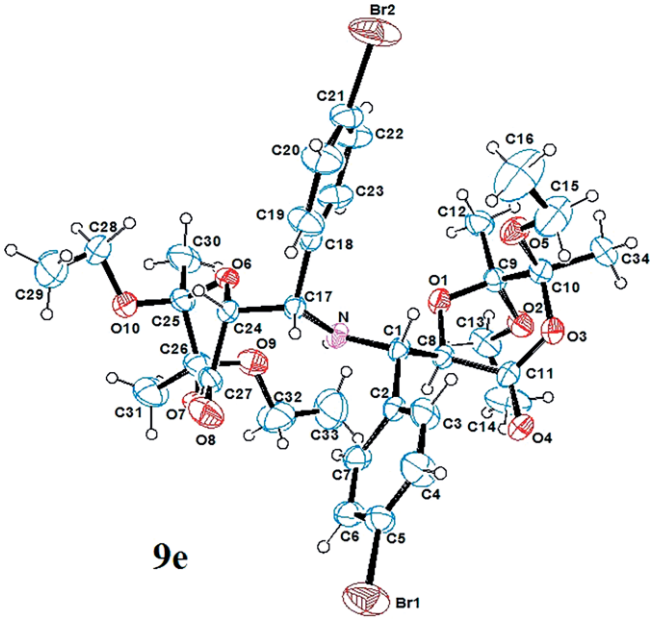
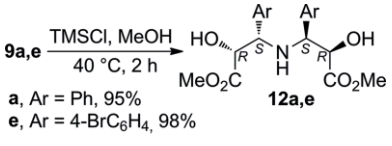


Figure 1. ORTEP[19]view of **9e**, showing the arbitrary atom-labeling scheme. Thermal ellipsoids are at the 40 % probability level.

Finally, with the aim to obtain the *dual* α-hydroxy-β-amino esters **12**, compounds **9a,e** were selected and a methanolysis (TMSCl/MeOH) was performed affording *duals* amino acids **12a,e** in a quasi-quantitative yield (Scheme 6).



Scheme 6. Preparation of *dual* α-hydroxy-β-amino esters **12a,e**.

Conclusion

In summary, we have described the straightforward preparation of *dual* α-hydroxy-β-amino acid derivatives **9/9′**, via imine intermediate **10**, by a highly stereoselective Mannich-like condensation between the silylketene acetal **8** derived from the enantiopure (5*S*,6*S*)-5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one and hydroarylamides **4**. By tuning the stoichiometry of the reagents, is it possible to obtain the dual compounds **9/9′** or the imine intermediate **10**, a valuable synthon for further Mannich like condensation reactions.

A mechanism hypothesis, which gives a rationale for the high diastereoselectivity of this procedure, integrates the description of the synthetic protocol proposed in this paper. Compounds **9** can be easily transformed into the corresponding β,β′-diaryl *dual* derivatives **2c**, a very attractive class of amino acids for the synthesis of non-conventional peptidomimetics.

Experimental Section

Mannich-Like Condensation (*Method B*). Synthesis of *duals* 9, 9′ and 10: Anhydrous MeCN solutions (1 mol L^{-1}) of the reagents **4**, **8** and $InCl_3$ have been used. In a flame-dried round flask, the $InCl_3$ solution (4 mL, 0.88 g, 4 mmol) was added to the hydroarylamide **4** solution (2 mL, 2 mmol), at 25 °C and under nitrogen. The resulting mixture was stirred at –30 °C until some solid crystallized (1 h). Then, the (*S*,*S*)-ketene acetal **8** solution (6 mL, 2.0 g, 6 mmol) was added and the mixture was stirred for further 10 min. Finally, the reaction was quenched by aqueous saturated solution of $NaHCO_3$ (4 mL) and extracted with AcOEt (3 × 20 mL). The collected organic phases were washed with brine (2 × 10 mL), dried with Na_2SO_4 and the solvent evaporated under vacuum (RV). The resulting crude was purified by FCC (AcOEt/hexane/TEA, from 10:1:0.01 to 3:1:0.01). Starting hydroarylamide **4**, yield and physical, spectroscopic, and analytical data of *duals* **9a–e** and **9a′–e′**, and of imines **10a–e** are as follows.

(3*R*,3′*R*,5*S*,5′*S*,6*S*,6′*S*)-3,3′-[(1*S*,1′*S*)-Azanediylbis(phenylmethylene)]bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9a): Hydrobenzamide (**4a**, 596 mg). **9a** (794 mg, 63 %); white solid, m.p. 130–131 °C; $[\alpha]_D^{20}$ = +195 (*c* 1.0, $CHCl_3$); ee > 99 % [HPLC: column KROMASIL 5-AK; 25 °C; *i*PrOH/hexane (1:10); flow 0.8 mL/min, t_R = 7.07 (**9a**) and 7.54 (**9a′**)]. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.31–7.29 (m, 6H), 7.21–7.18 (m, 4H), 4.13 (d, 2H, *J* = 5.8 Hz), 3.93 (d, 2H, *J* = 5.8 Hz), 3.66 (q, 4H, *J* = 7.0 Hz), 3.53–3.47 (m, 2H), 3.39–3.34 (m, 2H), 1.50 (s, 6H), 1.47 (s, 6H), 1.09 (t, 6H, *J* = 7.0 Hz), 1.02 (t, 6H, *J* = 7.0 Hz), (NH proton not visible); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.4 (2C), 138.3 (2C), 128.6 (4C), 128.0 (4C), 127.6 (2C), 104.7 (2C), 98.1 (2C), 75.7 (2C), 61.1 (2C), 58.1 (2C), 57.0 (2C), 18.9 (2C), 17.7 (2C), 15.4 (2C), 15.1 (2C). Anal. Calcd. for $C_{34}H_{47}NO_{10}$: C, 64.85; H, 7.52; N, 2.22; found C, 64.61; H, 7.33; N, 2.39.

(3*R*,3′*R*,5*S*,5′*S*,6*S*,6′*S*)-3,3′-[(1*R*,1′*S*)-Azanediylbis(phenylmethylene)]bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9a′): 64 mg (5 %); white wax; $[\alpha]_D^{20}$ = +120 (*c* 0.96, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.18 (s, 10H), 4.33 (d, 2H, *J* = 4.5 Hz), 4.29 (d, 2H, *J* = 4.5 Hz), 3.56 (q, 4H, *J* = 6.0 Hz), 3.51–3.28 (m, 4H), 1.44 (s, 6H), 1.38 (s, 6H), 1.11 (t, 6H, *J* = 4.5 Hz), 1.34 (t, 6H, *J* = 4.5 Hz), (NH proton not visible); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.9 (2C), 139.8 (2C), 127.8 (4C), 127.3 (4C), 126.6 (2C), 104.8 (2C), 97.8 (2C), 74.9 (2C), 62.3 (2C), 57.9 (2C), 56.9 (2C), 19.1 (2C), 18.0 (2C), 15.8 (2C), 15.4 (2C). MS (ESI) calcd. for $C_{34}H_{47}NO_{10}$ $[M + 1]^+$: *m/z* 630.33, found 630.3 $[M + 1]^+$, 652.2 $[M + 23]^+$. Anal. Calcd. for $C_{34}H_{47}NO_{10}$: C, 64.85; H, 7.52; N, 2.22; found C, 64.59; H, 7.28; N, 2.44.

(3*R*,5*S*,6*S*)-3-[(*S*)-(Benzylideneamino)(phenyl)methyl]-5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one (10a): 148 mg (18 %); white

wax; $[\alpha]_D^{20}$ = +47 (*c* 1.0, THF). *E and Z* mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.36 *and* 8.31 (s, 1H), 7.84–7.81 (m, 2H), 7.55 (d, 2H, *J* = 7.1 Hz), 7.47–7.30 (m, 6H), 5.10 *and* 5.00 (d, 1H, *J* = 4.1 *and* 4.5 Hz), 4.61 *and* 4.57 (d, 1H, *J* = 4.5 *and* 4.1 Hz), 3.74–3.61 (m, 2H), 3.58–3.42 (m, 1H), 3.38–3.31 (m, 1H), 1.52 *and* 1.51 (s, 3H), 1.43 (s, 3H), 1.17–1.09 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.0, 163.3 *and* 162.2, 139.6, 136.2, 130.8, 128.6 (2C), 128.3 (2C), 128.2 (2C), 128.1 (2C), 127.5, 105.7, 98.5, 74.7, 74.5, 58.6 *and* 58.4, 57.0, 19.6, 17.7, 15.5, 15.0. MS (ESI) calcd. for $C_{24}H_{29}NO_5$ $[M + 1]^+$: *m/z* 412.21; found MS (ESI) *m/z* 412.2 $[M + 1]^+$, 434.2 $[M + 23]^+$. Anal. Calcd. for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40; found C, 70.28; H, 7.39; N, 3.12.

Enantiomeric *duals* **ent-9a**, **ent-9a′** and **ent-10a** were prepared using the (*R*,*R*)-TES-ketene acetal **11**.

ent-9a: $[\alpha]_D^{20}$ = −196.5 (*c* 1.1, $CHCl_3$). ^{1}H NMR matches that of **9a**. Anal. Calcd. for $C_{34}H_{47}NO_{10}$: C, 64.85; H, 7.52; N, 2.22; found C, 64.62; H, 7.33; N, 2.47.

ent-9a′: $[\alpha]_D^{20}$ = −124 (*c* 1.0, $CHCl_3$). ^{1}H NMR matches that of **9a′**. Anal. Calcd. for $C_{34}H_{47}NO_{10}$: C, 64.85; H, 7.52; N, 2.22; found C, 64.74; H, 7.38; N, 2.38.

ent-10a: $[\alpha]_D^{20}$ = −48 (*c* 1.0, THF). ^{1}H NMR matches that of **10a**. Anal. Calcd. for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40; found C, 70.31; H, 7.41; N, 3.22.

(3*R*,3′*R*,5*S*,5′*S*,6*S*,6′*S*)-3,3′-[(1*S*,1′*S*)-Azanediylbis(*p*-tolylmethylene)]bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9b): Hydrotoluamide (**4b**, 680 mg). **9b** (672 mg, 51 %); wax; $[\alpha]_D^{20}$ = +214 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.11 (d, 4H, *J* = 8.2 Hz), 7.07 (d, 4H, *J* = 8.2 Hz), 4.10 (d, 2H, *J* = 5.8 Hz), 3.87 (d, 2H, *J* = 5.5 Hz), 3.64 (q, 4H, *J* = 7.0 Hz), 3.53–3.36 (m, 4H), 2.33 (s, 6H), 1.49 (s, 6H), 1.46 (s, 6H), 1.08 (t, 6H, *J* = 7.0 Hz), 1.00 (t, 6H, *J* = 7.0 Hz) (NH proton not visible); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.5 (2C), 136.9 (2C), 135.3 (2C), 128.8 (4C), 128.5 (4C), 104.7 (2C), 98.1 (2C), 75.8 (2C), 60.8 (2C), 58.1 (2C), 57.0 (2C), 21.2 (2C), 19.0 (2C), 17. 7 (2C), 15.3 (2C), 15.1 (2C). Anal. Calcd. for $C_{36}H_{51}NO_{10}$: C, 65.73; H, 7.81; N, 2.13; found C, 66.02; H, 8.05; N, 1.98.

(3*R*,3′*R*,5*S*,5′*S*,6*S*,6′*S*)-3,3′-[(1*S*,1′*R*)-Azanediylbis(*p*-tolylmethylene)]bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9′b): 106 mg (8 %); white wax; $[\alpha]_D^{20}$ = +123 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.31 (d, 4H, *J* = 7.9 Hz), 7.15 (d, 4H, *J* = 7.9 Hz), 4.51 (d, 2H, *J* = 1.9 Hz), 4.33 (d, 2H, *J* = 2.5 Hz), 3.81–3.66 (m, 4H), 3.52–3.44 (m, 2H), 3.35–3.29 (m, 2H), 2.36 (s, 6H), 1.53 (s, 6H), 1.41 (s, 6H), 1.20 (t, 6H, *J* = 7.0 Hz), 1.13 (t, 6H, *J* = 7.0 Hz) (NH proton not visible). Anal. Calcd. for $C_{36}H_{51}NO_{10}$: C, 65.73; H, 7.81; N, 2.13; found C, 65.84; H, 7.79; N, 2.02.

(3*R*,5*S*,6*S*)-5,6-Diethoxy-5,6-dimethyl-3-{(*S*)-[(4-methylbenzylidene)amino](p-tolyl)methyl}-1,4-dioxan-2-one (10b): 212 mg (24 %); wax; $[\alpha]_D^{20}$ = +43 (c 1.2, $CHCl_3$). *E and Z* mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.31 *and* 8.28 (s, 1H), 7.71 (d, 2H, *J* = 7.8 Hz), 7.42 (d, 2H, *J* = 7.8 Hz), 7.22–7.13 (m, 4H), 5.04 *and* 4.98 (d, 1H, *J* = 4.1 *and* 4.2 Hz), 4.61 *and* 4.55 (d, 1H, *J* = 4.2 *and* 4.1 Hz), 3.80–3.56 (m, 2H), 3.54–3.44 (m, 1H), 3.44–3.29 (m, 1H), 2.39 (s, 3H), 2.37 (s, 3H), 1.52 (s, 3H), 1.42 *and* 1.41 (s, 3H), 1.17–1.13 (m, 6H). Anal. Calcd. for $C_{26}H_{33}NO_5$: C, 71.05; H, 7.57; N, 3.19; found C, 70.81; H, 7.36; N, 3.38.

(3*R*,3′*R*,5*S*,5′*S*,6*S*,6′*S*)-3,3′-{(1*S*,1′*S*)-Azanediylbis[(4-methoxyphenyl)methylene]}bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9c): Hydro(4-methoxy)benzamide (4c, 776 mg). 9c (648 mg, 47 %); wax; $[\alpha]_D^{20}$ = +168 (*c* 1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.11 (d, 4H, *J* = 8.5 Hz), 6.84 (d, 4H, *J* = 8.7 Hz), 4.09 (d, 2H, *J* = 6.0 Hz), 3.86 (d, 2H, *J* = 6.0 Hz), 3.81 (s, 6H), 3.66 (d, 2H, *J* = 14.1 Hz), 3.64 (d, 2H, *J* = 14.1 Hz), 3.55–3.33 (m, 4H), 1.49 (s, 6H), 1.46 (s, 6H), 1.09 (t, 6H, *J* = 7.3 Hz), 1.02 (t, 6H, *J* = 7.0 Hz) (NH proton not visible); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.4 (2C), 158.9 (2C), 130.3 (2C), 129.5 (4C), 113.3 (4C), 104.6 (2C), 97.9 (2C), 75.6 (2C), 60.3 (2C), 57.9 (2C), 56.8 (2C), 54.9 (2C), 18.7 (2C), 17. 5 (2C), 15.2 (2C), 14.9 (2C). Anal. Calcd. for $C_{36}H_{51}NO_{12}$: C, 62.68; H, 7.45; N, 2.03; found C, 62.95; H, 7.74; N, 1.82.

(3*R*,3′*R*,5*S*,5′*S*,6*S*,6′*S*)-3,3′-{(1*S*,1′*R*)-Azanediylbis[(4-methoxyphenyl)methylene]}bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9c′): 82 mg (6 %); white wax; $[\alpha]_D^{20}$ = +78 (*c* 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.35 (d, 4H, *J* = 8.7 Hz), 6.89 (d, 4H, *J* = 8.7 Hz), 4.53 (d, 2H, *J* = 2.8 Hz), 4.40 (d, 2H, *J* = 2.8 Hz), 3.82 (s, 6H), 3.73–3.62 (m, 4H), 3.56–3.49 (m, 2H), 3.45–3.36 (m, 2H), 1.52 (s, 6H), 1.42 (s, 6H), 1.18–1.14 (m, 12H) (NH proton not visible); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.0 (2C), 159.0 (2C), 133.3 (2C), 128.4 (4C), 113.6 (4C), 105.3 (2C), 98.1 (2C), 74.5 (2C), 58.4 (2C), 57.3 (2C), 56.5 (2C), 55.2 (2C), 18.5 (2C), 17.6 (2C), 15.2 (2C), 15.0 (2C). Anal. Calcd. for $C_{36}H_{51}NO_{12}$: C, 62.68; H, 7.45; N, 2.03; found C, 62.97; H, 7.79; N, 1.83.

(3*R*,5*S*,6*S*)-5,6-Diethoxy-3-{(*S*)-[(4-methoxybenzylidene)amino]-(4-methoxyphenyl)methyl}-5,6-dimethyl-1,4-dioxan-2-one (10c): 236 mg (25 %); wax; $[\alpha]_D^{20}$ = +15.8 (*c* 1.0, $CHCl_3$). *E and Z* mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.25 *and* 8.22 (s, 1H), 7.74 (d, 2H, *J* = 8.7 Hz), 7.45 (d, 2H, *J* = 8.6 Hz), 6.91–6.88 (m, 4H), 5.00 *and* 4.95 (d, 1H, *J* = 4.2 *and* 4.5 Hz), 4.57 *and* 4.49 (d, 1H, *J* = 4.5 *and* 4.2 Hz), 3.82 (s, 3H), 3.80 *and* 3.78 (s, 3H), 3.74–3.59 (m, 2H), 3.52–3.44 (m, 1H), 3.43–3.27 (m, 1H), 1.50 (s, 3H), 1.41 (s, 3H), 1.16–1.10 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.0 *and* 167.6, 161.9 *and* 161.1, 161.7, 158.9, 132.1, 130.1 (2C), 129.4, 129.2 (2C), 113.7 (2C), 113.6 (2C), 105.5, 98.5, 74.8, 73.8, 58.5, 56.9, 55.3, 55.2, 19.7, 17.7, 15.5, 15.0. Anal. Calcd. for $C_{26}H_{33}NO_7$: C, 66.22; H, 7.05; N, 2.97; found C, 66.47; H, 7.23; N, 2.74.

(3*R*,3′*R*,5*S*,5′*S*,6*S*,6′*S*)-3,3′-{(1*S*,1′*S*)-Azanediylbis[(4-fluorophenyl)methylene]}bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9d): Hydro(4-fluoro)benzamide (**4d**, 708 mg). **9d** (572 mg, 43 %); white wax; $[\alpha]_D^{20}$ = +198 (*c* = 1.4 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.20–7.15 (m, 4H), 7.04–6.99 (m, 4H), 4.09 (d, 2H, *J* = 5.7 Hz), 3.90 (d, 2H, *J* = 5.7 Hz), 3.69 (q, 4H, *J* = 7.0 Hz), 3.58 (bs, 1H), 3.60–3.48 (m, 2H), 3.42–3.32 (m, 2H), 1.52 (s, 6H), 1.48 (s, 6H), 1.13–1.03 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.3 (2C), 162.4 (d, 2C, *J* = 245.4 Hz), 133.9 (2C), 130.1 (d, 4C, *J* = 8.1 Hz), 115.0 (d, 4C, *J* = 21.3 Hz), 104.9 (2C), 98.1 (2C), 75.5 (2C), 60.4 (2C), 58.2 (2C), 57.1 (2C), 18.8 (2C), 17.6 (2C), 15.3 (2C), 15.0 (2C). Anal. Calcd. for $C_{34}H_{45}F_2NO_{10}$: C, 61.34; H, 6.81; N, 2.10; found C, 61.43; H, 6.90; N, 2.02.

(3*R*,3′*R*,5*S*,5′*S*,6*S*,6′*S*)-3,3′-{(1*S*,1′*R*)-Azanediylbis[(4-fluorophenyl)methylene]}bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9d′): 94 mg (7 %); white wax; $[\alpha]_D^{20}$ = +48 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.42–7.38 (m, 4H), 7.08–7.03 (m, 4H), 5.12 (d, 2H, *J* = 4.4 Hz), 4.27 (d, 2H, *J* = 4.5 Hz), 4.03 (bs, 1H), 3.83–3.70 (m, 4H), 3.64–3.52 (m, 4H), 1.56 (s, 6H), 1.45 (s, 6H), 1.26 (t, 6H, *J* = 7.1 Hz), 1.19 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.9 (2C), 162.4 (d, 2C, *J* = 246.0 Hz), 134.0 (2C), 128.5 (d, 4C, *J* = 7.9 Hz), 114.9 (d, 4C, *J* = 21.4 Hz), 105.1 (2C), 98.1 (2C), 75.7 (2C), 73.9 (2C), 58.9 (2C), 57.5 (2C), 18.6 (2C), 17.5 (2C), 15.1 (4C). Anal. Calcd. for $C_{34}H_{45}F_2NO_{10}$: C, 61.34; H, 6.81; N, 2.10; found C, 61.47; H, 6.96; N, 2.00.

(3*R*,5*S*,6*S*)-5,6-Diethoxy-3-{(*S*)-[(4-fluorobenzylidene)amino]-(4-fluorophenyl)methyl}-5,6-dimethyl-1,4-dioxan-2-one (10d): 448 mg (50 %); wax; $[\alpha]_D^{20}$ = +37 (*c* 1.4, $CHCl_3$). *E and Z* mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.31 *and* 8.26 (s, 1H), 7.84–7.79 (m, 2H),

7.54–7.49 (m, 2H), 7.12–7.03 (m, 4H), 5.05 *and* 4.98 (d, 1H, *J* = 4.2 *and* 4.8 Hz), 4.54 *and* 4.47 (d, 1H, *J* = 4.8 *and* 4.2 Hz), 3.70–3.58 (m, 2H), 3.55–3.45 (m, 1H), 3.36–3.26 (m, 1H), 1.51 (s, 3H), 1.42 (s, 3H), 1.17–1.07 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.9, 164.5 (d, *J* = 249.0 Hz), 162.2 (d, *J* = 244.0 Hz), 161.8, 135.4 (d, *J* = 2.8 Hz), 132.4 (d, *J* = 2.5 Hz), 130.6 (d, 2C, *J* = 8.7 Hz), 129.7 (d, 2C, *J* = 7.7 Hz), 115.5 (d, 2C, *J* = 22.1 Hz), 115.1 (d, 2C, *J* = 21.0 Hz), 105.7, 98.5, 74.7, 73.7, 58.5, 57.0, 19.3, 17.7, 15.5, 15.0. Anal. Calcd. for $C_{24}H_{27}F_2NO_5$: C, 64.42; H, 6.08; N, 3.13; found C, 64.71; H, 6.29; N, 3.00.

Enantiomeric *duals* **ent-9d** and **ent-10d** were prepared using the silyl derivative (*R*,*R*)-TES-ketene acetal **11**.

ent-9d: $[\alpha]_D^{20}$ = –194 (*c* 1.4, $CHCl_3$). ^{1}H NMR matches that of **9d**. Anal. Calcd. for $C_{34}H_{45}F_2NO_{10}$: C, 61.34; H, 6.81; N, 2.10; found C, 61.53; H, 7.06; N, 1.95.

ent-10d: $[\alpha]_D^{20}$ = –34 (*c* 1.6, $CHCl_3$). ^{1}H NMR matches that of **10d**. Anal. Calcd. for $C_{24}H_{27}F_2NO_5$: C, 64.42; H, 6.08; N, 3.13; found C, 64.65; H, 6.33; N, 2.92.

(3*R*,3′*R*,5*S*,5′*S*,6*S*,6′*S*)-3,3′-{(1*S*,1′*S*)-Azanediylbis[(4-bromophenyl)methylene)]bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9e): Hydro(4-bromo)benzamide 4e (1.07 g). 9e (0.94 g, 60 %); white wax; $[\alpha]_D^{20}$ = +224 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.44 (d, 4H, *J* = 8.4 Hz), 7.07 (d, 4H, *J* = 8.3 Hz), 4.09 (d, 2H, *J* = 5.2 Hz), 3.84 (d, 2H, *J* = 5.2 Hz), 3.70–3.62 (m, 5H), 3.57–3.47 (m, 2H), 3.42–3.32 (m, 2H), 1.50 (s, 6H), 1.46 (s, 6H), 1.11 (t, 6H, *J* = 7.0 Hz), 1.03 (t, 6H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.2 (2C), 137.2 (2C), 131.3 (4C), 130.3 (4C), 121.7 (2C), 104.9 (2C), 98.2 (2C), 75.2 (2C), 60.6 (2C), 58.2 (2C), 57.1 (2C), 18.8 (2C), 17.6 (2C), 15.3 (2C), 15.0 (2C). Anal. Calcd. for $C_{34}H_{45}Br_2NO_{10}$: C, 51.85; H, 5.76; N, 1.78; found C, 52.03; H, 5.92; N, 1.61.

(3*R*,3′*R*,5*S*,5′*S*,6*S*,6′*S*)-3,3′-{(1*S*,1′*R*)-Azanediylbis[(4-bromophenyl)methylene)]bis(5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one) (9e′): 126 mg (8 %); white wax; $[\alpha]_D^{20}$ = +123 (*c* = 1.1 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.47 (d, 4H, *J* = 8.4 Hz), 7.30 (d, 4H, *J* = 8.5 Hz), 4.49 (d, 2H, *J* = 2.3 Hz), 4.28 (d, 2H, *J* = 2.3 Hz), 3.80–3.66 (m, 4H), 3.54–3.43 (m, 2H), 3.33–3.23 (m, 2H), 2.03 (bs, 1H), 1.53 (s, 6H), 1.39 (s, 6H), 1.20 (t, 6H, *J* = 7.0 Hz), 1.13 (t, 6H, *J* = 7.1 Hz). Anal. Calcd. for $C_{34}H_{45}Br_2NO_{10}$: C, 51.85; H, 5.76; N, 1.78; found C, 52.07; H, 5.94; N, 1.59.

(3*R*,5*S*,6*S*)-3-{(*S*)-[(4-Bromobenzylidene)amino](4-bromophenyl)methyl}-5,6-diethoxy-5,6-dimethyl-1,4-dioxan-2-one (10e): 296 mg (26 %); wax; $[\alpha]_D^{20}$ = +23 (*c* 1.2, $CHCl_3$). *E and Z* mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.27 *and* 8.24 (s, 1H), 7.68 (d, 2H, *J* = 8.4 Hz), 7.57–7.38 (m, 6H), 5.01 *and* 4.94 (d, 1H, *J* = 4.0 *and* 4.7 Hz), 4.51 *and* 4.46 (d, 1H, *J* = 4.6 *and* 4.1 Hz), 3.66–3.26 (m, 4H), 1.49 (s, 3H), 1.40 (s, 3H), 1.16–1.06 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.3 *and* 167.7, 162.2 *and* 161.3, 138.5, 134.9, 131.6 (2C), 131.3 (2C), 130.0 (2C), 129.9 (2C), 125.4, 121.5, 105.8 *and* 105.2, 98.5 *and* 98.1, 74.7 *and* 74.4, 73.8, 58.5, 57.3 *and* 57.0, 19.3, 17.7, 15.5, 15.0. Anal. Calcd. for $C_{24}H_{27}Br_2NO_5$: C, 50.64; H, 4.78; N, 2.46; found C, 50.40; H, 4.51; N, 2.68.

Synthesis of 9d from Imine 10d: Anhydrous MeCN solutions (1 mol L^{-1}) of **10d**, **8** and $InCl_3$ have been used. In a flame-dried round flask, the $InCl_3$ solution (0.5 mL, 110 mg, 0.5 mmol) was added to the immine **10d** solution (0.5 mL, 224 mg, 0.5 mmol), at 25 °C and under nitrogen. The resulting mixture was stirred at –30 °C until some solid crystallized (1 h). Then, the (*S*,*S*)-ketene acetal **8** solution (0.75 mL, 249 mg, 0.75 mmol) was added and the mixture was stirred for further 10 min. Finally, the reaction was quenched by aqueous saturated solution of $NaHCO_3$ (1 mL) and extracted with AcOEt (3 × 5 mL). The collected organic phases were washed with brine (2 × 5 mL), dried with Na_2SO_4 and the solvent evaporated under vacuum (RV). The resulting crude was purified by FCC (AcOEt/hexane/TEA, from 10:1:0.01 to 3:1:0.01) and **9d** was isolated (156 mg, 47 %). The physical, analytical and spectroscopic data match those of **9d** prepared by reaction of **4d** with **8**.

Synthesis of *dual* α-Hydroxy-β-amino Esters 12a,e: A solution of trimethylsilyl chloride (164 mg, 1.5 mmol) and compound **9** (1 mmol) in MeOH (4 mL) was stirred at 40 °C for 2 h. After evaporation of the solvent under vacuum, the residue was diluted with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with dichloromethane (2 × 10 mL). The collected organic phases were dried with Na_2SO_4, filtered and concentrated under vacuum affording pure compound **12**.

(2*R*,2′*R*,3*S*,3′*S*)-Dimethyl 3,3′-Azanediylbis(2-hydroxy-3-phenylpropanoate) (12a): *Dual* **9a** (630 mg). **12a** (366 mg, 98 %); white wax; $[\alpha]_D^{20}$ = +92 (*c* 0.9 $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.35–7.31 (m, 6H), 7.22–7.20 (m, 4H), 4.20 (d, 2H, *J* = 4.9 Hz), 3.65 (d, 2H, *J* = 4.9 Hz), 3.60 (s, 6H), 3.44 (bs, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.6 (2C), 138.8 (2C), 128.4 (4C), 128.1 (4C), 128.0 (2C), 75.2 (2C), 61.8 (2C), 52.2 (2C); IR (KBr) ν_{max} 3412, 3320, 1755, 1206, 1149, 744 cm^{-1}. MS (ESI) *m/z* 374.1 $[M + 1]^+$, 396.1 $[M + 23]^+$. Anal. Calcd. for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75; found C, 64.57; H, 6.51; N, 3.48.

(2*R*,2′*R*,3*S*,3′*S*)-Dimethyl 3,3′-Azanediylbis(3-(4-bromophenyl)-2-hydroxypropanoate) (12e): *Dual* **9e** (788 mg). **12e** (526 mg, 99 %); white wax; $[\alpha]_D^{20}$ = +140 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.48 (d, 4H, *J* = 8.3 Hz), 7.09 (d, 4H, *J* = 8.4 Hz), 4.14 (d, 2H, *J* = 4.7 Hz), 3.65 (s, 6H), 3.56 (d, 2H, *J* = 4.7 Hz), 3.09 (bs, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.7 (2C), 137.1 (2C), 131.1 (4C), 129.2 (4C), 121.5 (2C), 74.2 (2C), 60.6 (2C), 51.9 (2C). Anal. Calcd. for $C_{20}H_{21}Br_2NO_6$: C, 45.22; H, 3.98; N, 2.64; found C, 44.94; H, 3.68; N, 2.93.

Conflict of interest

The authors declare no conflict of interest.

Supporting Information (see footnote on the first page of this article): Synthesis of compounds **4a–e**, **8,11**. Copies of ^{1}H and ^{13}C NMR spectra of synthesized compounds.

CCDC 1533981 (for **9a**) and 1533983 (for **9e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Keywords: Diastereoselectivity · Enols · Mannich-like reaction · Hydroarylamides · Dual α-hydroxy-α-amino acids

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$$2^{n-1} + 2^{\frac{n-2}{2}}$$

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