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Asymmetric synthesis of all isomers of α-methyl-β-phenylserine

Alberto Avenoza,[a,*] Carlos Cativiela,[b,*] Francisco Corzana,[a] Jesús M. Peregrina[a] and María M. Zurbano[a]

[a]*Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de la Rioja, UA-CSIC, 26001 Logroño, Spain*

[b]*Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Universidad de Zaragoza-C.S.I.C., 50009 Zaragoza, Spain*

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Abstract

This report describes the synthesis of enantiomerically pure (2*R*,3*R*)-, (2*R*,3*S*)-, (2*S*,3*S*)- and (2*S*,3*R*)-2-amino-3-hydroxy-2-methyl-3-phenylpropanoic acids, four quaternary α-amino acids, using a stereodivergent synthetic route and starting from (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals. The key step involves the asymmetric Grignard additions to the above chiral aldehydes, in which high levels of asymmetric induction are observed.

1. Introduction

In recent years, α,α-disubstituted α-amino acids have attracted the attention of numerous research groups in connection with the design and synthesis of several conformationally constrained analogues of bioactive peptides (peptidomimetics).[1]

In this context and as a part of our research program on the synthesis of new quaternary α-amino acids,[2] we have been interested in the synthesis of hydroxy-α-amino acids.[3] Particularly, α-methyl-β-phenylserines have received our attention due to their role as important intermediates in the synthesis of biological useful compounds, such as florfenicol, thiamphenicol and L-methyldopa.[4] Moreover, α-alkylated β-hydroxy-α-amino acids can also be found as substructures in several biologically active molecules,[5] and some of them possess antihypertensive activity and are DOPA decarboxylase inhibitors.[6]

To the best of our knowledge, there are three methods in the literature for the synthesis of racemic 2-methyl-3-phenylserines[7] and three strategies for the preparation of their enantiomerically pure forms. Seebach described that the enolization of a bicyclo[3.3.0]aminal, prepared from L-cysteine,

* Corresponding authors. E-mail: alberto.avenoza@dq.unirioja.es

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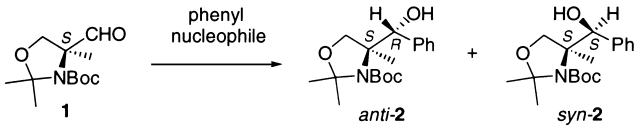
followed by aldol condensation with benzaldehyde, provided the corresponding carbinol with an excellent diastereoselectivity which was easily transformed into the (2*R*,3*R*)-2-methyl-3-phenylserine.[8] The asymmetric synthesis of the methyl ester derivative of (2*S*,3*R*)-2-methyl-3-phenylserine was reported by Schöllkopf using the well-know bis-lactim ether method.[9] More recently, (2*R*,3*R*)-2-methyl-3-phenylserine methyl ester was prepared by a highly regio- and stereocontrolled ring opening of *N*-(*p*-toluenesulfinyl)-2-methyl-2-methoxycarbonyl-3-phenylaziridine with 50% TFA/MeCN.[10]

2. Results and discussion

In this context, we have recently reported the preparation of both enantiomers of *N*-Boc-*N*,*O*-isopropylidene-α-methylserinal[11] (**1** and **7**) and their use as chiral building blocks in the synthesis of enantiomerically pure α-substituted alanines by transformation of the aldehyde group into ethyl, vinyl or ethynyl groups.[12] In this methodology, the oxazolidine ring contributes the amino acid moiety and the stereogenic centre was already created in the starting material. However, in this report we would also like to explore the fact that this oxazolidine ring can behave as an excellent chiral auxiliary to create another new centre in the asymmetric Grignard addition reactions to aldehydes.

Therefore, in order to demonstrate the synthetic utility of both *N*-Boc-*N*,*O*-isopropylidene-α-methylserinals (**1** and **7**) as chiral building blocks in the synthesis of enantiomerically pure α-methyl-β-phenylserines, we have tried the reaction of these aldehydes with two phenyl nucleophiles under different conditions (Scheme 1).



Scheme 1. Addition of phenyl nucleophiles to chiral aldehyde **1**

As shown in Table 1, different conditions were tested when we carried out the reaction of *N*-Boc-*N*,*O*-isopropylidene-α-methylserinal **1** with phenylmagnesium bromide. In the absence of a catalyst, high levels of diastereoselectivity were achieved in favour of the *anti*-**2** diastereoisomer and the reaction is quantitative in 3 h. We observed that the diastereoselectivity is affected by temperature, so at a low temperature (–78°C), a *syn*-**2**/*anti*-**2** ratio of ≥2/≤98 (*syn*-**2** is not detected) was achieved, while at 0°C this ratio decreased to 25/75.

Additions of phenylmagnesium bromide to α-amino aldehydes derived from L-α-amino acids, particularly to *N*-Boc-*N*,*O*-isopropylideneserinal (Garner's aldehyde), occur as a non-chelation controlled Felkin–Ahn attack on the least hindered face[13] and therefore, in our case, it is reasonable to think that a similar model is applicable to explain the results obtained. In this way, the addition of phenylmagnesium bromide to the L-α-methylserinal **1** would be expected to occur as a non-chelation attack on the *re*-face to give the *anti*-**2** isomer as the major adduct (Fig. 1). The same feature was observed when PhLi was used in the absence of a catalyst (entry 7).

On the other hand, a reversal in selectivity is not observed even when the reactions were carried out under conditions of chelation control (entries 3, 4, 5 and 8) indicating that the Cram chelation model[14] has not occurred, at least predominantly (Fig. 1). Simply an important decrease of

Table 1
Phenyl nucleophile additions to α-methylserinal **1**[a]

Entry	Phenyl nucleophile	Solvent	T (° C)	Lewis acid (equiv)	Solvent	% conv	*syn/anti*[b]
1	PhMgBr	THF	-78	none	THF	100	2/98
2	PhMgBr	THF	0	none	THF	100	25/75
3	PhMgBr	THF	-78 to 0	$CeCl_3$ (1.0)	THF	100	7/93
4	PhMgBr	THF	-78 to 0	$BF_3 \cdot Et_2O$ (1.0)	Et_2O	20	7/93
5	PhMgBr	Et_2O	-78	$AlCl_2Et$ (1.0)	Et_2O	100	29/71
6	PhMgBr	Et_2O	-78	none	Et_2O	100	30/70
7	PhLi	Et_2O	-78	none	Et_2O	100	31/69
8	PhLi	Et_2O	-78	$AlCl_2Et$ (1.0)	hexane	100	43/57

[a]Reactions were run with 4 equivalents of nucleophile for each equivalent of aldehyde.
[b]Determined by integration of the CH signals of products *syn*-**2** and *anti*-**2** in the ^1H NMR spectra.

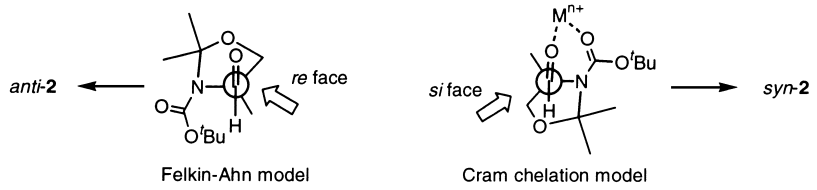


Figure 1. Models to explain the behaviour of phenyl nucleophile additions to α-methylserinal **1**

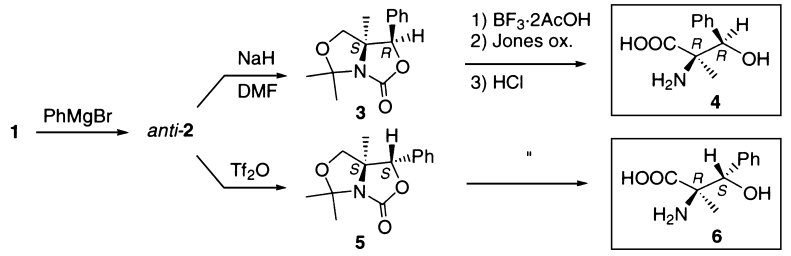
diastereoselectivity was observed in the case of PhLi in the presence of $AlCl_2Et$ (entry 7). The same feature occurs in the phenyl nucleophile additions to Garner's aldehyde.

Other additional proof that the pathway involving a non-chelation model is appropriate to explain the diastereoselectivity observed is the fact that the ratio *syn*-**2**/*anti*-**2** is influenced by the solvent as described in the literature.[13b,c,15] When the reaction of aldehyde **1** with phenylmagnesium bromide was carried out in diethyl ether, a solvent more likely to favor chelation,[13b] a decrease of the diastereoselectivity was observed (entry 6).

In general, the results obtained indicate that the model proposed to explain the diastereoselectivity observed in the nucleophile additions is similar to that described for Garner's aldehyde.[13b,16] The only difference observed is a significant increase of diastereoselectivity.

Starting from enantiomerically pure *anti*-**2**, which was obtained by the attack of phenylmagnesium bromide on methylserinal **1** (entry 1), we synthesised (2*R*,3*R*)-α-methyl-β-phenylserine **4** with an overall yield of 54%, using four steps: intramolecular cyclization in compound *anti*-**2**, promoted by the attack of the alkoxide ion on the carbonyl carbon of the Boc group to give the bicyclic compound **3**, selective deprotection of the acetonide moiety of **3** by the action of boron trifluoride–acetic acid complex or aqueous hydrochloric acid to give the corresponding oxazolidinone, subsequent Jones oxidation and acid hydrolysis using hydrochloric acid at reflux. Liberation of the amino acid **4** from its hydrochloride salt was achieved by refluxing with propylene oxide in ethanol. The spectral data of this compound proved to be identical to that previously reported[8] (Scheme 2).

The diastereoisomer (2*R*,3*S*)-α-methyl-β-phenylserine **6** was also obtained starting from *anti*-**2** but now by a different type of intramolecular cyclization described by Joullié et al.[13b,c] which uses

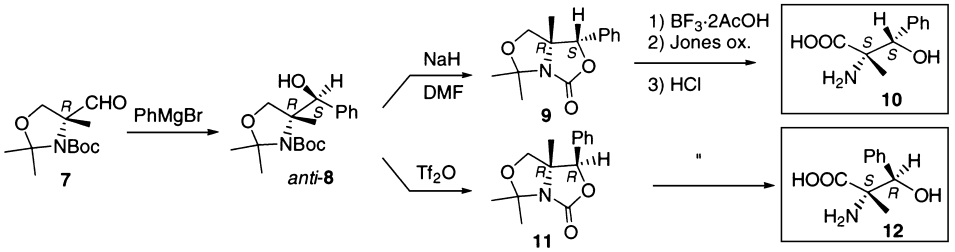


Scheme 2. Synthesis of (2*R*,3*R*)- and (2*R*,3*S*)-α-methyl-β-phenylserines (**4** and **6**)

triflic anhydride to give the bicyclic compound **5**, with inversion of configuration at the benzylic carbon. Similar rearrangements have previously been reported in the literature.[17]

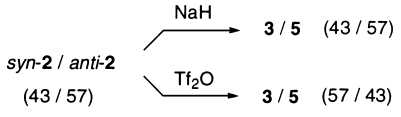
Using the same strategy used to prepare amino acid **4** from **3**, the amino acid **6** was obtained from compound **5** in a 43% yield. The spectral data of this compound proved to be identical to that previously reported[9] (Scheme 2).

The enantiomers (2*S*,3*S*)- and (2*S*,3*R*)-α-methyl-β-phenylserines (**10** and **12**) were obtained using the same strategy described above in Scheme 2, but starting from (*R*)-α-methylserinal **7** (Scheme 3). The spectral data of **10** and **12** were identical to those obtained for their enantiomers **4** and **6**, but their specific rotations were opposite in sign (Scheme 3).



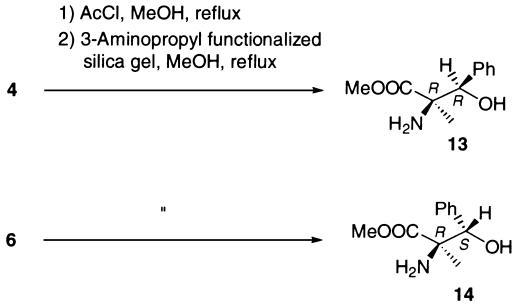
Scheme 3. Synthesis of (2*S*,3*S*)- and (2*S*,3*R*)-α-methyl-β-phenylserines (**10** and **12**)

The enantiomeric purity of the intermediates in the synthesis of amino acids was examined by NMR spectroscopy. Analysis of the ^{1}H NMR spectra of bicyclic diastereoisomers **3** and **5** showed that the enantiomeric purity of these compounds was at least 96% (only one diastereoisomer was observed). In order to be sure that compounds **3** and **5** were almost enantiomerically pure, we determined the cross-contamination by conversion of the mixture of alcohols *syn*-**2**/*anti*-**2** in a ratio 43/57 (starting from entry 6 of Table 1) into the corresponding mixture of bicyclic compounds **3**/**5** by the action of NaH, showing a ratio of 43/57. When the same transformation was carried out in the presence of triflic anhydride, a ratio of 57/43 was observed for the mixture of compounds **3**/**5** (Scheme 4).



Scheme 4. Determination of the cross-contamination in compounds **3** and **5**

The absolute stereochemistry of (2*R*,3*R*)- and (2*R*,3*S*)-α-methyl-β-phenylserines (**4** and **6**) was determined by their transformations into the corresponding methyl ester derivatives **13** and **14**, using acetyl chloride in methanol, and further comparison of their optical activities and spectroscopic data with the values reported[9c] (Scheme 5).



Scheme 5. Determination of the absolute stereochemistry of **4** and **6**

In summary, we have developed the asymmetric synthesis of the four stereoisomers of α-methyl-β-phenylserines: (2*R*,3*R*)-**4**, (2*R*,3*S*)-**6**, (2*S*,3*S*)-**10** and (2*S*,3*R*)-**12** via the highly diastereoselective Grignard addition reactions of phenylmagnesium bromide on the chiral aldehydes (*S*)-α-methylserinal **1** and (*R*)-α-methylserinal **7**. In this way, the oxazolidine ring of chiral building blocks (*S*)-**1** and (*R*)-**7** has been exploited as the precursor of the amino acid moiety and, moreover, as the chiral auxiliary to create another new stereogenic centre in the asymmetric reactions. The extension of this methodology to new asymmetric reactions is in progress.

3. Experimental

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and in CD_3OD and D_2O with TMS as the external standard using a coaxial microtube (chemical shifts are reported in ppm on the δ scale, coupling constants in hertz). 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, proton–proton COSY experiments and proton–carbon HETCOR experiments. Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter in an 1 dm cell of 1 mL capacity. Microanalyses were carried out on a CE Instruments EA-1110 analyser and were in good agreement with the calculated values. IR spectra were recorded on a Perkin–Elmer FT-IR spectrum 1000 spectrometer. Mass spectra were obtained by one of the following ionization techniques: electron impact (EI) or electrospray ionization (ESI) on a Hewlett–Packard 5989B mass spectrometer.

*3.1. (*S*)-*N*-(tert-Butoxycarbonyl)-4-[(*R*)-1′-phenylcarbinol]-2,2,4-trimethyl-3-oxazolidine* anti-*2*

To a precooled solution of **1** (1.06 g, 4.4 mmol) in THF (25 mL) at –78°C was added dropwise a 3 M solution of phenylmagnesium bromide (5.8 mL, 17.4 mmol) in THF over 5 min. The

resultant yellow solution was stirred for an additional 3 h at –78°C and then warmed to 0°C over 10 min. The reaction mixture was then diluted with diethyl ether (150 mL) and quenched with saturated NH_4Cl solution (50 mL). The organic layer was washed with a saturated NaCl (50 mL), dried (Na_2SO_4) and concentrated to give a pale yellow oil, which was purified by column chromatography (hexane/ethyl acetate, 4/1) to give *anti*-**2** (1.27 g, 90%) as a colourless oil. $[\alpha]_D^{25} = -35.6$ (*c* 0.40, MeOH); ^{1}H NMR ($CDCl_3$): δ 0.85 (s, 3H, CH_3), 1.34–1.73 (m, 15H, $(CH_3)_2C$, $(CH_3)_3CO$), 3.58–3.72 (m, 1H, CH_2), 4.03–4.15 (m, 1H, CH_2), 4.68–4.81 (m, 1H, C*H*Ph), 5.70–5.85 (m, 1H, OH), 7.20–7.40 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 21.8 ($(CH_3)_2C$), 24.5 ($C(CH_3)N$), 26.5 ($(CH_3)_2C$), 28.4 ($(CH_3)_3CO$), 67.4 ($C(CH_3)N$), 72.0 (CH_2), 78.1 ($(CH_3)_3CO$), 81.1 (*C*HPh), 95.6 ($(CH_3)_2C$), 127.5, 127.6, 127.8, 141.1 (Ph), 154.0 (CO); IR (CH_2Cl_2) 3325 (OH), 1685, 1655 (CO); MS (EI) (m/z) = 41, 57, 77; ESI$^+$ (m/z) = 322. Anal. calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.62; H, 8.35; N, 4.40.

Starting from entry 7 of Table 1 and after column chromatography of the crude reaction, an analytical sample of diastereomer *syn*-**2** could be achieved to characterize it. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.43–1.65 (m, 15H, $(CH_3)_2C$, $(CH_3)_3CO$), 3.24 (d, 1H, J = 9.9 Hz, CH_2), 3.94 (d, 1H, J = 9.9 Hz, CH_2), 5.02 (s, 1H, C*H*Ph), 5.43 (brs, 1H, OH), 7.24–7.47 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 17.7 ($(CH_3)_2C$), 25.9 ($C(CH_3)N$), 26.3 ($(CH_3)_2C$), 28.4 ($(CH_3)_3CO$), 67.6 ($C(CH_3)N$), 71.3 (CH_2), 78.9 ($(CH_3)_3CO$), 81.2 (*C*HPh), 95.6 ($(CH_3)_2C$), 127.7, 127.8, 127.9, 140.9 (Ph), 154.1 (CO); IR (CH_2Cl_2) 3325 (OH), 1685, 1655 (CO).

3.2. (1R,7aS)-1-Phenyl-5,5,7a-trimethyl-2,6-dioxa-4-azapentalen-3-one **3**

To a solution of *anti*-**2** (400 mg, 1.24 mmol) in DMF (25 mL) at 0 °C was added NaH (33 mg, 1.38 mmol). The resulting suspension was stirred at 0°C for 5 h before being quenched at 0°C with H_2O (20 mL). The resulting mixture was concentrated to obtain a pale yellow solid, which was washed with ethyl acetate (4×25 mL). After drying (Na_2SO_4) and evaporation of the solvent, the crude residue was purified by column chromatography (hexane/ethyl acetate, 4/1) to give **3** (260 mg, 85%) as a white solid. Mp: 102–103°C; $[\alpha]_D^{25} = -79.2$ (*c* 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.54 (s, 3H, $(CH_3)_2C$), 1.60 (s, 3H, CH_3), 1.72 (s, 3H, $(CH_3)_2C$), 3.10 (d, 1H, J = 9.0 Hz, CH_2), 3.29 (d, 1H, J = 9.0 Hz, CH_2), 5.32 (s, 1H, C*H*Ph), 7.20–7.45 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 23.3 (CH_3), 27.7, 28.7 ($(CH_3)_2C$), 69.8 ($C(CH_3)N$), 70.6 (CH_2), 82.3 (*C*HPh), 94.9 ($(CH_3)_2C$), 124.3, 128.8, 129.0, 136.0 (Ph), 156.1 (CO); IR (CH_2Cl_2) 1758 (CO); MS (EI) (m/z) = 42, 83, 105, 115, 207; ESI$^+$ (m/z) = 248. Anal. calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.27; H, 6.86; N, 5.63.

3.3. (2R,3R)-2-Amino-3-hydroxy-2-methyl-3-phenylpropanoic acid **4**

Method A: Compound **3** (200 mg, 0.81 mmol) was treated with boron trifluoride–acetic acid (2.3 g, 12.2 mmol) in MeOH (10 mL) at 0°C. The reaction was warmed and stirred at rt for 5 h before being quenched by slow addition of $NaHCO_3$ at 0°C. The resulting suspension was stirred for 20 min at rt and then concentrated to give a white solid, which was washed with ethyl acetate (4×20 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a crude residue, which was purified by column chromatography (hexane/ethyl acetate, 3/7) to give the (4*S*,5*R*)-4-(hydroxymethyl)-4-methyl-5-phenyl-3-oxazolidin-2-one (151 mg, 90%) as a white solid, which was used without further purification.

Method B: To a solution of **3** (200 mg, 0.81 mmol) in THF (10 mL) was added aqueous 6 M HCl (5 mL). After being stirred at rt for 2 h, the solvent was removed to give (4*S*,5*R*)-4-(hydroxymethyl)-4-methyl-5-phenyl-3-oxazolidin-2-one (167 mg, 100%) as a white solid, which was used without further purification. Mp: 103–104 °C; $[\alpha]_D^{25} = -98.7$ (*c* 0.52, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 3H, CH_3), 2.97 (d, 1H, $J = 11.4$ Hz, CH_2), 3.25 (d, 1H, $J = 11.4$ Hz, CH_2), 3.47 (brs, 1H, OH), 5.34 (s, 1H, C*H*Ph), 6.90 (s, 1H, NH), 7.35 (s, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 22.1 (CH_3), 62.6 (*C*(CH_3)N), 65.6 (CH_2), 86.5 (*C*HPh), 125.8, 128.5, 128.8, 133.3 (Ph), 159.6 (CO); IR (CH_2Cl_2) 3616 (OH), 3435 (NH), 1766 (CO); ESI$^+$ (m/z) = 208.

To a solution of (4*S*,5*R*)-4-(hydroxymethyl)-4-methyl-5-phenyl-3-oxazolidin-2-one (200 mg, 0.96 mmol) in acetone (10 mL), at 0°C, was added 1.5-fold excess of Jones reagent dropwise over 5 min. The mixture was stirred at 0°C for 1 h and then at rt for 4 h. The excess of Jones reagent was destroyed with 2-propanol. The mixture was then partitioned between brine (10 mL) and ethyl acetate (30 mL). The aqueous phase was extracted several times with ethyl acetate (4×20 mL). The organic phases were combined, dried (Na_2SO_4) and concentrated. The resulting white solid (184 mg) was dissolved in aqueous 6 M HCl (5 mL) and heated at 100°C for 12 h. The solution was then concentrated to give 2-amino-3-hydroxy-2-methyl-3-phenylpropanoic acid hydrochloride as a white solid (190 mg). This compound was dissolved in 4 mL of EtOH/propylene oxide (3/1) and the mixture was heated under reflux for 2 h. After this time, the amino acid partially precipitated as a white solid (60 mg). The filtrate was concentrated, the residue dissolved in distilled water and eluted through a C_{18} reverse-phase Sep-pak cartridge to give, after removal of the water, 73 mg of **4** as a white solid. Total amount: 133 mg (70%). $[\alpha]_D^{25} = -12.1$ (*c* 0.36, H_2O); ^{1}H NMR (D_2O): δ 1.58 (s, 3H, CH_3), 5.03 (s, 1H, C*H*Ph), 7.28–7.45 (m, 5H, Ph); ^{13}C NMR (D_2O): δ 20.0 (CH_3), 66.0 (*C*(CH_3)N), 74.7 (*C*HPh), 126.8, 128.7, 128.8, 137.6 (Ph), 174.4 (CO); ESI$^+$ (m/z) = 196; Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.71; H, 6.68; N, 7.14.

3.4. (1S,7aS)-1-Phenyl-5,5,7a-trimethyl-2,6-dioxa-4-azapentalen-3-one **5**

Triflic anhydride (289 μL, 1.71 mmol) was added to a solution of *anti*-**2** (460 mg, 1.43 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (700 mg, 3.41 mmol) in CH_2Cl_2 (20 mL) at 0°C. After stirring for 5 min at 0°C, the resultant white precipitate was filtered and the organic phases washed with a 5% aqueous solution of $NaHCO_3$ (10 mL) before being dried (Na_2SO_4) and concentrated to give a yellow oil, which was purified by chromatography (hexane/ethyl acetate, 4/1) to give **5** (235 mg, 66%) as a white solid. Mp: 84–85°C; $[\alpha]_D^{25} = +84.5$ (*c* 1.05, MeOH); ^{1}H NMR ($CDCl_3$): δ 0.94 (s, 3H, CH_3), 1.46 (s, 3H, $(CH_3)_2C$), 1.66 (s, 3H, $(CH_3)_2C$), 3.80 (d, 1H, $J = 8.7$ Hz, CH_2), 3.97 (d, 1H, $J = 8.7$ Hz, CH_2), 5.39 (s, 1H, C*H*Ph), 7.17–7.38 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 22.0 (CH_3), 23.8, 27.7 ($(CH_3)_2C$), 69.7 (*C*(CH_3)N), 74.1 (CH_2), 85.0 (*C*HPh), 94.6 ($(CH_3)_2C$), 125.5, 128.5, 128.6, 134.4 (Ph), 155.8 (CO); IR (CH_2Cl_2) 1762 (CO); MS (EI) (m/z) = 42, 83, 105, 115, 247; ESI$^+$ (m/z) = 248. Anal. calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.23; H, 6.90; N, 5.62.

3.5. (2R,3S)-2-Amino-3-hydroxy-2-methyl-3-phenylpropanoic acid **6**

Treatment of **5** (260 mg, 1.05 mmol) with boron trifluoride–acetic acid (2.82 g, 15.0 mmol) in MeOH (10 mL) at rt, according to the procedure described for compound (4*S*,5*R*)-4-(hydroxy-

methyl)-4-methyl-5-phenyl-3-oxazolidin-2-one, afforded (4*S*,5*S*)-4-(hydroxymethyl)-4-methyl-5-phenyl-3-oxazolidin-2-one (196 mg, 90%) as a white solid, which was used without further purification. Mp: 118–119°C; $[\alpha]_D^{25}=+16.5$ (*c* 0.40, MeOH); ^{1}H NMR (CD_3OD): δ 0.73 (s, 3H, CH_3), 3.54 (d, 1H, $J=11.6$ Hz, CH_2), 3.60 (d, 1H, $J=11.6$ Hz, CH_2), 5.56 (s, 1H, C*H*Ph), 7.27–7.45 (m, 5H, Ph); ^{13}C NMR (CD_3OD): δ 20.1 (CH_3), 63.7 (*C*(CH_3)N), 68.5 (CH_2), 83.7 (*C*HPh), 127.2, 129.5, 129.6, 137.7 (Ph), 161.2 (CO); IR (CH_2Cl_2) 3616 (OH), 3436 (NH), 1764 (CO); ESI$^+$ (m/z) = 208.

In a similar way to that described for compound **4**, compound **6** (138 mg, 73%) was obtained from (4*S*,5*S*)-4-(hydroxymethyl)-4-methyl-5-phenyl-3-oxazolidin-2-one (200 mg, 0.96 mmol). $[\alpha]_D^{25}=+33.0$ (*c* 0.35, H_2O). ^{1}H NMR (D_2O): δ 1.27 (s, 3H, CH_3), 5.12 (s, 1H, C*H*Ph), 7.38–7.50 (m, 5H, Ph); ^{13}C NMR (D_2O): δ 18.7 (CH_3), 65.1 (*C*(CH_3)N), 75.0 (*C*HPh), 127.3, 128.7, 128.9, 137.3 (Ph), 175.5 (CO); ESI$^+$ (m/z) = 196. Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.35; H, 6.66; N, 7.08.

3.6. (R)-N-(tert-*Butoxycarbonyl*)-4-[(S)-1′-*phenylcarbinol*]-2,2,4-trimethyl-3-oxazolidine anti-**8**

In a similar way to that described for its enantiomer *anti*-**2**, compound *anti*-**8** (1.27 g, 90%) was obtained from aldehyde **7** (1.06 g, 4.4 mmol). $[\alpha]_D^{25}=+36.0$ (*c* 0.41, MeOH). Anal. calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.36; H, 8.39; N, 4.30.

Using the same conditions as in entry 7 of Table 1, but starting from aldehyde **7** and after column chromatography of the crude reaction, an analytical sample of diastereomer *syn*-**8** could be achieved to characterize it, and the NMR spectra showed it to be identical to its enantiomer *syn*-**2**.

3.7. (1S,7aR)-1-Phenyl-5,5,7a-trimethyl-2,6-dioxa-4-azapentalen-3-one **9**

In a similar way to that described for its enantiomer **3**, compound **9** (260 mg, 85%) was obtained from compound *anti*-**8** (400 mg, 1.24 mmol). $[\alpha]_D^{25}=+79.7$ (*c* 0.52, $CHCl_3$). Anal. calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.42; H, 7.01; N, 5.69.

3.8. (2S,3S)-2-Amino-3-hydroxy-2-methyl-3-phenylpropanoic acid **10**

In a similar way to that described for its enantiomer (4*S*,5*R*)-4-(hydroxymethyl)-4-methyl-5-phenyl-3-oxazolidin-2-one, compound (4*R*,5*S*)-4-(hydroxymethyl)-4-methyl-5-phenyl-3-oxazolidin-2-one (151 mg, 90%) was obtained from compound **9** (200 mg, 0.81 mmol). $[\alpha]_D^{25}=+94.8$ (*c* 0.53, MeOH).

In a similar way to that described for its enantiomer **4**, compound **10** (133 mg, 70%) was obtained from compound (4*R*,5*S*)-4-(hydroxymethyl)-4-methyl-5-phenyl-3-oxazolidin-2-one (200 mg, 0.96 mmol). $[\alpha]_D^{25}=+12.6$ (*c* 0.36, H_2O). Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.40; H, 6.74; N, 7.19.

3.9. (1R,7aR)-1-Phenyl-5,5,7a-trimethyl-2,6-dioxa-4-azapentalen-3-one **11**

In a similar way to that described for its enantiomer **5**, compound **11** (235 mg, 66%) was obtained from compound *anti*-**8** (460 mg, 1.43 mmol). $[\alpha]_D^{25}=-84.2$ (*c* 1.05, $CHCl_3$). Anal. calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.36; H, 6.89; N, 5.68.

3.10. (2S,3R)-2-Amino-3-hydroxy-2-methyl-3-phenylpropanoic acid **12**

In a similar way to that described for its enantiomer (4*S*,5*S*)-4-(hydroxymethyl)-4-methyl-5-phenyl-3-oxazolidin-2-one, compound (4*R*,5*R*)-4-(hydroxymethyl)-4-methyl-5-phenyl-3-oxazolidin-2-one (190 mg, 90%) was obtained from compound **11** (260 mg, 1.05 mmol). $[\alpha]_D^{25} = -16.3$ (*c* 0.40, MeOH).

In a similar way to that described for its enantiomer **6**, compound **12** (138 mg, 73%) was obtained from compound (4*R*,5*R*)-4-(hydroxymethyl)-4-methyl-5-phenyl-3-oxazolidin-2-one (200 mg, 0.96 mmol). $[\alpha]_D^{25} = -35.6$ (*c* 0.35, H_2O). Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.12; H, 6.75; N, 7.20.

3.11. Methyl (2R,3R)-2-amino-3-hydroxy-2-methyl-3-phenylpropanoate **13**

Acetyl chloride (5 mL, 70.3 mmol) was added dropwise to MeOH (10 mL) at 0°C. After stirring for 10 min, the solid amino acid **4** (40 mg, 0.20 mmol) was added and the resulting solution was stirred for 1 h at rt and additional 24 h at reflux. The solvent was removed to give a residue corresponding to the methyl ester hydrochloride derivative. In order to obtain the free amino ester **13**, this crude residue was treated with 3-aminopropyl functionalized silica gel (0.44 g) in MeOH (10 mL). After stirring the mixture for 2 h at reflux, the silica gel was removed by filtration and the solution was concentrated to give 25 mg of a yellow oil, which was purified by column chromatography (CH_2Cl_2/MeOH, 95/5) to give a white solid corresponding to compound **13** (15 mg, 36%). $[\alpha]_D^{25} = +3.7$ (*c* 0.47, $CHCl_3$) (lit.[10] $[\alpha]_D^{25} = +5.0$ (*c* 0.68, $CHCl_3$)). Anal. calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 64.07; H, 7.30; N, 6.77. Spectral data were identical to those reported in the literature (Ref. 9c).

3.12. Methyl (2R,3S)-2-amino-3-hydroxy-2-methyl-3-phenylpropanoate **14**

In a similar way to that described for its diastereomer **13**, compound **14** (13 mg, 31%) was obtained from compound **6** (38 mg, 0.194 mmol). $[\alpha]_D^{25} = -10.9$ (*c* 0.44, $CHCl_3$). Anal. calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 64.12; H, 7.33; N, 6.75. Spectral data were identical to those reported in the literature (Ref. 9c).

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