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A concise synthesis of (*R*)- and (*S*)-α-alkyl isoserines from D- and L-malic acids

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Abstract—A simple and diastereoselective method for the synthesis of (*R*)- and (*S*)-α-alkyl isoserines has been developed in four steps starting from commercially available D- and L-malic acid, respectively. This approach features stereocontrolled alkylation of 2-(2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl)acetic acid and proceeds through a methylcarbamate via a Curtius rearrangement.

1. Introduction

Non-proteinogenic α-hydroxy-β-amino acids (isoserine derivatives) are probably the most important members of the β-amino acid family. They are an essential moiety of a large number of well-known naturally occurring products, which are endowed with a powerful biological activity.[1] The most striking examples are those incorporated into many biologically active peptides, such as bestatin,[2] amatatin,[3] norstatine[4] and taxol.[5] When incorporated into peptides their conformational restraints induce a large variety of stable secondary structures[6] and tertiary structures,[7] and these β-peptides are capable of adopting stable helical, turn and sheet conformations in solution.[8] These conformational properties of β-peptides depend on the main chain torsional angles θ of the β-amino acid units, as depicted in Figure 1.[9]

(*R*)-**1** (*S*)-**1**

Figure 1.

Moreover, the synthesis of the constrained analogues of the active compounds is a common procedure adopted in medicinal chemistry to restrict possible low energy conformations.[10] For example, 2′-methyl taxoids, the analogues of *paclitaxel* and *docetaxel* (Fig. 2), with an additional methyl substituent at the 2′-position should create some additional torsional strain associated with rotation.[11] These constrained analogues display a higher cytotoxic activity, probably due to a reduction in the degree of freedom of rotation at the C'_2–C'_3 bond or of some additional hydrophobic interactions between the 2′-methyl and the microtubule binding sites.[12] With this in mind, α-substituted isoserine is of great interest since the presence of an alkyl substituted at the 2-position favors a gauche conformation about the torsion angle.[13]

Many procedures have been developed to synthesize β-substituted isoserines in optically active forms,[14] but little attention has been paid to the synthesis of chiral α-substituted isoserines. Only three papers have reported the synthesis of enantiomerically pure α-methyl isoserine.[15] Herein, a concise and efficient method is reported for the synthesis of enantiomerically pure α-alkyl isoserines (*R*)-**1** and (*S*)-**1**.

2. Results and discussion

Our protocol utilizes Seebach's 'self-regeneration of stereocenters (SRS)' synthetic principle[16] to build the new stereocenter. The shortest route to enantiomerically pure α-alkyl isoserines was developed in four steps from D- and L-malic acids. First, dioxolanone acids (2*R*,4*R*)-**4** were obtained

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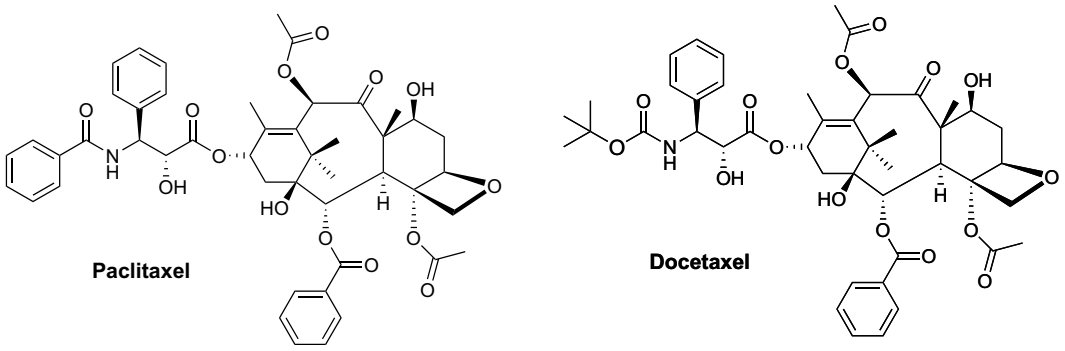
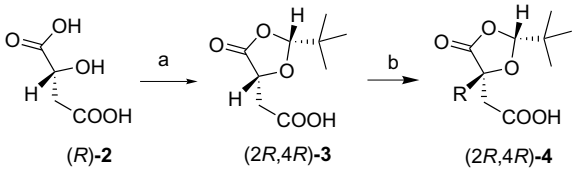


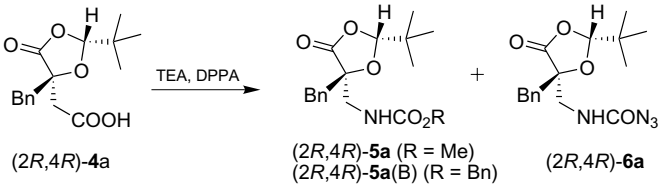
Figure 2.

with good yields and excellent diastereoselectivities (de >98%) starting from D-malic acid (*R*)-**2** (Scheme 1).[17]



Scheme 1. Reagents and conditions: (a) pivaldehyde, *p*-toluenesulfonic acid and concd H_2SO_4, pentane, reflux, 36 h, 98%; (b) (i) LHMDS, THF, −78 °C, 5 min; (ii) RX, THF, −78 °C, 30 min then warm up to −23 °C, 6 h (RX = EtI, additional 10 h at −5 °C); (iii) quenched with 1 M HCl; **4a**: R = benzyl, 81%, **4b**: R = ethyl, 63%, **4c**: R = allyl, 79%, **4d**: R = methyl, 80%.

With the dioxolanone acids (2*R*,4*R*)-**4** in hand, we attempted to convert the carboxylic acid into the carbamate (2*R*,4*R*)-**5** via Curtius rearrangement. This approach failed to give the desired products (2*R*,4*R*)-**5** but an unidentified mixture produced in our case according to the conditions used for the classic Curtius rearrangement procedure.[18–20] This might be due to the rapid Curtius rearrangement of acyl azide followed by trapping of the active intermediate isocyanate by N_3^-, H_2O and other nucleophiles. To solve this problem, we treated (2*R*,4*R*)-**4a** with triethylamine and diphenylphosphoryl azide (DPPA) to produce the intermediate isocyanate, which was then trapped by the alcohol to give the desired carbamate (2*R*,4*R*)-**5** in a moderate chemical yield (Scheme 2). In order to improve the chemical yield, we explored different conditions for the Curtius rearrangement and the results are summarized in Table 1.



Scheme 2.

It was found that the low yields were given by treatment of (2*R*,4*R*)-**4** with triethylamine and DPPA in ROH without another solvent (Table 1, entries 1–4). Interestingly, carbamoyl azide (2*R*,4*R*)-**6** was obtained as the major product when *t*-BuOH was used (entries 3 and 4), which provided a good way to synthesize carbamoyl azide. Fortunately, when a mixture of (2*R*,4*R*)-**4a**, triethylamine and DPPA was stirred in either benzene or toluene at room temperature for 1 h prior to the addition of the alcohol, the yields were improved significantly with toluene being a better choice than benzene (entries 5 and 6). When we changed the amount of TEA from 1.5 to 2 and 3 equiv, it was found that 2 equiv of TEA gave the best yield (entries 6–8).

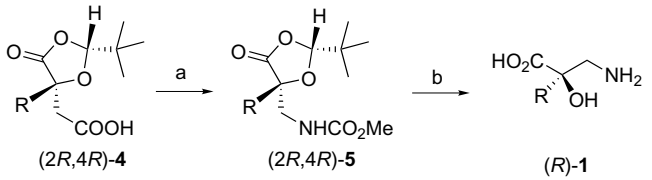
Table 1. Optimizing experimental conditions for the Curtius rearrangement of acids (*R*)-**4a**[a]

Entry	TEA (equiv)	DPPA (equiv)	Conditions[b]	Product[c]	Yield[d] (%)
1	1.0	1.0	BnOH (1 equiv), refluxed 24 h	**5a**(B)	48[e]
2	1.0	1.0	MeOH (5 equiv), refluxed 10 h	**5a**	59
3	1.0	1.0	*t*-BuOH (5 equiv), refluxed 24 h	**6a**	42
4	2.2	2.0	*t*-BuOH (5 equiv), refluxed 24 h	**6a**	76
5	1.5	1.0	Benzene, rt, 1 h, MeOH, reflux 16 h	**5a**	67
6	1.5	1.0	Toluene, rt, 1 h, MeOH, reflux 16 h	**5a**	77
7	2.0	1.0	Toluene, rt, 1 h, MeOH reflux 16 h	**5a**	86
8	3.0	1.0	Toluene, rt, 1 h, MeOH reflux 16 h	**5a**	82
9	2.0	1.5	Toluene, rt, 1 h, MeOH reflux 16 h	**5a**	85

[a] Each reaction was carried out under an argon atmosphere and solvents were dried via a standard method.
[b] Entries 5–9: MeOH (5 equiv).
[c] (2*R*,4*R*)-**6a** = **6a**, (2*R*,4*R*)-**5a** = **5a**, (2*R*,4*R*)-**5a**(B) = **5a**(B).
[d] Isolated yield based on **4**.
[e] It proved difficult to separate **5a**(B) from BnOH.

However, increasing the amount of DPPA to 1.5 equiv led to a slightly decreased yield (entry 9).

Using the optimized reaction conditions of entry 7 in Table 1, 4-alkyl carbamate (2*R*,4*R*)-**5** can also be obtained in good yields. Deprotection of the acetal and carbamate using 6 M HCl in a sealed tube at 110–120 °C afforded (*R*)-α-alkyl isoserine as its hydrochloride salt, which was finally transformed into the free β-amino acid (*R*)-**1** by interaction with propylene oxide under reflux in EtOH, (four steps, 51–66% from D-malic acid, 98% ee) (Scheme 3).



Scheme 3. Reagents and conditions: (a) TEA, DPPA, toluene, rt, 1 h then MeOH, reflux, 16 h, **4a**: R = benzyl, 86%, **4b**: R = ethyl, 86%, **4c**: R = allyl, 84%, **4d**: R = methyl, 82%; (b) (i) 6 M HCl, sealed tube, 110–120 °C, 11 h; (ii) propylene oxide, EtOH, reflux, 1 h, **1a**: 94%, **1b**: 96%, **1c**: 95%, **1d**: 96%.

The enantiomers, α-alkyl isoserine (*S*)-**1**, were obtained following the same strategy starting from L-malic acid.

3. Conclusions

We have developed an efficient four-step protocol for the synthesis of optically active α-alkyl-α-hydroxy-β-amino acids starting from the commercially available D- or L-malic acid in a good overall yield (51–66%) and an excellent stereoselectivity (98% de). This approach features the stereocontrolled alkylation of 2-(2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl) acetic acid in the second step, which was the key step to build the stereocenter of (*R*)-**1** and (*S*)-**1**. α-Alkyl isoserines (*R*)-**1** and (*S*)-**1** were successfully obtained via a modified Curtius rearrangement in the third step. The application of this new method in the stereoselective synthesis of 2,3-dialkyl substituted isoserines is being investigated and will be reported in due course.

4. Experimental

4.1. General procedures

All reactions were carried out under an argon atmosphere and the solvents were purified according to the established procedures. Reactions were monitored by thin layer chromatography (TLC). Column chromatography purifications were carried out using silica gel (200–400 mesh). Melting points were recorded on an X-4 melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-300 and 400 MHz, and Varian Inova-500 MHz spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and in D_2O (chemical shifts are reported in ppm on the δ scale, coupling constants in hertz). IR spectra were obtained on a Nicolet 170 SX FT-IR. Optical rotations were recorded on a Perkin–Elmer Model 341 polarimeter. HR-MS spectra were measured with a FT-MS Bruker Apex II mass spectrometer.

4.2. 2-((2*R*,4*R*)-2-*tert*-Butyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (2*R*,4*R*)-3

To a solution of pivalaldehyde (20 g, 232 mmol) in pentane (300 mL) were added *p*-toluensufonic acid (2 g), concentrated sulfuric acid (three drops), and D-malic acid (20 g, 150 mmol). The reaction mixture was stirred under reflux for 36 h, and then cooled to room temperature. The resulting suspension was filtered. The filter cake was dissolved in CH_2Cl_2 (200 mL) and washed twice with 20 mL of 8% aqueous phosphoric acid. The solution was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a white solid. Yield 29.7 g (98%); mp 104–106 °C; $[\alpha]_D^{22} = +2.2$ (*c* 1.2, $CHCl_3$). IR (cm^{-1}): 3292 (br), 2968 (br), 1786 (s), 1741 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.67 (1H, octet, $J = 1.5$, 3.5, 7.5 Hz), 3.02 (1H, dd, $J = 3.5$, 17 Hz), 2.84 (1H, dd, $J = 7.5$, 17 Hz), 0.99 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.90, 172.11, 109.88, 71.40, 34.23, 23.40.

4.3. 2-((2*S*,4*S*)-2-*tert*-Butyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (2*S*,4*S*)-3

As described for enantiomer (2*R*,4*R*)-**3**, compound (2*S*,4*S*)-**3** (29.7 g, 98%) was obtained from L-malic acid (20 g, 150 mmol); mp 104–106 °C; $[\alpha]_D^{22} = -2.3$ (*c* 1.5, $CHCl_3$). IR (cm^{-1}): 3292 (br), 2968 (br), 1788 (s), 1742 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.67 (1H, octet, $J = 1.5$, 3.5, 7.5 Hz), 3.02 (1H, dd, $J = 3.5$, 17 Hz), 2.84 (1H, dd, $J = 7.5$, 17 Hz), 0.99 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.90, 172.11, 109.88, 71.40, 34.23, 23.40.

4.4. 2-((2*R*,4*R*)-2-*tert*-Butyl-4-alkyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (2*R*,4*R*)-4a–d

General procedure for the reaction of the enolate from the dioxolanone (2*R*,4*R*)-**3** with various RX: Under argon, LHMDS (2.0 mmol, in 2 mL dry THF) was added to a solution of (2*R*,4*R*)-**3** (202 mg, 1.0 mmol) in 8 mL dry THF at −78 °C. After 5 min at −78 °C, the RX (1.5 mmol, in 2 mL dry THF) was added and the reaction mixture was stirred at this temperature for 30 min, then the temperature was allowed to warm up to −23 °C over a period of 6 h (RX = EtI, additional 10 h at −5 °C). The reaction was quenched with 1 M aqueous HCl (4 mL). The mixture was then extracted twice with 15 mL ether. The organic layer was washed with brine, and water to pH 2, dried over $MgSO_4$, and concentrated under vacuum. The pure product was obtained by column chromatography (petroleum ether/ethyl acetate, 8:1–1:1) in a good yield.

4.4.1. 2-((2*R*,4*R*)-2-*tert*-Butyl-4-benzyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (2*R*,4*R*)-4a. Yield: 81%, 236 mg; mp 134–136 °C; $[\alpha]_D^{22} = -64.2$ (*c* 1.0, $CHCl_3$). IR (cm^{-1}): 2926, 1795 (s), 1702 (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24–7.34 (m,

5H), 4.61 (s, 1H), 3.21 (d, 1H, $J = 14$ Hz), 3.03 (d, 1H, $J = 14$ Hz), 2.91 (q, 1H, $J = 16$ Hz), 2.77 (d, 1H, $J = 16$ Hz), 0.89 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.31, 133.70, 130.37, 128.67, 127.67, 108.73, 80.78, 40.13, 40.02, 34.24, 23.47. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.64; H, 6.83.

4.4.2. 2-((2*R*,4*R*)-2-*tert*-Butyl-4-ethyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (2*R*,4*R*)-4b. Yield: 63%, 145 mg; mp 90–92 °C; $[\alpha]_D^{22} = -29.9$ (c 1.0, $CHCl_3$). IR (cm^{-1}): 3301, 2795, 1780 (s), 1743 (s); ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 5.20 (s, 1H), 2.89 (d, 1H, $J = 16$ Hz), 2.85 (d, 1H, $J = 16$ Hz), 1.90 (q, 2H, $J = 7.5$ Hz), 1.07 (t, 3H, $J = 7.5$ Hz), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.62, 173.90, 108.29, 80.37, 38.90, 34.36, 26.69, 23.55, 7.73. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.55; H, 7.45.

4.4.3. 2-((2*R*,4*R*)-2-*tert*-Butyl-4-allyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (2*R*,4*R*)-4c. Yield: 79%, 191 mg; oil; $[\alpha]_D^{22} = -65.2$ (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.73–5.82 (m, 1H), 5.19–5.24 (m, 3H), 2.82 (s, 2H), 2.54 (d, $J = 6.3$ Hz, 2H), 0.91 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4, 173.4, 129.9, 121.2, 108.3, 79.7, 39.4, 38.0, 34.2, 23.5.

4.4.4. 2-((2*R*,4*R*)-2-*tert*-Butyl-4-methyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (2*R*,4*R*)-4d. Yield: 80%, 173 mg; mp 136–138 °C; $[\alpha]_D^{22} = -21.2$ (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.16 (s, 1H), 2.94 (d, 1H, $J = 16.5$ Hz), 2.81 (d, 1H, $J = 16.5$ Hz), 1.47 (s, 3H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 174.2, 107.6, 41.2, 34.2, 23.6, 19.6.

4.5. 2-((2*S*,4*S*)-2-*tert*-Butyl-4-alkyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (2*S*,4*S*)-4a–d

As described for enantiomers (2*R*,4*R*)-**4a**–**d**, compounds (2*S*,4*S*)-**4a**–**d** were obtained from dioxolanone (2*S*,4*S*)-**3**.

4.6. Methyl ((2*R*,4*R*)-2-*tert*-Butyl-4-alkyl-5-oxo-1,3-dioxolan-4-yl)carbamate (2*R*,4*R*)-5a–d

Under argon, a solution of 2-((2*R*,4*R*)-2-*tert*-butyl-4-alkyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (2*R*,4*R*)-**4** (2 mmol), diphenyl phosphoryl azide (0.44 mL, 2 mmol), and triethylamine (0.56 mL, 4 mmol) in dry toluene (4.0 mL) was stirred at room temperature for 1 h. MeOH (10 mmol) was then added. After the mixture was stirred at reflux for 16 h, the solvent was removed under reduced pressure to give the crude product as a pale yellow oil. The pure product was obtained by column chromatography (petroleum ether/ethyl acetate, 20:1–2:1) in good yield.

4.6.1. Methyl ((2*R*,4*R*)-2-*tert*-butyl-4-benzyl-5-oxo-1,3-dioxolan-4-yl)carbamate (2*R*,4*R*)-5a. Yield: 85%, 546 mg; $[\alpha]_D^{17} = -30.0$ (c 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.30 (m, 5H), 5.02 (br, 1H), 4.23 (s, 1H), 3.67 (s, 3H), 3.59 (d, 2H, $J = 6.3$ Hz), 3.15 (d, 1H, $J = 14$ Hz), 2.98 (d, 1H, $J = 14$ Hz), 0.82 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.75, 156.86, 133.86, 130.13, 128.65, 127.55, 109.33, 83.46, 52.38, 45.76, 39.21, 34.25, 23.18. HRMS (m/z): Calcd for $C_{17}H_{23}NO_5$: $[M+Na]^+$ 344.1468. Found: $[M+Na]^+$ 344.1464.

4.6.2. Methyl ((2*R*,4*R*)-2-*tert*-butyl-4-ethyl-5-oxo-1,3-dioxolan-4-yl)methylcarbamate (2*R*,4*R*)-5b. Yield: 426 mg, 82%. $[\alpha]_D^{17} = -18.1$ (c 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.16 (s, 1H), 5.04 (br, 1H), 3.65 (s, 3H), 3.47–3.50 (t, 2H, $J = 5.6$ Hz), 1.73–1.80 (dq, 2H, $J = 7.2$, 2.4 Hz), 0.98 (t, 3H, $J = 7.2$ Hz), 0.88 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.88, 156.81, 108.79, 82.69, 52.20, 44.20, 34.46, 26.10, 23.26, 7.70. HRMS (m/z): Calcd for $C_{12}H_{21}NO_5$: $[M+NH_4]^+$ 277.1758. Found: $[M+NH_4]^+$ 277.1756.

4.6.3. Methyl ((2*R*,4*R*)-2-*tert*-butyl-4-allyl-5-oxo-1,3-dioxolan-4-yl)carbamate (2*R*,4*R*)-5c. Yield: 81%, 440 mg. $[\alpha]_D^{17} = -26.0$ (c 1.3, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (m, H), 5.21–5.27 (m, 3H), 4.96 (br, 1H), 3.65 (s, 3H), 3.55 (q, 2H, $J = 3.9$ Hz), 2.53 (q, 2H, $J = 4.5$ Hz), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.44, 156.83, 130.04, 121.08, 108.96, 82.34, 52.37, 44.89, 37.15, 34.52, 23.35. HRMS (m/z): Calcd for $C_{13}H_{21}NO_5$: $[M+NH_4]^+$ 289.1756 Found: $[M+NH_4]^+$ 289.1754.

4.6.4. ((2*R*,4*R*)-2-*tert*-Butyl-4-methyl-5-oxo-1,3-dioxolan-4-yl)carbamate (2*R*,4*R*)-5d. Yield: 435 mg, 88%; $[\alpha]_D^{17} = -9.3$ (c 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17 (s, 1H), 5.02 (s, 1H), 3.66 (s, 3H), 3.50–3.54 (t, 2H, $J = 6.6$ Hz), 1.38 (s, 1H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.12, 156.87, 107.63, 79.90, 52.29, 54.74, 35.20, 23.33, and 17.23. HRMS (m/z): Calcd for $C_{11}H_{19}NO_5$: $[M+NH_4]^+$ 263.1601. Found: $[M+NH_4]^+$ 263.1597.

4.7. Methyl ((2*S*,4*S*)-2-*tert*-butyl-4-alkyl-5-oxo-1,3-dioxolan-4-yl)carbamate (2*S*,4*S*)-5a–d

As described for enantiomers (2*R*,4*R*)-**5a**–**d**, compounds (2*S*,4*S*)-**5a**–**d** were obtained from compounds (2*S*,4*S*)-**4a**–**d**.

4.8. Azido-*N*-(((2*R*,4*R*)-4-benzyl-2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl)methyl)formamide (2*R*,4*R*)-6a

Under argon, a solution of 2-((2*R*,4*R*)-2-*tert*-butyl-4-benzyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (2*R*,4*R*)-**4a** (290 mg, 1 mmol), diphenylphosphoryl azide (0.404 mL, 2 mmol), and triethylamine (0.28 mL, 2 mmol) in dry toluene (2.0 mL) was stirred at room temperature for 1 h. *t*-BuOH (5 mmol) was then added. After the mixture was stirred at reflux for 24 h, the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL), washed with brine, saturated Na_2CO_3 solution, and water, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 20:1–2:1) to give (2*R*,4*R*)-**6a** as a white solid (252 mg, 0.76 mmol); yield: 76%. $[\alpha]_D^{22} = -24.0$ (c 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.30 (m, 5H), 5.37 (s, 1H), 4.28 (s, 1H), 3.55–3.69 (m, 2H), 3.16 (d, 1H, $J = 14$ Hz), 2.97 (d, 1H, $J = 14$ Hz), 0.84 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ

173.47, 156.75, 133.52, 130.11, 128.73, 127.71, 109.44, 83.04, 45.39, 39.18, 34.26, 23.20. HRMS (*m*/*z*): Calcd for $C_{16}H_{20}N_4O_4$: $[M+Na]^+$ 355.1377. Found: $[M+Na]^+$ 355.1368. IR (cm^{-1}): 3351 (s), 3063 (br), 2970 (s), 2935 (s), 2161 (s), 1779 (s), 1718 (s), 1543 (s), 1230 (s).

4.9. (*R*)-3-Amino-2-hydroxy-2-alkylpropanoic acid (*R*)-1a–d

Under argon, a sealed tube was charged with carbamate (2*R*,4*R*)-**5** (0.2 mmol), 6 M aqueous HCl (2 mL). The mixture was stirred at 110–120 °C for 1 h, the solvent removed under reduced pressure and the residue treated at 110–120 °C with 6 M aqueous HCl (2 mL) for 10 h. The mixture was cooled to room temperature, diluted with water (2 mL), washed with ethyl acetate (2 × 3 mL), and concentrated to give the desired amino acid hydrochloride salt. Treatment of this amino acid hydrochloride salt with ethanol/propylene oxide gave (*R*)-**1** as a white solid.

4.9.1. (*R*)-3-Amino-2-hydroxy-2-benzylpropanoic acid (*R*)-1a. Yield: 94%; mp 254–256 °C (dec); $[\alpha]_D^{18} = -53.0$ (*c* 0.45, H_2O). ^1H NMR (400 MHz, D_2O): δ 7.09–7.15 (m, 3H), 7.03 (d, 2H, $J = 8$ Hz), 3.30 (d, $J = 13.2$ Hz, 1H), 2.91–3.00 (m, 2H), 2.79 (d, 1H, 13.1). HRMS (*m*/*z*): Calcd for $C_{10}H_{13}NO_3$: $[M+H]^+$ 196.0968. Found: $[M+H]^+$ 196.0969.

4.9.2. (*R*)-3-Amino-2-hydroxy-2-ethylpropanoic acid (*R*)-1b. Yield: 96%, mp 237–239 °C (dec); $[\alpha]_D^{18} = -18.0$ (*c* 1.0, H_2O). ^1H NMR (400 MHz, D_2O): δ 3.15 (d, $J = 13.6$ Hz, 1H), 2.92 (d, $J = 13.6$ Hz, 1H), 1.71 (q, 2H, $J = 7.2$ Hz), 0.98 (t, 3H, $J = 7.2$ Hz). HRMS *m*/*z* Calcd for $C_5H_{11}NO_3$: $[M+H]^+$ 134.0814. Found: $[M+H]^+$ 134.0816.

4.9.3. (*R*)-3-Amino-2-hydroxy-2-allylpropanoic acid (*R*)-1c. Yield: 95%; mp 243–245 °C (dec); $[\alpha]_D^{18} = -43.7$ (*c* 0.50, H_2O). ^1H NMR (400 MHz, D_2O): δ 5.70 (m, 1H), 4.95–5.04 (m, 2H), 3.13 (d, $J = 13.6$ Hz, 1H), 2.90 (d, $J = 13.6$ Hz, 1H), 2.46 (dd, 1H, $J = 14$, 6.8 Hz). 2.18 (q, 1H, $J = 14$, 7.2 Hz). HRMS (*m*/*z*): Calcd for $C_6H_{11}NO_3$: $[M+H]^+$ 146.0812. Found: $[M+H]^+$ 146.0816.

4.9.4. (*R*)-3-Amino-2-hydroxy-2-methylpropanoic acid (*R*)-1d. Yield: 96%; mp 225–227 °C; $[\alpha]_D^{18} = -11.5$ (*c* 1.0, H_2O). ^1H NMR (400 MHz, D_2O): δ 3.13 (d, $J = 13.6$ Hz, 1H), 2.93 (d, $J = 13.6$ Hz, 1H), 1.25 (s, 3H). HRMS (*m*/*z*): Calcd for $C_4H_9NO_3$: $[M+H]^+$ 120.0655. Found: $[M+H]^+$ 120.0652.

4.10. (*S*)-3-Amino-2-hydroxy-2-alkylpropanoic acid (*S*)-1a–d

As described for enantiomers (*R*)-**1a**–**d**, compounds (*S*)-**1a**–**d** were obtained from compounds (2*S*,4*S*)-**5a**–**d**.

4.10.1. (*S*)-3-Amino-2-hydroxy-2-benzylpropanoic acid (*S*)-1a. Yield: 95%; mp 254–256 °C (dec); $[\alpha]_D^{18} = +53.2$ (*c* 0.23, H_2O).

4.10.2. (*S*)-3-Amino-2-hydroxy-2-ethylpropanoic acid (*S*)-1b. Yield: 96%; mp 237–239 °C (dec); $[\alpha]_D^{18} = +18.0$ (*c* 1.0, H_2O).

4.10.3. (*S*)-3-Amino-2-hydroxy-2-allylpropanoic acid (*S*)-1c. Yield: 95%; mp 243–245 °C (dec); $[\alpha]_D^{18} = +43.5$ (*c* 0.54, H_2O).

4.10.4. (*S*)-3-Amino-2-hydroxy-2-methylpropanoic acid (*S*)-1d. Yield: 94%; mp 225–227 °C (dec); $[\alpha]_D^{18} = +11.2$ (*c* 1.0, H_2O).

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